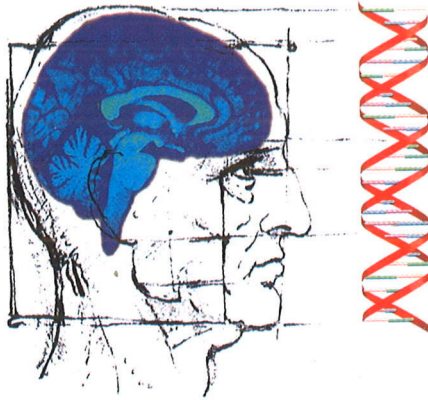


HUMAN FRONTIER



WORKSHOP V

BRAIN AND MIND evolutionary perspectives

EDITORS

Michael S. Gazzaniga and Jennifer S. Altman

CO-EDITORS

Paul M. Corballis • Elizabeth A. Disbrow • Jeffrey Hutsler • David J. Kemmerer

CONTRIBUTORS

Ira B. Black
Susan Carey
Leo M. Chalupa
Michael Corballis
Leda Cosmides

Daniel C. Dennett
C. Randy Gallistel
Michael S. Gazzaniga
Leah Krubitzer
Steven Pinker

Pasko Rakic
Giacomo Rizzolatti
Paul Rozin
Wolf Singer
John Tooby

Chapter 1

Constructing the neocortex: influences on the pattern of organization in mammals

Leah Krubitzer

*in collaboration with Kelly Huffman and Zoltán Molnár**

To understand the process of evolution it is necessary to examine its products, i.e., present-day morphology, in a variety of species. Comparisons reveal similarities and differences, from which inferences can be made about the mechanisms that might have led to the present structures. Features that are common to species in different lineages may be inherited from a common ancestor, i.e., homologous, or the result of independent convergent evolution. If a structure is not present in intervening species, it is assumed to have evolved independently, presumably in response to similar environmental conditions or as a solution to the demands of physics. A well-known example of convergent evolution is the similarity of the eyes in cephalopod molluscs and vertebrates.

In all mammals, the neocortex is divided into many functional subunits, each with a distinct appearance in histological sections, a unique pattern of connections and containing neurons with common stimulus preferences. The increase in the overall size of the neocortex, the number of its functional subdivisions and the complexity of the internal organization of the subdivisions all tend to parallel the increasing complexity of behaviour. A broad definition of behaviour is the sensory, perceptual and cognitive processing abilities and the motor skills displayed by a species, ranging from electrosensory processing in the platypus to language in humans.

* Department of Physiology, Oxford University and Inst. Biol. Cellulaire et de Morphol., Lausanne, Switzerland.

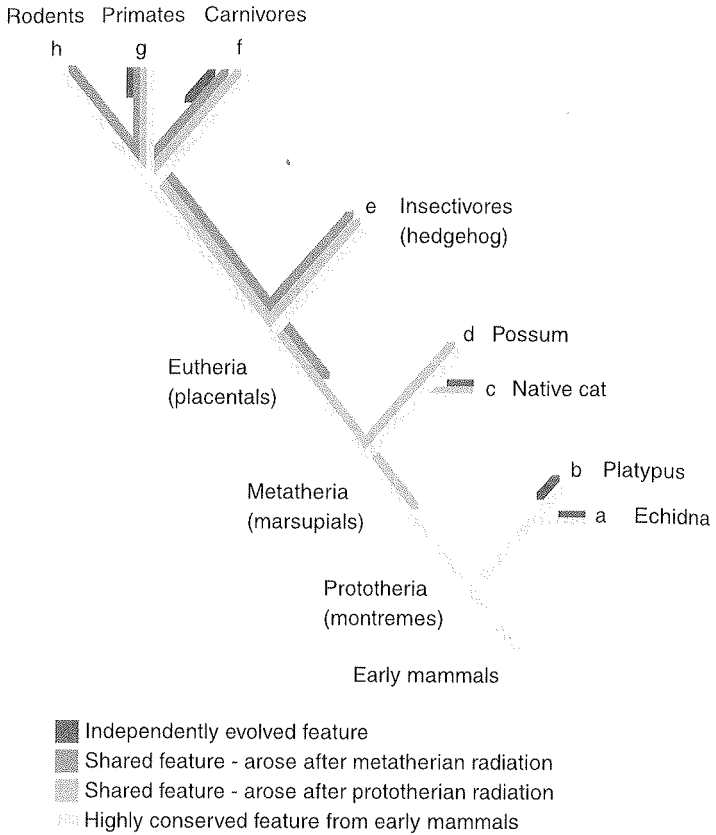


Figure 1. A simplified evolutionary tree showing the relationships between the three main mammalian radiations and mapping the common and independently acquired features of cortical organization. Light grey, structures common to all species examined (a–h), such as the primary somatosensory and visual areas, which are probably derived from the ancestral stem; mid and dark greys, areas added later in evolution and shared only by some groups, such as the secondary somatosensory area in metatherians and eutherians (c–h); black, structures that seem similar but have been added independently, e.g., the modules in the somatosensory area (a, b, c, f and g). Modified from Krubitzer, 1995.

The similarities and differences in cortical organization between species are consistent, including the number of cortical fields and their internal organization, structure and connections. The challenge is to determine how these changes in size and number of parts occurred and how they relate to changes in behaviour. We are tackling this problem by comparing the sensory neocortex in representatives of the three main mammalian radiations, the prototherians or monotremes, the metatherians or marsupials and the eutherians or placental mammals (*Fig. 1*).

This approach has revealed a common basic plan for the cortex across the mammals and has enabled us to propose some ways in which the plan may have been modified. Because the types of changes seen in the common plan are prevalent across species and restricted in nature, we consider that a common mechanism underlies them. Here we propose that the size of the neocortex and number of cortical fields could increase through the addition of new sensory inputs from an expanded periphery, together with an expansion of the embryonic rudiment of the neocortex, the cortical plate, during development. We contend that the changes occur through changes in the development of the nervous system and provide evidence that the identity of cortical areas results from the patterns of activity of their inputs during development. We consider that the evolution of the neocortex is the evolution of cortical development.

Neocortical organization

We have determined the number, relative positions and internal organization of functional subdivisions in the sensory neocortex of selected species (*Fig. 2*). Sensory fields in the neocortex can be differentiated because each contains a complete representation of a particular part of the peripheral sensory system, e.g., the retina, the cochlea or the skin. The neurons in each area also display specific response properties or stimulus preferences. Maps of these responses have been constructed using multiunit

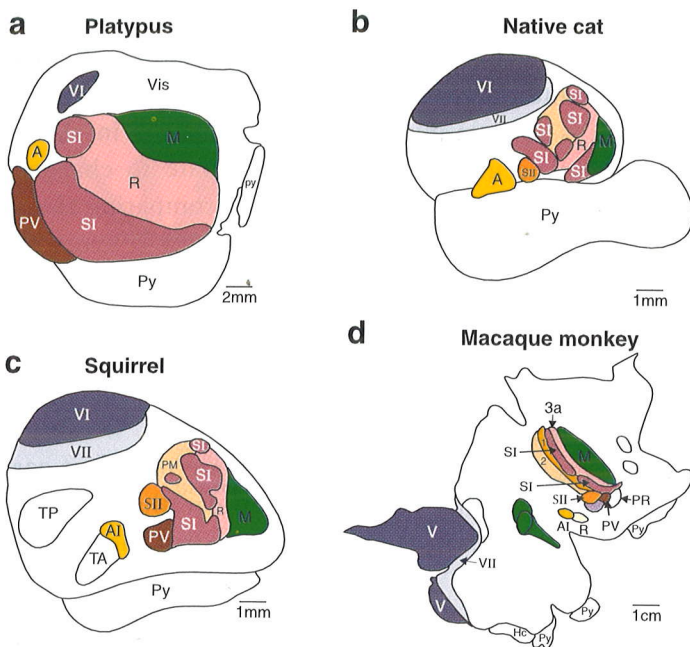


Figure 2. Comparison of the number, extents and relative positions of functional areas in the neocortex of four mammals from various branches of the evolutionary tree. All four have primary auditory (A), motor (M), somatosensory (SI) and visual (VI) areas. Other common areas include the second somatosensory area (SII), parietal ventral area (PV), rostral area (R) and the presumptive primary motor area (M). For further explanation, see text. Fields mapped with electrophysiological and histochemical methods are displayed on a drawing of the flattened cortex. *He*, hippocampus; *PM*, medial parietal; *PR*, rostral parietal; *Py*, pyriform cortex; *TA*, anterior temporal; *TP*, posterior temporal; 1, 2, 3a, somatosensory fields 1, 2, 3a.

electrophysiological recordings, correlated with studies of cortical structure using myelin staining, enzymatic reactions and immunohistochemistry; patterns of subcortical, interhemispheric and intrahemispheric connections have also been examined.

The organization of the neocortex has several common features in all the species investigated. The most noteworthy is the presence of several distinct functional areas, including

separate primary fields representing vision, body surface (somatosensory) and hearing (auditory), as well as several secondary fields. This is counter to the claim that those mammals with ancestors that appeared early in evolution, such as monotremes and marsupials, have an undifferentiated cortex with indistinct boundaries to the cortical fields (see Krubitzer *et al.*, 1997). Even the platypus, a monotreme, has several representations of the sensory periphery with three somatosensory areas containing well-developed maps of the body surface as well as primary visual, auditory and motor areas (*Fig. 2a*). Equivalents of all these areas can be identified in other mammals (*Fig. 2b-d*; Krubitzer, 1998).

The size, shape and relative location of the fields does, however, change across species. In the monotremes, i.e., the platypus and echidna, the auditory area is embedded in the somatosensory area (*Fig. 2a*), whereas in Australian marsupials, such as the native cat (quoll), the auditory cortex is more posterior and larger, located lateral to the visual cortex (*Fig. 2b*). The primary visual area in the native cat is much larger than in the platypus; located at the back of the brain, it contains several representations of the visual field. There is also a secondary visual cortex containing several areas.

In general, the size of a cortical area seems to be related to the extent to which the peripheral organ is used. The native cat has specialized pads on its forepaws, possibly for identifying and capturing prey, and has an enlarged hand representation in the primary somatosensory cortex. The increased size of its auditory area may also indicate an increase in functional specialization. Another example is the bill of the platypus, which is specialized for electrosensory detection of prey and has a large representation in the cortex, not seen in other mammals (see *Fig. 3c*).

The organization of the cortex also seems to reflect social behaviour, as seen in the striped possum, which has the most complex social behaviour of all marsupials. Possums live in large

troops, mobbing predators if one of the troop is threatened and using signals to alert others to the presence of predators. Their brain:body-weight ratio is the largest among marsupials (J. Nelson, personal communication) and the neocortex contains at least five somatosensory areas (Huffman *et al.*, 1999). Possums use the specialized fourth digit for extracting insects from trees and, as in the native cat, the representation of this digit occupies much of the primary somatosensory cortex.

The diversity of cortical organization among rodents provides another example of specialization related to function. In the mouse and rat, the organization of the visual cortex is relatively simple, with a small primary visual area surrounded by a belt of visual cortex. In contrast, the somatosensory area is large, with about half the space dedicated to the representation of the facial whiskers (vibrissae) in the 'barrel' fields (see *Fig. 3a*). The squirrel, in comparison, has a well-developed visual system, divided into several areas. About half the cortex is dedicated to processing visual information, whereas much less is devoted to somatosensory or auditory information (*Fig. 2c*).

Thus all mammals have a common constellation of cortical fields and the modifications to this constellation are limited. Although the size and internal organization of the fields may change, cortical fields never completely disappear; even when a sensory function is poorly developed, a small field remains. Although the platypus makes minimal use of vision, it has a primary visual field with normal inputs from the sub-cortical visual nuclei in the thalamus. In the star-nosed mole, a nocturnal, burrowing insectivore that relies on its nose for detecting food, the visual cortex is present but reduced (see *Fig. 3b*). Even in the most extreme example, the blind mole rat, which is a subterranean rodent with tiny eyes covered with facial skin, the primary visual area is present and receives inputs from the retina through the thalamus (Cooper *et al.*, 1993). The primary visual area can also persist when no eye is present during development: in a

monkey with an eye removed before the visual pathway was well established, the primary visual area and its inputs still formed but were smaller than normal (Rakic, 1988).

Another trend is the increase in the amount of cortex between primary sensory areas. Primates have significantly more cortex between the primary visual, somatosensory and auditory areas than the animals discussed so far, reflecting an increase in the extent and number of higher-order fields (*Fig. 2d*). Whereas the platypus has three somatosensory fields, humans have ten or more; marsupials typically have two or three visual areas but macaque monkey has more than 20. Although the exact extent and organization of the cortical fields involved in processing complex visual stimuli in primates are not yet fully appreciated (for review, see Kaas, 1989), the important point is the increase in cortical area and number of fields lying between the primary fields, not the details of how the space is divided.

In some species, cortical fields have been added with a concomitant change in the pattern or weighting of the connections between areas that alters the relationship between existing fields (reviewed in Krubitzer, 1998). As a result, structures that are retained from the common ancestor may take on new functions, i.e., they are homologous. The receptors represented in the primary somatosensory area, for example, have changed during evolution: in the platypus both mechanosensory and electrosensory receptors are represented, whereas in primates representations of rapidly and slowly adapting mechanosensory receptors interdigitate. The connections of the primary somatosensory area also differ between species because of changes such as the addition of a new receptor type, e.g., electrosensory receptors in the platypus, or of more cortical fields and thalamic nuclei for processing different types of mechanosensory inputs, as in primates.

The basic plan of cortical organization has also become modified by the formation of modules within a field (*Fig. 3*).

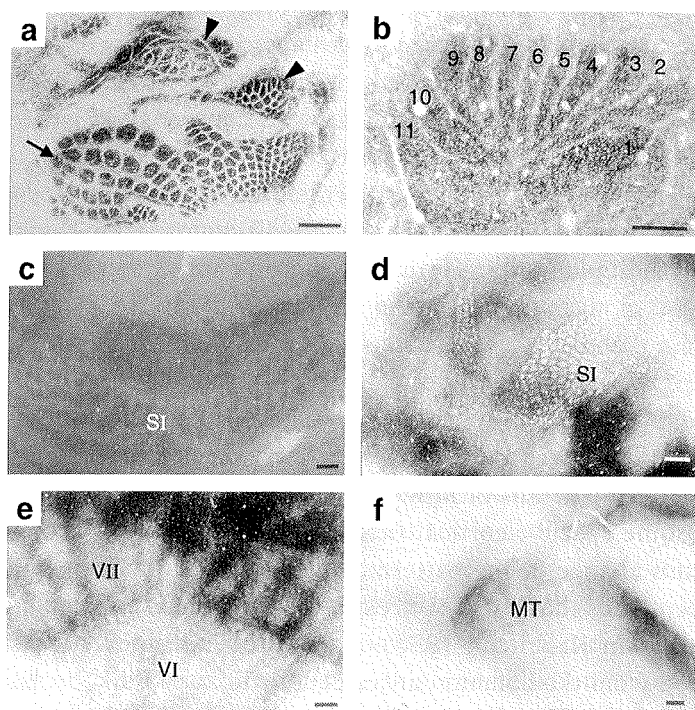


Figure 3. Modular organization in the neocortex, revealed by a variety of histochemical methods. **a**, 'barrel' fields in the rat SI (arrow); each module represents the input from one vibrissa. Arrowheads, fore- and hind-paw fields. **b**, separate modules (1-11) representing the individual lobes of the nose of the star-nosed mole. **c**, representation of the platypus bill in SI; light areas receive inputs from electro- and mechanoreceptors, dark areas only from mechanoreceptors. **d**, modules in SI of the brush-tailed possum associated with the vibrissae. **e**, in the squirrel monkey bands in the secondary visual area (VII) and the lattice-work in VI are related to differential patterns of connections and different neuronal properties. **f**, bands in middle temporal visual area (MT) in the marmoset are related to patterns of ipsi- and contralateral cortical connections. Abbreviations as in Figure 2. Scale bars, 1 mm. Modified from Krubitzer, 1995.

Modules are broadly defined as structurally and physiologically distinct regions within a classically defined cortical field; they are often related to morphological specializations, such as the vibrissae in the rat and the lobes of the nose in the star-nosed mole (*Fig. 3a, b*). Like the rodents, the brush-tailed possum has barrel fields in the somatosensory cortex for processing information from the vibrissae (*Fig. 3d*). As these must have evolved separately, there may be certain constraints on the types of cortical organization that can evolve.

In summary, distantly related species belonging to the three main radiations of the mammalian evolutionary tree show some similarities in the basic divisions of the neocortex. All have distinct cortical subdivisions containing neurons that respond preferentially to one or more sensory modalities. Each field has a similar gross topographic organization, microscopic appearance and connections across species, which indicates that fields are homologous or inherited from a common ancestor, rather than arising independently in each lineage. The basic plan is robust as it is present in highly specialized animals, such as the platypus or the star-nosed mole, and persists even in the absence of significant input, as with the visual area of the blind mole rat. The distinct differences between species seem to be superimposed on the basic plan, indicating the independent evolution of particular features. These include the amount of cortex devoted to a particular function, the shapes of fields and the detailed organization and connections of the fields representing specific peripheral structures.

Possible mechanisms for cortical change

Having identified some of the changes that have occurred during evolution, the next step is to determine the mechanisms that produced them. It seems likely that different processes are involved in the changes in size and complexity of an area, in the number of areas and in their locations. Gene mutations that directly alter

the number of cell divisions during the development of the cortex are obviously a possible cause of overall increases in cortical area. Mutations could also directly affect field size or complexity through changes in the timing of developmental events (see Rakic, this volume). Changes in the sensory periphery as a result of mutations that alter the number and types of receptors in a sense organ might influence the size of a cortical field by modifying the developmental conditions, as well as contributing to the organization of the field in the individual adult through use-dependent mechanisms (see below).

More subtle molecular changes that influence cell-cell communication may indirectly have profound effects on the overall organization of the neocortex, for instance, in use-dependent changes in the sensory and motor cortex of adult mammals (Recanzone *et al.*, 1992, 1998; Kaas, 1995). Use-dependent changes include increases in the size of the cortical representation of a body part as a result of exercise, so may be analogous to the expansion of cortical fields representing specialized body parts. These changes could be a consequence of the evolution of postsynaptic neurotransmitter receptors, such as the NMDA type of glutamate receptor, that seem to allow for changes in the efficacy of neocortical synapses throughout the lifetime of an individual (Black, 1995; see Black, this volume). Thus, several of the differences in the cortex observed in a wide sample of mammals could have occurred without requiring a genetic change that directly affected the organization of a cortical map.

In a broader sense, environmental events, such as the emergence of culture or social learning, might also influence cortical development, as well as contributing to dynamic changes in the adult brain. For example, we should expect to find similar types of use-dependent changes in cortical organization in the human cortex related to the development of spoken language. Broca's area, the primary area for speech production, can indeed be considered as a use-dependent expansion of the representation of

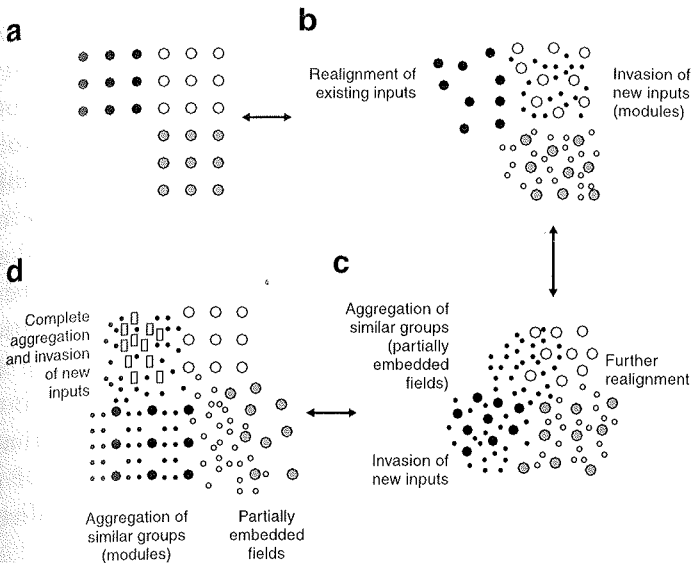


Figure 4. Ways that cortical fields might be modified or added during evolution. **a**, hypothetical stage with three separate fields, each with uniform appearance and connections. **b–d**, new but related inputs (small circles) invade and existing inputs realign and aggregate to form modules within a field, or segregate to form a new field or a field partially embedded in the original field. The process can occur in either direction. Modified from Krubitzer, 1995.

the oral structures in the motor cortex, much like the representation of the platypus bill is a specialization of the representation in the primary somatosensory area. Both types of cortical specialization are driven by structural and functional modifications in the periphery.

None of these mechanisms are adequate to explain how cortical areas change their locations or new fields are added. New cortical fields might be generated as a result of changes in inputs, which may create novel combinations of inputs, perhaps through correlation of the patterns of activity in the inputs. Addition of a new type of sensory receptor or a change in the peripheral morphology might also give rise to a new cortical

field, either with or without an increase in the size of the neo-cortex. If the activity of new inputs is correlated with that of existing inputs from the same part of the body, modules could form within a field by assimilation of the new inputs into an existing field (Fig. 4). Aggregation of these functionally similar modules, with redistribution to a location other than the one where they arose, could also lead to formation of a new field and establishment of a new representation of the sensory periphery.

Such a series of events may occur very rapidly in evolution, as illustrated by the somatosensory fields of the flying fox (Fig. 5; Krubitzer *et al.*, 1995). The flying fox belongs to the Megachiroptera, thought to be an early branch from the primate line, and may represent an early stage in the evolution of the primate cortex. The primary somatosensory cortex, specifically

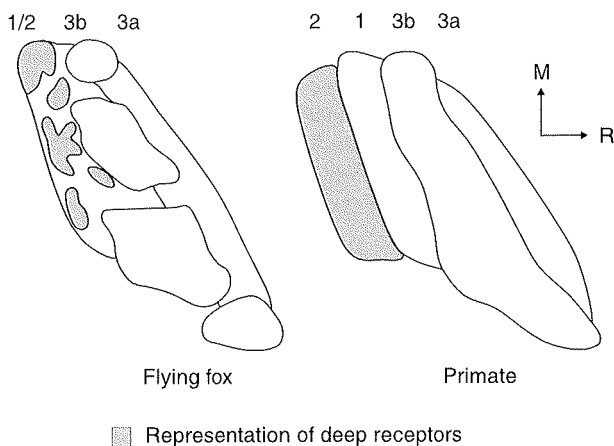


Figure 5. *a*, the flying fox may represent the early primate organization of the somatosensory cortex, with a primary somatosensory area (S1 or area 3b), a rostral deep field (area 3a) and a field partially embedded in area 3b that contains complete representations of both cutaneous and deep receptors (area 1/2). The representations of deep receptors form small aggregates or modules within area 1/2. *b*, in advanced primates, area 2 is a separate field. Selective pressure over time in this lineage may have caused the projections of deep receptors to aggregate and eventually separate. M, medial; R, rostral. Modified from Krubitzer and Calford, 1992.

Brodman's area 3b, in the flying fox and primates has a similar organization. In primates, areas 1 and 2 lie caudal to area 3b. Neurons in area 1 respond to cutaneous stimulation and those in area 2 to deep receptors. In the flying fox, the equivalent of areas 1 and 2 is partially embedded in area 3b and the representations of the deep receptors form islands interspersed within the representation of cutaneous inputs (Krubitzer and Calford, 1992). This is one of several examples in extant species in which fields seem to lie within other fields and where modules that represent one type of sensory receptor are embedded in a representation of another type. In this example, we consider that there was selection for segregation of deep and cutaneous receptor terminals in area 1/2 in the primate lineage, with the eventual complete separation into the areas 1 and 2 seen in advanced primates.

Cortical field specification in development

One issue that has to be resolved is whether the identity of a cortical field is determined intrinsically, by a component that assigns its unique identity, or extrinsically, through its dominant connections. If the mechanism is intrinsic, a part of the cortex will become the primary visual or somatosensory area irrespective of its location. Thus a change in its geographical location would be akin to continental drift (Krubitzer *et al.*, 1995). An extrinsic mechanism assumes that the developing cortex is a homogeneous sheet and the specific functions of each area are determined by the sensory inputs it receives via the thalamus and by its connections with other cortical and subcortical areas. With an extrinsic mechanism, small changes in timing during development, such as the number of cells generated in the thalamus or cortex (see Rakic, this volume), could influence both the division of the cortex into fields and the size of the fields by changing the pattern of inputs from the thalamus.

To investigate which of these mechanisms operates, we have changed the size of the cortex before inputs arrive from the

thalamus. We are using the opossum, *Monodelphis domestica*, a South American marsupial, because the young are born very immature and the entire process of formation and innervation of the neocortex occurs postnatally. As litters are large and the young mature rapidly, development can be followed easily. The cortical organization is well understood, so any changes that are induced can readily be detected.

The first axonal projections between the thalamus and cortex were traced after staining with crystals of carbocyanine dye

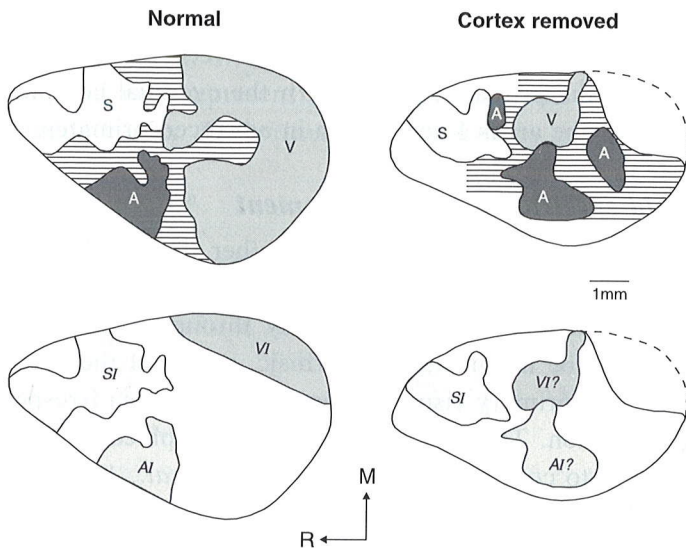


Figure 6. Neocortical areas in the opossum, *Monodelphis domestica*, are reorganized after removal of part of the cortical plate in one hemisphere, which supports the hypothesis that cortical areas are not intrinsically specified. The remaining tissue forms relatively normal visual (VI, VII), auditory (AI) and somatosensory (SI, SII) fields, although compressed compared with the normal cortex. The diagrams show the flattened neocortex; left, normal; right, lesioned. Top, the regions of cortex in which neurons responded only to stimulation in one sensory modality (solid), such as visual (V), auditory (A) or somatosensory (S), or to more than one modality (stripes). Bottom, the locations of the primary sensory areas. M, medial; R, rostral.

implanted in paraformaldehyde-fixed brains of various ages between postnatal days 2 and 30. The formation of the cortex and outgrowth of the first axons from the thalamus and the cortex start just after birth, when the first neurons arrive under the pial surface of the lateral cortex. Maturation occurs in a distinct gradient across the hemisphere, with approximately four days difference between the most mature lateral segments and the newly formed cortex at the extreme dorsal convexity (Molnár *et al.*, 1998).

In preliminary investigations, about half the developing cortex (the cortical plate) of one hemisphere was removed before it was invaded by thalamic inputs. The cortex was mapped in mature animals using electrophysiological and histological techniques, comparing the lesioned and normal sides. The cortex was smaller on the lesioned side but all areas were present, although reduced in size; some had shifted slightly and the primary sensory areas were compressed (*Fig. 6*). These results support the hypothesis that cortical fields are determined by patterns of activation during development. Some aberrant organization was observed, mostly at the posterior pole adjacent to the site where the cortical plate was removed, which implies that position in the early cortex may to some degree determine the general location of visual, somatosensory and auditory cortex. To test whether the expansion of the cortex alone is sufficient to generate a new cortical field, we are currently adding generative neuroepithelium to the cortical plate before the inputs from the thalamus arrive.

Cortical organization and behaviour

We consider that the large differences in neocortical organization observed in extant mammals may be accounted for by changes in the morphology of the body, including the addition or modification of sensory receptors; environmental influences; and changes in the size of the developing cortical sheet. As 'higher-

order' behaviours, such as cognition and language, are clearly tied to the cortex, they must have arisen through a similar process. This perspective leads to a new set of rules for the study of cognition, because the increases in cognitive capacity, language and social skills associated with humans are enslaved by changes in external morphology, the environment and the internal sensory processing network. The higher-order functions cannot be divorced from these factors. The evolution of the mind is thus the evolution of the brain, which depends on genetic and epigenetic effects on the developing nervous system.

Cortical development and evolution

Pasko Rakic

Modern developmental neurobiology provides insight into how the cerebral cortex develops and how it may have evolved. Through the course of evolution, the cerebral cortex has increased enormously in surface area but not in thickness, a trend that can be seen even in the relatively short period of primate evolution: the human cortex is only about 15% thicker than that of the macaque monkey but is at least 10 times greater in area. To understand how this complex structure has enlarged over the course of mammalian evolution, we need to examine the cellular changes that may take place during brain ontogeny, an approach that has been extensively used in evolutionary biology (see Gould, 1977).

The genes and molecules that control the early stages of corticogenesis are good candidates for determining the species-specific size and basic pattern of cortical organization. I have proposed that the developing cerebral cortex is composed of a large number of radial units, each consisting of a group of clonally