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The Evolution of Isocortex

Key Words
Isocortex
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Abstract

There are several reasons why we lack detailed and comprehensive theories of how isocortex evolved in the various lines of mammalian evolution. Although current methods allow cortical areas to be defined with a high degree of assurance, few taxa have been studied in detail, and even the most-studied taxa are incompletely understood. In addition, concepts persist from early studies, based on limited data, that confound current theories, and some theories of isocortical evolution have been based on questionable premises. Nevertheless, some conclusions are clearly supportable. Early mammals had small brains with proportionately little isocortex. Mammals with larger brains and proportionately more isocortex evolved in several lines of descent. All mammals appear to have roughly 20 cortical areas, 'the organs of the brain', in common as retentions from an early ancestor, with primary and secondary sensory fields occupying much of cortex. Some of these cortical areas have been greatly modified in some taxa to become significantly expanded in size, highly laminated structurally, or both. Numbers of areas have increased independently in several branches of mammalian evolution, and the functioning of large brains may be enhanced by having more subdivisions. Finally, over many generations new areas may emerge from old by the formation of functionally distinct modules within areas, followed by the fusion of modules to ultimately form separate areas.

Introduction

The brains, especially the isocortices, of different species of mammals clearly vary. The most obvious variable feature of isocortex is size. This can be clearly demonstrated from any extensive brain collection, since dramatic differences exist even within members of a single order or family. Since isocortex is not so variable in thickness, a useful measurement is the surface area of isocortex of a single hemisphere, which is something on the order of 4–5 cm^2 in the smallest primate, *Microcebus*, and over 1,000 cm^2 in humans. Much of this difference correlates with overall body size. Mammals with larger bodies have larger brains. Intuitively, this seems to make sense, until one considers the question of why one needs a larger computer to do basically the same things in a larger animal. Why, for example, does a lion need a much larger brain to process information and execute actions than a house cat? Part of the answer is that brains do not increase in size with the body at a 1:1 ratio, but by considerably less. In addition, to some extent, a larger brain is needed for a larger body, since input and output pathways are longer and require larger and possibly more neurons. Another factor is that increases in size create scaling problems [Schmidt-Nielsen, 1984]. Microcircuits

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based on neurons cannot be simply increased in size without changing how they work [Ringo et al., 1994]. Distance means time in the nervous system, and larger brains may compensate for a reduction in efficiency by becoming even larger.

Another type of enlargement, an increase that does not reflect body size, has received more attention and interest. Hedgehogs and squirrel monkeys, animals of the same body size, differ by a factor of five or more in brain size [Radinsky, 1975; also see Finlay and Darlington, 1995]. Much of this difference is reflected in isocortex. The assumption that the proportionately larger brain provides more functions is supported by the evidence that the range of behavior is greater in squirrel monkeys. Because brain and isocortical sizes are easily measured, and they can even be determined for extinct species from brain endocasts, we know a lot about phyletic variation for these parameters [Jerison, 1973, 1990]. Such comparative evidence supports the conclusion that early mammals had proportionately small brains with little isocortex, that there was little change in this measure over most of mammalian evolution, and that major increases in the size of isocortex have occurred independently in a number of lines of descent over the last 65 million years.

The internal organization of brains is another variable that relates to function. From the time of Broca, we have known that regions of isocortex are specialized for specific functional roles. Visual processing largely occurs in the occipital and temporal cortices, for example, while the frontal cortex has been associated with cognitive planning and social abilities. Occipital and temporal regions of the brain are greatly enlarged in highly visual but relatively non-social squirrels, tree shrews and tarsiers, demonstrating the independent enlargement of cortical centers for processing visual information. Greatly expanded frontal cortex, of course, characterizes human brains, but moderate expansions also are found in highly social mammals such as dogs and other canids [Radinsky, 1969]. Thus, brain shape can provide additional functional information that is also available for extinct species. Finally, the pattern of fissures in isocortex is influenced by the functional organization of the brain, and this information has been used to compare brain specialization of somatosensory cortex in extinct and extant species [Radinsky, 1969, 1975; Welker, 1990]. But these types of measures, though useful, do not provide enough information to construct comprehensive theories of isocortical evolution. For this, we need detailed information of how isocortex in different species is subdivided into areas and modules, and how these compartments are interconnected into processing systems.

The Areas of Isocortex

Brodmann [1909], perhaps more than any other investigator, popularized the concept that isocortex is divided into a number of functionally distinct regions or areas. Using local differences in histological appearance, he subdivided cortex into various numbers of areas in a range of mammalian species, thereby providing a theory of phyletic differences and similarities in numbers and kinds of areas. Modern studies support the concept that isocortex consists of a patchwork of areas, and that cortical function can best be understood in terms of systems of interconnected cortical areas, subcortical structures, and the local circuits and modules within areas. To understand the evolution of isocortex, then, we need to determine how species differ in these cortical features and how these differences evolved.

If we concentrate on just one aspect of this goal, determining how taxa differ in their complements of cortical areas, we can start to appreciate the magnitude of the task. The early and overly optimistic view was that cortical areas, as the functionally significant subdivisions, could be easily and reliably identified by variations in histological appearance. This optimism has been dampened by a history of disagreement over the identity of valid subdivisions by those using the architectonic method; in addition, recent experimental evidence indicates that early investigators identified few valid areas [Kaas, 1989a], and even these were inconsistently identified across taxa. However, we now have the means to identify cortical areas with more assurance. Cortical areas, as 'the organs of the brain' [Brodmann, 1909], are likely to be characterized by a number of features related to their functional roles. Primary visual cortex (V1) has a caudomedial location, a number of marked histological and histochemical (architectonic) traits, a unique pattern of connections with the lateral geniculate nucleus and other structures, and neurons that respond to visual stimuli in specific ways. All these and other features vary in detail across taxa, and such variability has led to misidentifications of even V1 (area 17). Yet, V1 is probably the most easily identified area of cortex, and this area can be reliably identified by using multiple criteria [Kaas, 1987a]. Thus, the use of multiple criteria and experimental approaches has the potential of reliably identifying cortical areas across species. Nevertheless, it still may be difficult to get widespread agreement about the identities of homologous areas. This in part is because the concept of homology and the methods of comparative neurobiology are not widely appreciated by neuroscientists. However, there are reasons for optimism. For some species, great progress in understanding cortical organization has been made over the last few years, and some results are very compelling. This progress both allows a number of important conclusions at this time and suggests that it will soon be possible to formulate comprehensive and highly specific theories of cortical evolution.

All Mammals Share a Small Number of Areas

The reasonable supposition that all mammals have a few areas in common, those inherited from the last common ancestor, is more difficult to support than one might suppose. There has been a history of difficulty in identifying homologous areas across taxa, and this difficulty persists. In part this is because early theories of cortical organization, based on limited experimental data, continue to have impact and add confusion. For example, all mammals appear to have the primary somatosensory field, S1. However, the region of anterior parietal cortex originally identified as S1 in early studies of monkeys [Marshall et al., 1937] included four strip-like architectonic zones (areas 3a, 3b, 1 and 2), each of which is now known to contain a separate representation of the body and constitute a functionally distinct and separate cortical area. Researchers have argued from a multitude of similarities that only the area 3b representation ('S1 proper') is the homologue of S1 in other mammals investigated, such as rats and cats [Kaas, 1983]. The S1 can be reliably identified by its representation of cutaneous receptors in a characteristic pattern that is highly isomorphic with the body surface, as well as by dense inputs from the ventroposterior nucleus, a well developed layer 4, and other criteria. Thus, there is now compelling evidence for S1 in such a wide distribution of species [Kaas, 1983; Johnson, 1990; Krubitzer, 1995] that there can be little doubt about the early emergence and retention of the area. I would advocate the consistent use of a single architectonic term for S1, such as 'area 3b' or 'somatic koniocortex', but a confusing use of terms persists, so that different parts of S1 or area 3b of rats and cats, and even prosimian primates, continue to be labeled as area 3b, 1, or 2. One unfortunate outcome of considering parts of S1 as valid areas is that the connections of 3b, 1 and 2, actually parts of S1 in cats and three different areas in monkeys, have been compared without even a mention of the possibility that the 'areas' are not homologous [e.g. Schwark et al., 1992]. We can expect this problem of persisting misidentifications and neglect of new criteria to be even greater for subdivisions of isocortex that are less easily identified than S1. The undesirable result of this problem is that many studies of connections and other features of cortical 'areas' are of limited comparative value. We are only misled by invalid comparisons across taxa, and yet such comparisons are common.

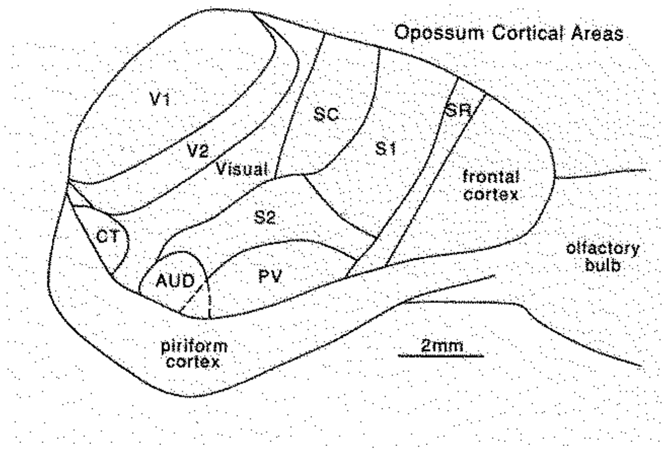

Fig. 1. A dorsolateral view of an opossum brain showing proposed subdivisions of isocortex. The first or primary somatosensory area (S1) is bordered laterally by two other representations of the body surface, the parietal ventral area (PV) and the second somatosensory area (S2). S1 projects in topographically parallel patterns to rostral (SR) and caudal (SC) fields of somatosensory cortex for a total of at least five somatosensory areas. Visual cortex includes the first (V1) and second (V2) areas, a medial limbic area with input from V1, and a lateral target zone for four or more visual areas. Caudotemporal cortex (CT) may be visual. An auditory zone (AUD) includes the first auditory area, A1, and possibly other auditory fields. There is yet no conclusive evidence for separate motor areas. Based on Beck et al. [1995].

In spite of the problem of proper identification, many investigators will agree that something on the order of 20 cortical areas can be identified with assurance across such a range of species that they must have been inherited from a common ancestor. The isocortex of opossums contains many of the areas that we consider to be of early origin and basic to mammals (fig. 1). Opossums have relatively little isocortex. In general appearance, their brains resemble the oldest known endocasts of brains of mammals from 40–60 million years ago [Kielan-Jaworowska, 1984].

Opossums, as all other investigated mammals, have an S1. This field represents the body from tail to tongue in a mediolateral cortical sequence, receives inputs from the ventroposterior nucleus, and projects to four adjoining regions of cortex [Beck et al., 1995]. Two of these regions, just caudolateral to S1, contain additional representations of cutaneous receptors of the body. Most of this cortex formerly would have been assigned to the second somatosensory area, S2, but recent experimental studies indicate that there are two representations of the body in this region in a wide range of eutherian mammals [see Krubitzer et al., 1995, for review], the classical S2 and a parietal ventral area, PV. The S1 also projects in topographic sequences to strips of cortex rostral and caudal to S1. For convenience, these potential areas are termed the somatic rostral (SR) and somatic caudal (SC) fields. These fields correspond in position to areas 3a and 1 of monkeys, and it seems reasonable to hypothesize that the more differentiated areas 3a and 1 of anthropoid primates evolved from less differentiated border zones of early mammals. More importantly, projections from S1 in comparable caudal and rostral regions have been found in all species investigated. Thus, it is likely that five somatosensory areas arose early in mammalian evolution and have been retained in most modern mammals. They are highly interconnected and typically relate to other areas and structures such as motor cortex, entorhinal cortex, the amygdala and hippocampus [see Krubitzer and Kaas, 1990]. Monotremes have at least four of these areas, although they appear to have a PV and lack S2 [Krubitzer et al., 1995]. If so, S2 may have emerged in therian mammals after the split from prototherian mammals over 150 million years ago.

Similar arguments can be made for the early emergence and retention of a collection of at least four visual areas. All mammals without regressed visual systems appear to have primary (Vl) and secondary (V2) visual areas (fig. 2, see Kaas and Krubitzer [1991]). These areas can be reliably identified by their retinotopic maps, connections, and other characteristics. However, there is not universal agreement on the existence of these visual areas in some mammals. Some investigators hold that rats and mice have a sequence of other small visual areas in the position of V2 [e.g., Montero, 1993], and the suggestion has even been made that V2 of cats is not homologous to V2 of other mammals. These views seem inconsistent with the comparative evidence for V1 and V2 [see Kaas, 1980].

The connections of V1 and V2 can be used to help identify other visual areas. In all mammals investigated, V1 projects to V2, to limbic cortex medial to V2, and to one or more regions just lateral to V2. Various terms have been applied to these targets, and the medial and lateral targets of V1 may not be homologous in all species. Clearly, further study is needed. Yet, a reasonable assumption is that at least four visual areas have been widely retained from early mammals.

The organization of the auditory region of cortex in various mammals is much less well understood [see Luethke et al., 1988; Beck et al., 1995]. A primary field, A1, can be identified by its characteristic pattern of high to low frequency representation of tones, koniocortical appearance, and dense input from the principal (ventral) medial geniculate nucleus. The A1 seems to have been reliably identified in a wide enough range of mammals (evidence is limited for monotremes, see Krubitzer et al. [1995]) to support the view that A1 emerged with the first mammals. Additional auditory areas have been found in a number of mammals, but homologues have been so difficult to identify that different 'neutral' terminologies have been developed for different taxa. A 'second' area, A2, was originally defined in cats, but this A2 has been redefined several times, and even now its boundaries are uncertain. Although the term, A2, also has been applied to a portion of auditory cortex in rodents and monkeys, it remains quite uncertain if the term has been applied to homologous fields, and the term A2 has been largely abandoned except for carnivores. Another complication is that part of the somatosensory field, PV, is also responsive to auditory stimulation. In studies where only auditory stimuli are used, part of PV could be misidentified as a purely auditory field. For now, it seems reasonable to conclude that A1 and possibly other auditory fields have been widely retained from early mammals.

There is evidence for the existence of at least a primary motor field (M1) and a supplementary motor field (M2) in a wide range of eutherian mammals, but the evidence is equivocal in marsupials [see Beck et al., 1995]. Neither motor area is included in the summary of cortical organization in opossums presented herein (fig. 1; Beck et al. [1995]), because cortex rostral to S1 failed to exhibit architectonic and connectional features of motor cortex, and electrical stimulation of this cortex did not evoke movements. The S1 in opossums and other marsupials has been described as being a composite of both M1 and S1, since movements can be evoked by electrically stimulating S1 [Lende, 1963]. However, movements are similarly evoked from S1 of eutherian mammals, and S1 of opossums exhibits somatotopic, architectonic, and connectional features of S1, not M1. Thus, there is little reason to consider S1 in marsupials as a composite field of both S1 and M1. Remarkably, there is evidence for a separate M1 rostral to S1 in monotremes [see Krubitzer et al., 1995] and even some marsupials. We need further evidence to evaluate the possibilities that M1 emerged early in mammalian evolution and was lost in some lines, evolved independently in several lines, or evolved early and was retained in the evolution of eutherian mammals.

In addition to sensory and motor areas, all mammals appear to have two or more medial limbic areas (identified by architectonic features and thalamic connections), orbital-frontal areas, and entorhinal areas. Altogether, there is evi-

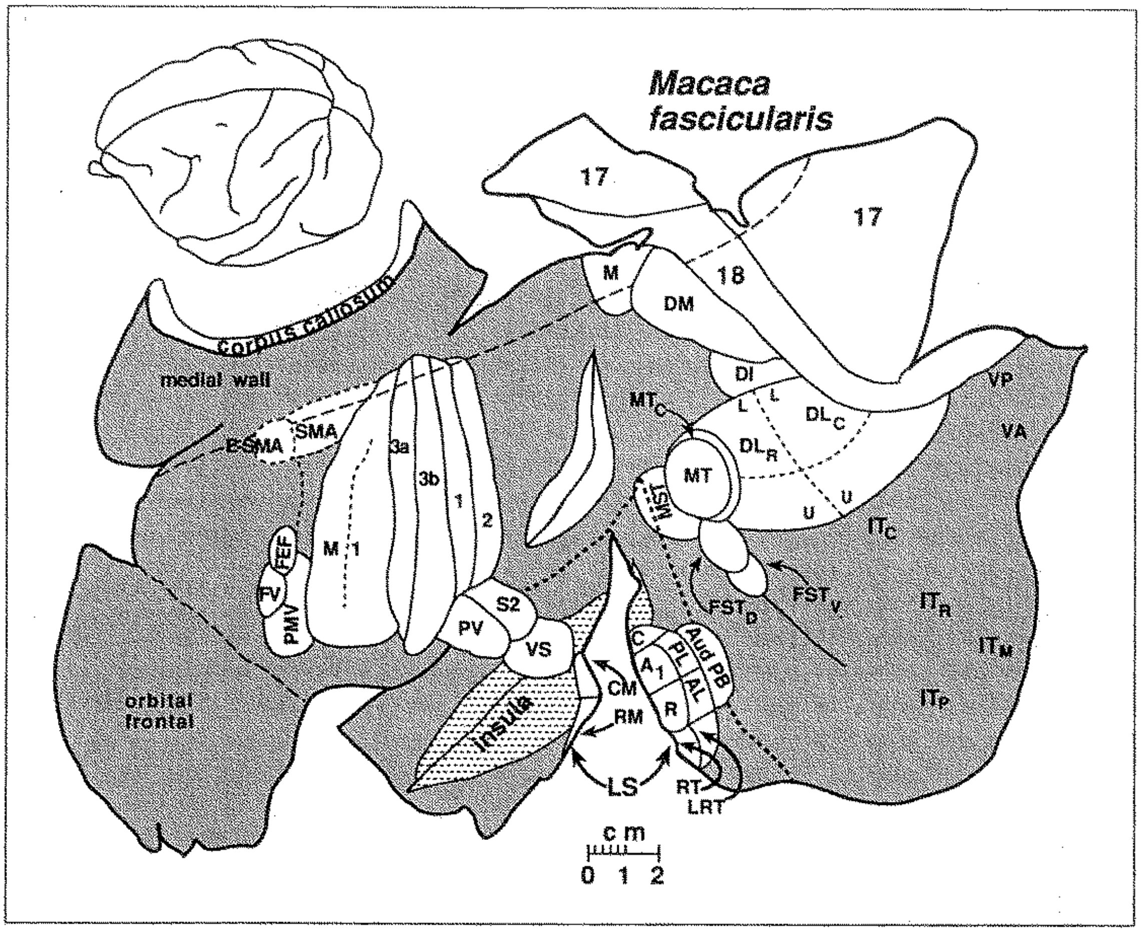

Fig. 2. Some of the proposed sensory and motor areas of isocortex in an Old World macaque monkey. More elaborate proposals show as many as 32 visual areas alone [Felleman and Van Essen, 1991]. A dorsolateral view of the brain on the upper left shows only part of the cortex. The total extent of isocortex is shown as a flattened sheet below. The flattening involved unfolding the cortex in the fissures, splitting cortex in several locations, and unfolding cortex of the medial and ventral surfaces. Names of areas stem from Brodmann's numbers for areas (3a, 3b, 1, 2, 17 and 18), and newer terms reflect location (middle temporal, MT), function (supplementary motor area, SMA) or both (ventral premotor area, PMV). Visual areas include primary (V1) and secondary (V2) areas in architectonic areas 17 and 18, respectively; dorsomedial (DM), dorsointermediate (DI), and dorsolateral areas with rostral (DLr) and caudal (DLc) divisions; caudal (ITc), rostral (ITr), medial (ITm), and polar (ITp) divisions of inferotemporal cortex; the middle temporal area (MT) and a crescentlike area (MTc) surrounding it; dorsal (FSTd) and ventral (FSTv) divisions of the fundal area of the superior temporal sulcus; a medial area (M), and ventral posterior (VP) and ventral anterior (VA) areas. Auditory cortex includes a core of the primary area (A1) and primary-like rostral (R) and rostrotemporal (RT) areas. An auditory belt of anterior lateral (AL), posterior lateral (PL), caudal (C), caudomedial (CM), rostromedial (RM), medial rostrotemporal (MRT), and lateral rostrotemporal areas (LRT). An auditory parabelt region (Aud. P.B.) receives auditory projections and relays to the adjoining temporal lobe. Somatosensory cortex includes areas 3a, 3b, and 1, and 2 of anterior parietal cortex; the second area (S2); the parietal ventral area (PV), and the ventral somatic area (VS). Motor and visuomotor areas of the frontal lobe include primary motor cortex (MIr and MIc); the supplementary motor area (SMA) with a rostral part devoted to eye movements (E-SMA); dorsal and ventral premotor fields (PMD and PMV); the frontal eye field (FEF); and the frontal visual area (FV). LS = Lateral sulcus.

dence for nearly twenty areas emerging early in mammalian evolution and being retained in most or all taxa. Given regions of cortex of uncertain identity, even a figure of 20 areas is probably an underestimate.

Conclusions about what areas have been retained from a common ancestor should be based on extensive comparative evidence from extant species and a cladistic analysis [see Northcutt and Kaas, 1995]. Unfortunately, even widely accepted theories of cortical evolution have been based on clearly questionable premises. A common mistake has been to postulate an evolutionary sequence of origin of cortical areas from characteristics of that area in one or a few species of mammals. For example, secondary fields such as S2 were assumed to be phylogenetically older than primary fields such as S1, because they appeared to be less 'differentiated' in cats and monkeys [e.g., Bishop, 1959]. The secondary fields are typically less densely myelinated, have neurons with larger receptive fields, and contain representations of sensory surface that appear to be less precise. These characteristics were seen as primitive, and thus investigators proposed that secondary fields evolved first. In a later form of this approach, Sanides [1970, 1972] hypothesized that cortex evolved by successively producing new areas from the inner ring of a series of 'growth rings' of cortex, with each successive ring being more structurally differentiated than the last. Early rings retained their less differentiated and phylogenetically earlier state. It seems easy to question this premise by pointing out that primary areas are structurally quite distinct in some mammals, such as monkeys, and much less so in others, such as hedgehogs. To address this difficulty, Sanides argued the seemingly untenable proposition that hedgehogs and bats do not have primary areas. The comparative evidence indicates most clearly that cortical areas are capable of evolutionary change in appearance, as well as in other characteristics such as connection patterns. Remarkably, the view that more differentiated cortical fields are necessarily more recent phylogenetically continues to receive support.

Numbers of Cortical Areas Have Increased in Some Lines of Evolution

New World monkeys such as owl monkeys have a greatly expanded isocortex, and there is experimental evidence for more cortical areas than in mammals with less isocortex such as rats and opossums. In owl monkeys, there is evidence for over 20 visual areas, over 10 auditory areas, and over 15 sensorimotor areas [Kaas, 1994]. Similar or greater numbers of areas (over 30 visual areas) have been claimed for Old World macaque monkeys [Felleman and Van Essen, 1991]. The evidence for some of these areas is very compelling, and these fields are likely to be valid. Other proposed areas may turn out to be invalid, and with further results and reinterpretation they may be incorporated in new and somewhat different schemes of cortical organization. Nevertheless, the number of reliably defined fields in each domain is likely to increase rather than decrease. In addition, monkeys have a greatly expanded frontal lobe, which appears to contain a number of fields not present in rats [Preuss, 1995]. While the validity of some of the areas in current proposals can be questioned, the conclusion that owl and macaque monkeys (fig. 2) have more cortical fields than hedgehogs, rats, and opossums is well-supported.

Cortical organization has also been rather extensively studied in domestic cats. Although more questions remain about the identities of areas, the same broad conclusion emerges that cats have more cortical areas than many other mammals. Given the great expansion of isocortex in some ungulates and cetacea, we can suppose that the number of fields has increased in these lines of evolution as well. Thus, Brodmann's [1909] general theory that the number of cortical areas varies across species is quite supportable. However, many aspects of his specific proposals of how cortex is subdivided are not. Since all or most extant mammals appear to have retained only a limited set of areas from their early ancestors, the additional areas in different lines of descent should be considered as innovations that are not homologous (except in the sense that if they evolved through replications of existing areas, they may be considered serial homologues; see Wiley [1981]).

New areas in different lines appear to have been placed in middle levels of cortical processing hierarchies. This conclusion is based on evidence that early distribution centers of sensory information (primary sensory areas) and terminal effector stations (motor, motivational and emotional centers) have been retained, while more stages of intermediate levels of processing have been added. Of course, adding stages of processing at intermediate levels of hierarchies removes constraints so that early and late stages can be and have been modified. For example, V1 does not have to be such a general purpose area in mammals with many visual areas, and visual areas higher than V1 can be used to access motor cortex. Thus, primary visual cortex projects directly or more directly to motor cortex in mammals with fewer visual areas.

Some Areas Have Been Greatly Modified

Areas may change so much in different lines of evolution that homologies become difficult to recognize. Primary visual cortex varies in surface area from 4 mm^2 or less in small, non-visual mammals such as mice to over 3,000 mm^2 in humans [Kaas, 1989a], and the lamination pattern ranges from rather indistinct in hedgehogs [Kaas et al., 1970] to pronounced and multilayered in tarsiers [Hassler, 1967]. Of course, we expect such differences to be functionally significant. Remarkably, Brodmann [1909], based on Nissl appearance alone, correctly identified V1 (area 17) in most species he studied, including hedgehogs, presumably because intermediate states of area 17 lamination persisted, and a graded series of changes could be used to identify extremely derived forms. Intermediate states may not always persist, thus complicating the identification of derived and primitive forms of an area.

One such area may be the middle temporal visual area, MT, of primates (fig. 2). This area, first described in New World owl monkeys [Allman and Kaas, 1971], has now been identified with assurance in all primates studied [see Kaas and Krubitzer, 1991]. The MT is one of the more easily recognized subdivisions of the brain, so there is widespread agreement on its existence, location, and boundaries [see Kaas, 1993a]. It represents the visual hemifield as a mirror image of V1, receives direct projections from V1, is densely and distinctively myelinated, and has neurons that are highly selective for direction of motion and unselective for color. No such visual area has been identified in any non-primate.

While some mammals, such as cats, have a V1 projection target that is in the approximate location of MT in the upper temporal lobe, most mammals do not [Kaas, 1980]. Instead, V1 projects to one or more locations along the outer border of V2. The closest relatives of primates, i.e. bats and tree shrews [see Kaas and Preuss, 1993], are typical in this regard. In these mammals, no V1 projection zone exists in the expected location of MT in temporal cortex. Both tree shrews and the highly visual megachiropteran bats, however, do have a V1 projection zone centered along the outer border of V2. This oval of cortex is less myelinated than MT but more myelinated than adjoining visual areas. Furthermore, the input pattern indicates a retinotopic organization that corresponds to that in MT. Other features remain to be studied, but one tantalizing implication of the observed similarities is that the primitive location of MT was along the V2 border. According to this theory, MT became structurally more differentiated and was also displaced by other visual areas into the temporal lobe in the line leading to primates. This supposition is consistent with the observation that the proportional distance of MT to V2 varies in primates, with more displacement in anthropoid primates than prosimians. The conclusion that MT in primates evolved from an area along the border of V2 suggests that the displaced Vl projection zone in cats (PMLS), often considered a homologue of MT because of its location in upper temporal cortex [e.g., Creutzfeld, 1985; Payne, 1993], became displaced into the temporal lobe independently of the displacement in the line leading to primates, or PMLS is not MT.

New Areas May Differentiate from Old

New areas may emerge by the process of the differentiation and segregation of modular classes within areas, followed by a merging of modules within a class. The concept that some fields have differentiated into two or more is apparent from the illustrations of brain areas by Brodmann [1909], in which a single area in one species is sometimes shown as a combination of two or more separate areas in another species. For example, a single somatosensory field in prosimian primates (numbered 1–3 in Brodmann's scheme) is differentiated into three separate somatosensory fields (1, 2 and 3) in simians [see also Clark and Le Gros, 1931]. The concept of single areas differentiated into several areas has been widely accepted [e.g. Lende, 1963; Ebbesson, 1984], but it is not clear how one area gradually becomes two or more while maintaining or improving function for each step or generation in the process. As an alternative, Allman and Kaas [1974] suggested that a given brain area might suddenly replicate from one generation to another as a result of a mutation. Thereafter, each of the two 'daughter' areas would be free to gradually diverge and expand in structure and function without ever producing a decrement in function, much like the forelimbs of birds and humans assumed new roles once released from old roles in locomotion (in these cases, not by duplication). The duplication of body parts has been a common mechanism in vertebrate evolution, but it is not certain that duplication has played a role in brain evolution. Thus, we should also consider how new areas might emerge in more gradual steps without disrupting function.

A more explicit theory of how single cortical areas might divide into more has been presented elsewhere [Kaas, 1989b; Kaas, 1993a; Krubitzer et al., 1995; Krubitzer, 1995]. The essential element in the theory is a recognition of the tendency of cortical areas to segregate functional classes of neurons into sets of processing modules within areas [Kaas, 1982, 1993b]. Synaptic connections in the nervous system are now thought to be strengthened and maintained by synchronous activity and weakened and lost by asynchronous activity in pre- and postsynaptic cells [see Brown et al., 1990]. The outcomes of a selection mechanism in the development of cortical fields would be highly variable, depending on such factors as maturation, receptor transduction properties, numbers of connections, and the properties of local circuits that create neuron response characteristics. The overproduction of efferent fibers in development allows considerable flexibility in the selection process, and the gradual loss of connections during development would progressively reduce this flexibility. In such a modifiable system, new functional classes of neurons could easily emerge in any cortical area. Classes could be mixed at the neuronal level or they could group due to the effect of activity on local connections. The tendencies to mix or segregate neurons by class would be subject to selection, and groups of segregated neurons (modules) of the same class could merge to form an area. All steps in the process may result in advantages and disadvantages in function, but the persistence of seemingly intermediate stages in various cortical areas suggests that any stage may be functionally appropriate under some circumstances. For instance, V1 of primates is divided into 'blob' and 'interblob' regions so that the area has a pattern of spot-like modules embedded in a surround [see Kaas and Preuss, 1993]. The V2 of primates has a different modular pattern of three sets of alternating band-like modules. Bands may have emerged by a fusing of spot-like modules [Florence and Kaas, 1992]. Sometimes bands of the same functional type are joined at the base and partially fused. Further fusion could produce two adjoined areas with parallel representations of the visual hemifield but with quite different neural, connectional, and architectonic characteristics. Each area would, of course, be subject to further modification and specialization. The tendency for adjoining sensory areas to contain parallel representations of sensory surfaces may reflect this proposed mechanism of duplication.

Brain Evolution and the Problem of Scaling

A reasonable concern in interpreting the evidence that mammals vary in number of cortical areas is the possibility that the increase in numbers of areas in mammals with proportionately large brains is more apparent than real. Could the difference be one of resolution? Clearly, some of our methods, such as microelectrode mapping of representations of sensory surfaces, are more easily applied to larger subdivisions of the brain. Thus, it could be easier to miss smaller areas in an experimental investigation. If small brains simply expanded to become large brains, one might be able to document more areas in the large brains and wrongly conclude that the number of areas had increased. Indeed, the currently favored hypothesis about the organization of visual cortex in rats and mice is that primary visual cortex is surrounded by a ring of six to eight visual areas of 0.5–1 mm in diameter [e.g. Montero, 1993]. While the alternative hypothesis, that most of these 'visual areas' are actually modules of a lateral V2 and a medial visual area [Kaas and Krubitzer, 1991], is more consistent with the comparative data, the possibility remains that we have greatly underestimated the numbers of areas in the cortex of small-brained mammals.

One argument against this possibility of size as the only significant difference is that large brains simply cannot work in the same way as small brains. To an anatomist accustomed to working on large monkey brains, it is rather astonishing to consider the proportions of the forebrain of small brained insectivores, such as the Madagascar tenrecs, in which isocortex is not only unimaginably small – 12 mm^2 of surface area per hemisphere – but proportionately almost a trivial portion of the forebrain, with the hippocampal 'cortex' being about as large, piriform cortex three to four times as large, and the olfactory bulb matching the size of isocortex. In contrast, the isocortex of each hemisphere in humans is roughly 20,000 mm^2 in surface area, and this structure dwarfs the hippocampus, piriform cortex, and olfactory bulb. The first mammals were small and had small brains, with proportions approximately those of living insectivores [Kielan-Jaworowska, 1984]. Thus, mammals with large brains and proportionately and absolutely large amounts of isocortex evolved from mammals with little isocortex. Clearly some areas became bigger in the process. The V1 is approximately 100 times larger in a macaque monkey than in a mouse [Kaas, 1983] and the difference in the size of S1 (area 3b) is similar. These large areas cannot function in the same ways as small areas. Problems created by increasing the sizes of areas need to be solved.

The difficulty in evolving larger brains is that neurons cannot be made simply bigger and function in the same way. One reason is that larger neuronal sizes and longer conduction distances translate into slower processing. Larger size creates additional problems. Thus, larger brains have more neurons rather than just larger neurons, and this alone means that if neurons maintain about the same amount of connectivity with other neurons, they still are connected to proportionately less of the processing system [Ringo, 1991; Ringo et al., 1994]. To maintain the same proportion of connectivity, neurons in larger brains would have to connect with more neurons and have more connections. Larger brains do seem to devote proportionately more neural tissue to connections, but full compensation is unlikely, and neurons are connected to proportionately less of the brain. In addition, the costs of communication over longer distances must be met. The logical solution in large brains is that the more efficient local processing circuits are used more extensively, and long connections are used only where they are critically necessary. This can be achieved by subdividing large areas locally into smaller processing modules that have only limited interactions with more distant modules within the area. Thus, the large V1 of macaque monkeys is proportionately much less interconnected than the small V1 of mice. But macaques also have more areas, and the additional areas are often rather small compared to V1. Thus, visual area MT is $^1/_{10}$ the size of V1 in monkeys, and connectional distances across the field are much less. A large area can be effective only in local processing, while greater connectivity allows a small area to be also effective in global processing. We propose that increasing the number of cortical areas reduces the problem of interconnecting cortical circuits. Along this line of reasoning, the specialization of processing within each hemisphere of the very large human brain (lateralization of function) reduces the need for excessive long-distance corpus callosum connections [Ringo et al., 1994].

Just as brains would not scale up very effectively in size without modification of the processing framework, they would not scale down very easily without losing numbers of subdivisions. Perhaps a difficulty in remodeling is what limits the rapid evolution of smaller brains, so that miniaturized species have much larger brains than their body size would predict. The dwarfed Old World talapoin monkey, about the size of a squirrel monkey, has a brain nearly as large as its much larger macaque monkey relatives [Florence and Kaas, 1992]. Our miniature breeds of dogs have mis-shapened heads as their brains similarly remain proportionately large.

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