Title

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The mammalian neocortex varies greatly in size and internal organization across species. However it is often difficult to attribute specific cognitive abilities to corresponding cortical specializations. Here mammals with different sensory specializations are compared with their less, or differently, specialized relatives in order to identify trends in mammalian cortical evolution associated with increased behavioral abilities and sensory processing. In addition, some of the features of small versus large brains are considered in the context of evolution. The enlargement of cortex, changes to the organization of cortical areas, and the subdivision of cortex into additional areas, are seen as important trends correlated with the ability to process greater volumes of complex sensory information. Recent advances in the ability to manipulate gene expression during development suggest some of the mechanisms that have produced these changes. These mechanisms include alterations to a sensory surface (retina, cochlea, and skin) that affect neocortical maps through a cascade of inductive influences during development and more dramatic changes in brain organization that may result from duplication and subsequent specialization of cortical areas.

How brains have changed in the course of evolution and what changes are correlated with increased cognitive abilities remain among the most fundamental and intriguing questions regarding mammalian evolution. Ancestral mammals were shrew-like in size and habits with relatively small brains that had proportionately little neocortex (Jerison, 1990; Kielan-Jaworowska, 1983, 1984, 1986). It is obvious from these observations that brain size has increased in many mammalian lineages, and that with this expansion has come an increase in the repertoire and complexity of mammalian behaviors. Humans represent an extreme in this regard, and it is natural to wonder how evolution has "built" large brains and what kinds of structural changes are associated with brain enlargement. The neocortex is of particular interest, as it accounts for much of the expansion of brain volume in humans and other mammals (Jerison, 1973, 1990; Kaas, 2000; Northcutt & Kaas, 1995) and it is the processing center underlying complex cognitive abilities.

There have been a number of historical theories about the composition of ancestral brains that gave rise to modern lineages and a number of different mechanisms proposed for how the mammalian brain, particularly the neocortex, has been modified to produce the diversity of anatomical configurations observed today (Allman & Kaas, 1971; Deacon, 1990; Kaas, 1982, 1987a, 1989, 1993; Krubitzer, 1995, 2000; Krubitzer et al., 1993; Krubitzer & Huffman, 2000). Because of their similarity to ancestral mammals, the modern mammalian order Insectivora has figured prominently in many theories and discussions of brain evolution (Allman, 1999; Batzri-Izraeli et al., 1990; Catania, 2000a; Deacon, 1990; Ebner, 1969; Glezer et al., 1988; Kaas et al., 1970; Krubitzer et al., 1997; Lende, 1969; Michaloudi et al., 1988; Radinsky, 1976). One conclusion drawn from the

investigation of such small-brained mammals, is that large brains are not simply scaled up versions of small brains; rather, the number of cortical areas has increased in the course of evolution, such that large-brained mammals with complex behaviors have more cortical subdivisions than small-brained mammals (see Kaas, 1987a, 1993; Krubitzer, 1995, 2000, for reviews). However there is much uncertainty and disagreement as to the number and identity of cortical areas for individual species and how the cortex has been modified to produce different configurations in the course of evolution.

Despite this uncertainty, the continued improvement of methods for histochemically processing brain tissue and recording electrophysiological responses from neurons, in conjunction with the addition of new species to comparative studies of brain organization, has added greatly to the information available to guide theories of mammalian brain evolution. This is particularly true for recent advances in genetics that reveal potential patterning mechanisms for different areas and nuclei, and allow the manipulation of gene expression at different stages of development (Fukuchi-Shimogori & Grove, 2001; Ohsaki et al., 2002; O'Leary & Nakagawa, 2002). Here I review some of these recent findings that support specific conclusions for how brains may have been modified in the course of evolution and the mechanisms that may underlie these changes. Conclusions are drawn primarily from studies of small-brained mammals for which we have the greatest confidence in defining cortical areas and tracking evolutionary changes related to behavioral and sensory specializations.

Organization of the Neocortex in Ancestral Mammals

Fossil endocasts from early Triassic mammals indicate that primitive taxa had small bodies and brains, approaching the size of the smaller shrews and moles found today (Jerison, 1990; Kielan-Jaworowska, 1983, 1984, 1986). In some of these endocasts the rhinal fissure can be discerned and from these examples it is apparent that early mammals had proportionately little neocortex. Thus mammalian evolution has been marked by an increase in overall brain and body size, as well as an increase in the relative proportion of the brain taken up by neocortex (Jerison, 1990).
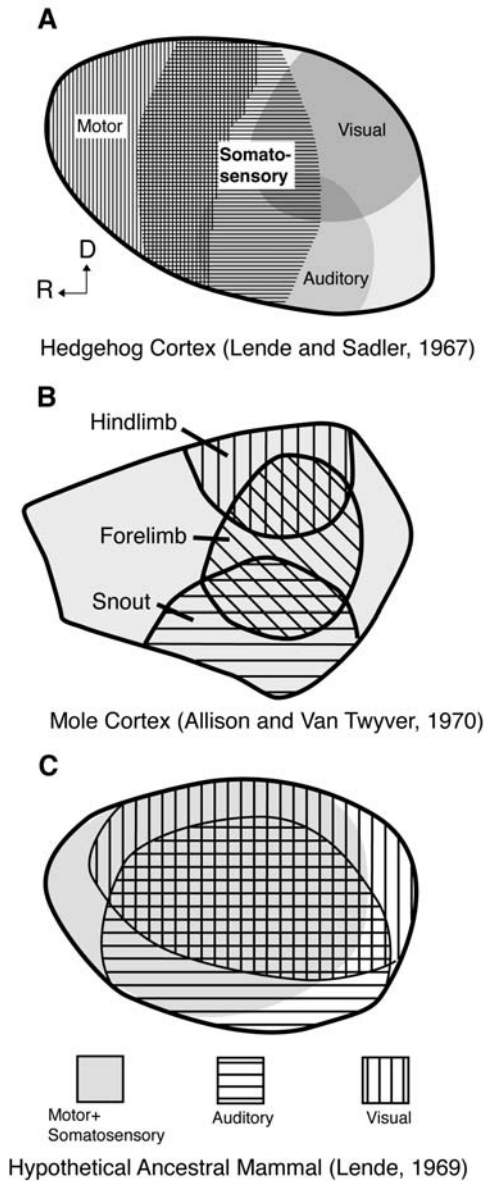
Because modern members of the Insectivore order (Figure 1) resemble ancestral taxa in many respects (Eisenberg, 1981), this mammalian order (including shrews, moles, and hedgehogs) has been the subject of a number of studies aimed at determining how ancestral brains may have been organized. Early studies of hedgehogs (Lende & Sadler, 1967) and moles (Allison & Van Twyver, 1970) using surface electrodes to map cortical subdivisions suggested that cortical areas overlapped extensively (Figure 2A, B) and were not well organized into the topographic maps that are characteristic of cortical subdivisions in other species. In hedgehogs primary somatosensory cortex (S1), primary visual cortex (V1) and primary auditory cortex (A1) were found to overlap with one another, and motor cortex (M1) was partially embedded in somatosensory cortex. This led to the proposal (Lende, 1969) that cortical areas may have gradually differentiated from one another by slowly separating apart from an ancestral, overlapping condition in stem mammals (Figure 2C).
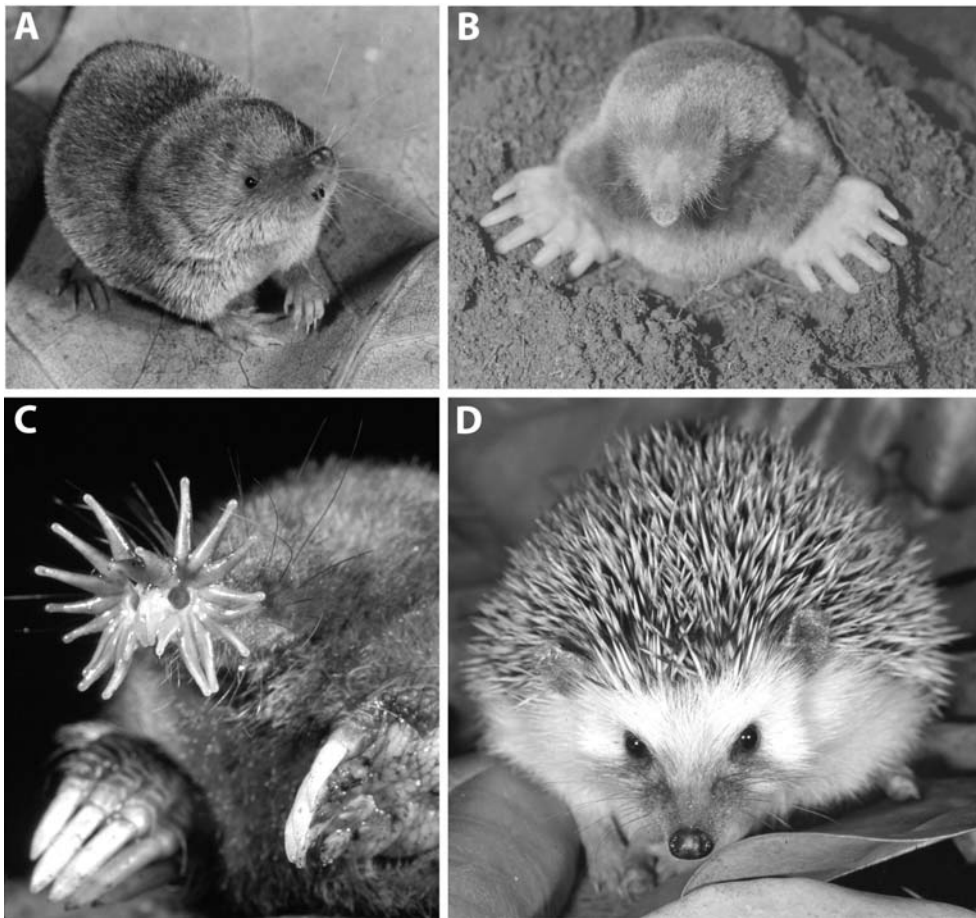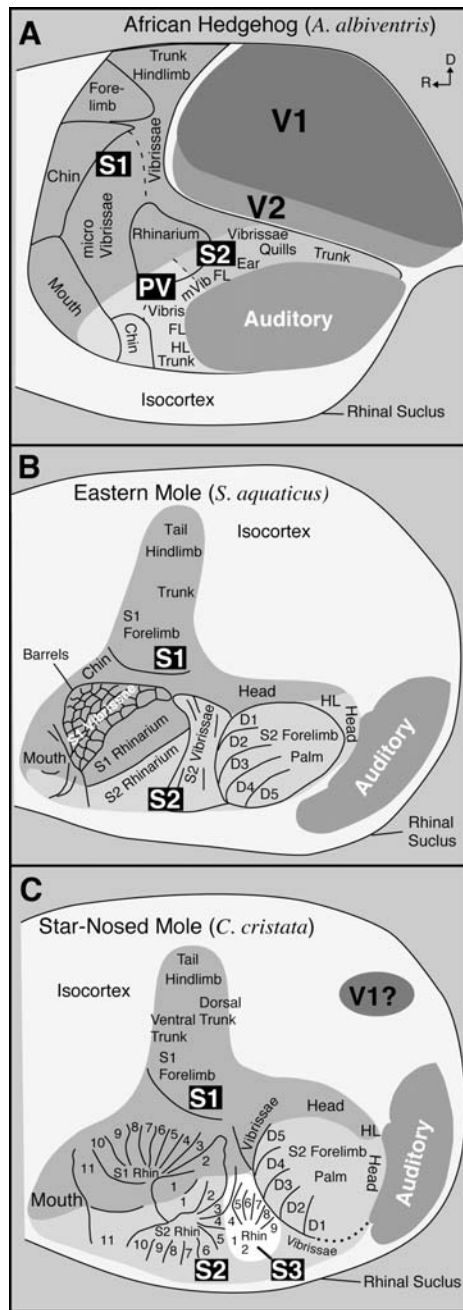
Figure 1. Some members of the order Insectivora. (A) A tiny shrew (*Cryptotus parva*) weighing only a few grams. Shrews are thought to resemble ancestral mammals in many respects. (B) The eastern American mole (*Scalopus aquaticus*) with tiny eyes and ears and large clawed forelimbs. (C) The star-nosed mole (*Condylura cristata*) with nostrils surrounded by 22 fleshy appendages used to explore the environment through touch. (D) A hedgehog (*Altelerix albiventris*) with defensive spines and relatively large eyes and ears.

However comparative studies from a wide range of mammals have consistently revealed well organized, nonoverlapping cortical subdivisions in the vast majority of mammalian lineages. Thus from the outset Lende's conception of brain evolution depended on the assumption that modern insectivores alone, in contrast to other small-brained mammals, have retained a brain organization similar to the ancestral condition. A second problem with theories of gradual separation based on studies of extant insectivores comes from more recent investigations of insectivore brains using modern histochemical cortical stains and microelectrode recording methods. These findings clearly indicate that shrews (Catania et al., 1999), moles (Catania & Kaas, 1995), and hedgehogs (Batzri-Izraeli et al., 1990; Pobirsky, 1998; Catania et al., 2000) have well-organized and nonoverlapping cortical subdivisions on a par with cortical areas found in most other mammalian species (Figure 3). Therefore the overlap of cortical areas documented in previous investigations was the result of the poor resolution of neuronal responses obtained from surface electrode recordings. Taken together with a number of other recent investiga-

tions of cortical organization across mammals (Huffman et al., 1999; Krubitzer et al., 1993, 1995, 1997) that have revealed discrete and well organized cortical subdivisions, the most parsimonious conclusion is that small-brained ancestral mammals also had a few well organized and nonoverlapping cortical sensory areas (Northcutt & Kaas, 1995; Kaas, 1995; Krubitzer, 1995).

A

Hedgehog Cortex (Lende and Sadler, 1967)

B

Mole Cortex (Allison and Van Twyver, 1970)

C

Hypothetical Ancestral Mammal (Lende, 1969)

Figure 2. Early investigations of cortical organization in insectivores using surface electrode techniques. (A) Results of Lende and Sadler (1967) suggested that visual, auditory, and somatosensory areas overlapped extensively in the hedgehog cortex. (B) Results of Allison and Van Twyver (1970) suggesting a similar organization in the eastern American mole (*S. aquaticus*). In this case the details of somatosensory cortex were explored and the representation of different body parts in S1 were found to overlap extensively. (C) The overlap of cortical areas described for hedgehogs (A) suggested that ancestral mammals might have had a similar organization of cortex but with an even greater degree of overlap, as illustrated above. More recent investigations of insectivore cortex using microelectrodes (Figure 3) have instead revealed well organized and nonoverlapping cortical areas.

A African Hedgehog (*A. albiventris*)

B Eastern Mole (*S. aquaticus*)

C Star-Nosed Mole (*C. cristata*)

Figure 3. The results of recent investigations of cortical organization in members of the order Insectivora. (A) In contrast to studies of hedgehog cortical organization using surface electrodes, subsequent investigations have revealed well organized visual (Kaas et al., 1970), somatosensory (Catania et al., 2000) and auditory (Batzri-Izraeli et al., 1990) cortical sensory areas. These areas have sharp borders as indicated by microelectrode recordings and cortical architecture (cytochrome oxidase histochemistry). (B) Similarly, the eastern American mole has well organized somatosensory areas (compare to Figure 2B) that include visible barrels much like those identified in rodent cortex. (C) Finally, the star-nosed mole also has well organized topographic representations including an interconnected network of somatosensory areas representing the star. Each of three representations of the star (S1, S2, and S3) is visibly reflected as a series of modules, much like the whisker-barrel system of rodents.

## Cortical Areas May Be Added to Processing Networks

Modern studies of cortical organization using sensitive neuroanatomical tracers, new histological stains, and microelectrode recordings have confirmed the early conclusions of Brödmann (1909), based on cytoarchitecture alone, that different mammals have different numbers of cortical subdivisions or areas (see Kaas, 1995, for review). Large-brained mammals such as primates and carnivores have more subdivisions than small-brained mammals such as rodents and insectivores. Historically this was a matter of some debate (Lashley & Clark, 1946) and even recently it has been suggested that some small-brained mammals have a primate-like cortical organization. For example it has been suggested that rodents may have 10 visual areas adjacent to V1 forming a complex processing network in caudal cortex (Montero, 1993), and that many of these areas are homologues to the cortical visual areas found in primates. However more recent assessments of the organization of visual cortex across rodents and other mammal species suggest that rodents and most other small mammals have instead a relatively simple visual system consisting of primary and secondary visual cortex (V1 and V2) and few other areas (Rosa & Krubitzer, 1999).

In mathematical analyses, great clarity often comes from determining the behavior of a complex function when variables are at extreme values–that is, determining a function's limits. Similarly, we may look at the extremes of mammalian brain size for the clearest examples of how mammals differ in numbers of cortical areas. The masked shrew (*Sorex cinereus*) provides this opportunity as it approaches theoretical size limits for mammals (Schmidt-Nielsen, 1984) and is the smallest mammal for which cortical organization has been explored (Catania et al., 1999). The results are unequivocal; shrews have only a very small number of cortical areas directly adjacent to one another leaving virtually no room for additional cortical subdivisions (Figure 4). These areas include primary and secondary somatosensory cortex (S1 and S2), primary auditory cortex (A1), primary visual cortex (V1), and at least one separate motor area (M1). Considering the small space between V1 and S1 in shrews (Figure 4) and the correspondingly sharp transition from visual to somatosensory responses for neurons at the V1 to S1 border (Catania et al., 1999) there is little room for even a single secondary visual area (V2). The similarity between the shrew's cortex and that of ancestral mammals (Kielan-Jaworowska, 1984) suggests that stem mammals had a similarly simple cortical plan.

In contrast, it is clear that some primates, representing the opposite extreme of brain size and complexity, have as many as 20-30 visual areas (Fellman & Van Essen, 1991; Kaas, 1994), 15 auditory areas (Kaas & Hackett, 1998), 10-15 somatosensory areas (see Kaas, 1995, for review) and 10 or more motor areas (Wu et al., 2000). Thus a major and important trend in the course of mammalian evolution has been an increase in both the size of neocortex and in the number of cortical subdivisions (Figures 5-6).

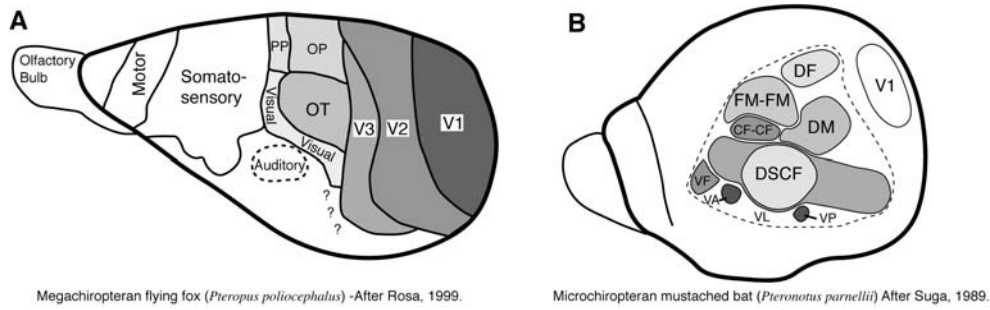It should be noted in this regard, that most cortical areas are characterized by topographic representations of sensory surfaces. Thus somatosensory areas (such as S1 and S2) contain maps of the mechanoreceptors in the skin, visual areas (such as V1 and V2) contains maps of the retina which are in turn maps of the visual field, and auditory areas (A1) contain maps of the cochlea which are in turn

maps of frequency (but see also Suga, 1989, for examples of computational maps). The presence of a complete representation of a sensory surface is one of the characteristics that is often used to define an individual cortical area. Some additional criteria include unique connections, cytoarchitecture, and response properties of cortical neurons (see Kaas, 1987b).
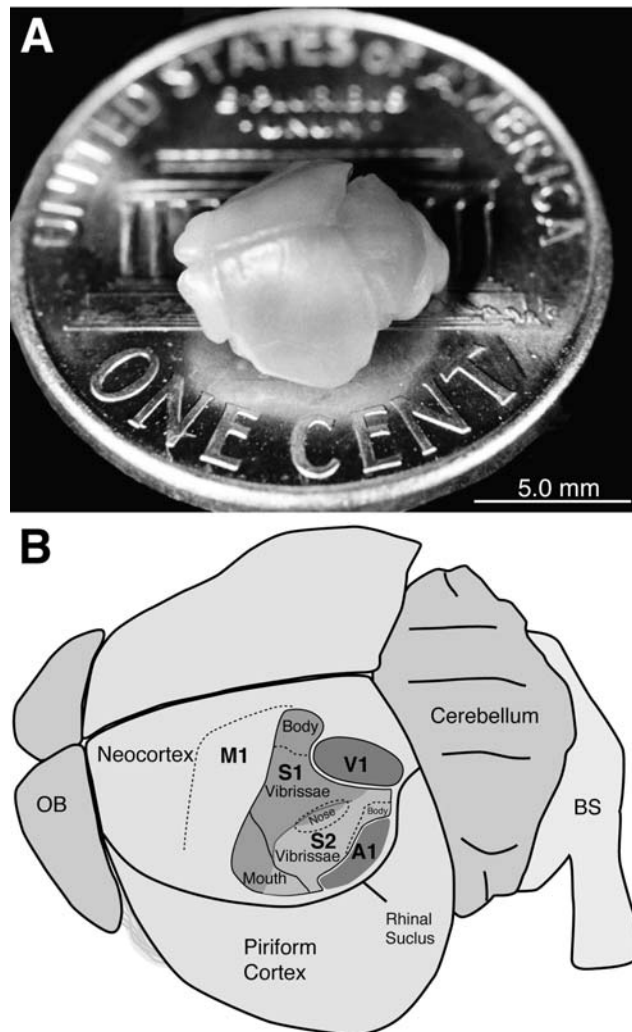

Figure 4. The small brain and neocortex of the shrew. (A) The brain of a least shrew (*Cryptotus parva*) resting on a penny for scale. (B) The organization of cortical areas in shrews (data from Catania et al., 1999). Shrews have a small total area of neocortex, and are thought to resemble ancestral mammals in this respect. The cortex contains a small number of cortical areas that are closely adjacent to one another, leaving little room for additional subdivisions. These areas include primary and secondary somatosensory cortex (S1 and S2), primary visual cortex (V1) and presumptive primary auditory cortex (A1). Note the close adjacency of V1 to the somatosensory areas, leaving little room for V2 or other visual areas. Comparative studies of insectivores and other mammals suggests that ancestral mammals had a similar cortical organization consisting of only a few, but well organized, sensory areas.

A Megachiropteran flying fox (*Pteropus poliocephalus*) -After Rosa, 1999.

B Microchiropteran mustached bat (*Pteronotus parnellii*) After Suga, 1989.

Figure 5. Cortical organization in megachiropteran and microchiropteran bats, demonstrating visual and auditory specializations respectively. (A) Summary of cortical areas in the megachiropteran flying fox (*Pteropus poliocephalus*). This fruit-eating species relies heavily on vision and this is reflected in the proportion of cortex devoted to vision and the number of corresponding visual areas (data from Rosa, 1999). Roughly half of the cortex is taken up by a series of at least 6 visual areas (shaded areas) and a number of additional areas are likely to be found in more rostral-lateral cortex. (B) Summary of cortical areas in the microchiropteran mustached bat (*Pteronotus parnellii*). In contrast to megachiropteran bats, microchiropteran bats have reduced visual systems and depend heavily on echolocation to navigate and locate flying prey. This is reflected in the organization of their neocortex which is dominated by a network of 8 or more auditory areas (shaded areas) that largely process information in the frequency range of returning echolocation pulses (data from Suga, 1989). These closely related species provide an example of how cortex has evolved in parallel with the more complex visual or auditory abilities of each respective species.
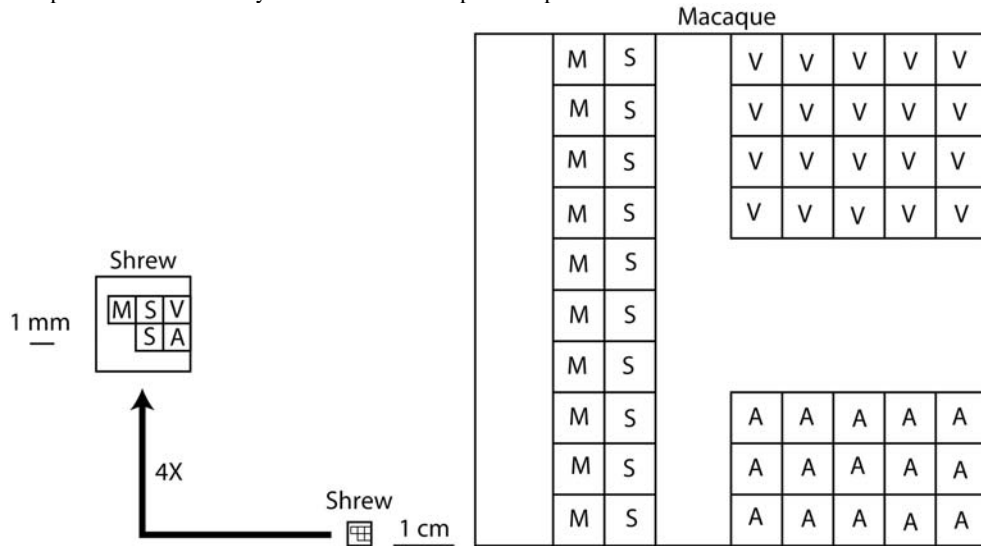
Figure 6. A schematic representation of cortical organization in a small-brained (shrew) and large-brained (macaque monkey) mammal. Shrews have as little as 0.15 cm^2 of neocortex whereas macaques have roughly 72 cm^2–a 480 fold difference. Humans, with approximately 800 cm^2 of neocortex, do not fit on the figure, but have neocortex with over 5000 times the surface area of a shrew. Given that shrews are similar in size and habits to ancestral mammals, there has clearly been a tremendous enlargement of cortex in many mammalian lineages. In addition to getting larger, the internal organization of cortex has changed as well. Many cortical subdivisions have been added in larger brained mammals, and this can be appreciated by comparing the enlarged shrew brain (far left) to the macaque brain. The letters denote visual (V), auditory (A), somatosensory (S) and motor areas (M). Shrews have only a few cortical subdivisions, whereas macaques have many (see text for references). The illustration is not intended to show the relative size or location of cortical areas.

Cortical Correlates of Behavioral Complexity

Although brain size has increased drastically in some lines of mammalian evolution and this is usually correlated with an increase in the number of cortical subdivisions, these changes are not necessarily correlated with increased behavioral sophistication or intelligence. If one considers brain size in rodents, for example, it would be difficult to make the case that a 70 kg capybara is particularly more intelligent than a 100 g rat, or that a rat is behaviorally more sophisticated than a diminutive, 10 g, pygmy mouse. This is in part because a larger brain is needed to run a larger body. The reasons for this likely include the need to control more muscles and to process larger volumes of sensory inputs, at least for somato-sensation. Additionally, larger cell bodies are needed to support longer axons in larger brains (and spinal cords) and further size increases in axons and dendrites-and hence cell bodies-are likely to result from the need to increase the conduction velocity of action potentials for many neurons. These and other factors contribute to the relationship between brain and body weight observed for many species (Jerison, 1973).

Similarly, the addition of cortical areas to a processing network does not necessarily provide an increase in computational abilities. As individual cortical areas increase in size, the local connections must increase in length to maintain a similar degree of global connectivity relative to sensory inputs. As pointed out above, such increases in the lengths of axons or dendrites must be accompanied by increases in their respective diameters in order to maintain similar conduction rates between cells (Ringo et al., 1994). The end result may be that some cortical areas become subdivided simply to remain locally efficient while maintaining global interactions with a few larger and longer connections between areas (Ringo, 1991, and see Kaas, 2000, for review).

Despite the fact that some regional subdivision of the cortex may be needed to simply maintain the status quo as brain size increases, there are nevertheless likely to be significant benefits to sensory processing that accompany more extensive subdivision of the cortex into separate processing areas, just as increases in brain size beyond that needed to control a larger body are likely to provide extra computation ability. A major potential benefit to subdividing cortex may come from the ability to process different facets of sensory stimuli in different areas (Zhang et al., 2001). This is thought to be the case for primates and carnivores which are more intelligent than smaller brained species with fewer cortical subdivisions, such as rodents and insectivores (Kaas, 1982). But intelligence is difficult to define and comparisons that relate specific behaviors to specific brain specializations are often difficult to make.

One way to more clearly appreciate the relationship between brain organization and behavioral complexity is to examine closely related species that differ primarily in a single dimension of sensory and behavioral specialization. This kind of comparison has been made for Talpid moles (Catania, 2000a) which include the common and relatively unspecialized eastern American mole (*Scalopus aquaticus*) and the closely related but very specialized star-nosed mole (*Condylura cristata*). Although both of these species depend heavily on touch to navigate and explore their environments, the star-nosed mole has an elaborate mechanosensory organ on its face consisting of 22 fleshy appendages surrounding the nostrils, each covered

with many hundreds of small, sensitive mechanosensory receptors called Eimer's organs. This structure is accompanied by a complex behavior pattern such that the star acts like a mechanosensory eye with a small tactile fovea and a larger, surrounding area of low resolution touch (Catania & Kaas, 1997a). In contrast, the eastern American mole, which also explores its environment with the tip of its snout, has a more typical mammalian nose without appendages or the complex mechanosensory Eimer's organs (Catania, 2000b) and the behavior of the eastern American mole is relatively simpler.

Corresponding to the larger and more complex sensory structures and associated behaviors in the star-nosed mole, the amount of cortex devoted to the nose in this species is very large and includes 3 separate somatosensory maps, or areas, representing the mechanosensory star. Within each of these maps, there is a series of modules that represent each separate mechanosensory appendage (Catania & Kaas, 1995). In contrast, the cortex of the eastern American mole contains only two cortical areas representing the snout in a much smaller total area without the modular subdivisions characteristic of the star-nosed mole cortex (Catania & Kaas, 1997b; Catania, 2000a). Thus the star-nosed mole, which handles much greater volumes of tactile information and uses the snout in a relatively complex set of foraging behaviors, has both a larger proportion of cortex devoted to the star and more cortical areas devoted to the nose than is typical of other species of mole (see Figure 3).

Another useful comparison can be made between megachiropteran and microchiropteran bats. These two major subdivisions of bat species (order Chiroptera) differ drastically in their diets and foraging strategies and hence the priorities of their sensory systems. Microchiropteran bats rely heavily on echolocation to navigate and capture food (flying insects) and thus have exquisitely sensitive auditory systems. Megachiropteran bats (flying foxes) are primarily fruit eaters and do not echolocate. Rather they depend heavily on their visual systems to navigate and locate food. These sensory priorities are reflected in the corresponding organization of the neocortex of each species and, like the star-nosed mole's sensory system, this can provide evidence for how the neocortex has evolved to handle larger volumes of more complex information.

The differences between megachiropteran and microchiropteran cortex are dramatic (Figure 5). Nearly half of the megachiropteran cortex is devoted to vision, forming a network of interconnected visual areas in the caudal half of the cortex (Rosa, 1999). This includes at least 6 characterized visual areas and additional visual cortex that has not yet been fully explored. In contrast, the cortex of the echolocating mustached bat (*Pteronotus parnellii*) is dominated by a network of at least 8, and probably many more, auditory areas (Figure 5), many of which are tuned specifically to the harmonics of the echolocation frequencies used by the mustached bat (Suga, 1989; Misawa & Suga, 2001).

Such comparisons of closely related species, that differ primarily in sensory and behavioral specializations, support the broad conclusion drawn from a wide range of species, that subdividing the neocortex into multiple processing areas is an important component of increased cognitive ability. This presumably allows for the parallel processing of different facets of sensory information within different parts of the neocortex. Similar specializations for parallel processing have been reported for central nervous structures in a number of specialized vertebrates,

notably barn owls (Takahashi et al., 1984) and weakly electric fish (Heiligenberg & Bastian, 1984).

An additional sensory specialization evident in the species described above is the segregation of sensory systems into high resolution and low resolution components, or functional foveas. This is most familiar to us in the form of the retinal fovea, with which we have personal experience. We constantly shift our eyes (make saccades) to position behaviorally relevant images on the high resolution area of the retina, which has the greatest number of photoreceptors, associated ganglion cells (output of the retina), and corresponding cortical representational area. The fovea is said to have a high degree of cortical magnification because a huge amount of cortex is devoted to this region despite the relatively small proportion of the visual field that is viewed by the retinal fovea.

It has also been recognized that some echolocating bats have a similar organization for their auditory system. For example in the mustached bat (*Pteronotus parnellii*) much of the cochlea and the central nervous system is devoted to the analysis of only a very narrow frequency range corresponding to one harmonic of returning echos. This has been called an acoustic fovea (Suga & Jen, 1976) because of its similarity to a retinal fovea. Bats even have the equivalent of an auditory saccade (analogous to eye movements in a visual system). This is necessary because echos are Doppler shifted by different amounts depending on the relative velocity of the bat and its echolocation target, and therefore the returning echo may not fall on the frequency of the acoustic fovea. When this occurs, bats shift the frequency of their outgoing echolocation pulses appropriately, such that the Doppler shifted returning echos will fall on the frequency of the acoustic fovea. This behavior is called Doppler shift compensation (Schnitzler, 1968).

Finally, the star-nosed mole has a somatosensory fovea consisting of a pair of tactile appendages just above the mouth (Catania & Kaas, 1997a). Star-nosed moles also make saccadic movements of the star so that objects of interest can be explored in greatest detail with the foveal appendages. As is the case for the retinal fovea of primates and the acoustic fovea in bats, the tactile fovea of the star has a greatly expanded representation in the cortex.

The obvious benefit of a fovea-periphery organization is the conservation of computational space in the brain. This is accomplished by specializing only a very small part of a sensory surface for detailed analysis of incoming information and devoting a large area of the brain to sensory inputs from this region (Azzopardi & Cowey, 1993). A larger low-resolution area of the sensory surface is used to guide the fovea, whether it be the retinal fovea, tactile fovea, or acoustic fovea.

Mechanisms of Cortical Evolution

As described above, much of the neocortex is characterized by multiple maps of sensory surfaces and changes in the number and nature of these cortical maps has clearly been an important trend in mammalian evolution that accompanies increased behavioral complexity and cognitive abilities. There are a number of proposals for how the cortex may have been altered in the course of evolution and recent studies seem to support some specific conclusions. There are two levels of organization addressed below, including (1) how details of cortical sensory maps

may be altered and (2) how completely new areas in the form of maps of the sensory periphery may have been added to the neocortex.

Instructive Influence of the Sensory Surface

There is considerable evidence from experimental manipulations during development suggesting that sensory surfaces (the retina, skin, or cochlea) play an instructional role in guiding the formation of the details of cortical (and subcortical) sensory maps, or representations (here I refer to the retina as the periphery, although it is part of the CNS). Some of the strongest evidence comes from the somatosensory system of rodents, where each whisker is represented by a separate histologically visible unit (barrel) in primary somatosensory cortex - S1 (Woolsey & Van der Loos, 1970). Development of the sensory system begins with the skin surface and ends at the cortex such that whiskers form before cortical barrels and thus have the opportunity to instruct cortical development (see Killackey et al., 1995). In support of this possibility, early damage to the whiskers disrupts the formation of corresponding cortical barrels (Andres & Van der Loos, 1985; Woolsey, 1990).

A related observation was made by Van der Loos and Dörfl (1978) who noted that strains of mice born with extra whiskers also developed extra, corresponding barrels in representational cortex. They argued that it was unlikely for a single mutation to have simultaneously altered the skin surface, subcortical nuclei, and somatosensory cortex. Rather, a mutation acting at the level of the early developing skin surface was more likely to have been communicated to the subcortical representations (trigeminal sensory nuclei and thalamus) and subsequently to the later developing cortex. Recently this interpretation has received strong support from experiments in which altered whisker patterns have been induced during prenatal development by transfecting the epidermis of mice with an adenovirus harboring *Sonic Hedgehog* (*Shh*). This genetic manipulation does not affect gene expression in the central nervous system, however the altered whisker patterns induced in the periphery were consistently reflected in the later-forming pattern of cortical barrels (Ohsaki et al., 2002). This study seems to confirm the extrinsic nature of the signal guiding the formation of supernumerary barrels, as suggested by Van der Loos and Dörfl (1978).

Another possible role for the periphery in guiding the formation of cortical representations may come in the form of a competition for cortical space during development. Evidence for this possibility has come from the primate visual system where suturing one eye shut during critical periods of development results in a reduction in the size of corresponding ocular dominance columns related to the sutured eye and an expansion in the size of columns devoted to the open eye (Hubel et al., 1977). Activity-dependent expansions of cortical areas have also been documented for rodent barrel cortex where the most active cortical regions undergo the greatest amount of growth during development (Riddle et al., 1993; Purves et al., 1994). Thus activity from the sensory surface may play an important role in determining how much cortical territory is allocated to the representation of different parts of a sensory surface.

Given these observations, it seems likely that some evolutionary changes in the cortex (and subcortical stations) may simply be the result, at least initially,

of alterations to the sensory periphery that are communicated to the cortex by a cascade of inductive events during a relatively plastic developmental program. The examples of laboratory mice with supernumerary whiskers no doubt have their analogues in wild strains and this may be one of the historical sources of variation upon which natural selection has acted to produce the various configurations of whiskers, and cortical barrels, observed today. Direct evidence for this kind of naturally occurring variation has been observed in star-nosed moles (Catania & Kaas, 1997c) where approximately 5% of wild-caught specimens have been found with extra or fewer nasal appendages and corresponding alterations to the maps (modules) in somatosensory cortex.

Another peripherally-centered influence on cortical evolution might be found in the timing of development of different parts of a sensory surface. For example both the retinal fovea of primates and the tactile fovea of star-nosed moles are the earliest parts of the retina and star, respectively, to develop (Rapaport & Stone, 1984; Catania, 2001). Sensory inputs (ganglion cells and trigeminal afferents respectively) from these areas are allocated larger areas of cortex than inputs from the surrounding and later developing, nonfoveal, sensory surfaces (Azzopardi & Cowey, 1993; Catania, 2001). Thus the earliest developing parts of a sensory surface may have a competitive advantage in capturing cortical territory, perhaps through activity dependent mechanisms (Hubel et al., 1977).

These examples suggest that one mechanism by which evolution has altered cortical representations is by relatively simple changes to the sensory surface that are developmentally linked to the cortex. This is not to suggest that the cortex can equally accommodate any alterations to the sensory periphery. It seems more likely that cortical and subcortical areas, though flexible, are optimized for the normally expressed development of the sensory periphery. The accommodation of an altered sensory periphery may result in a less than optimal cortical configuration, despite a net selective advantage provided by the altered sensory surface. However subsequent selection could then act to fine tune the central nervous system in later generations. For example, for the cortex to accommodate the representation of an expanded sensory surface there may be a reduction in the average representational area of each sensory input. An extra barrel in the barrel field could result in less cortical territory devoted to each barrel. Alternatively, there might be an expansion of the somatosensory system overall such that each barrel, including the supernumerary barrel, maintained the premutation amount of representational space, resulting in an overall increase in somatosensory cortex at the expense of, for example, visual cortex.

The main point is that consequences of an initial perturbation of the cortex by a mutation acting at the level of the sensory surface might provide a net advantage despite a resulting cortical configuration that was less than optimal. Natural selection could then act to favor local changes in the cortex (and subcortical areas) that better accommodate the altered sensory surface. Such subsequent changes could include alterations to the overall size of the neocortex and other brain areas, or changes to the number, organization, or configuration of cortical sensory areas and their connections. Recent fossil evidence for this trend has been found for anthropoid primates, which seem to have evolved high acuity vision before developing corresponding specializations in the central nervous system (Bush et al., in press).

Addition of Cortical Areas to Processing Networks

Although some evolutionary changes to the mammalian brain may begin with the sensory surface, many larger scale and more significant changes to the mammalian brain have certainly occurred more centrally. What are some of the potential mechanism that have brought about large-scale organizational changes? Recent investigations and manipulations of gene expression patterns in the developing mouse neocortex have shed light on potential mechanisms that may control many aspects of the development, position, and number of cortical areas (Cecchi, 2002; Fukuchi-Shimogori & Grove, 2001; Ohsaki et al., 2002; O'Leary & Nakagawa, 2002). An important finding from these investigations is that graded expression of patterning proteins is found in the developing neocortex, and manipulation of these expression patterns results in predictable alterations in the position of entire cortical subdivisions. One growth factor in particular–FGF8, a member of the fibroblast growth factor family–has a dramatic effect on the rostro-caudal position of cortical areas. FGF8 is normally expressed at the rostral pole of the developing neocortex, and increases or decreases of the production of FGF8 cause caudal and rostral shifts, respectively, of somatosensory and other cortical areas (Fukuchi-Shimogori & Grove, 2001).

A key experiment was to introduce a second source of FGF8 at the caudal pole of developing mouse neocortex (Fukuchi-Shimogori & Grove, 2001). This manipulation resulted in the partial, mirror image duplication of the barrel field (Figure 7) in somatosensory cortex that is presumed to be supplied by its own set of thalamocortical axons (O'Leary & Nakagawa, 2002).
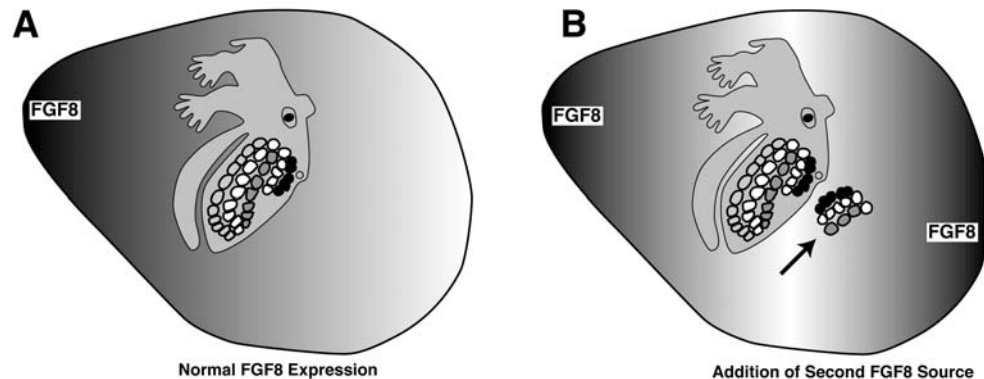
Figure 7. A schematic illustration of recent experiments that have induced the partial duplication of the cortical barrel field by adding a new source of FGF8 to the caudal part of developing cortex (from Fukuchi-Shimogori and Grove, 2001). (A) FGF8, a member of the fibroblast growth factor family, is normally expressed rostrally in developing cortex. (B) When a second source of FGF8 was introduced by electroporation during fetal development, adults were later found to have a partially duplicated barrel field (arrow). This result suggests a mechanism by which mirror image duplications of a cortical area might occur in the course of mammalian evolution.

In essence Fukuchi-Shimogori and Grove (2001) manipulated gene ex-