Neuron
Minireview

The Magnificent Compromise: Cortical Field Evolution in Mammals

Leah Krubitzer[1,*]
[1]Center for Neuroscience and Department of Psychology, University of California, Davis, Davis, CA 95618, USA
*Correspondence: lakrubitzer@ucdavis.edu
DOI 10.1016/j.neuron.2007.10.002

The neocortex of mammals is composed of cortical fields that have a unique organization associated with the animal's ecological niche and lifestyle. Each cortical field has a specific pattern of connections with other cortical fields and brain structures, and together they comprise a neocortical network that generates a variety of behaviors. These networks and the behaviors they generate are variable across mammals, and are particularly complex in some species such as humans. Here I discuss the mechanisms that contribute to neocortical organization in mammals, and how this organization has been altered to generate the variability that exists in different lineages.

Introduction

The brain is not a well-designed machine, but a magnificent compromise. It has a long and demanding history, and it is the product of a number of competing factors that constrain its future form and function. These factors include the genes that construct a viable organism during development, and the parameters of the physical world, both animate and inanimate, that it must translate, predict, and ultimately instruct the body to act upon. Of particular interest to my laboratory, and the focus of this issue of *Neuron*, is the neocortex. The neocortex is involved in a variety of complex functions and is considered by many to be the defining feature of mammalian brain evolution, and its expansion, the pinnacle of human evolution. How is this structure generated in evolution and how do alterations to the phenotype arise? To what extent are phenotypic characteristics of the neocortex genetically based and thus evolutionary, and to what extent are they context dependent, and thus persist only in relatively stable environments? While my laboratory and others have generated several proposals on how complex brains evolve and have begun to address the questions posed above using a variety of different approaches, there are a number of obstacles that make it difficult to study brain evolution directly.

For example, brains evolve over tens of thousands of years, and neural tissue does not fossilize. Therefore, the physical evidence of brain evolution comes from endocasts of skulls, which provide information only on overall brain size, shape, and fissure pattern, but not on the functional organization and connections of cortical fields in our ancient ancestors. These problems can be circumvented by comparing the brains of a variety of mammals to determine the features of neocortical organization that are similar, due to inheritance from the common mammalian ancestor (homology), and the features that are a specialization of a particular lineage and related to alterations in lifestyle and ecological niche (Bullock, 1984). While the comparative approach is a powerful method that has been used to great advantage by a number of investigators, results from this type of analysis can be difficult to interpret. Specifically, any mammalian brain that we observe is a frozen moment in the process of evolution; it has its own evolutionary history and at some point has evolved independently. Because we examine the brain at a fixed point in time, this approach tells us little about how phenotypic transformations occur. This is where studies of cortical development can inform comparative studies.

Phenotypic changes occur when some aspect of development is modified either by intrinsic, genetically mediated mechanisms, and/or by epigenetic events such as changes in the physical environment that alter neural activity in the developing organism. Studies of cortical development have demonstrated that each has a profound effect on the ultimate cortical phenotype that emerges, and that these mechanisms operate in concert to generate a particular type of neocortex (described below).

Finally, a particularly salient challenge associated with studying neocortical evolution is the anthropocentric nature of our quest. Currently, there is an enormous effort to understand which genes and proteins are unique to humans, and which features of brain organization and behavior distinguish us from other mammals, particularly our close relatives the chimpanzees. While it is inherently interesting to understand the features of the brain and the types of behavior that make us different, in reality, the similarities in the brains of mammals, including humans, far outweigh the differences (see Krubitzer, 1995). Thus, it is equally fruitful to examine the similarities that exist in mammalian brains, and *then* explore the derivations or specializations of the human brain with an understanding of the rules that underlie how brains are constructed in development, the factors that contribute to phenotypic variation and species specializations, and the constraints under which the evolving nervous system operates.

How Are Brains Similar?

Comparative analysis from a variety of mammals that represent major branches of evolution has demonstrated that

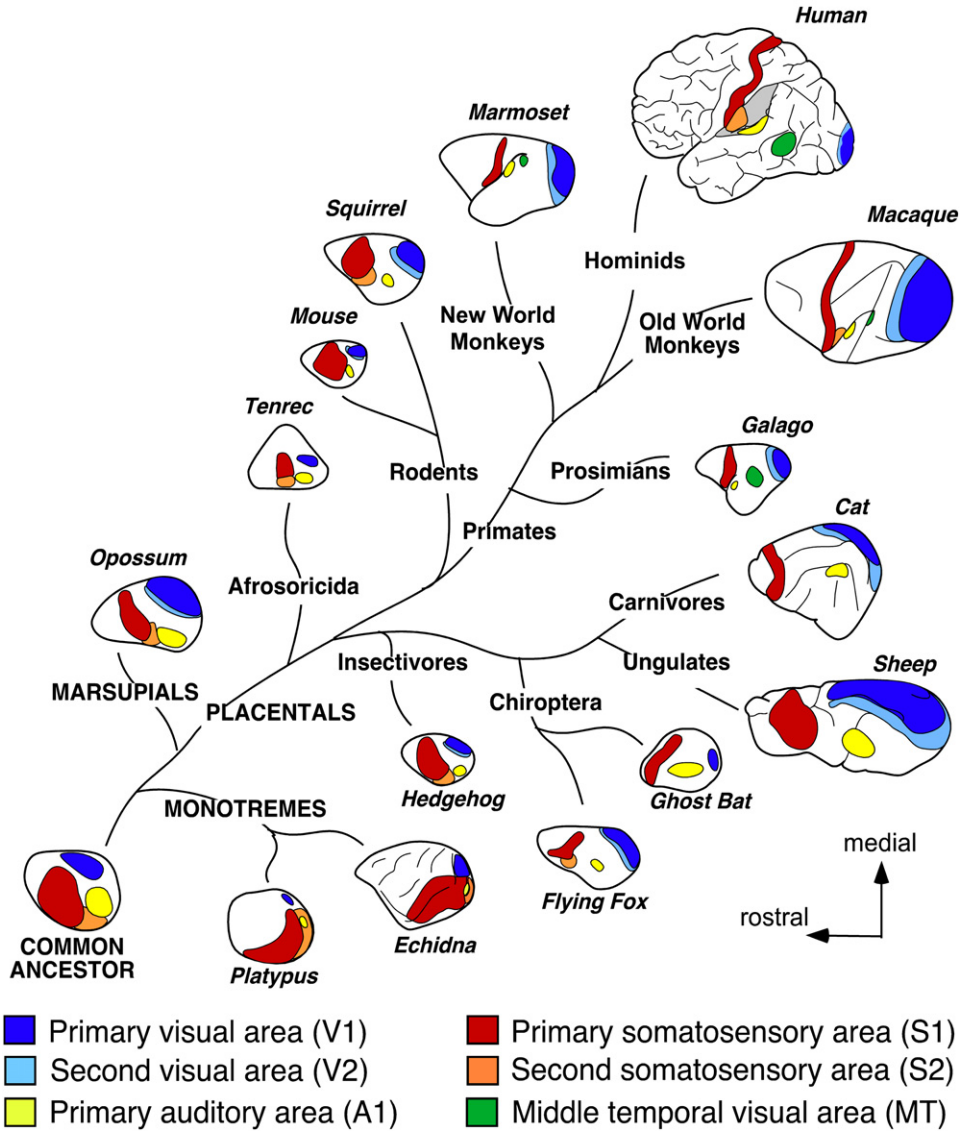

Figure 1. A Phylogenetic Tree Illustrating the Relationship between Major Groups of Mammals
Common cortical fields have been identified in all species examined. The genes involved in specifying these areas in development were likely inherited from the common ancestor of all mammals. Modified from Krubitzer and Kahn, 2003.

there is a constellation of cortical fields that all mammals posses. For example, all mammals possess primary sensory areas (V1, S1, A1), second sensory areas (V2, S2, PV), and multimodal cortical areas (MM) that reside between primary areas (Kaas, 2006; Krubitzer and Hunt, 2006; Figure 1). While the presence of the motor cortex in marsupials and monotremes is contentious (Haight and Neylon, 1979; see Karlen and Krubitzer, 2007 for review), placental mammals also posses at least one separate cortical motor area (M1). Finally, all mammals investigated share many features of thalamocortical and corticocortical connections (Krubitzer and Hunt, 2006).

It should be noted that even when a sensory system is not used, cortical fields associated with that system still persist. For example, in blind mole rats the eyes are greatly reduced in size and are covered by specialized skin, and the visual system in these animals is only used for circadian functions (Tobler et al., 1998). Despite this, these animals still posses a geniculo-cortical pathway and a V1, although these visual structures are dramatically smaller and have been co-opted by other sensory systems (Cooper et al., 1993; Doron and Wollberg, 1994). Experimentally induced loss of both eyes very early in development in primates (Rakic et al., 1991) and opossums (Kahn and

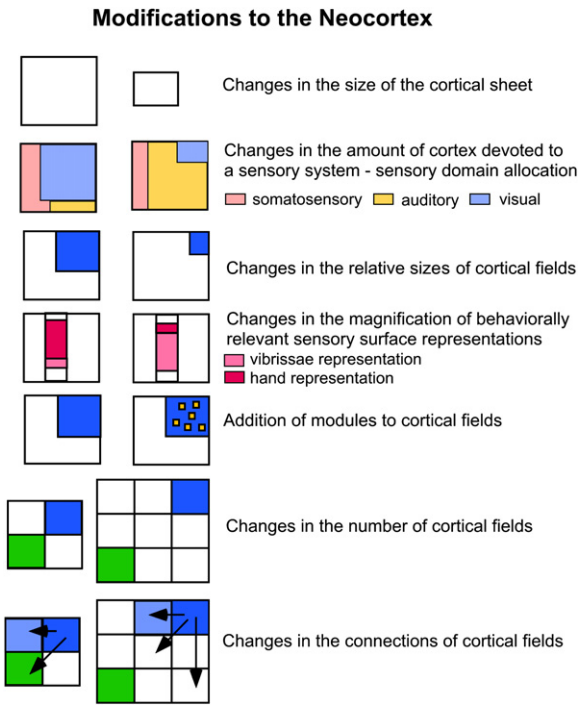

Figure 2. A Schematic Representing the Types of Changes That Have Been Made to the Neocortex in Mammals

These changes, although few in number, form the neural substrate for a wide range of behaviors observed in mammals. It should be noted that these features of organization that vary in different species are often linked. For example, a disproportionate increase in the size of the cortical sheet is most often accompanied by an increase in cortical field number; and an increase in cortical field number is often accompanied by alterations in the connections of cortical fields. Similarly, differences in cortical domain allocation often covary with changes in the magnification of behaviorally relevant body parts. From Krubitzer and Kaas, 2005; and Krubitzer and Hunt, 2006.

Krubitzer, 2002) also results in characteristics of the neocortex that are invariant, including the presence of a V1 and a geniculo-cortical system. However, as in naturally blind animals, alterations in the size, organization, and connections of V1 are observed (Rakic et al., 1991; Kahn and Krubitzer, 2002; Karlen et al., 2006). Thus, in both naturally and experimentally modified sensory systems, aspects of cortical organization persist, even with the loss or reduction of the sensory apparatus. The very presence of these cortical areas and their associated connections in the absence of use indicates that cortical evolution is constrained by the interactions of genes that generate cortical fields during development (see below).

What Are the System-Level Modifications That Have Been Made to the Brain?

Although variability exists in the organization of the neocortex, the types of system-level alterations that can be made are limited. Specifically, alterations can occur in the size of the cortical sheet, the amount of cortex devoted to a particular sensory system (sensory domain), the relative size of cortical fields, the functional organization within cortical fields, the addition of modules to cortical fields, the number of cortical fields, and the connections of cortical fields (Figure 2).

These alterations can occur individually or in conjunction with each other. For example, the size of the cortical sheet in some groups, such as primates, is relatively large compared with the size of the body and the rest of the brain. In a subset of species, this encephalization is accompanied by an increase in the number of cortical fields, and by changes in the connectivity of cortical fields. The combination of these changes results in a neocortex that is more complexly organized.

Studies on the cell-cycle kinetics of neocortical progenitor cells in the ventricular zone indicate that there are a number of possible ways in which cortical sheet size can be increased. In general terms, the number of cells can be increased by extending the length of time that cells undergo symmetric divisions, the rate at which cell divisions occur, or the amount of naturally occurring cell death (Kornack and Rakic, 1998; Kornack, 2000; Kuida et al., 1998). Several hypotheses have been proposed regarding the types of alterations to the kinetics of cell division that are possible and how these changes are genetically mediated. For example, the intracellular protein beta-catenin is expressed in neuroepithelial precursor cells during neurogenesis (Chenn and Walsh, 2002). Overexpression of beta-catenin in mice results in a dramatic increase in the size of the cortical sheet, due to an increase in the proportion of progenitor cells that re-enter the cell cycle and continue mitotic division. Another candidate gene, *Brain Factor-1* (*BF-1* or *Foxg1*), is expressed in telencephalic progenitor cells (Tao and Lai, 1992) and regulates cell proliferation and differentiation in the developing neocortex (Hanashima et al., 2002). Alterations in this gene could also lead to changes in the size of the cortical sheet. *BF-1* is regulated by FGF2, which also regulates cortical sheet size by determining the number of cycles of division that progenitor cells undergo during cortical neurogenesis. Injections of FGF2 into the ventricle of embryonic rats results in a substantial increase in cortical volume (Vaccarino et al., 1999), and FGF2 knockout mice have smaller neocorticies (Raballo et al., 2000). Finally, recent studies have shown that differences in the number of intermediate progenitor cells in the subventricular zone during neurogenesis can account for differences in the size of the cortical sheet (see Kriegstein et al., 2006 for review). Data to support this come from comparative studies in rats, ferrets, and primates that demonstrate that the subventricular zone, which contains intermediate progenitor cells, is significantly larger in species with a larger cortical sheet (Kriegstein et al., 2006 for review). Taken together, these studies indicate that the disproportionate size of the neocortex in different lineages could be regulated in several ways by utilization of different genes and proteins, and indeed different lineages may have evolved distinct mechanisms for cortical sheet expansion. Nevertheless, all of the potential mechanisms that have been proposed to

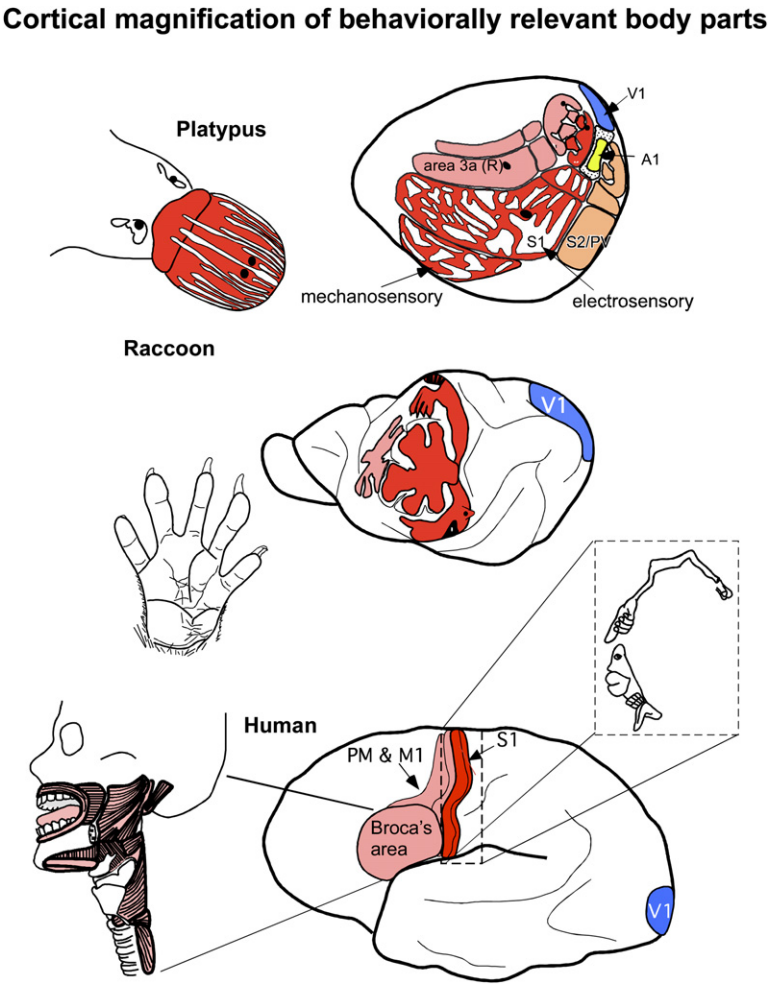

Figure 3. Examples of Cortical Magnification in Platypuses, Raccoons, and Humans

In the platypus, the bill representation occupies the majority of S1, while in the raccoon, the hand representation in S1 is extremely large, larger than the magnification of the hand in humans. In humans, the lips, tongue and other oral structures also assume a large portion of S1, M1, and PM. If one considers human specialization in light of specializations observed in other mammals, then one could propose that Broca's area is a magnification of the muscle, bone, soft tissue, and joint representations in M1 and PM associated with oral and throat specializations that have been modified for speech. Of course, connections of these specialized or magnified representations often change as well. In the human and raccoon brain, A1 is buried in the lateral sulcus. The fissure pattern in the human brain is highly simplified. Platypus cortex is modified from Krubitzer et al. (1995); platypus bill is modified from Pettigrew (1999); raccoon is modified from Welker and Seidenstein (1959) and Herron (1978); human is modified from Penfield and Boldrey (1937).

underlie cortical sheet expansion affect the kinetics and timing of cell division of progenitor cells during neurogenesis.

While the genetic factors that contribute to increased encephalization in mammals are becoming increasingly clear, why an increase in the size of the cortical sheet results in an increase in the number of cortical fields in some species, but not in others, is not well understood. Further, although the question of how cortical scaling can occur has recently been addressed computationally and experimentally (see Changizi, 2006; Finlay and Brodsky, 2006; Stevens, 2006; Herculano-Houzel et al., 2007), the issue of how cortical fields are added in evolution is still purely theoretical (e.g., Allman and Kaas, 1971; Ebbesson, 1980; Krubitzer, 1995).

In addition to alterations to the size of the cortical sheet, alterations in the amount of space devoted to a particular sensory system and the relative size of a cortical field can also occur (Figure 2), and in some species these changes are accompanied by alterations in the functional organization of the cortical field. For example, the duck-billed platypus has a large S1 compared with both other primary areas in its neocortex and the relative size of S1 in other mammals (Krubitzer et al., 1995; Figure 1 and Figure 3). In addition, the internal organization of S1 has been modified such that 90% of S1 is occupied by the representation of the bill. This expansion, called cortical magnification, is related to the density and arrangement of mechanosensory receptors on the bill, the evolution of new electrosensory receptors, and the specialized behaviors associated with the bill. In the platypus, other sensory areas such as the rostral area, R, and S2/PV also exhibit cortical magnification and together with S1 comprise most of the cortical sheet. Thus, the cortex is dominated by the somatosensory system, and cortical fields within the somatosensory domain are dominated by representations of the bill. Other examples of cortical magnification can be observed in a variety of species, including the expansion of auditory cortex associated with alterations in the cochlea in echolocating bats (e.g., Suga et al., 1975; Asanuma et al., 1983; Kujirai and Suga, 1983), and the magnification of the hand representation in S1 associated with changes in the structure of the hand and receptor distribution and density in the hand of primates and raccoons (e.g., Nelson et al., 1980; Welker and Seidenstein, 1959). In humans alterations in the larynx, tongue, lips, and other

oral structures are accompanied by an expansion of the oral representations in somatosensory cortex, motor cortex, and premotor cortex. The location of motor (M1) and premotor (PM) cortex coincides with the location of Broca's area. Thus, Broca's area can be considered as a cortical magnification of behaviorally relevant body parts in M1 and PM associated with speech production (Figure 3).

These system-level alterations to the cortical phenotype, while limited, are ubiquitous across mammals and sensory and motor systems. How these organizational differences occur has only recently been examined (see below). However, it is clear that the same types of alterations occur in all mammals, and that the derivations of the human brain follow a predictable pattern (Figure 3). Thus, if one can appreciate the factors that contribute to aspects of the phenotype, the rules by which brains are constructed, how alterations occur, and what constraints are imposed on the nervous system, specific questions regarding the evolution of speech and language areas in motor and premotor cortex of the human brain, for instance, can be more readily addressed.

Contributions to the Cortical Phenotype

The cortical phenotype is the product of both intrinsic, genetically mediated mechanisms and epigenetic events. As noted above, genes can regulate cortical sheet size, and increases in size are often associated with changes in the organization and number of cortical fields present on the cortical sheet. Further, recent studies indicate that genes can also directly contribute to the emergence of cortical fields during development and ultimately to their organization and function.

During the last decade numerous studies have shed light on the molecular cascades involved in the patterning of the forebrain. For example, very early in the developing telencephalon, well before cortical fields have emerged, early signaling centers secrete molecules such as Fgf8, Wnt, Shh, and Bmp4, which direct the graded expression of transcription factors, or regulatory genes, such as *Emx2*, *Pax 6*, and *Lhx2*, which in turn regulate patterning in the developing cortex (see Grove and Fukuchi-Shimogori, 2003; O'Leary and Nakagawa, 2002; O'Leary et al., 2007 [this issue of *Neuron*]; Sur and Rubenstein, 2005 for review). Signaling centers are regionally organized, and alterations in their pattern of expression result in large alterations in cortical field size and location (e.g., Fukuchi-Shimogori and Grove, 2001; Garel et al., 2003). Transcription factors, such as *Emx2* and *Pax6*, regulate the region-specific expression of other genes that are believed to encode cell adhesion molecules such as the cadherins (e.g., *Cad 6*, *Cad 8*, and *Cad 11*), other transcription factors such as *Tbr1*, and axon guidance molecules such as *ephrinA-5*. As with the signaling centers, disruption of these transcription factors alters the size and relative location of emerging cortical fields (e.g., Bishop et al., 2000; Hamasaki et al., 2004; see O'Leary and Nakagawa, 2002 for review). Some transcription factors, such as COUP-TFI, appear to balance the pattering of genes known to be involved in the arealization of cortical fields by repressing the identities of some cortical areas during development (Armentano et al., 2007). For example, COUP-TFI has a high caudolateral/low rostromedial graded expression, and its deletion results in a compression of S1, V1, and A1 to the caudal portion of the neocortex and an expansion of cortex rostral to S1. These results led Armentano et al. (2007) to propose that in normal mice, COUP-TFI represses "motor-like identities in cortical progenitors" and thereby restricts the size of M1 in normal animals.

Genes regulated by early transcription factors (e.g., *Cad 6, Cad 8, Cad 11*, *Tbr1*, and *ephrinA-5*) are regionally expressed in the neocortex and localized to one or more cortical fields. These genes are involved in the establishment of the histological, functional, neuroanatomical, and molecular identities of individual cortical fields during development (Bulfone et al., 1995; Suzuki et al., 1997; Mackarehtschian et al., 1999; Nakagawa et al., 1999; Vanderhaeghen et al., 2000; Vanderhaeghen and Polleux, 2004; Hevner et al., 2001, 2002). Like *Emx2* and *Pax6*, their expression is intrinsically mediated, at least until birth, and their expression persists even in the absence of thalamocortical inputs (Nakagawa et al., 1999; Miyashita-Lin et al., 1999). Disruption of these transcription factors alters the size and relative location of emerging cortical fields (e.g., Bishop et al., 2000, 2003; Hamasaki et al., 2004; Armentano et al., 2007). Thus, experimentally altering gene expression at different stages of development can modify the neocortex in a way that is consistent with how the brain is naturally modified in evolution (Figure 2).

Genes that regulate other portions of the brain and body also influence cortical field organization. For example, small alterations in the spatial extent of *Hox* genes that regulate forelimb development in bats and mice generate large modifications in the structure of the forelimb in these two species (Chen et al., 2005; Cretekos et al., 2005). This difference in forelimb morphology and use is reflected in the allocation of different body part representations in S1 in each species. In bats, the forelimb (wing), with its touch domes, occupies a relatively large amount of space compared with the representation of the forelimb in the mouse (Woolsey, 1967; Calford et al., 1985; Zook, 2006). As noted previously, alterations in peripheral morphology and sensory receptors that occur naturally (blind mole rats) or are induced experimentally (bilaterally enucleated primates and opossums) result in dramatic changes in the size, organization, and connections of cortical areas. Natural differences in limb and head morphology, as well as sensory receptor type, distribution, and density, are at least in part genetically mediated.

The data presented above on cortical and body development indicate that genes contribute to the emergence of the phenotype, and differences in their expression can account for differences in cortical organization. However, genes also constrain development, and in turn limit the types of phenotypic modifications that occur in evolution. Specifically, because a single gene can control a number

of activities in development (pleiotropy; Hall, 1994), the number of viable changes that could be made to or effected by any particular gene is limited. Further, genetically mediated events are most often dependent (contingent) on one or more prior genetic events and in turn may instruct some combination of downstream genetic events (as described above). This makes it rather difficult to substantially modify an organism by extreme genetic manipulations, and suggests that small genetic alterations such as changes in the timing and spatial distribution of genes via base substitutions, recombination, and transposition can generate large phenotypic modifications.

In addition to genetically mediated mechanisms, epigenetic events also contribute considerably to the cortical phenotype. (I use the term epigenetic to mean a characteristic or feature resulting from external experiences.) At the level of the individual, the use of a body part during development affects the morphology of the body part itself (which in turn may affect some aspect of cortical organization). For example, alterations in mastication behavior in development, brought about by changes in diet, have a direct effect on craniofacial morphology (He, 2004), skull dimensions (Katsaros et al., 2002), mandibular morphology (Bresin, 2001), and bone density (Davies et al., 2005). Other epigenetic factors such as temperature, salinity, humidity (see Johnston and Gottlieb, 1990 for review) and even gravity (e.g., Singh et al., 2005) also contribute to the development of body morphology. At a larger level of organization, the pattern of sensory-driven activity that occurs during development has an enormous impact on the resulting cortical phenotype.

For example, alterations in the relative patterns of sensory-driven activity between sensory systems that occur with congenital blindness (bilateral enucleation) or deafness result in massive changes in sensory domain allocation, cortical field size, and cortical and subcortical connectivity (e.g., Kahn and Krubitzer, 2002; Hunt et al., 2006). Specifically, cortex that would normally be devoted to the lost sensory system becomes activated by the remaining sensory systems, and the primary cortical area of the lost system (e.g., V1 or A1) decreases in size. Finally, primary areas that would normally receive unimodal sensory inputs from the thalamus and other cortical fields receive both thalamic and cortical inputs from the remaining sensory systems in both congenitally deaf and congenitally blind animals.

In natural environments, sensory-driven activity in the developing animal is dependent on the unique combination of stimuli present in different environments, and the type, density, and distribution of sensory receptors present in a particular species. For example, the activation of different types of sensory receptors in semiaquatic, nocturnal animals such as the platypus would be different than for a burrowing, terrestrial rodent, or for a diurnal, arboreal primate. While sensory receptors from all species transduce particular types of physical stimuli, such as photons, displacement of skin and hairs, and movement of molecules within a particular medium, such as air or water, the relative amounts and magnitude of the stimuli are different in different environments. Further, the sensory apparatus, which is under both genetic and epigenetic control, is often specialized in different species (such as the presence of electrosensory receptors on the bill of the platypus). Thus, the epigenetic factors that influence the development of the neocortex cannot be separated from the genes that direct the construction of both neural and nonneural tissue.

As with genes, the physical environment itself exerts large constraints on the developing and evolving organism. The types of physical energy within the environment are finite, clearly defined, and obey the laws of physics. The invariant nature of these stimuli clearly constrains how sensory receptors evolve to transduce these stimuli, and in turn constrains the neocortical regions associated with different sensory systems.

Conclusions

The cortical phenotype is constructed by genes that regulate aspects of the brain and body during development, and by the distribution of physical energy and associated sensory-driven activity generated in particular environments. These intrinsic, extrinsic, and epigenetic factors work as an integrated network that operates under formidable constraints present at each level of organization. Thus, the brain of any extant animal is a compromise, it is not perfectly designed in any aspect of organization, but functions optimally as a whole.

Despite the constraints imposed by genes and the physical environment, the cortical phenotype can be highly variable, and flexibility can be generated in several ways. First, genes intrinsic to the neocortex and genes that regulate peripheral morphology and receptor distribution can vary in their spatial location and timing of expression during development. Second, variability in use of the structure also allows for phenotypic flexibility. Finally, although the laws of physics are invariant, the magnitude and patterns of physical stimuli (e.g., photons and sound waves) may be distributed differently in different environments (e.g., terrestrial, aquatic, burrowing, diurnal, nocturnal), and thus generate unique patterns of sensory-driven activity in the developing nervous system. The phenotypic differences in cortical organization that emerge as a result of this flexibility generate a wide range of behaviors, which are the target of selection. Because the neocortical phenotype that generates this diverse behavior is determined through both genetic and epigenetic interactions, only some aspects of the cortical phenotype can be inherited and evolve, while other aspects of the cortical phenotype may masquerade as a product of evolution, but are actually context dependent and persist only in particular environments.

ACKNOWLEDGMENTS

This work was supported by the McDonnell Foundation and in part by a grant from the National Institute of Neurological Disorders and Stroke (R01-NS035103-11).

REFERENCES

Allman, J.M., and Kaas, J.H. (1971). Brain Res. *31*, 85–105.

Armentano, M., Chou, S.J., Srubek Tomassy, G., Leingartner, A., O'Leary, D.D., and Studer, M. (2007). Nat. Neurosci. *10*, 1277–1286.

Asanuma, A., Wong, D., and Suga, N. (1983). J. Neurophysiol. *50*, 1182–1196.

Bishop, K.M., Goudreau, G., and O'Leary, D.D. (2000). Science *288*, 344–349.

Bishop, K.M., Garel, S., Nakagawa, Y., Rubenstein, J.L., and O'Leary, D.D. (2003). J. Comp. Neurol. *457*, 345–360.

Bresin, A. (2001). Swed. Dent. J. Suppl. *150*, 1–49.

Bulfone, A., Smiga, S.M., Shimamura, K., Peterson, A., Puelles, L., and Rubenstein, J.L. (1995). Neuron *15*, 63–78.

Bullock, T.H. (1984). Science *225*, 473–478.

Calford, M.B., Graydon, M.L., Huerta, M.F., Kaas, J.H., and Pettigrew, J.D. (1985). Nature *313*, 477–479.

Changizi, M.A. (2006). Scaling the brain and its connections. In The Evolution of Nervous Systems in Mammals, J. Kaas and L. Krubitzer, eds. (Oxford: Academic Press), pp. 181–187.

Chen, C.H., Cretekos, C.J., Rasweiler, J.J., 4th, and Behringer, R.R. (2005). Evol. Dev. *7*, 130–141.

Chenn, A., and Walsh, C.A. (2002). Science *297*, 365–369.

Cooper, H.M., Herbin, M., and Nevo, E. (1993). J. Comp. Neurol. *328*, 313–350.

Cretekos, C.J., Weatherbee, S.D., Chen, C.H., Badwaik, N.K., Niswander, L., Behringer, R.R., and Rasweiler, J.J., 4th. (2005). Dev. Dyn. *233*, 721–738.

Davies, J.H., Evans, B.A., and Gregory, J.W. (2005). Arch. Dis. Child. *90*, 373–378.

Doron, N., and Wollberg, Z. (1994). Neuroreport *5*, 2697–2701.

Ebbesson, S.O. (1980). Cell Tissue Res. *213*, 179–212.

Finlay, B.L., and Brodsky, P. (2006). Cortical evolution as the expression of a program for disproportionate growth and the proliferation of areas. In The Evolution of Nervous Systems in Mammals, J. Kaas and L. Krubitzer, eds. (Oxford: Academic Press), pp. 73–96.

Fukuchi-Shimogori, T., and Grove, E.A. (2001). Science *294*, 1071–1074.

Garel, S., Huffman, K.J., and Rubenstein, J.L. (2003). Development *130*, 1903–1914.

Grove, E.A., and Fukuchi-Shimogori, T. (2003). Annu. Rev. Neurosci. *26*, 355–380.

Haight, J.R., and Neylon, L. (1979). J. Anat. *129*, 673–694.

Hall, J.C. (1994). Pleiotropy of behavioral genes. In Flexibility and Constraint in Behavioral Systems, R.J. Greenspan and C.P. Kyriacou, eds. (Chichester: John Wiley and Sons), pp. 15–27.

Hamasaki, T., Leingartner, A., Ringstedt, T., and O'Leary, D.D. (2004). Neuron *43*, 359–372.

Hanashima, C., Shen, L., Li, S.C., and Lai, E. (2002). J. Neurosci. *22*, 6526–6536.

He, T. (2004). Swed. Dent. J. Suppl. *165*, 1–72.

Herculano-Houzel, S., Collins, C.E., Wong, P., and Kaas, J.H. (2007). Proc. Natl. Acad. Sci. USA *104*, 3562–3567.

Herron, P. (1978). J. Comp. Neurol. *181*, 717–727.

Hevner, R.F., Shi, L., Justice, N., Hsueh, Y., Sheng, M., Smiga, S., Bulfone, A., Goffinet, A.M., Campagnoni, A.T., and Rubenstein, J.L. (2001). Neuron *29*, 353–366.

Hevner, R.F., Miyashita-Lin, E., and Rubenstein, J.L. (2002). J. Comp. Neurol. *447*, 8–17.

Hunt, D.L., Yamoah, E.N., and Krubitzer, L. (2006). Multisensory plasticity in congenitally deaf mice: how are cortical areas functionally specified? Neurosci. *139*, 1507–1524.

Johnston, T.D., and Gottlieb, G. (1990). J. Theor. Biol. *147*, 471–495.

Kaas, J.H. (2006). Reconstructing the organization of neocortex of the first mammals and subsequent modifications. In The Evolution of Nervous Systems in Mammals, J. Kaas and L. Krubitzer, eds. (Oxford: Academic Press), pp. 27–48.

Kahn, D.M., and Krubitzer, L. (2002). Proc. Natl. Acad. Sci. USA *99*, 11429–11434.

Karlen, S.J., and Krubitzer, L. (2007). Prog. Neurobiol. *82*, 122–141.

Karlen, S.J., Kahn, D.M., and Krubitzer, L. (2006). Neuroscience *142*, 843–858.

Katsaros, C., Berg, R., and Kiliaridis, S. (2002). J. Orofac. Orthop. *63*, 5–13.

Kornack, D.R. (2000). Brain Behav. Evol. *55*, 336–344.

Kornack, D.R., and Rakic, P. (1998). Proc. Natl. Acad. Sci. USA *95*, 1242–1246.

Kriegstein, A., Noctor, S., and Martinez-Cerdeno, V. (2006). Nat. Rev. Neurosci. *7*, 883–890.

Krubitzer, L. (1995). Trends Neurosci. *18*, 408–417.

Krubitzer, L., and Kahn, D.M. (2003). Prog. Neurobiol. *70*, 33–52.

Krubitzer, L., and Kaas, J. (2005). Curr. Opin. Neurobiol. *15*, 444–453.

Krubitzer, L., and Hunt, D.L. (2006). Captured in the net of space and time: Understanding cortical field evolution. In The Evolution of Nervous Systems in Mammals, J. Kaas and L. Krubitzer, eds. (Oxford: Academic Press), pp. 49–72.

Krubitzer, L., Manger, P., Pettigrew, J., and Calford, M. (1995). J. Comp. Neurol. *351*, 261–306.

Kuida, K., Haydar, T.F., Kuan, C.-Y., Gu, Y., Taya, C., Karasuyama, H., Su, M.S., Rakic, P., and Flavell, R.A. (1998). Cell *94*, 325–337.

Kujirai, K., and Suga, N. (1983). Auris Nasus Larynx *10*, 9–24.

Mackarehtschian, K., Lau, C.K., Caras, L., and McConnell, S.K. (1999). Cereb. Cortex *9*, 601–610.

Miyashita-Lin, E.M., Hevner, R., Wassarman, K.M., Martinez, S., and Rubenstein, J.L. (1999). Science *285*, 906–909.

Nakagawa, Y., Johnson, J.E., and O'Leary, D.D. (1999). J. Neurosci. *19*, 10877–10885.

Nelson, R.J., Sur, M., Felleman, D.J., and Kaas, J.H. (1980). J. Comp. Neurol. *192*, 611–643.

O'Leary, D.D., and Nakagawa, Y. (2002). Curr. Opin. Neurobiol. *12*, 14–25.

O'Leary, D.D.M., Chou, S.-J., and Sahara, S. (2007). Neuron *56*, this issue, 252–269.

Penfield, W., and Boldrey, E. (1937). Brain *60*, 389–443.

Pettigrew, J.D. (1999). J. Exp. Biol. *202*, 1447–1454.

Raballo, R., Rhee, J., Lyn-Cook, R., Leckman, J.F., Schwartz, M.L., and Vaccarino, F.M. (2000). J. Neurosci. *20*, 5012–5023.

Rakic, P., Suner, I., and Williams, R.W. (1991). Proc. Natl. Acad. Sci. USA *88*, 2083–2087.

Singh, R., Carvalho, T., and Gerstner, G.E. (2005). Acta Astronaut. *56*, 357–366.

Stevens, C.F. (2006). Principles of brain scaling. In The Evolution of Nervous Systems Theories, Development, Invertebrates, J. Kaas and L. Krubitzer, eds. (Oxford: Academic Press), pp. 272–282.

Suga, N., Simmons, J.A., and Jen, P.H. (1975). J. Exp. Biol. *63*, 161–192.

Sur, M., and Rubenstein, J.L. (2005). Science *310*, 805–810.

Suzuki, S.C., Inoue, T., Kimura, Y., Tanaka, T., and Takeichi, M. (1997). Mol. Cell. Neurosci. *9*, 433–447.

Tao, W., and Lai, E. (1992). Neuron *8*, 957–966.

Tobler, I., Herrmann, M., Cooper, H.M., Negroni, J., Nevo, E., and Achermann, P. (1998). Behav. Brain Res. *96*, 173–183.

Vaccarino, F.M., Schwartz, M.L., Raballo, R., Nilsen, J., Rhee, J., Zhou, M., Doetschman, T., Coffin, J.D., Wyland, J.J., and Hung, Y.-T.E. (1999). Nat. Neurosci. *2*, 246–253.

Vanderhaeghen, P., and Polleux, F. (2004). Trends Neurosci. *27*, 384–391.

Vanderhaeghen, P., Lu, Q., Prakash, N., Frisen, J., Walsh, C.A., Frostig, R.D., and Flanagan, J.G. (2000). Nat. Neurosci. *3*, 358–365.

Welker, W.I., and Seidenstein, S. (1959). J. Comp. Neurol. *111*, 469–501.

Woolsey, T.A. (1967). Johns Hopkins Med. J. *121*, 91–112.

Zook, J.M. (2006). Somatosensory adaptation of flying mammals. In The Evolution of Nervous Systems in Mammals, J. Kaas and L. Krubitzer, eds. (Oxford: Academic Press), pp. 49–72.