Emergence of Novel Functions During Brain Evolution

Using a cladistic approach to investigate how new brain functions evolve

Kiisa C. Nishikawa

From comparative studies of both vertebrates and invertebrates, a common theme has emerged: Brains have evolved rather conservatively compared with other morphological features. Edwards and Palka (1991) likened neural evolution in insects to a fugue rather than to an opera, because despite large differences in behavior among species, most of the differences among insect nervous systems are found in the details of synaptic connections among highly conserved sets of neurons. Likewise, the vertebrate brain is commonly thought to have evolved conservatively because vertebrates, from lampreys to humans, are strikingly similar in their overall brain organization. Indeed, few novel brain structures have appeared since the origin of vertebrates.

Over the last 15 years, the cladistic approach to phylogenetic analysis has revolutionized our understanding of brain evolution by demonstrating that many structures that had previously been assumed to be homologous actually evolved many times independently (Northcutt 1984). Examples of convergent evolution that have recently come to light include pathways that control song production and learning, which evolved independently in songbirds and parrots (Brauth et al. 1994, Striedter 1994); sound-processing circuits associated with ear asymmetries in owls, which may have evolved as many as five to seven times independently (Volman 1994); and divisions of the mammalian isocortex, several of which appear to have evolved independently in different lineages of mammals (Northcutt and Kaas 1995). The cladistic approach, combined with ever-improving anatomical techniques, demonstrates that "there's been a whole lot of evolution going on" in brains, much more than was previously thought.

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The general pattern that has emerged from recent cladistic studies is that, in both invertebrates and vertebrates, major changes in brain structure have occurred only rarely, whereas changes in neural connections, neurotransmitters, and membrane properties (i.e., receptors and ion channels), as well as changes in the relative sizes of different parts of the brain, have occurred frequently and convergently during evolution. Thus, the brains of animals are mixtures of innumerable small novelties that appear against a background of conserved features.

Evolution of novel brain functions

Brain evolution is fundamentally an interdisciplinary subject, integrating information across all levels in the biological hierarchy: molecular, cellular, anatomical, physiological, and behavioral. Brain evolution has been studied extensively at the anatomical level during the last century (e.g., Ariens-Kappers et al. 1936, Butler and Hodos 1996, Northcutt 1984), and ever-improving techniques continue to provide exciting new insights. Recently, brain evolution has received some attention at the molecular and cellular levels (Arbas et al. 1991) and at the physiological and behavioral levels (Volman 1990), although comparative studies at these levels are still rare (Bullock 1993). For most parts of the brain, we still know little about their function and evolutionary origins.

Why is it important to understand the evolution of brain function? For several reasons. First, we want to understand how our unique human brain evolved and to know in what respects it is similar to, as well as different from, the brains of other animals. Second, identifying homologues of novel brain structures may provide important insights into pathological conditions of the brain

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and may suggest how such pathologies could be alleviated. For example, evolutionary studies may reveal why the forebrain, especially the hippocampus, is most subject to plaque formation in Alzheimer's disease. Third, convergent evolution of neural circuits that serve similar functions may provide insights into the functional architecture of nervous systems. For example, features such as parallel, distributed processing and population coding (in which a signal is encoded in the activity of a population of neurons instead of a single cell) have evolved convergently in distantly related species throughout the animal kingdom; these features likely represent analagous solutions to similar problems in different animals (Liebenthal et al. 1994).

In this article, I review the results of a handful of recent studies that provide insights into the evolution of brain function. These studies make use of several methodological advances in "evolutionary neurobiology," including not only the development and application of cladistic methods to reconstruct relationships among species but also the development of molecular techniques that help to reveal the homologues of novel features. Using these tools in a comparative context, it has been possible to study how novel brain functions emerged during evolution.

I begin with an overview of how phylogenetic analysis can be used to study the evolution of novel brain functions. I then review recent studies that have examined four different types of changes in brain characteristics: major new features that appeared during metazoan evolution; changes in interconnections among existing groups of neurons; changes in membrane properties of neurons; and changes in the relative sizes of different parts of the brain. Next, I suggest a process that may be responsible for many evolutionary changes in brain function. The process begins with overproduction of neurons by mechanisms such as correlated growth. Redundant neurons, freed from the constraints of their previous functions, may evolve new connections, neurotransmitters, and membrane properties, and these changes may lead to the emergence of novel functions. I conclude the article with a discussion of how recent studies have changed our views of the evolution of brain function.

The phylogenetic approach

Several recent studies provide examples of how to use a phylogenetic approach to examine the emergence of new brain functions during evolution. The first step is to identify a feature, such as sound localization in owls, that is present in some, but not all, species within a group. New features are most often identified at behavioral or anatomical levels. Huge numbers of such features are already known to exist, but their evolutionary appearance has never been investigated. The second step is to examine the feature in at least three species. (Although the comparative method can be used to study two species, at least three species are required for generating a phylogenetic hypothesis.)

The third step is to investigate the evolutionary history of the feature by mapping its distribution onto a cladogram, that is, a branching diagram that illustrates a phylogenetic hypothesis about the evolutionary relationships among the species. (Obvious limitations of this method are that cladograms are not available for all groups of species and that not all phylogenetic hypotheses will withstand the test of time.) A cladistic analysis determines the most parsimonious explanation for the distribution of character states among species. Thus, it provides information about the location and direction of transitions from one character state (e.g., absence of a function) to another (e.g., presence of the function). Because loss of function has occurred commonly during evolution, the absence of a characteristic is often derived from its presence, rather than the reverse.

The next step is to identify the homologous ancestral feature from which the new feature was derived. New features do not appear de novo during evolution. They are always derived from some antecedent feature, which may be very different in form from the new feature and therefore difficult to recognize as such. Identifying homologous features is usually accomplished through studies of morphology and development at the anatomical, cellular, and—most recently—molecular levels. Finally, cellular and molecular characteristics, as well as anatomy and physiology, can be compared between species that possess the primitive versus derived condition. From these comparisons, it is possible to infer the changes in these characteristics that are responsible for the emergence of the new feature.

In addition to cladistic studies, neurophysiological analyses of network properties are also important for inferring changes that led to new functions. However, such analyses may not necessarily reveal the complex functions of a circuit in the whole animal. Thus, an important final step is to design ecologically relevant behavioral tests to understand the function of the novel structure in those species that possess it. Such tests may also, perhaps, shed light on the selection pressures that produced the novel structure. This step has been performed for only a few of the novel neural features that have appeared during animal evolution.

Major changes in neural organization

Major reorganizations of the nervous system have occurred relatively rarely during evolution. Unraveling the origins of major new structures that appeared during these reorganizations is especially difficult because these structures have departed drastically in form and function from their ancestral homologues. Comparative studies of the expression of regulatory genes (e.g., François and Bier 1995) promise to provide new insights into the evolutionary origins of major new structures. By providing a test of homology based on gene expression, in addition to those based on morphological and developmental similarities, such comparative studies of regulatory gene expression during development may illuminate many of the morphological transformations of the nervous system that have occurred during metazoan evolution.

Two recent examples illustrate the problems associated with studying the origin of major new structures: the appearance of the dorsal

hollow nerve cord in chordates (Arendt and Nübler-Jung 1994) and the appearance of the mammalian isocortex (formerly termed the neocortex; Northcutt 1995). These examples also demonstrate the promise of comparative studies of regulatory gene expression in finding putative homologues for these structures.

Origin of the dorsal hollow nerve cord. Across the animal phyla, a major reorganization of the nervous system occurred among the brains of invertebrates and those of vertebrates, the so-called "great divide." Most invertebrates (i.e., the protostome phyla, including annelids, molluscs, and arthropods) possess solid ventral nerve cords with ganglia that contain relatively few neurons. Many of these neurons are individually identifiable on the basis of their size, morphology, and biochemistry. By contrast, the vertebrate nervous system is composed of a dorsal hollow nerve tube with a brain at the anterior end. The vertebrate nervous system contains many more neurons, few of which are individually recognizable.

How did the dorsal hollow nerve cord of vertebrates evolve from the ventral solid nerve cord of invertebrates? The nature philosophers of the early nineteenth century, such as Geoffroy St.-Hilaire, proposed that vertebrates were upside-down protostomes (the "dorsoventral reversal" hypothesis). This hypothesis received little attention for most of the twentieth century because it seemed likely that attempts to test it would be futile. However, recent data on the expression of regulatory genes during development have resurrected this old hypothesis. François and Bier (1995) showed that homologous genes in frogs and fruit flies (the *chordin* gene of *Xenopus* and the *short gastrulation* gene of *Drosophila*) are involved in determining the dorsoventral axis in embryos but that the polarity of their expression is reversed. The *chordin* gene is expressed on the dorsal side of the frog embryo, whereas its homologue, *short gastrulation*, is expressed on the ventral side of the fly embryo. The hypothesis that the dorsal side of vertebrates is homologous to the ventral side of insects is supported by the fact that these regions express homologous regulatory genes. If true, the dorsoventral reversal hypothesis has important implications for understanding the evolutionary origin of the dorsal hollow nerve cord.

Origin of the mammalian isocortex. Once the major reorganization that gave rise to the vertebrate brain occurred, subsequent major changes in structure have been rare. Some major new structures include the cerebellum, which is present in gnathostome vertebrates but appears to be absent in hagfishes and lampreys (Fritzsch and Sonntag 1987); the auditory papillae, which are present in sarcopterygians (the lobe-finned fishes and their descendants, which include all terrestrial vertebrates) but absent in cartilaginous and ray-finned fishes (McCormick 1988, Wilczynski 1984); and the cerebrospinal tracts and isocortex, which are present in mammals but absent in all other vertebrates (Northcutt and Kaas 1995). Of course, these structures must have been derived from homologous structures in ancestors, but in most cases the homologues remain to be identified.

Among these novel brain features, the origin of the mammalian isocortex has, for obvious anthropocentric reasons, received much attention. The isocortex plays a role in a wide variety of perceptual, cognitive, and motor functions. Primitively, the isocortex is composed of six laminae and 10 to 20 functional subdivisions, including visual, somatosensory, auditory, gustatory, limbic, and motor fields (Northcutt and Kaas 1995). The evolutionary appearance of the mammalian isocortex had a dramatic effect in terms of brain function. In broad terms, the isocortex is associated with the appearance of a number of new cognitive abilities, including uniquely human attributes, such as self-awareness (Povinelli and Preuss 1995).

The origin of the mammalian isocortex remains controversial. All living mammals possess an isocortex that is situated between the lateral and medial pallial areas of the forebrain (Northcutt and Kaas 1995). All vertebrates possess lateral, dorsal, and medial pallial formations, any one or more of which might plausibly have given rise to the mammalian isocortex (Northcutt and Kaas 1995). Two alternative hypotheses for cortical origins have been proposed. Shimizu and Karten (1991) and Butler (1994) argue that the isocortex evolved from the dorsal ventricular ridge of sauropsids (living reptiles and birds). Their hypothesis is based on the morphological and physiological similarity between neurons in the two areas. By contrast, Northcutt (1995) proposed that the dorsal ventricular ridge of sauropsids and the isocortex of synapsids (mammal-like reptiles and mammals) evolved as independent enlargements of the cerebral hemispheres. On somewhat different grounds, Bruce and Neary (1995) also argue that the mammalian isocortex did not evolve from the dorsal ventricular ridge of sauropsids. As in the case of the dorsoventral reversal hypothesis, current research is focused on comparing the expression of regulatory genes in the isocortex and its putative homologues to settle this important issue.

Changes in neural connections

Whereas relatively few major new structures have appeared during brain evolution, minor changes in the pathways that interconnect brain areas are ubiquitous in both invertebrates and vertebrates. In most cases, little is known about the function of these novel pathways. Three recent examples—the evolution of prey capture in frogs, the evolution of sound localization in owls, and the evolution of jamming avoidance in electric fish—illustrate how relatively small changes in neural interconnections have led to the emergence of novel functions.

Evolution of prey capture in frogs. All frogs possess relatively simple tongues that contain only two pairs of muscles, which protract and retract the tongue, respectively, during prey capture. Two different mechanisms of tongue protraction (mechanical pulling and inertial elongation) have evolved among frogs; each is characterized by different biomechanical properties and dif-

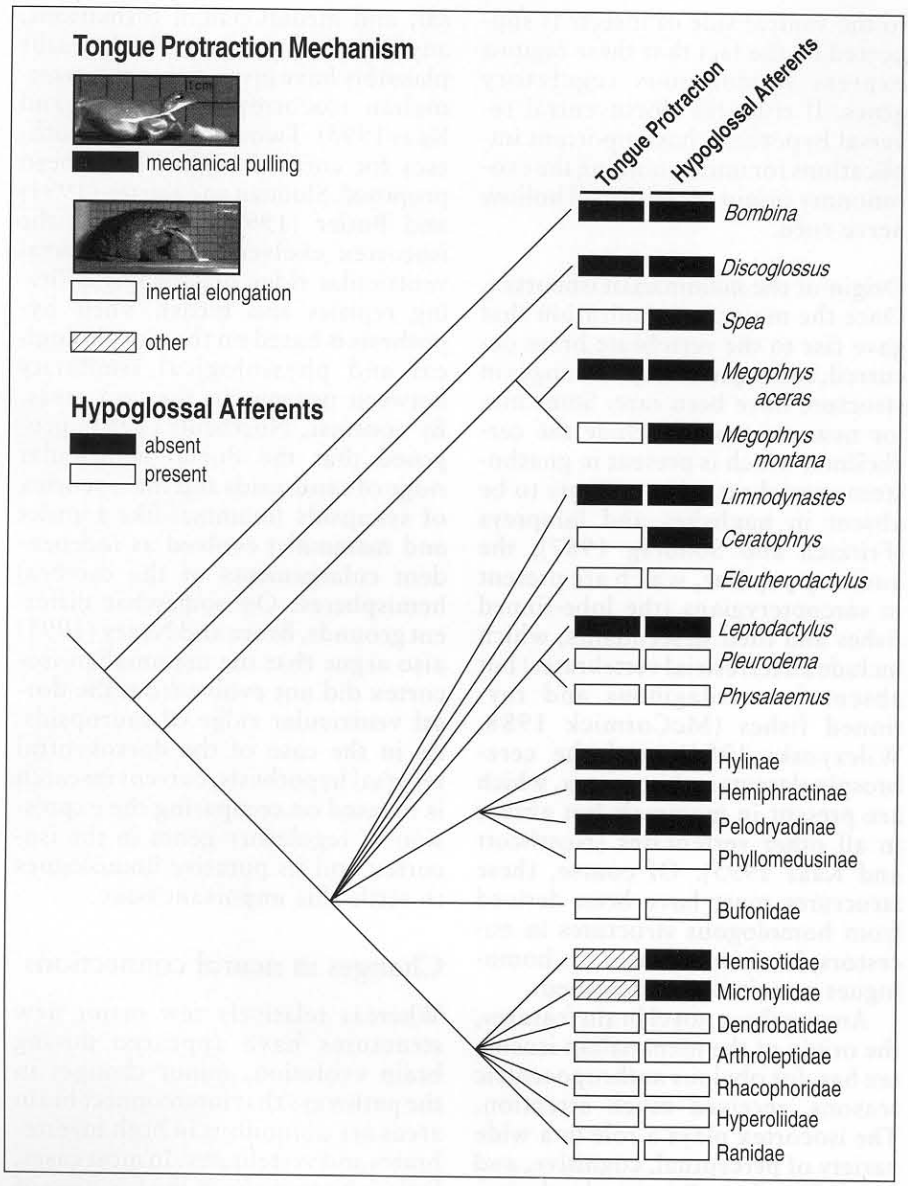

Figure 1. A cladogram illustrating the evolution of tongue protraction mechanisms and hypoglossal afferents among frogs. For both characteristics (tongue protraction mechanism and hypoglossal afferents), black boxes indicate the primitive condition; white and hatched boxes indicate derived character states. In most cases, the taxa included in the figure are anuran genera. For simplicity, subfamilies are given when all of the genera examined possessed the same character state. For mechanisms of tongue protraction, mechanical pulling is the primitive condition and inertial elongation is a derived condition, which evolved up to eight times independently. Hypoglossal afferents are primitively absent among frogs. These afferents also have evolved several times independently, but only in frogs that use inertial elongation to protract the tongue.

ferent mechanisms of neural control (Nishikawa et al. 1992).

Frogs primitively possess short tongues that are protracted by mechanical pulling (Figure 1). In mechanical pullers, the resting length of the tongue is approximately equal to the length of the jaws, but during feeding, the tongue shortens as the protractor muscles pull it forward (Deban and Nishikawa 1992). The tongues of inertial elongators are similar morphologically to those of mechanical pullers, but the fibers of the protractor and retractor muscles are somewhat longer and the muscles contract much more rapidly, generating accelerations of more than 30 *g* during protraction. These accelerations are 18 times greater than those of mechanical pullers. In both mechanical pullers and inertial elongators, the tongue shortens at first, as the protractor muscles contract and accelerate the tongue pad upward and forward. However, in inertial elongators, the tongue elongates under its own inertia by as much as 180% of its resting length after the initial shortening phase (Nishikawa and Gans 1996). By contrast, the tongue of mechanical pullers does not elongate but shortens during protraction. Frogs with inertial elongation of the tongue have evolved as many as eight times independently from ancestors that used mechanical pulling to protract the tongue (Figure 1).

Neural control of these tongue types differs in two respects. First, inertial elongators use only feedforward, open-loop (i.e., no feedback) control to coordinate jaw and tongue movements. In inertial elongators, there is no opportunity for feedback correction after the tongue is launched because tongue protraction is ballistic (Nishikawa and Gans 1996). By contrast, mechanical pullers can rely on both feedforward and feedback control of tongue movements because there is no inertial stage of tongue elongation. Second, in inertial elongators, accurately placing the tongue on the prey requires precise coordination of tongue and jaw movements because the long tongue is attached to the lower jaw but can also move independently. However, precise coordination is not necessary in mechanical pullers because the movement of the short tongue pad relative to the lower jaw is restricted to a few millimeters, so that the tongue pad will always end up in nearly the same location as the tips of the jaws.

Surprisingly, novel sensory fibers (i.e., afferents) in the tongue have evolved independently four to five times in frogs that use inertial elongation to protract their tongues (Figure 1). Frogs primitively possess a hypoglossal nerve that innervates the hyolingual muscles and that contains no sensory fibers. In toads of the family Bufonidae, sensory fibers from the glossopharyngeal nerve have invaded the hypoglossal nerve in the tongue (Nishikawa et al. 1993), whereas cervical spinal afferents have invaded the hypoglossal nerve in frogs of the family Ranidae (Ander-

son and Nishikawa 1995). As they invaded these new territories, the sensory fibers changed their peripheral pathways as well as their central connections but not the location of their cell bodies or the basic class of sensory receptors that they innervate. Similar independent evolution of novel sensory fibers has occurred during tongue evolution within birds (Wild 1990) and mammals (Lowe 1981).

A great deal is known about the function of the novel sensory fibers in frog tongues. These mechanosensory afferents of the tongue serve a variety of novel functions in feedforward control of jaw and tongue movements during prey capture. In all anurans that possess them, hypoglossal afferents modulate the phase of activity in the mouth-opening and mouth-closing muscles (Anderson and Nishikawa 1993, Nishikawa and Gans 1992). In intact frogs, the mouth-opening muscles are active before the mouth-closing muscles, whereas in deafferented frogs, the opening and closing muscles are activated simultaneously (Figure 2). Thus, when deafferented frogs attempt to feed, the mouth remains closed. By modulating the activity of the jaw muscles, tongue afferents precisely coordinate tongue and jaw movements during feeding. Proprioceptive afferents such as these, which detect the tongue's movements, commonly play a role in modulating patterns of motor output (Rossignol et al. 1988).

In frogs, sensory information from the tongue also interacts with visual input (Anderson and Nishikawa 1993). The modulatory effect of the tongue afferents depends on attributes of the visual stimulus that elicits feeding. Frogs use their tongues (tongue prehension) to capture small prey, but they use their jaws (jaw prehension) to capture large prey (Anderson 1993). When presented with small prey, the mouths of deafferented frogs remain closed, whereas the same frogs open their mouths normally when presented with large prey (Figure 3).

The hypoglossal afferents of frogs not only subserve typical motor control functions, such as modulating motor output, but also, suprisingly, have become involved in more cognitive processes, such as behavioral decision making (Anderson and Nishikawa 1996). Intact frogs switch from tongue prehension to jaw prehension at a particular threshold of prey size (which increases with the size of the frog). The threshold corresponds to the size at which the weight of the prey becomes greater than the force of adhesion between prey and tongue. Frogs with inactivated tongue afferents alternate randomly between tongue prehension and jaw prehension when offered intermediate-sized prey (Figure 3). The varied roles of hypoglossal afferents in frogs suggest that they have been deeply integrated into the previously existing prey-capture circuitry.

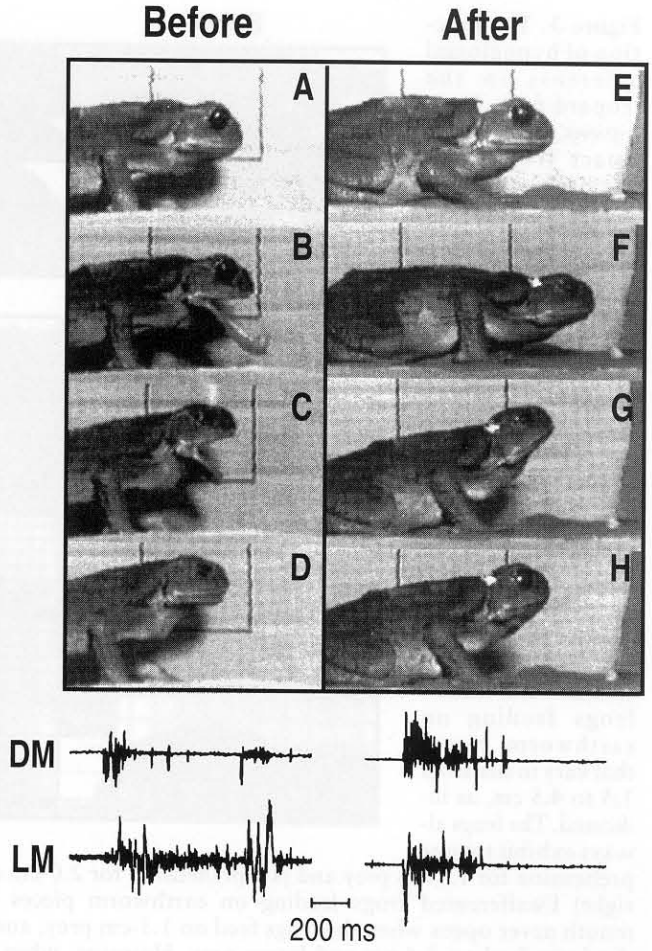

Figure 2. The function of hypoglossal afferents in the marine toad, *Bufo marinus*, before and after deafferentation. (upper left) Normal feeding in an intact toad, illustrating inertial elongation. The toad orients toward the prey (A), the mouth opens and the tongue is protracted (B), the tongue is retracted (C), and the mouth closes (D). (upper right) After deafferentation, toads orient normally (E) but the mouth fails to open during the feeding attempt (F–H). (lower left) Electromyographic traces show activity in the jaw muscles depressor mandibulae (DM) and levator mandibulae (LM) in intact toads before deafferentation. DM reaches its peak activity approximately 90 ms before LM. (lower right) After deafferentation, DM and LM reach their peak activity simultaneously. These results demonstrate that hypoglossal afferents modulate the phase of activity in the jaw muscles during feeding.

In this example, small changes in the central and peripheral connections of sensory neurons in inertial elongators have led to the emergence of a novel function: precise coordination of tongue and jaw movements during feeding. Similar circuits have evolved convergently in at least four frog lineages (Figure 1). Although these circuits function similarly at the behavioral level, both cladistic analyses and comparative anatomical studies show that the circuits are convergent rather than homologous in the different frog lineages. Our ongoing studies are exploring physiological differences in the convergent neural circuits.

Evolution of sound localization in owls. Asymmetrical ears, in which one ear is higher than the other, may have evolved independently as many as five to seven times among owls (Norberg 1977). This adaptation enables owls to locate the source of a sound in two dimensions simultaneously (i.e., both the azimuth, or compass direction, and the elevation of a sound relative to the owl's head). By contrast, owls with symmetrical ears must listen from at least two different head positions to

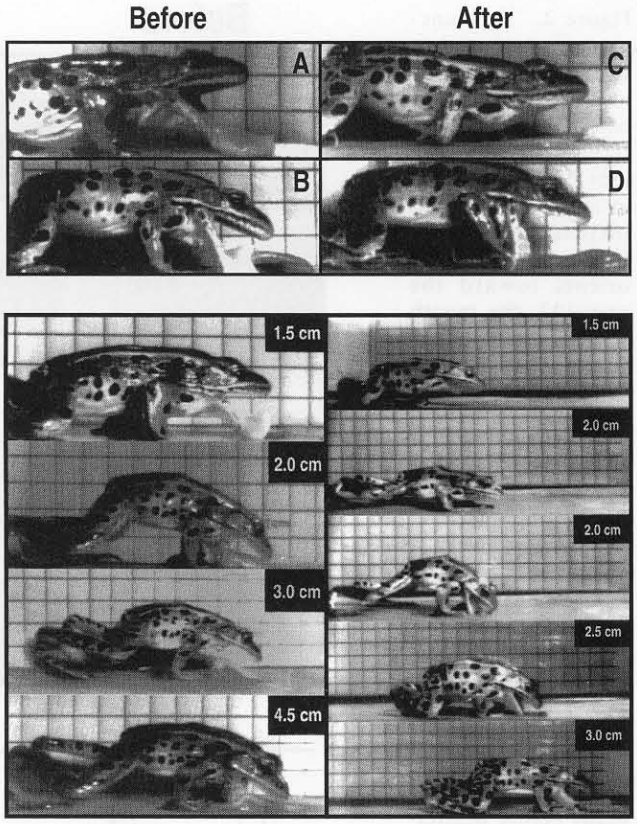

Figure 3. The function of hypoglossal afferents in the leopard frog, *Rana pipiens*. (upper left) Intact frogs feed normally on both small prey, for which they exhibit tongue prehension (A), and large prey, for which they exhibit jaw prehension (B). (upper right) After deafferentation, the mouth fails to open for small prey (C), but it opens normally for large prey (D). These results demonstrate that the effect of deafferentation depends on the visual stimulus that is presented to the frog. (lower left) Intact frogs feeding on earthworm pieces that vary in size from 1.5 to 4.5 cm, as indicated. The frogs always exhibit tongue prehension for 1.5-cm prey and jaw prehension for 2.0-cm and larger prey. (lower right) Deafferented frogs feeding on earthworm pieces of varying sizes. The mouth never opens when the frogs feed on 1.5-cm prey, and it always opens when the frogs feed on 2.5-cm and larger prey. However, when the frogs feed on 2.0-cm prey, they alternate randomly between opening and not opening the mouth. This result demonstrates that hypoglossal afferents in the tongue influence motor-program choice.

get the same information (Volman 1994). Barn and saw-whet owls, and other owls with asymmetrical ears, readily capture prey in total darkness, whereas owls with symmetrical ears, such as the great horned owl, are reluctant even to attempt to fly in total darkness (Payne 1971).

This novel function results from several minor changes in brain structure and sound-processing circuits (Volman and Konishi 1990). However, these minor changes in the anatomy and physiology of the sound-processing circuits are sufficient to produce a major change in sound-localization abilities. By mounting magnetic search coils on owls' heads, Moiseff (1989) found that owls with asymmetrical ears orient to phantom stimuli played to their ears through headphones by changing head position in two dimensions: azimuth and elevation. Volman and Konishi (1990) studied the neurophysiological responses of midbrain neurons to sounds played to the two ears through headphones (Figure 4). Their results showed that all owls use the same cues to locate sounds in space. These cues are the difference in the time at which a sound arrives at the two ears (interaural time difference; ITD) and the difference in intensity of the sound in the two ears (interaural intensity difference; IID). Both kinds of owl use ITD as an azimuth cue. However, owls with symmetrical ears use IID as an additional azimuth cue, whereas owls with asymmetrical ears use it as an elevation cue (Volman 1994).

Owls with asymmetrical ears have also evolved the ability to hear sounds of higher frequency than symmetrical-eared owls. All else being equal, spatial resolution is higher for high-frequency sounds than for low-frequency sounds. The shift to higher frequencies, by improving the resolution of the ITD cue, may have allowed owls to exploit chance asymmetry that appeared in the ears and to use the IID as an elevation cue. Thus, the novel function performed by the sound-processing circuits of asymmetrical owls is the use of IID, not as a cue for sound localization, but rather as a cue to determine sound elevation.

Evolution of jamming avoidance in electric fishes. Weakly electric fishes live in turbid water and emit electrical signals that they use to defend territories and to detect stationary and moving objects in their environment. To avoid interference between its own and a neighbor's signal, a fish will shift the frequency of its electric discharge away from that of its neighbor. To implement this jamming avoidance response, the fish must be able to detect the direction of the difference in phase between its own signal and that of its neighbor (Rose et al. 1987).

A jamming avoidance response is present in African (*Gymnarchus*) and South American (*Eigenmannia*) electric fishes and may have evolved independently in these two groups (Kawasaki 1993). Only one living genus of electric fish, *Sternopygus*, is known to lack a jamming avoidance response, and it is a close relative of *Eigenmannia*. Absence of the jamming avoidance response in *Sternopygus* may be a primitive characteristic.

Because *Sternopygus* lacks the jamming avoidance response, one might expect that it is also unable to detect the direction of difference in phase between its own signal and that generated by another fish. Contrary to expectation, however, *Sternopygus* does possess the neural circuitry for detecting phase differences between its own and other electrical signals, but it appears to use this ability for locating stationary and moving objects in the environment rather than for jamming avoidance (Kawasaki 1993, Rose et al. 1987). Thus, as for sound localization in owls, the jamming avoidance response appears to have been acquired among electric fishes through relatively small changes in

the physiology and interconnections of existing neurons that were used previously for a different purpose.

Current investigations of the evolution of the jamming avoidance response are comparing the anatomical and physiological properties of the electrosensory system in the different lineages of electric fishes in which it has evolved convergently (Heiligenberg et al. 1996, Kawasaki and Guo 1996). These studies show that similar jamming avoidance functions have emerged in circuits that differ in many details, including connections, neurotransmitters, and membrane properties.

Evolution of membrane properties

In conjunction with changes in connectivity, changes in neurotransmitters and membrane properties (i.e., types and density of ion channels or receptors in the membranes of neurons) have undoubtedly played a role in the evolution of brain function. The physiological properties of many of the ion channels found in neuronal membranes have been well studied, and mutations in genes that code for ion channel proteins are known to have profound effects on neuronal excitability. However, few studies have compared natural variation in membrane properties of neurons among species, and even fewer studies have associated changes in membrane properties with changes in behavior.

One such study, by Wright et al. (1996), compared the physiological properties and excitability of mechanosensory neurons involved in the tail withdrawal reflex among six closely related genera of gastropod molluscs. The tail withdrawal reflex of the marine gastropod *Aplysia californica* has long been a model system for studies of learning and memory at the cellular level. For each of the six genera, including *Aplysia*, Wright et al. (1996) tested the responses of homologous mechanosensory neurons involved in the tail withdrawal reflex to serotonin-mediated increases in spike duration (i.e., spike broadening) and excitability (i.e., increased spike frequency), which normally are associated with simple forms of learning. As in *Aplysia*, most of the species showed increases in both spike duration and spike frequency in response to bath-applied serotonin (Figure 5). However, one species (*Dolabrifera dolabrifera*) showed neither spike broadening nor increased excitability. As a consequence of these changes in membrane properties, *D. dolabrifera* has also evolved decreased behavioral sensitization, possibly because it experiences less predation in its natural habitat than the other species. This study demonstrates that the membrane properties of neurons, like their connectivity, may evolve in response to natural selection and may play an important role in the emergence or disappearance of brain functions.

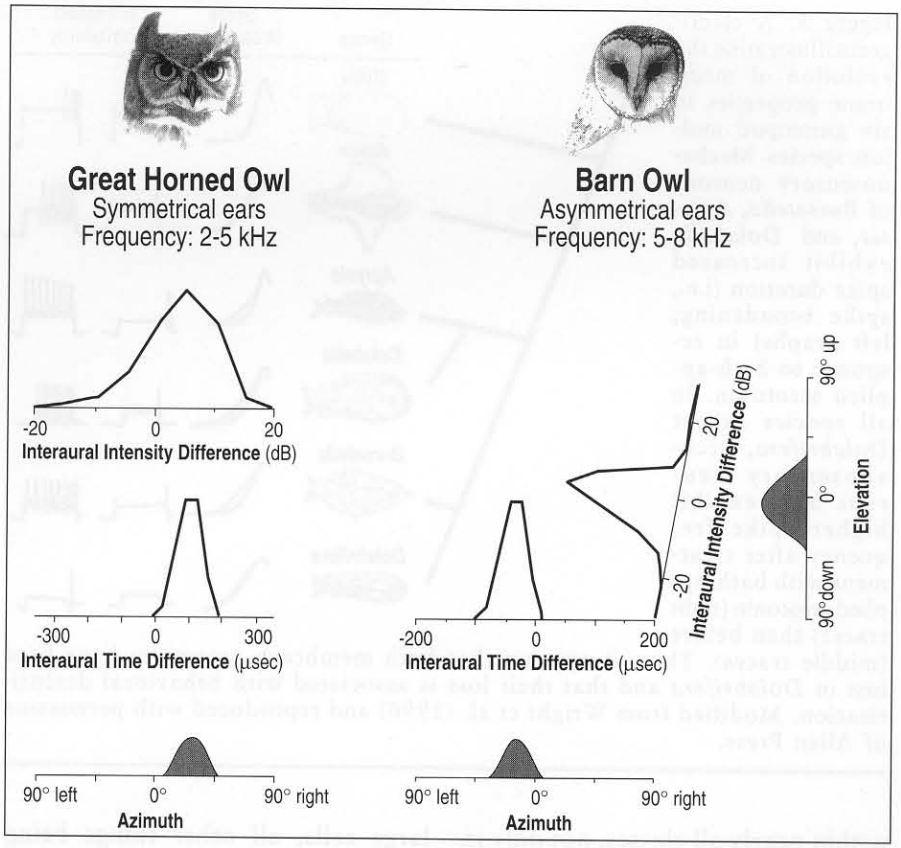

Figure 4. Behavioral experiments illustrating how interaural time (ITD) and intensity (IID) differences are used as directional cues in owls. Azimuth curves (at bottom) and elevation curves (at right) indicate amount and direction of head turning for a stimulus with a given ITD and IID. The graphs show spike frequency of single neurons as a function of IID and ITD. In the case of the great horned owl (left), the neuron shows a maximum spike frequency when IID is approximately +5 dB, which corresponds to an azimuth of approximately 25° toward the right. Other neurons would respond maximally to different values of IID and azimuth. In the case of the barn owl, spike frequency is highest when IID is approximately –3 dB, which corresponds to an elevation of approximately 15° below the horizon. Both symmetrical- and asymmetrical-eared owls use ITD as an azimuth cue. However, owls with symmetrical ears, such as the great horned owl, use IID as an additional azimuth cue, whereas owls with asymmetrical ears, such as the barn owl, use IID as an elevation cue. Modified from Volman (1990, 1994) and reproduced with permission of Springer-Verlag.

Changes in relative sizes of brain areas

Changes in the relative sizes of different parts of the brain have occurred frequently during evolution in both vertebrates and invertebrates. Among molluscs, snails tend to have smaller brains than cephalopods, and among annelids, polychaetes have larger, more complex brains than oligochaetes (Bullock and Horridge 1965). Among insects, there is considerable variation in the size and complexity of parts of the brain, such as the mushroom bodies (Strausfeld et al. 1995). Among vertebrates, brain size has increased independently, sometimes numerous times,

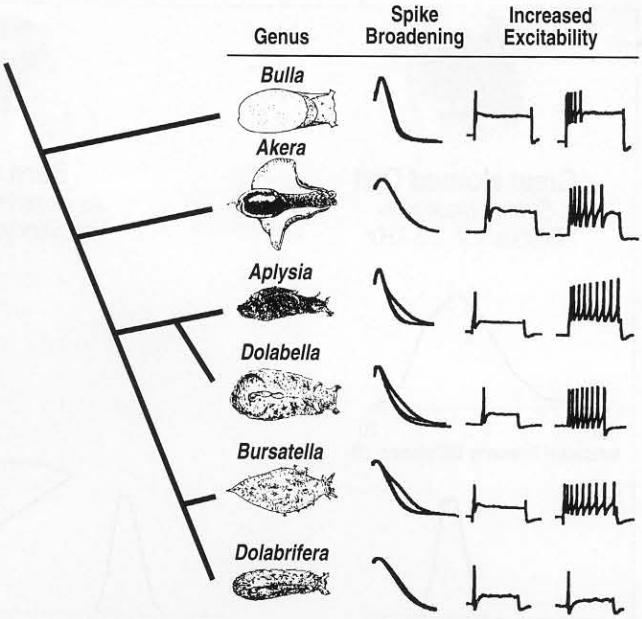

Figure 5. A cladogram illustrating the evolution of membrane properties in six gastropod mollusc species. Mechanosensory neurons of *Bursatella*, *Aplysia*, and *Dolabella* exhibit increased spike duration (i.e., spike broadening; left graphs) in response to bath-applied serotonin. In all species except *Dolabrifera*, mechanosensory neurons also exhibit higher spike frequency after treatment with bath-applied serotonin (right traces) than before (middle traces). Thus, it appears that both membrane properties have been lost in *Dolabrifera* and that their loss is associated with behavioral desensitization. Modified from Wright et al. (1996) and reproduced with permission of Allen Press.

within nearly all classes, not only in birds and mammals (Jerison 1973) but also in cartilaginous and bony fishes (Northcutt 1995).

There are also lineages in which both the size and complexity of the brain appear to have decreased during evolution. For example, the relative size and complexity of the brain appear to have decreased in lungfishes and amphibians as a consequence of large increases in genome size in these taxa (Roth et al. 1993, in press). Amphibians and lungfishes possess from 10 to 200 times more DNA than most vertebrates, and the difference is principally in the amount of middle to highly repetitive DNA (sometimes referred to as "selfish DNA"), which does not code for proteins. Because cell size is closely correlated with genome size, the brains and other organs of lungfishes and amphibians are composed of relatively small numbers of huge cells. This situation severely compromises the integrity of several brain functions. For example, the increase in cell size and decrease in cell numbers place severe limits on the resolving power of the visual system, particularly on the retina. A retina with many small cells will have much greater acuity than a retina with few large cells, all other things being equal.

Perhaps the best example of how genome size affects brain organization comes from the bolitoglossine salamanders (Roth et al. 1993, in press), whose genomes, with 20 times more DNA than those of an average frog or mammal, are the largest among terrestrial salamanders. Their retinas contain one-twentieth the number of photoreceptors of an average frog or mammal—the fewest photoreceptors among salamanders that rely on vision for prey capture. However, compensatory mechanisms have evolved that appear to maintain the functional integrity of the visual system despite the large size and small numbers of neurons (Roth et al. in press). One compensatory feature is a 1:1 ratio of photoreceptors to retinal ganglion cells in the entire bolitoglossine retina, as compared with a 10:1 ratio in the retina of a typical frog. In the mammalian retina, a 1:1 ratio of photoreceptors to retinal ganglion cells is found only in a small part of the retina, the fovea, where visual acuity is highest.

An evolutionary decrease in the size and complexity of the nervous system has clearly had a profound, and rather complex, effect on numerous aspects of brain function in amphibians and lungfishes (Roth et al. 1993, in press). In other cases, an evolutionary increase in the relative size of brain structures appears to be related to the emergence of novel functions. I explore two such examples, the expansion of the isocortex in mammals, particularly in humans, and the expansion of the hippocampus in food-storing birds.

Expansion of the mammalian isocortex. Perhaps the best-known example of an evolutionary increase in the relative size of a particular brain structure is the expansion of the isocortex in mammals, which culminated in the appearance of the modern human brain. Based on endocranial casts, it appears that the expansion of the human brain occurred rapidly, approximately 2 million years ago, during the transition from *Homo habilis* to *Homo erectus*. Both taxa probably represent several different species (Tattersall 1995), and a cladistic analysis of these new species may change our views about the evolutionary appearance of the modern human brain.

During the past 50 years, numerous anatomical, physiological, and behavioral studies have compared the brains of humans with those of the great apes (i.e., chimpanzee, gorilla, and orangutan). Surprisingly, there are few qualitative differences across the ape-to-human transition. On the basis of cellular topology, Geschwind (1965) claimed that the only new structure to appear in the brain during human evolution is Wernicke's area, a part of the isocortex that is involved in speech. However, more recent anatomical studies suggest that structural homologues of Wernicke's area are present in macaques (Deacon 1988), which implies that there may, in fact, be no qualitative differences between the brains of humans and chimpanzees.

By contrast, there are many quantitative differences between apes and humans in the relative sizes of different parts of the brain. Not all brain areas are larger in humans than apes. Some areas (e.g., the medulla oblongata) maintained the same relative size across the ape-to-human transi-

tion, whereas others, such as the olfactory bulb, actually decreased in relative size (Baron et al. 1988). However, most areas of the brain increased in size. Even after accounting for differences in body size across taxa, the corpus striatum, cerebellum, and hippocampus doubled in relative size during the transition from apes to humans, and the isocortex tripled in relative volume (Baron et al. 1988). There also are differences in the relative sizes of different parts of the isocortex (Penfield and Roberts 1959). In particular, the thumb and finger areas of the motor cortex, as well as Wernicke's and Broca's areas (both related to speech), are relatively much larger in humans than in the great apes.

It has long been known that the parts of the brain that are largest in humans relative to apes are also the last to be myelinated during embryonic development (Fleichsig 1920). This observation fits well with the widely held idea, originally developed in the early nineteenth century by Karl von Baer (1828), that more general, widespread features of organisms appear early during development, whereas specific adaptations shared by fewer species appear at later developmental stages.

The differences in relative sizes of brain areas between humans and great apes are commonly believed to represent specific adaptations for particular functions (e.g., Eccles 1989). The scenario begins with the evolution of bipedal locomotion in the early australopithecines. Erect posture freed the hands for functions other than locomotion. The expansion of the human brain then occurred in the context of tool manufacture and group foraging, with most, if not all, of the relative increases in specific parts of the brain relating either to increased manual dexterity or to verbal communication and the ability to plan for future events (Eccles 1989).

However, a recent comparative study of relative brain sizes and growth rates during embryonic development provides a new perspective on the ape-to-human transition, as well as on the evolution of mammalian brains in general. An analysis of the relative sizes of 12 different parts of the brain in 131 species of mammal (Finlay and Darlington 1995) showed that the relative sizes of most parts of the brain (with the exception of the olfactory lobes) are closely correlated with absolute brain size. As the mammalian brain increases in overall size, specific areas of the brain (such as the isocortex, corpus striatum, and hippocampus) increase predictably and disproportionately in their relative size. (By predictably, I mean that if total brain size is known, then the relative size of specific brain areas can be predicted with 99% accuracy. By disproportionately, I mean that the relative size of these areas increases not in linear proportion, but exponentially, with total brain size.)

Finlay and Darlington (1995) also studied the timing of neurogenesis (the terminal differentiation step during which mature neurons are produced) in different parts of the brain in seven mammalian species. They found that the order of neurogenesis in different brain areas is the same in all species and, more important, is tightly correlated with the relative size of different brain areas, so that the areas that develop latest are largest. The larger the brain structure, the longer neurogenesis is postponed during embryonic development. Thus, the largest brain structures are the ones that spend the longest periods of time in the exponential cell division stage before terminal differentiation. These structures thereby generate a larger pool of neuronal precursor cells and thus an exponentially larger population of differentiated neurons (Caviness et al. 1995).

The implications of Finlay and Darlington's (1995) observations for understanding the evolution of the human brain are profound. The brains of mammals appear to have followed simple allometric and developmental rules during their evolution, and the human brain is no exception. If absolute brain size alone can predict the relative size of most brain areas, then any selection pressure that increased brain size would result in the evolution of a brain with the same relative proportions of various areas as the human brain (i.e., a huge isocortex, a large corpus striatum and hippocampus, and perhaps even a large Wernicke's area). Due to the coordinated disproportionate growth of different brain regions, it is not necessary to argue that each and every structure that increased in relative size across the ape-to-human transition did so because it experienced independent selective pressures that provided a specific performance advantage. Instead, it appears that selection for any one attribute could account for nearly the entire pattern of change in the relative sizes of a variety of different structures.

The widespread occurrence of genetic and phenotypic correlations among the characteristics of organisms, such as the correlated growth of brain structures discussed above, vastly complicates efforts to reconstruct the "whys" of evolutionary history, not only of the brain, but also of all other characteristics as well (Lauder et al. 1993). The existence of such correlations among traits makes it difficult to reconstruct the selection pressures responsible for evolutionary change. Selection on a trait itself will cause it to evolve, but so will selection on any other trait with which it is genetically correlated. Thus, for many traits, it may be impossible to infer the selection pressures that were responsible for their evolution.

There are, however, some caveats to Finlay and Darlington's (1995) conclusions. First, although their study applies to all brain areas except for the olfactory bulbs (which appear to follow a different allometric rule), at present it applies only to mammals because no other group has been investigated. Second, although their nonlinear model of relative brain size explains most of the differences in relative sizes of most brain areas, it does leave room for some selective modification of the relative sizes of brain structures, up to a difference of approximately 2.5-fold, which is the limit of resolution of their model. This difference is small in proportion to the huge, exponential differences in relative brain size (more than 200-fold after accounting for differences in body size) that are explained by nonlinear, correlated growth. The third, and perhaps most important, caveat is that reallocation of function has probably occurred within particular brain

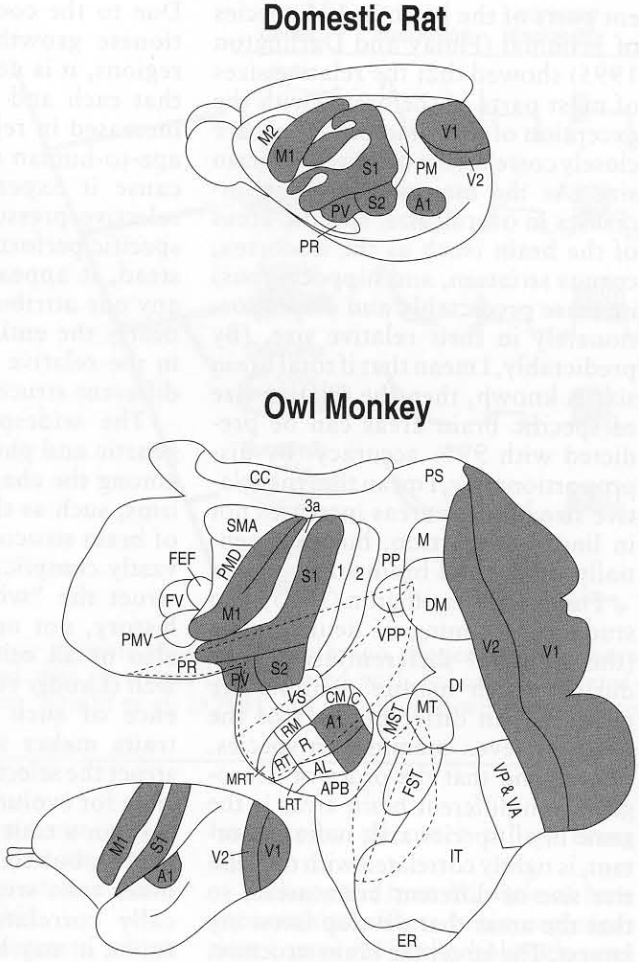

Figure 6. Comparison of identified cortical areas in rats and owl monkeys. The monkey brain is shown in its normal orientation in the cranium (bottom left) and with the isocortex flattened (bottom right; the sulci [i.e., convolutions of the brain] are indicated by broken lines). Shading indicates areas in both rat and monkey brains that are thought to be homologous. Homologues include the first and second somatosensory areas (S1 and S2), the parietal ventral sensory area (PV), the primary motor area (M1), the primary auditory area (A1), and the primary and secondary visual areas (V1 and V2). Additional homologues may exist. For example, the supplementary motor area (M2) of rats may be homologous to the supplementary motor and eye areas (SMA) of owl monkeys. White areas in owl monkey brains appear to be absent in rat brains. These include the dorsal (PMD) and ventral (PMV) premotor areas; the frontal eye (FEF) and frontal ventral (FV) areas; the rostral (R), rostral temporal (RT), caudal (C), caudal medial (CM), rostral medial (RM), medial rostral temporal (MRT), lateral rostral temporal (LRT), anterior lateral (AL), and posterior lateral (PL) auditory areas, as well as the auditory parabelt (APB); the medial (M), dorsomedial (DM), dorsointermediate (DI), ventroposterior (VP), ventroanterior (VA), ventral posterior parietal (VPP), middle temporal (MT), middle superior temporal (MST), and fundal superior temporal (FST) visual areas; and the inferior temporal cortex (IT). For orientation, the corpus callosum (CC), entorhinal cortex (ER), posterior parietal cortex (PP), parietal rostral field (PR), and the area prostriata (PS) are labeled. Modified from Northcutt and Kaas (1995) and reproduced with permission of Elsevier Trends Journals.

areas, especially within the isocortex (see below). Despite these caveats, Finlay and Darlington's (1995) study suggests that "extra brain structure" evolved in mammals through correlated growth and was subsequently put to use in adaptive ways (e.g., in language or fine control of hand movements). Their findings challenge the conventional hypothesis—that natural selection increased the size of neural structures that were already committed to a particular adaptive function.

Despite differences in relative size, several attributes of the isocortex are relatively constant across mammalian species, including overall thickness and cell density, laminar organization, and the basic set of primary sensory projections. Thus, changes in neuron number translate primarily into an increase in surface area and, hence, into an increase in the number and size of cortical modules (Rakic 1995). To investigate how changes in the relative size of cortical areas are, in turn, related to cortical function, Northcutt and Kaas (1995) have begun to map the evolution of cortical areas onto a cladogram of mammalian species. Their analysis shows that the number of functionally distinct cortical subdivisions has increased during mammalian evolution (Figure 6). In visual cortex alone, the number of functional subdivisions ranges from 5 to 8 in rats, to more than 20 in owl monkeys, and to more than 32 in macaques (Northcutt and Kaas 1995). This increase in the number of functional subdivisions has occurred independently numerous times among mammals, and therefore novel cortical subdivisions are, by definition, not homologous across mammalian species (Northcutt and Kaas 1995). Relatively few cortical areas appear to be homologous among all living species of mammals. Homologous areas include the first and second somatosensory areas, the parietal ventral sensory area, the primary motor area, the primary auditory area, and the primary and secondary visual areas (Figure 6). Although a few additional areas may also be homologous among all mammalian species, most of the other cortical areas probably expanded independently among different lineages (Northcutt and Kaas 1995).

An example of a functionally distinct cortical subdivision whose evolutionary history is relatively well known is the middle temporal (MT) area of visual cortex (Figure 6). This area is present in all primates so far investigated but is absent in all nonprimates. Thus, area MT is an evolutionary novelty that appeared early during primate evolution. Neurons of MT are highly selective for the direction of moving stimuli but not at all selective for color (Northcutt and Kaas 1995). The behavioral function of this cortical subdivision has remained obscure, but now that its distribution among mammals is known, ecologically relevant behavioral comparisons can be carried out among species in which it is present and absent.

Area MT probably evolved from some other area of visual cortex by a reorganization of its connections with other parts of the cortex. Such changes in interconnections among existing brain areas are undoubtedly an important source of novel brain functions (Krubitzer 1995), although

most such changes remain to be studied in detail.

Although there has been much recent progress in our understanding of the anatomy and development of the mammalian isocortex (Innocenti and Kaas 1995), the functional implications of increases in cortical size remain largely unknown. A major reason for this lack of knowledge is that transitions in relative size of the cortex (with body size taken into account) have not been mapped onto a cladogram. Thus, it is not clear which species should be compared to study this question.

Expansion of the hippocampus in food-storing birds. Among birds, all species of corvids (crows and jays) store seeds to some extent, but there is great variation in the extent to which different species depend on stored seeds for survival during the winter. Clark's nutcrackers, which inhabit high elevations, are the record holders, storing more than 33,000 seeds per bird per year in more than 6600 locations (Vander Wall and Balda 1977). Most other corvid species are less dependent on stored seeds for survival. Several recent studies have compared performance on a variety of spatial memory tasks among food-storing versus non–food-storing birds. Nutcrackers perform better in simple operant tests of spatial memory than other corvids (Olson et al. 1995). However, the differences among species are less distinct in open-room tests, in which the birds may choose to use a variety of different spatial cues. Similar differences have been observed between food-storing and non–food-storing tits (Paridae), in which cleverly designed, naturalistic experiments showed that storers and nonstorers use different strategies to search for seeds (Clayton and Krebs 1994a). The relative performance of the different species thus depends on what types of cues are available.

Several recent studies show that relative hippocampal volume is associated with performance on spatial memory tests in food-storing birds. Basil et al. (1996) found that Clark's nutcrackers have relatively larger hippocampal volumes than other corvids. Likewise, Healy and Krebs (1993) found that, among seven species of Old World corvids, food-storing species have relatively larger hippocampal volumes than nonstorers. Clayton and Krebs (1994b) also found that the growth rate of the hippocampus depends on food-storing experience. Young, hand-raised birds that were permitted to store seeds had larger hippocampal volumes at a given age than birds that were deprived of food-storing experience.

Birds and mammals differ in the cellular changes that occur in the hippocampus with learning. In mammals, most neurons are produced before birth; few, if any, new neurons are added later in development. Thus, learning-related changes in the mammalian hippocampus are expressed as modifications of existing neurons (e.g., numbers of synaptic spines) rather than as addition of new neurons. By contrast, birds and other nonmammals can undergo adult neurogenesis, in which new neurons may be added throughout life.

In birds, adult neurogenesis may be associated with the storage of new memories (reviewed in Clayton and Krebs 1995). Seasonal increases and decreases in numbers of hippocampal neurons have been observed in birds, with the largest numbers occurring in October, when food-storing activity increases (Barnea and Nottebohm 1994). In the context of food storing, seasonal increases and decreases in the number of hippocampal neurons would appear to be a relatively efficient mechanism for memorizing, as well as forgetting, the locations of stored seeds.

The hippocampus of food-storing birds provides a compelling demonstration of the relationship between the relative size of a neural structure (the hippocampus) and a specific cognitive ability (spatial memory). However, our understanding of the evolution of spatial memory in birds is hampered by a lack of information about the neural circuitry and neurophysiology of the hippocampus, and much disagreement remains about its function (Clayton and Krebs 1994a).

Mechanisms of change in brain function

A common process in evolutionary change of function involves the duplication of existing structures. After duplication, the redundant structures are freed from the constraint of having to perform their previous functions and may subsequently evolve a new function. Many structures, from jaw joints to genes, appear to have evolved in this way (Lauder and Liem 1989). For example, during the transition from reptiles to mammals, the bones of the old reptilian jaw joint evolved into the incus and malleus of the mammalian middle ear. This change in function was possible because the intermediate mammal-like reptiles possessed two jaw joints, both the old reptilian one, formed from the quadrate and articular bones, and the new mammalian one, formed from the dentary and squamosal bones. In mammals, the incus and malleus were free to change their function from jaw joint to middle-ear amplifiers because the new dentary–squamosal joint was already present. Similarly, genes that code for slightly different proteins, such as hemoglobin and myoglobin, appear to have evolved in the same way, that is, by duplication and subsequent differentiation.

Likewise, in the evolution of novel brain functions, redundant neurons must somehow be produced. It has been suggested (Fritzsch 1995) that populations of functionally uncommitted neurons may arise through the loss of previously existing connections between neurons and their ancestral inputs or targets. An important implication of Finlay and Darlington's (1995) correlated growth model, although one they did not mention, is that the allometric increase in the relative sizes of specific parts of the brain with increasing overall brain size is an important mechanism for producing a population of functionally uncommitted neurons that are free to evolve new functions. Presumably, the functions of these neurons may be influenced by natural selection, even if the original overproduction of neurons was not. Disproportionate growth is likely to have played an important role in the evolution of many novel brain functions. If so, then many questions regarding disproportionate growth will deserve further inquiry: How widespread is

disproportionate growth among different brain regions and among different species of vertebrates? What controls the rate of neurogenesis in a given brain area? How can the rate of neurogenesis be altered?

Studies of evolutionary changes in relative sizes of brain areas suggest that proportional increases in numbers of neurons with body size allow larger animals to do the same things that small animals do, whereas disproportionate increases in the relative size of particular brain areas may allow animals to do different things. However, it is clear that size differences alone cannot explain the emergence of novel functions during brain evolution: New functions have emerged through changes in neurotransmitters, membrane properties, and interconnections in the new population of functionally uncommitted neurons. Both the vertebrate nervous system in general and the mammalian isocortex in particular are notorious for producing more neurons and more connections during development than persist in adults (Innocenti 1995). This exuberant growth may provide variability in connectivity on which natural selection could act.

Conclusions

Our views of brain evolution are changing rapidly as new data force us to develop new perspectives. Whereas previous views emphasized similarities in brain structure among organisms, cladistic analyses have shifted the emphasis toward the many convergent novelties that have appeared during animal evolution. Major reorganizations in structure have occurred only rarely during brain evolution, whereas changes in the relative sizes of different structures and in neuronal connections, neurotransmitters, and membrane properties have occurred frequently. These small changes, originating within a species, have been amplified over evolutionary time to produce the pattern of seemingly large differences in behavior that we observe today among distantly related species.

I believe that the large degree of similarity in the brains of different species and the apparent conservatism of brain evolution may have misled us into believing that brain function is also similar across species, when in fact small changes in brain structure may actually have led to profound differences in function. Many of the studies reviewed here suggest that novel brain functions emerge from tinkering with interconnections among existing neurons. This view implies that closely related species may use similar information in different ways and that the cognitive abilities and other brain functions of a given species should be closely tied, rather than broadly tuned, to its ecology and natural history.

There are several challenges for future studies on the evolution of brain function. First, there is a great need for more comparative studies of brain function at behavioral and physiological levels (Bullock 1984, 1993). For many neural structures, alternative character states have been identified anatomically in different species. Yet, for nearly all of these characteristics, we know almost nothing about their evolution. Second, for each novel structure, we need to identify the homologue from which it was derived and investigate the changes in neuronal connections and membrane properties that led to the emergence of its novel function. Finally, we need to ask ecologically relevant questions about differences in performance and behavior among species in which the novel structure is present and absent (Bullock 1984). The tools are available, and a multitude of interesting brain functions beg for investigation.

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