

In Search of a Unifying Theory of Complex Brain Evolution

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The neocortex is the part of the brain that is involved in perception, cognition, and volitional motor control. In mammals it is a highly dynamic structure that has been dramatically altered in different lineages, and these alterations account for the remarkable variations in behavior that species exhibit. When we consider how this structure changes and becomes more complex in some mammals such as humans, we must also consider how the alterations that occur at macro levels of organization, such as the level of the individual and social system, as well as micro levels of organization, such as the level of neurons, synapses and molecules, impact the neocortex. It is also important to consider the constraints imposed on the evolution of the neocortex. Observations of highly conserved features of cortical organization that all mammals share, as well as the convergent evolution of similar features of organization, indicate that the constraints imposed on the neocortex are pervasive and restrict the avenues along which evolution can proceed. Although both genes and the laws of physics place formidable constraints on the evolution of all animals, humans have evolved a number of mechanisms that allow them to loosen these constraints and often alter the course of their own evolution. While this cortical plasticity is a defining feature of mammalian neocortex, it appears to be exaggerated in humans and could be considered a unique derivation of our species.

Key words: evolution; cortex; complexity

Introduction

How does evolution produce a complex brain? What are the factors that contribute to aspects of cortical expansion and organization in different mammals? How did human brains become so large and complex, and are they fundamentally different than the brains of other mammals? While these questions are inherently interesting, generating theories about brain evolution is a tricky business because one must strike a balance between known experimental data from extant mammals and inferences that can be made from these data regarding the unknown form of ancestral brains. For

this reason, studies of brain evolution have not been at the forefront of neuroscience research until quite recently. Without question, it can be more rewarding to directly record from a neuron and characterize its response properties or identify cells on a microscope than to assemble data from diverse disciplines to weave a cohesive story about a process that has been occurring for over four billion years.

However, within the last 5 years one can find numerous research papers, books, and popular press articles about brain evolution, and this resurgence of interest is due in large part to the development of new techniques. For example, recent advances in genetics have allowed us to sequence the genome of a number of animals including humans (Venter et al. 2001; see also Gregory et al. 2002; Waterston et al. 2002; The Chimpanzee Sequencing and Analysis Consortium 2005; Mikkelsen et al.

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2007). By comparing the genomes from these different species we are beginning to appreciate the genetic similarities that species share as well as the unique genetic alterations that have evolved in different species, especially in humans (e.g., Enard et al. 2002a,b; Hill & Walsh 2005; Mekel-Bobrov & Lahn 2006; Vallender & Lahn 2006). Another contributing factor to the resurgence of interest in brain evolution is the advancement of molecular techniques that have expanded our knowledge of the genetic and molecular mechanisms involved in neural development. Results from these studies enable us to make inferences about how developmental mechanisms may have been altered during evolution to produce variant phenotypes (see below). Finally, the use of noninvasive brain imaging techniques has allowed us to directly study the human brain and appreciate its stunning complexity in terms of sheer size, number of cortical fields, space allocation, and cognitive processing capacity. Our increased understanding of the brain and its development garnered from the techniques mentioned above has sparked a new interest, or at least revived a sleeping dinosaur in the field of neuroscience, and permits us to move out of the realm of speculation and into the realm of testable hypotheses.

What Is a Cortical Field and Why Study It?

Despite disagreement about how complex brains may have evolved and the relative contribution of genetic versus activity-dependent mechanisms to cortical development (see Krubitzer & Hunt 2007; Larsen & Krubitzer 2008 for review), most would agree that for mammals the major structure of the brain associated with higher level processes such as perception, cognition, and voluntary motor control is the neocortex. Support for this is particularly compelling in comparative studies of both primates and nonprimate mammals that demonstrate that the neocortex has

changed dramatically in different lineages in terms of size and organization compared to other structures. In addition, increases in size and complexity of organization are particularly pronounced in species that are considered “sentient” or those that exhibit complex behavior such as dolphins, elephants, and humans.

The neocortex is subdivided into basic units of processing that we term cortical fields. Cortical fields are identified and segregated from each other based on a number of criteria including a unique set of cortical and subcortical connections, neural response properties, a distinct appearance in histologically processed tissue, and sometimes a unique molecular signature. These criteria provide an important and useful means of subdividing the neocortex into distinct cortical fields and allow us to appreciate how cortical fields function collectively to generate particular types of perceptual, cognitive, and motor behaviors. However, theories of cortical evolution and studies of developmental and adult plasticity suggest that a cortical field is not a static structure, but rather a dynamic process or an event that changes throughout the life of an individual, either dramatically during development, or in a more limited fashion in adulthood. Because of this it is important to keep in mind that how we define a cortical field should be relative to the time during development or adulthood at which it is studied. Further, this view of a cortical field as a dynamic process or event underscores the difficulty inherent in the study of brain evolution.

How Do We Study Cortical Evolution?

One of the largest problems confronting the study of brain evolution is that it cannot be studied directly. For example, while a great deal can be learned about evolutionary trends and the genetic underpinning of mechanisms that generate specific phenotypes in a variety of different animals, it is much more difficult, and probably impossible, to directly study

how complex circuits in mammalian brains evolve. Fortunately, there are two approaches—the comparative approach and the developmental approach—that can be used to uncover the types of alterations that have occurred in the neocortex throughout the course of mammalian evolution and how those alterations were achieved.

The Comparative Approach

The comparative approach is a compelling method for examining similar features that all brains share as well as derivations or specializations that have arisen in different mammalian brains as a consequence of adaptation to a unique lifestyle and environment (Kaas 2007; Krubitzer 2007). This approach involves comparing distinct features of the neocortex of select mammals that ideally represent a number of phylogenetic branches of evolution, rather than just a few species such as monkeys, cats, and Mice (Fig. 1). There are a number of techniques that have been used to study the neocortex in different mammalian brains so that comparisons in the number, location, and connections of cortical fields can be made across different brains (Kaas 1982).

The traditional method used to make comparisons of the neocortex of different mammals is the architectonic method. This includes the use of cytoarchitecture, myeloarchitecture, chemoarchitecture, and a variety of other histological stains in different animals to examine various characteristics of a cortical field such as laminar organization, neurotransmitters utilized, and types of receptors present. Another set of techniques that are used to subdivide the neocortex are electrophysiological recording techniques for sensory cortex and intracortical microstimulation for motor cortex. Multi-unit and single-unit electrophysiological recording techniques allow us to determine the topographic organization of cortical fields, or cortical maps, as well as the response properties of neurons when stimulated with a unique type of sensory stimulus. Using these types of data we

can segregate cortical fields based on modality to which neurons respond as well as the features of a stimulus (e.g., direction, orientation) that neurons within a particular cortical field or cortical module prefer. Comparisons across brains can be quite compelling when electrophysiological recording data are combined with architectonic and histochemical distinctions. Studies that have combined these techniques have revealed an underlying organization of sensory and motor areas of the neocortex that all species share. This organization consists of a constellation of cortical fields including a primary visual area (V1), somatosensory area (S1; 3b in primates), and auditory area (A1), second sensory areas (e.g., V2, AAF or R, S2 and/or PV), a small posterior parietal region, and in eutherian mammals a primary motor area (Fig. 1; Krubitzer & Hunt 2007 for review).

In addition to electrophysiological and architectonic techniques, neuroanatomical tracing techniques that reveal the connections of a cortical field are also used to make comparisons between species. These comparisons reveal that there are basic patterns of thalamocortical and cortico–cortical connections present in different species, but that elaborations in connectivity have been made with the addition of new cortical fields in some lineages (Fig. 2). Similarities in cortical field organization, connectivity, and architectonic appearance that are ubiquitous across species are considered to be inherited from a common ancestor and thus homologous. On the other hand, there are aspects of organization, connectivity, and architecture that can be remarkably similar in one or two groups of mammals but are found to be independently evolved through a comparative analysis. Such similarities are homoplasious and indicate that there are serious constraints imposed on evolving nervous systems (see below). Taken together, the comparative approach allows us to appreciate similarities in brains that may be homologous or homoplasious. This approach also allows us to identify the differences that have evolved in different lineages, and to determine if the ways in which brains have

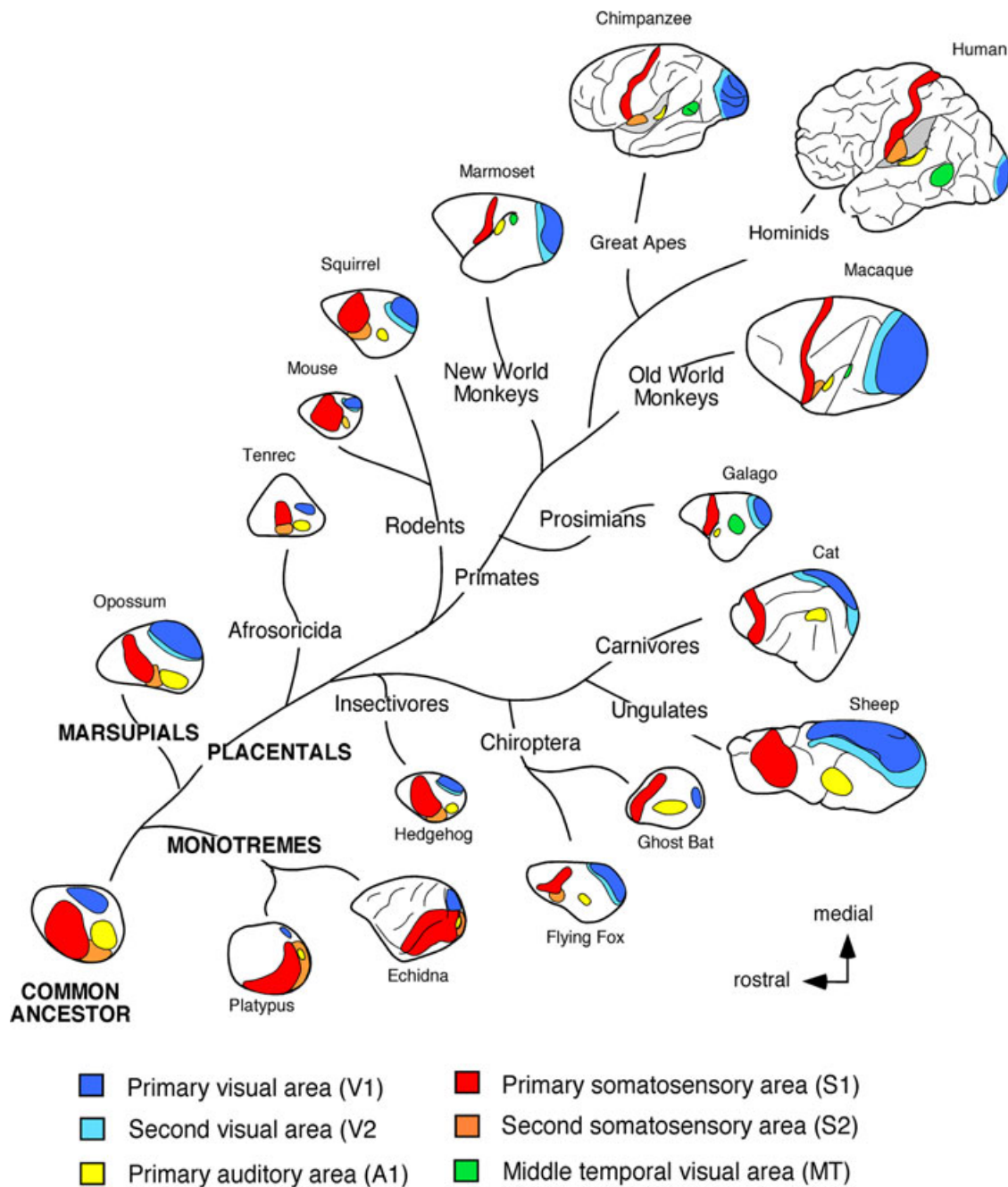


Figure 1. A phylogenetic tree illustrating the relationships between major mammalian lineages. All mammals contain a constellation of cortical fields that includes primary sensory areas as well as second sensory areas. These areas are likely due to inheritance from a common ancestor, and the ubiquity of their organization indicates that there is an underlying developmental blueprint that all mammals share. Some areas, such as MT are found only in primates. A comparative analysis allows us to infer how the brain of the common ancestor of all mammals was organized. Modified from Krubitzer & Hunt 2007.

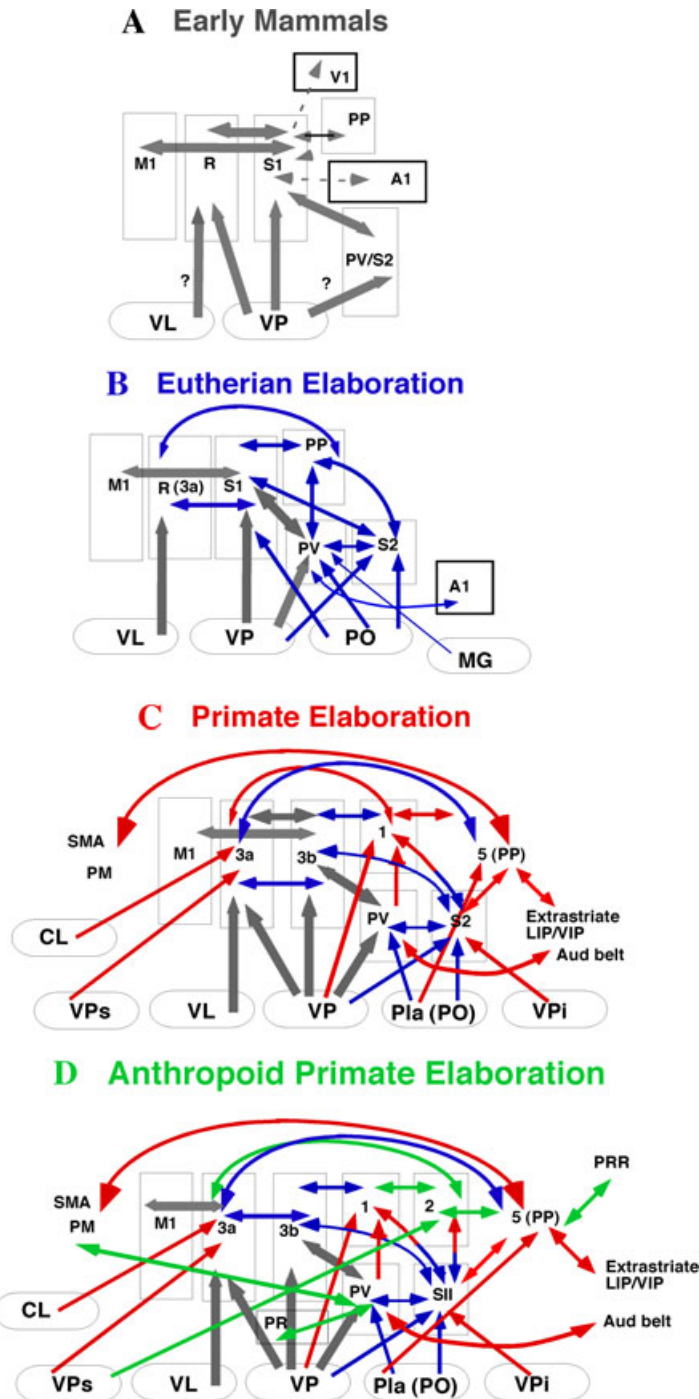


Figure 2. The pattern of connectivity of somatosensory cortex and thalamus in several groups of mammals. Comparative studies indicate that early mammals (**A**) had a very basic pattern of organization with only a few interconnected fields. (**B**) Eutherian mammals have retained the basic patterns of connectivity (grey arrows) but with the evolution of new areas they evolved novel patterns of connectivity (blue arrows). Primates in general (**C**) have an increased number of cortical areas and a further elaboration of connectivity (red arrows); the anthropoid primates (**D**) have further elaborations in terms of cortical number and connectivity

been modified is restricted (Krubitzer & Kaas 2005).

Because the cortical field is a dynamic event rather than a concrete immutable structure, any type of analysis we perform on the brain of an extant (living) mammal only provides a snapshot in the process of evolution. While the comparative approach has provided a lens with which to view these snapshots, it tells us little about the time-dependent mechanisms that drive these alterations or how these alterations are produced.

The Developmental Approach

The study of the evolution of a cortical field or any other portion of the brain is actually the study of the evolution of developmental mechanisms that give rise to an adult phenotype. Presumably developmental mechanisms are “tweaked” during evolution and these changes in developmental regimes produce variant adult phenotypes. Studies of development have revealed that both genetic and activity-dependent mechanisms contribute to the formation of the body and the brain and that alterations in both produce species differences. In terms of the former, there is a large body of work that demonstrates that the expression patterns for genes involved in the patterning of the body plan and basic brain morphology are highly conserved (e.g., Tallafub & Baily-Cuif 2002; Hirth & Reichert 2007 for review). For example, homeobox genes from the *Hox* family are involved in forelimb development in all mammals that have been studied, and in mammals with specialized forelimb morphology, such as bats, the expression pattern of these genes is slightly altered during forelimb development (Chen et al. 2005, Fig. 3). These “tweaks” are thought to be involved in

the transformation of the forelimb/hand morphology into a wing (Cretokos et al. 2001; Sears 2008; Sears et al. 2006). Specifically, retention of the webbing is accomplished through a combination of increased FGF and reduced BMP signaling, elongation of wing skeletal elements is thought to arise from increased BMP during chondrocyte maturation, and reduction of wing skeletal elements appears to arise from a posteriorization in the expression of *Hoxd13* in comparison to the expression of these genes in mice. Like portions of the body the emergence of the vertebrate forebrain and its major subdivisions is also accomplished by highly conserved homeobox genes from the *Hox* and *Otx* families, and similar combinatorial patterns of expression of these genes that generate basic forebrain organization are observed in both mammalian and nonmammalian vertebrates (Boncinelli et al. 1995, 2000; Hirth & Reichert 2007).

Regarding the mammalian neocortex there has been tremendous progress in identifying the early patterning genes that specify the location and size of cortical fields (e.g., Shimamura & Rubenstein 1997; Monuki et al. 2001; Grove & Fukuchi-Shimogori 2003; see O’Leary et al. 2007 for review). For example, early in development signaling molecules are expressed in patterning centers in the commissural plate (Fgfs), the cortical hem (Bmps and Wnts), and the ventral telencephalon (Shh). These signaling molecules define the major axes of the cortex (e.g., anterior/posterior, dorsal/ventral), and direct the graded expression of transcriptional factors such as Pax6, Emx2, and COUP-TFI. These transcriptional factors provide positional identities to cortical progenitors and their progeny in the cortical plate (e.g., Bishop et al. 2000; Fukuchi-Shimogori & Grove 2001; Armentano et al. 2007) and, in turn, guide the expression of other genes (e.g., cadherins

(green arrows). The connections shown here represent only a subset of all connections that have been demonstrated for primates. The basic plan of connectivity for early mammals and eutherians is inferred from comparative studies in monotremes, marsupials (early mammals) and rodents (Eutherian elaboration). From Krubitzer & Disbrow 2008.

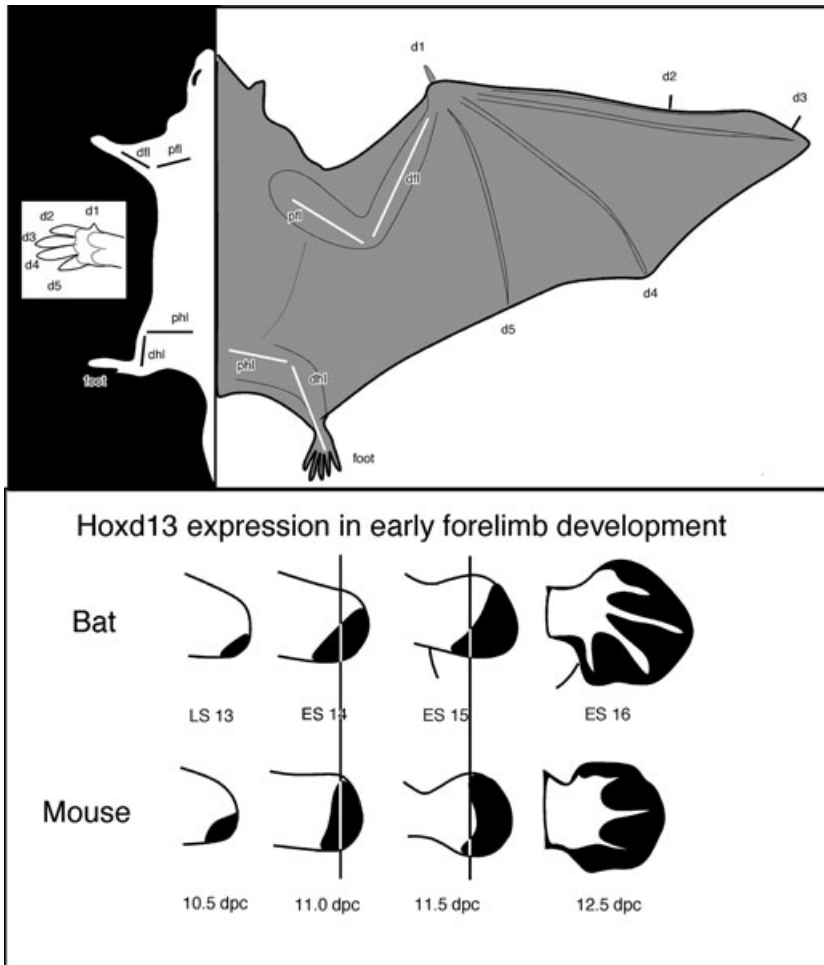


Figure 3. An illustration of the body plan of mice and bats (top) that depicts the major alterations to the forelimb that have emerged in bats. In bats, the digits (d) have elongated, the proximal and distal forelimb (pfl and dfl) have changed their relative lengths, and elongated membranes have grown between the digits, forelimbs and hindlimbs (distal dhl, and proximal phil). The expression of Hox 13 (bottom) in the developing forelimb of the bat and mouse has slightly different expression patterns (black areas), and these differences, in part, account for the very large differences in forelimb morphology in bats and mice. From Krubitzer & Hunt 2007.

and ephrins) that are localized to regions of the developing cortex and particular layers of the cortex. The genes expressed later in development are involved in a variety of functions that establish the identities of individual cortical fields (see O'Leary et al. 2007 for review). In addition to specifying the axis and location of cortical fields, a number of genes, including the ephrins, slits, and semaphorins, through a process of attraction and repulsion are involved in

axon guidance and fasciculation and synaptic development (Strochlic et al. 2007 for review). Studies in which the signaling molecules and transcription factors expressed early in development have been disrupted demonstrate that aspects of cortical organization including size and position of cortical fields can be altered dramatically (e.g., Bishop et al. 2000; Hamasaki et al. 2004; Armentano et al. 2007), but are never lost (Fig. 4).

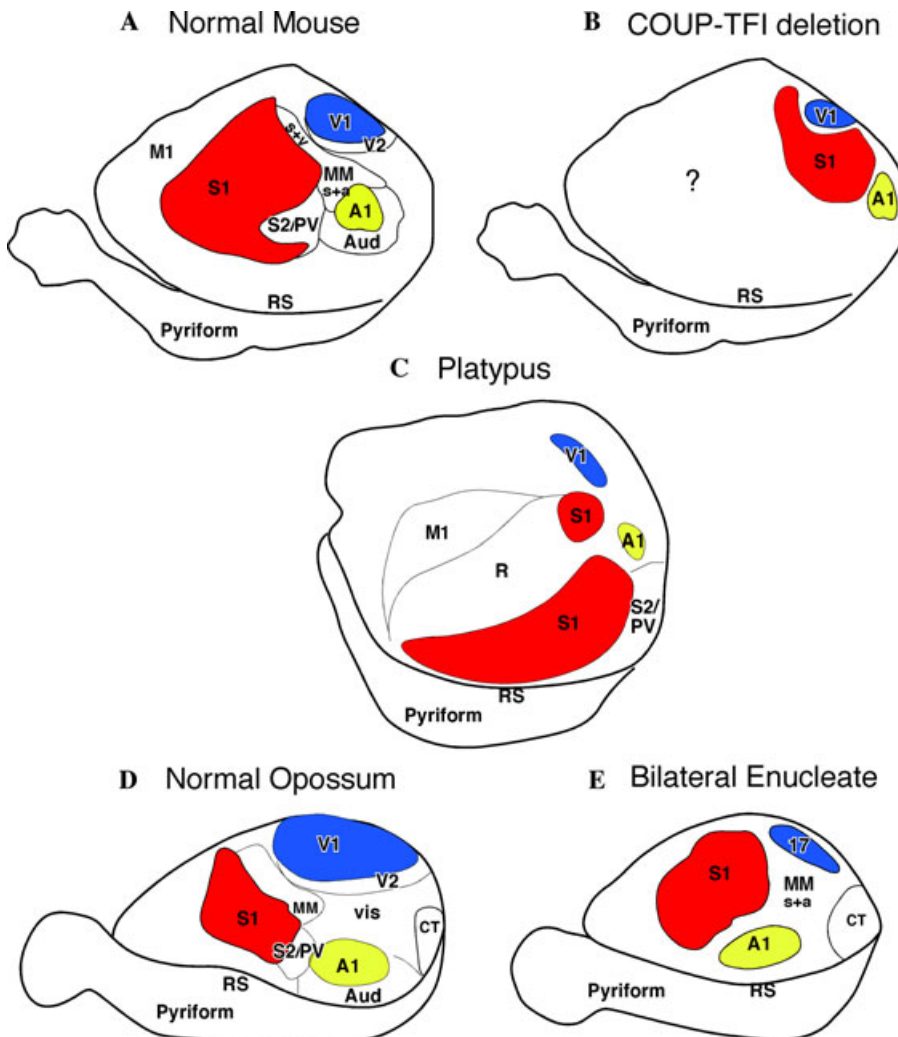


Figure 4. The organization of cortex in experimentally modified and normal mammals. In mice that lack COUP-TF1, cortical areas S1, V1 and A1 are smaller and are compressed at the caudal pole of the cortex compared to the location of these fields in normal mice (**A** and **B**). COUP-TF1 is expressed early in development and is believed to repress the identities of cortical progenitor cells that will become motor cortex. The caudalization of primary sensory areas in mice in which COUP-TF1 has been deleted looks remarkably like the caudalization of primary sensory areas in the normal platypus (**C**). It is possible that alterations in transcription factors such as COUP-TF1 in some lineages accounts for some of the variability observed in cortical field size and location in different mammals (see Fig. 1). Alterations in the size of cortical fields are also observed in mammals in which sensory input is removed, such as early bilaterally enucleated opossums (**D** and **E**). When considered together, these data indicate that both genetic and activity dependent mechanisms can alter features of cortical organization in different lineages. Modified from Armentano et al. 2007, Krubitzer et al. 1995, Kahn & Krubitzer 2002.

In addition to intrinsic genetic mechanisms, activity-dependent processes also play a major role in development. There is a plethora of studies that demonstrate that both spontaneous and

sensory-driven activity in development play a role in the emergence of a number of aspects of cortical and subcortical organization, including cortical field size, map formation,

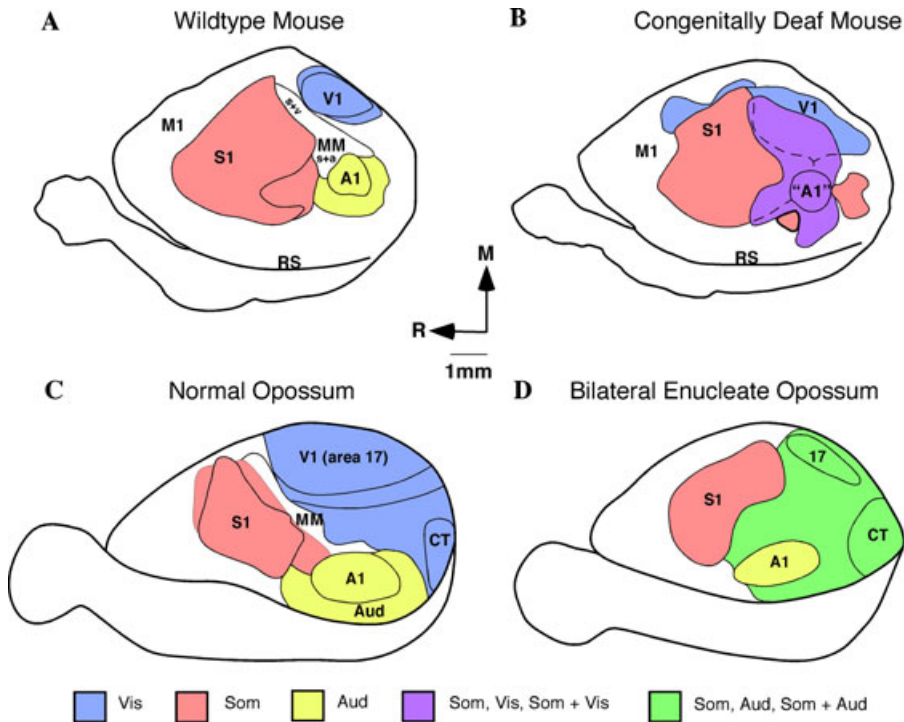


Figure 5. The organization of cortex in normal and congenitally deaf mice (**A** and **B**), and normal and bilaterally enucleated opossums (**C** and **D**). In both animals, loss of sensory driven input early in development results in a re-assignment of cortical space normally occupied by the lost sensory system. In congenitally deaf mice, the primary auditory area is taken over by the somatosensory and visual system and in bilaterally enucleated opossums, the primary visual area and all of visual cortex is taken over by the somatosensory and auditory system. See Hunt et al. 2006 and Kahn & Krubitzer 2002.

and connectivity (e.g., Feller & Scanziani 2005; Smith & Trachtenberg 2007; White & Fitzpatrick 2007 for review). The contributions of sensory input and sensory-driven activity to cortical organization are well demonstrated in studies that have removed sensory inputs or have modified sensory-driven neural activity. For example, both classic and modern studies in the visual system in cats and monkeys in which one or both eyes were sutured or removed early in development demonstrate that features of the organization of V1 and the response of neurons in V1 such as ocular dominance, orientation selectivity, and direction preference are altered (White & Fitzpatrick 2007 for review). At a systems level, bilateral enucleation, which results in complete loss of visual input to subcortical structures, results in a reduced size of V1 in both monkeys (Dehay et al. 1991; Rakic et al.

1991) and opossums (Kahn & Krubitzer 2002; Karlen & Krubitzer 2008). Further, the internal organization of V1 and both cortical and subcortical connections are altered (Karlen et al. 2006). Specifically, neurons in V1 respond to stimulation of other sensory modalities (Fig. 5), and V1 receives cortical and subcortical inputs from both visual and nonvisual structures. Major rerouting of subcortical connections has also been observed in congenitally blind and bilaterally enucleated mice in that ascending somatosensory projections from the dorsal column nucleus innervate the lateral geniculate nucleus (LGD) (Asanuma & Stanfield 1990). In bilaterally enucleated hamsters and blind mole rats, the inferior colliculus, normally associated with auditory processing, innervates the LGd (Izraeli et al. 2002; Piche et al. 2004; Doron & Wollberg 1994).

Experiments in the auditory system in mice in which the cochlea was still present but functionally impaired (Hunt et al. 2006) demonstrate similar alterations in the organization and connections of the primary auditory area (A1). In these mice A1 is reduced in size and neurons in A1 respond to somatosensory and visual stimulation (Fig. 5). Studies in rats in which the cochlea was intact and fully functioning but acoustic stimulation was greatly modified early in development demonstrate that cortical maps of A1 were dramatically altered, as were neural response properties (de Villers-Sidani et al. 2008; Zhou et al. 2008; Zhou & Merzenich 2008). These types of changes in map organization, cortical field size, and neural response properties have also been demonstrated in adults when sensory-driven activity is altered with loss of input or with skilled learning (e.g., Kaas 2000; Recanzone 2000). This sensory-driven neural activity and tremendous plasticity that occurs during development to construct cortical fields, and the persistence of cortical plasticity throughout adulthood to more subtly alter cortical maps, neural response properties, and connections is a defining and extraordinary feature of the mammalian neocortex.

The detailed molecular changes that allow for this plasticity in cortical organization are often driven by changes in gene expression during development (Hooks & Chen 2007 for review). However, the resulting phenotype produced by such molecular based changes is not heritable, and thus only persists when the environment in which the individual develops is relatively static.

While much of the work described above was done in mice, it is likely that the early genetic patterning of cortex involving the same genes exists in all species. This would explain the persistence of a common plan of organization in every mammal examined (Fig. 1) and the existence of vestigial sensory apparatus and cortical areas in mammals that do not appear to use a particular sensory system (see below). Many of the alterations to the cortical

phenotype in terms of cortical field size, number, and connectivity, occur via alterations in transcription factors and the genes they regulate, but can also be achieved through activity-dependent mechanisms (Figs. 4 & 5). However, unlike the known mechanisms for the formation of the wing of a bat, we do not know how these early genetic cascades are modified in the cortex of different species to produce variable phenotypes. Alterations in gross morphology of the brain, including the proportion of neural tissue devoted to the telencephalon, diencephalon, and midbrain structures, for example, are likely due to alterations in the expression patterns of early homeobox genes. But again, how these genes are altered in different species of mammals with different gross brain morphologies has only been studied in a limited fashion. Developmental studies identifying the genes and genetic cascades involved in cortical development provide an important foundation for future investigations of brain evolution. Specifically they have introduced the “major players” we can examine across multiple species with markedly different cortical organization (Fig. 4). This type of comparative gene expression analysis would allow us to determine if alterations in both spatial and temporal patterns of expression have actually occurred in the past to produce the plethora of different cortical phenotypes observed in living mammals.

Levels of Organization and Complexity

Two important factors to consider in any discussion of the evolution of complex nervous systems is how we define and measure complexity (Bullock 2007) and what level of organization we are interested in. The *Oxford English Dictionary* defines *complex* as: “consisting of parts,” “formed by combination,” “intricate, not easily analyzed or disentangled.” Thus, a good definition from a biological perspective is to consider brains with many parts complex, and a

complex neocortex as one with multiple cortical fields. When we examine the brain we can look at many levels of organization from the macro level that includes social systems, individuals, and cortical networks to the micro level that includes individual neurons, synapses, and molecules.

At a macro level of organization, groups of individuals (brains) interact to form social systems, and this level of organization has been observed in a variety of mammals from prairie voles to primates to dolphins. Some social systems are relatively simple such as that of the prairie vole, in which alloparenting and pair bonding occur (Carter & Getz 1993), while others are more complex. For example, a number of primate species have been observed to form cooperative alliances, engage in alloparenting, and disseminate culture and tradition throughout the group (e.g., Whiten et al. 1999; Perry 2008). It is interesting that other species, such as dolphins (e.g., Marino 2002) and elephants (Shoshani et al. 2006), also engage in some of these behaviors and like many primates have advanced cognitive abilities (Connor 2007). All of these species that have complex social interactions also have an extremely large cortical sheet (Fig. 6).

While this increase in the size of the cortical sheet was independently evolved in elephants, cetaceans, and primates, developmental studies suggest that increases in the size of the cortical sheet can be accomplished by altering cell cycle kinetics during neurogenesis in a variety of ways (e.g., Kriegstein et al. 2006; Chenn & Walsh 2002; see Fish et al. 2008). For example, the period of neurogenesis may be lengthened, the rate at which cells divide may be increased, and/or the number of cells that reenter the cell cycle and divide may be increased in mammals with a large cortical sheet compared to animals that have a small cortical sheet (e.g., Kornack & Rakic 1998; Kornack 2000). Regardless of the mechanism employed during evolution to produce changes in the size of the neocortex, it appears that increasing the size of the cortical sheet is necessary, although it may not be

sufficient, to generate the type of cortical complexity necessary to support sophisticated social systems.

Not only is the overall size of the cortical sheet variable in different mammals, the number of cortical fields is variable as well. Some mammals such as mice have about 10 cortical fields; other mammals such as macaque monkeys have more than 50 cortical fields (Fig. 7), and it is likely that humans have over a hundred cortical fields. While different areas are often associated with a particular function, in large brains with multiple cortical fields processing is distributed in networks so that a single cortical field often participates in multiple tasks or behaviors, and a given behavior is generated by multiple cortical fields. Further, larger brains with multiple cortical areas have increased the numbers of connections and this increased connectivity endows the brain with both tremendous processing power and flexibility in processing (Fig. 2).

In addition to an increase in the number of cortical fields and their connections, there is a change in the type of connectional network that has evolved, and this may fundamentally alter how bigger brains process information compared to smaller brains. For example, larger brains appear to have relatively fewer long range connections that connect distant areas of the cortex or the cerebral hemispheres, and they have more short, local connections necessary for time critical tasks (Ringo 1991; Ringo et al. 1994). These connections have optimal layouts based on the number, size, and location of cortical areas (e.g., Charniak et al. 2004), and it has been proposed that such “small-world” networks within the cortex have evolved to maximize complexity of processing with minimal costs (Bassett & Bullmore 2006). Selection for minimizing wiring costs such as is seen in decreasing the length of axons, decreasing brain size, and reducing of conduction delays is exemplified in a number of aspects of cortical organization, including the segregation of gray and white matter (Wen & Chklovskii 2005), the dimensions of axonal

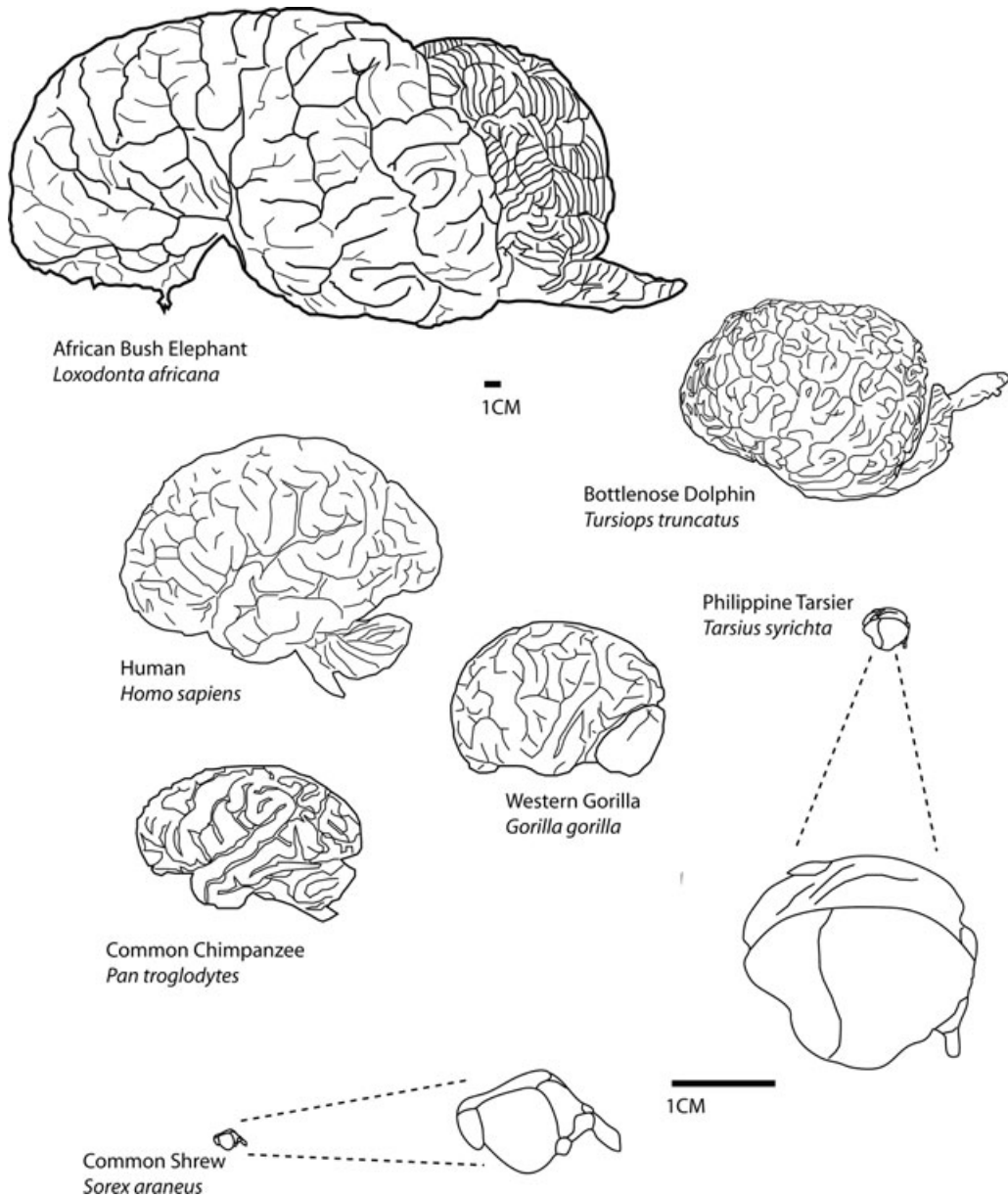


Figure 6. Illustrations of the brains of mammals that have evolved a large brain and a large cortical sheet. The enlargement of the elephant, dolphin, and anthropoid primate brains (apes and humans) is an example of convergent evolution since these increases in brain size were achieved independently. It is interesting to note that not all primates have a large neocortex. For example, the tarsier has a relatively small neocortex. The shrew is a nonprimate with an extremely small brain. Note that although tarsiers and shrews have relatively small brains, the proportion of the brain devoted to the neocortex is larger in the tarsier than in the shrew. All brains are drawn to scale; enlarged brains of shrew and tarsier are drawn to scale.

and dendritic arbors, and the existence of topographic maps, to name a few (see Chklovskii et al. 2002; Bassett & Bullmore 2006 for review).

Micro levels of organization, like the macro levels discussed above, also vary in terms of their complexity in different mammals. At a cellular level, one can count the number of



Figure 7. The organization of neocortex in the macaque monkey and mouse. The neocortex in each species has been flattened so that the relative size and location of cortical fields can be appreciated. In mice the neocortex is small, and a small number of cortical fields are identified. In the macaque monkey the cortical sheet is greatly expanded and there is a tremendous increase in the number of cortical fields. Despite differences in size and cortical field number, common (homologous) fields are still present and their relative location is the same in each species. Subdivisions for the monkey are from Hackett 2007, Lyon 2007, Wise 2007, Krubitzer & Disbrow 2008.

neurons in larger brains with more cortical areas and ask if neurons become more plentiful if they become more densely packed, or if they simply get larger. Using a technique called isotropic fractionation, Herculano-Houzel and colleagues (2007, 2008) found that for primates larger brains have more neurons (and more glia) and that the number of neurons scale linearly with the increased size of the brain. Thus, the average size of neurons does not increase in bigger brains: neurons are just more plentiful, although there are some exceptions. This conclusion is supported by comparative studies of basic cellular morphology in large-brained macaque monkeys and small-brained dunnarts (Tyler et al. 1998). These studies demonstrate

that despite the differences in the size of the primary visual area (V1) and the thickness of the cortex, the size of pyramidal neurons and their branching patterns are constant, as are the patterns of intrinsic connections (Tyler et al. 1998). In general, other features of cellular organization including the types of cortical neurons present and the percentage, length, and density of synapses appear to be constant in mammals (DeFelipe et al. 2007). Thus, certain features of cellular morphology are relatively stable across species.

However, alterations to these conserved features of cellular morphology have been observed. For example, in primates specialized dendritic branching patterns and increases in

spine density have been observed in pyramidal cells in sensory, motor, and prefrontal cortex (e.g., Elston et al. 2005a,b), and some of these specializations appear to be linear (e.g., more spines) as brains increase in size. Comparative studies of cell morphology demonstrate that humans and some great apes have distinct cellular subtypes such as spindle-shaped cells in anterior cingulate, frontoinsular, and primary motor cortex, and that only humans have a distinct type of pyramidal cell (CR-ir) in anterior paracingulate cortex (Sherwood & Hof 2007). Further, humans appear to have more interneurons and more types of interneurons (DeFilipe et al. 2007). Finally, the basic electrochemical properties of neurons are highly conserved across the animal kingdom. The presence of sodium and potassium channels, aspects of membrane permeability, and synaptic transmission, for example, are observed universally. However, the addition of pre- and postsynaptic elements, such as the evolution of new receptor types or the cooperative function of receptors (e.g., NMDA and AMPA) in some groups of animals, change the conditions under which neurons fire and have important implications for learning and plasticity.

The observations that, in general, neurons do not change in size and basic synaptic structure and that basic electrochemical properties of neurons are highly conserved suggest that there are large constraints on cellular evolution. Recent computational studies provide some insight into this issue and suggest that dendritic branching patterns of neurons have evolved to minimize costs while optimizing information processing of synaptic inputs that combine nonlinearly (Wen & Chklovskii 2008). These investigators demonstrate that the optimal dendritic arbor for the Purkinje cell, for example, which reduces the cost of plasma membrane (associated with energy to maintain the resting potential) would be planar, compact, and centripetal. Thus, although subject to a number of constraints, neurons tend to optimize their morphology based on a few simple requirements.

There appears to be a loose correlation between the emergence of complexity at the different levels of organization; complex social systems are associated with a larger and complex neocortex, and a large complexly organized neocortex has more neurons that have morphological specializations associated with increased processing capacity. What is not clear is whether similar principles or rules for generating more parts are applied to all levels of organization, and how changes that have evolved at one level affect the organization of other levels. It is likely that these interactions are complex and nonlinear. Further the resultant phenotype at any given level may be functionally optimal, but not necessarily the best independent solution to a particular challenge.

Finally, it is important to note that while brains have generally increased in size from that of the common ancestor, this is not always the case for all lineages (Kaas 2002). From an evolutionary standpoint a neocortex that is more complex does not necessarily provide a selective advantage. For example, rodents are a highly successful order composed of species occupying terrestrial, arboreal, aquatic, and fossorial habitats as well as diurnal and nocturnal lifestyles, and, with few exceptions, rodents have relatively small brains. In fact, most mammals have relatively small brains that are functionally optimized for cortical processing in their respective environments (Catania 2007).

Convergent Evolution and Constraints Imposed on Nervous Systems

Before we discuss the factors that constrain evolution it is important to establish that such constraints exist. Examples of both homologous and homoplastic features of cortical organization are compelling evidence for these constraints. For instance, the ubiquity of a common mammalian plan of cortical organization (homology) with a consistent spatial layout is remarkable. This is particularly compelling when

one considers that some animals may not use the visual system for activities other than circadian rhythms (as in the case of blind mole rats), but still maintain a primary visual area (V1) (Heil et al. 1991; Bronchti et al. 2002). Further, in experimental paradigms in opossums in which both eyes were removed very early in development (Kahn & Krubitzer 2002) V1 is still present (Fig. 5). In both blind mole rats and opossums V1 is reduced in size and some aspects of connectivity are maintained while others are altered (e.g., Bronchti et al. 1989; Karlen et al. 2006), suggesting that while some features of a primary cortical field can be altered, primary cortical fields cannot be eliminated. This persistence of highly conserved features of structure and function occurs at cellular and molecular levels as well (see above).

Another indication that very large constraints are imposed on evolving nervous systems is that structures or aspects of organization look remarkably similar despite distant phylogenetic relationships (homoplasy). This convergent evolution is observed at all levels of organization. Anthropoid primates and cetaceans (dolphins, whales, and porpoises) have differences in body and brain morphology and cortical organization compared to other mammals. Despite these differences—and the differences in the environments they inhabit (aquatic vs. terrestrial/arboreal)—both groups have similar social structure (fission—fusion), both groups form cooperative alliances or coalitions, and both engage in alloparenting, tradition, and culture (see Marino 2002, 2007; Marino et al. 2007 for review). In addition, both groups have evolved complex communication systems and self-recognition ability. Finally, as noted in the previous section of this review, both groups have independently undergone extreme cortical expansion. This convergence of complex, high-level social and cognitive abilities in primates and cetaceans is remarkable given that the divergence between the ancestral mammal groups that eventually led to cetaceans and primates occurred around 90–95 million years ago (MYA; Kumar & Blair Hedges 1998).

At the level of the cortex, convergent layouts of visual areas and their interconnections have emerged independently in squirrels and tree shrews (see Kaas 2002). In the somatosensory cortex, individual cortical areas that are similar in location, organization and connectivity have emerged in New World cebus monkeys and anthropoid primates (Fig. 8; Padberg et al. 2007). The cebus monkeys has an opposable thumb that evolved independently from that of anthropoid primates (Napier & Napier 1967; Fleagel & Simons 1995, Rose 1996). In addition, they have the highest encephalization quotient of all New World monkeys (Rilling & Insel 1999) and are considered socially complex because of sophisticated tool use and social transmission of culture and tradition (Fernandes 1991; Fragaszy et al. 2004; Waga et al. 2006; Perry 2008). Despite 60 million years of independent evolution, like anthropoid primates but unlike other New World monkeys, cebus monkeys have a cortical proprioceptive area, termed area 2, and an expanded posterior parietal cortical area, area 5 (Fig. 8), and both of these areas are involved in intentional reaching and grasping.

Convergence has also been observed at the level of modules within cortical fields in that many rodents and at least one species of marsupial (Weller 1993; see Karlen & Krubitzer 2007 for review) have evolved a barrel field in S1 associated with the mystacial vibrissae. The ancestral mammals that ultimately gave rise to rodents and marsupials diverged about 180 MYA. Similar barrel-like arrangements of cells have been observed in insular cortex in dolphins (Manger et al. 1998) (Fig. 9). It is interesting that although the dolphin brain is about 3000 times larger than the brains of most rodents and marsupials, the size of the “barrels” observed in each is similar. In fact, a comparative analysis of module size in different cortical areas in a variety of mammals indicates that the range of module size is limited, regardless of the overall size of the brain or cortical field (Manger et al. 1998). It has been suggested that selection for minimal wiring length drives the

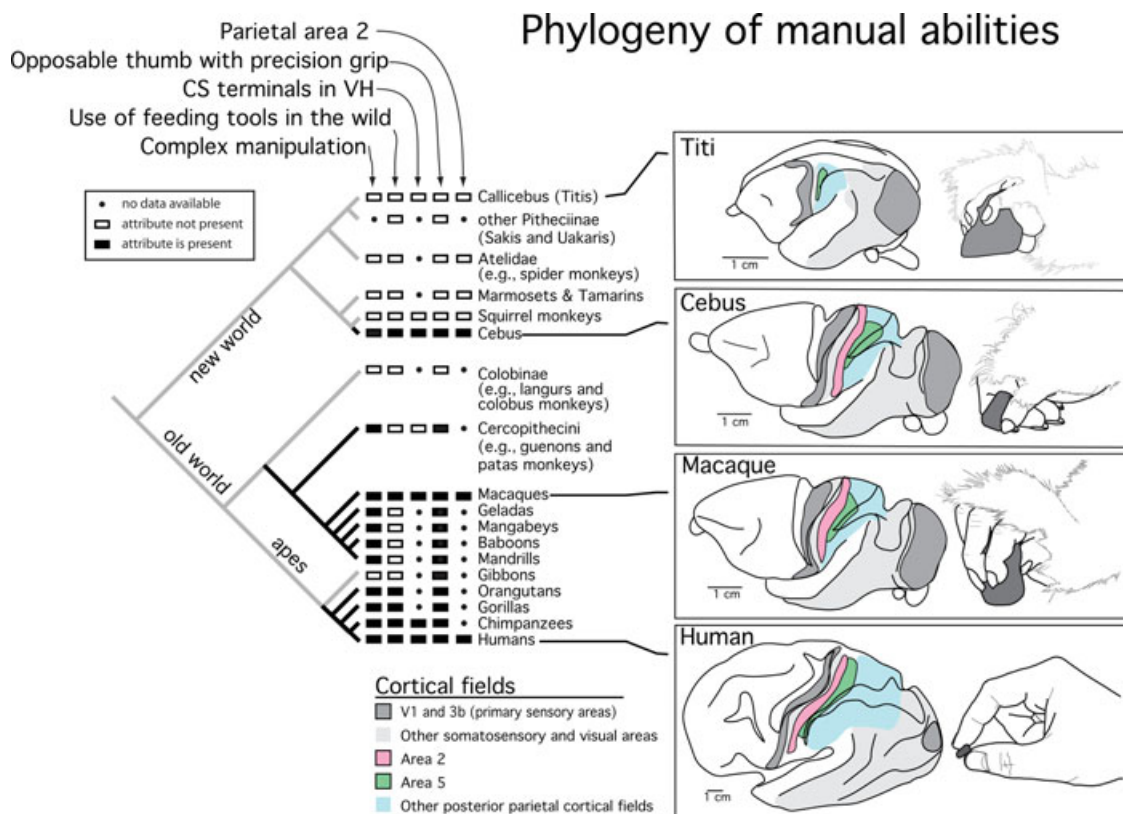


Figure 8. The evolution of manual abilities in primates and cortical areas associated with hand use. Although the titi monkey and cebus monkey are closely related, the morphological structure of the hand, the corticospinal terminations in the ventral horn, the use of tools, complex manipulation, encephalization, and cortical organization is more like that of their distant cousins, macaque monkeys and humans. In particular the cebus monkey has evolved a cortical area 2 (pink) and an expanded area 5 (green), which are both involved in manual abilities. This is a remarkable example of independent evolution at a number of levels of organization, from hand morphology, to cortical field, to complex abilities such as tool use. From Padberg et al. 2007.

size of modules in all mammals (Manger et al. 1998). Finally, convergence has been observed at the level of individual neurons. Electrophysiological recordings in V1 of the diurnal wallaby indicate that a number of response properties including orientation selectivity and spatiotemporal tuning are similar to that of primates, but not other marsupials (Ibbotson & Mark 2003), most of which are nocturnal.

The studies cited above represent only a few of the many examples of convergent evolution in mammals, from the level of social systems and cognition to the level of neural response properties. These examples of independent emergence of behaviors, brains, and

cortical fields indicate that the evolution, and thus the development of the nervous system, is highly constrained. Although genes are the cornerstones of evolution, natural selection acts on individuals and behaviors, rather than on larger or smaller levels of organization. Because the constraints imposed on developing nervous systems are the same for all animals, it is not surprising that cortical phenotypes are highly predictable. In fact, it has been argued that homologous developmental programs that are subject to similar selective pressures and the same intrinsic and extrinsic constraints generate inescapable outcomes at all levels of organization (e.g., Padberg et al. 2007).

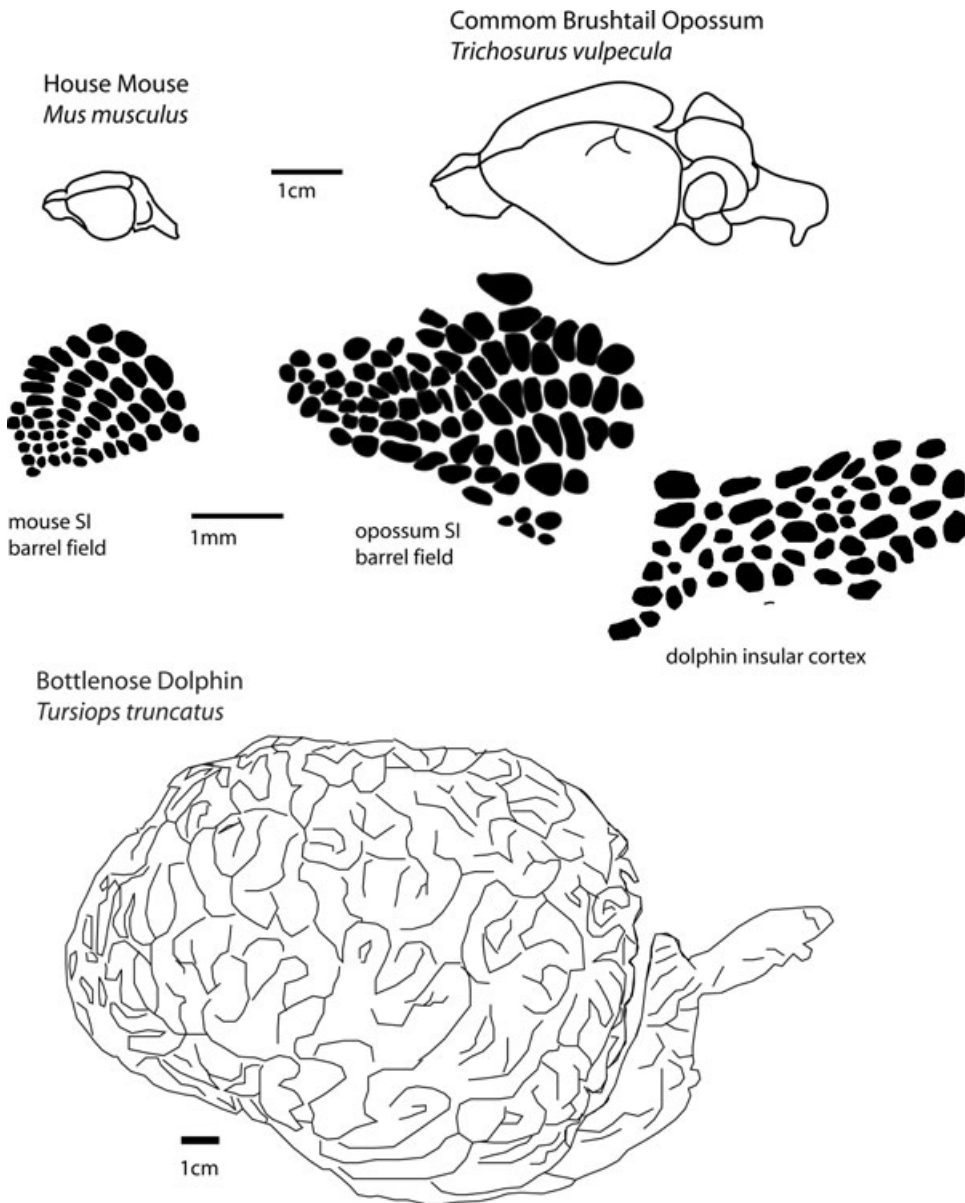


Figure 9. The arrangement of modules in mice, opossum, and dolphin neocortex. In mice and opossum, these modules (middle row) are located in the primary somatosensory area and form the barrel field of the mystacial vibrissae. In dolphins, these modules are in insular cortex and are probably associated with auditory processing. Despite about 180 million years of independent evolution of the lineages that led to modern mice and brush-tailed opossums, and 90 million years of independent evolution of the lineages that gave rise to modern mice and dolphins, the size and shape of the modules is remarkably similar. This is noteworthy since the overall size of the neocortex is so large in dolphins compared to the other two species. Modified from Manger et al. 1998; barrels of opossum are from Weller 1993.

The persistence of a common plan of organization and the independent evolution of similar types of modifications to this basic plan are due to two major constraints imposed on

developing and evolving nervous systems: the genetic code and the laws of physics. There are several ways in which genes constrain the evolution of the nervous system. First, several

highly conserved genes expressed early in development in animals ranging from arthropods to mammals generate immutable aspects of body plan development including establishing the anterior/posterior axis, segmentation of limbs, and midline designation (see Hirth & Reichert 2007 for review). Second, highly conserved homeobox genes such as those from the *Otx* and *Hox* families, *Emx* genes and *Pax* families, and columnar genes (e.g., *Msx*, *Dsh*, *Nkx*) regulate the major axes of the brain including the head/trunk boundary (Tallafub & Bailey-Cuif 2002), the dorsoventral axis (see Urbach & Technau 2008) and anterior/posterior axis (see Lichtneckert & Reichert 2008). While the amount of territory devoted to different major brain subdivisions varies across species, these subdivisions are never lost, the axes of organization is maintained, and their spatial relationship is highly consistent. Third, recent evidence has shown that there are very old, highly conserved noncoding elements of genes in both vertebrates and invertebrates, and these elements (*cis*-regulatory) regulate genes involved in major developmental processes such as body patterning and morphogenesis (McEwen et al. 2006; Vavouri et al. 2007). Thus, not only are genes that regulate major aspects of the brain and body highly conserved, but also the way that they are coordinated appears to predate vertebrates.

A final way in which genes constrain cortical evolution is in how they are deployed during development. As noted above in The Developmental Approach, there is a cascade of genetic events, possibly coordinated by duplication of highly conserved, *cis*-regulatory elements that set up contingencies that effectively constrain how development proceeds. If we consider cortical development as an “if/then” proposition, then the removal of one event will halt or disrupt the subsequent cascade of events necessary for individual and brain viability. The earlier in development that some change to this genetic cascade occurs, the greater the probability for significant change to the phenotype, but also for decreased viability. Thus, while evo-

lution is the continuing process of modifying contingencies, selection acts to reduce change that results in early death or decreased neural viability.

The second major constraint on evolving nervous systems is the shared physical environment that includes but is not limited to light, sound, temperature, heat, and gravity. The nervous system must interpret the patterns and intensity of these stimuli as they occur in different combinations and different media. There is a large body of evidence that these factors directly affect the developing body and behavior, which in turn affects brain organization, and further evidence indicates that these factors can also affect the developing brain directly. For example, different gravitational forces can alter body morphology by affecting bone density (Singh et al. 2005) and the extracellular matrix of tissue such as muscle via changes in gene expression (Silver & Siperko 2003). Thus, different gravitational stress conditions (e.g., terrestrial vs. aquatic) produce different and optimal morphological phenotypes, and these types of alterations to the body can affect the organization of both sensory and motor cortical areas. Gravity also has a direct effect on the development of descending pathways of the spinal cord, motor neuron development (Brocard et al. 2003), the levels of nerve growth factor and brain-derived nerve growth factor produced, and even behavior (Santucci et al. 2008). Salinity and humidity can affect body morphology (Johnston & Gottleib 1990), and temperature can affect body mass, body length, and ear and tail length (e.g., Villarreal et al. 2007). Temperature can also affect the genes associated with neural development whose pattern of expression is thermosensitive (Tsai et al. 2007). In some amniotes such as lizards, temperature can determine the sex of the offspring, and different incubation temperatures differentially affect male versus female fitness (Warner & Shine 2008).

At a more refined level, there is a wealth of data that demonstrates the important role of sensory-driven activity during early development. For example, alterations in the acoustic

environment can result in changes in the size and internal organization of the primary auditory area (A1), and the neural response properties of A1 (de Villers-Sidani et al. 2008; Zhou et al. 2008; Zhou & Merzenich 2008). Complete loss of input or lack of sensory-driven activity from one sensory system can dramatically alter cortical field size, functional organization, and connectivity (Fig. 5; Kahn & Krubitzer 2002; Karlen et al. 2006; Karlen & Krubitzer 2008; see Krubitzer & Hunt 2007 for review). I use these examples of the systems level changes that can occur when sensory-driven activity is altered or lost during development to underscore that the amount and types of physical stimulation present during development are crucial for determining the phenotype that emerges. These stimuli, even when they take the form of a mother's voice, screaming siblings, or a television droning, are nothing more than complex packages of physical stimuli present in any given environment.

Given that the laws of physics are invariant, it is not surprising that sensory-driven activity not only plays a major role in shaping the cortex to function optimally in a given environment, but that the physical parameters of any form of energy place formidable constraints on brain evolution (see Krubitzer 2007 for review).

Questions Posed

If I return to the questions posed at the beginning of this review I think we can begin to answer them. We have some understanding about how brains become larger; we also know that genes provide the basic framework of body plan and brain organization. On the other hand, the ultimate adult phenotype that is produced owes as much to the specific parameters of the physical environment in which it develops as it does to genes. Because all mammals are enslaved by the same rules of construction during development and by the laws of physics, there are far more similarities between species than there are differences.

But what about humans? Are they fundamentally different? Human brains have undergone enormous expansion during evolution, and cortical asymmetries have emerged that allow particular tasks to be processed intrahemispherically (Corbalis 2007). Human brains have more cortical fields, cortical fields have more neurons, and specific cortical fields are associated with unique behavioral specializations such as language. Humans have unique types of neurons and more and varied interneurons, and several features of the genome that have been characterized as unique to humans are involved in brain development. So, of course humans have specializations that make them unique, but so do all other species. The difficult part lies in figuring out how these varied specializations, observed at all levels of organization, make us uniquely human rather than uniquely cat or uniquely platypus.

Probably the most remarkable feature of the human neocortex is one that is difficult to measure and cannot be reduced to a cell type or a particular cortical field. This is our ability to loosen the constraints imposed on the development and evolution of our own nervous system; the ability to be plastic; the ability of our neocortex, and, in turn, our behavior to change dramatically throughout a lifetime. This plasticity is present in all mammals, but appears to be exaggerated in humans. Thus, the dynamic alterations to the physical environment that include changes in voice cadence, light levels, and even global temperature, which humans so notoriously produce, allow us to directly and often knowingly influence the development and evolution of our own brains and the brains of other mammals.

Is There a Unifying Theory for Brain Evolution?

Yes. Darwin provided the most important unifying theory in biology with his discovery that evolution is driven through natural selection of variant phenotypes. While his theory

is still the foundation of all biological science, at the time it was proposed it was incomplete because there was no information about molecules or genes, and our understanding of brains was in its infancy. Since that time there has been tremendous progress on all fronts of biology as well as in physics. Today, science is becoming more multidisciplinary, and we have more information from more disciplines on brain evolution and development than we have ever had in the history of science. However, despite our progress we are restricted by our own capacity to understand the larger levels of organization and their boundary conditions, and the interplay between different levels of organization to produce complex biological systems (Polyani 1968; Streidter 2007).

What we know is that the brain and particularly the neocortex is not a static entity, but a dynamic process that is continually shifting and changing within the life of an individual and in species over time. When we consider larger levels of organization in which groups of individuals within and across species interact within a common physical environment, we have a collective biomass or an emergent entity in which the behavior of individuals and populations substantially alters the physical environment in which an individual develops, and thus the brain itself. Because of this we need to put the neurons that we study back into the brain, the brain back into the body, and the body back into a physical environment if we hope to achieve an understanding of the larger story of the evolution of complex nervous systems.

Conflicts of Interest

The author declares no conflicts of interest.

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