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Intrinsic and Extrinsic Determinants of Neocortical Parcellation: A Radial Unit Model

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Abstract. This chapter offers the *radial unit model* to explain complex cellular events during cortical development and evolution by addressing the issue of genetic and epigenetic regulation of cortical areal parcellation. In this model, the proliferative zone at the surface of the cerebral ventricle is regarded as a two-dimensional mosaic of *proliferative units*, which established a universal genetic blueprint for cortical cytoarchitectonic maps. Each unit produces about one hundred genealogically related neurons that, after their last cell division, migrate to the cortex along a common radial glial guide. In the cortex, they bypass each other and form radial *ontogenetic columns*. The competence for differentiation into neuronal phenotypes within each column are established prior to their entrance into the cortical plate, while their radial position depends on their time of arrival. The size of a given cytoarchitectonic area depends on the number of proliferative units contributing ontogenetic columns, while the thickness of the cortex depends on the magnitude of cell production within the units and their selective death. Although the initial number of proliferative units devoted to each area may be set up early by regulatory genes, our recent experiments and the pattern of cortical malformations indicate that their final number can be modified by extrinsic factors. A genetic alteration or lesion of a distant but synaptically related structure, or reduced input to the cortex occurring at the critical developmental period, may exert structurally limited but functionally significant changes that, in turn, influence subsequent developmental events and provide the setting for new neural relationships. The net outcome of this is the emergence of a unique neocortical map. Recent advances in neurobiological techniques enable experimental testing of the radial unit hypothesis and provide new insight into genetic and epigenetic regulation of cortical parcellation.

INTRODUCTION

In this chapter, I will review some developmental principles and several lines of evidence in support of the radial unit model of neocortical ontogeny and phylogeny. This model, which involves the kinetics of cell proliferation, neuronal migration, competitive interactions, and selective cell elimination, has implications for understanding the genetic and epigenetic regulation of neocortical parcellation during development, and provides a new view on the pathogenesis of certain cortical malformations in man.

I will draw background information mostly from the analysis of cortical development in rhesus monkeys, which has become accessible to experimental analysis with modern methods including axonal tracing, electron microscopy, immunocytochemistry, *in situ* hybridization, receptor binding, and ^{3}H-thymidine autoradiography. Advances made in techniques of neurosurgery on the fetal cerebrum *in utero* make experimental manipulations that were traditionally limited to avian and amphibian embryos possible in large mammals (Rakic and Goldman-Rakic 1985). The size of the monkey's cerebrum during the second half of gestation and the presence of visible morphological landmarks at its surface allows precise localization for excision of specific cortical areas, while protracted development provides high temporal resolution of cellular events. Finally, the similarity between man and monkey of the convoluted cerebral surface and of distinct boundaries between major cytoarchitectonic fields enables comparison between findings obtained from animal research and findings from normal and pathological human autopsy specimens.

I will concentrate on the formation of cytoarchitectonic areas during ontogenetic and phylogenetic development. A comparison of cytoarchitectonic maps in various species reveals four important points relevant to the proposed developmental model. First, the neocortex expands enormously during phylogeny (e.g., the surface of rat's neocortex is less than 1% of a monkey's and 0.1% of a human's). Second, all cytoarchitectonic areas do not expand equally (e.g., striate cortex occupies only 3% of the cerebral surface in humans but more than 15% of the cerebral surface in monkeys). Third, new cytoarchitectonic areas become introduced during evolution (e.g., monkeys do not have Broca's area). Fourth, there are large interspecies variations in the sizes of cortical areas, as well as differences between the hemispheres of the same individual (e.g., the auditory cortex may be three times larger on the left side in right-handed humans).

How are differences in cortical parcellation between species and individuals generated? Is the number of neurons in each cytoarchitectonic area genetically determined? Do environmental factors and functional activity play any role? If so, when does the capacity for structural change stop? To answer some of these questions, we first must know when and where cortical

neurons are generated and how they assume their positions within the cortex. Then we have to determine whether their fate can be experimentally manipulated.

ORIGIN OF CORTICAL NEURONS

Classical histological studies suggested that the majority of cortical neurons in man are generated outside of the cortex itself, probably well before birth (Sidman and Rakic 1973). However, only the introduction of the DNA labeling method using ^{3}H-thymidine provided sufficiently precise data on the onset and end of corticogenesis. For example, analysis of a series of adult rhesus monkeys that were exposed to ^{3}H-thymidine during various pre- and postnatal stages revealed that all cortical neurons in this species are generated during the middle of gestation (Rakic 1974; Rakic and Goldman-Rakic 1982). The first cortical neurons arise around the 40th embryonic day (E40); the last at a more variable time. Thus, corticogenesis in the cingulate cortex stops at E70; in the striate cortex at E100. No neocortical neurons are produced during the last two prenatal months nor at any time after birth, which in rhesus monkeys occurs around E165 (Rakic 1985). This contrasts with reports of neurogenesis in the cortex of mature rodents (Kaplan 1981). Comparative cytological analysis indicates that in humans, with a normal gestation of about E265, the first cortical neurons are also generated around E40, and their production is complete by E125 (Rakic 1978). Thus, unlike rodents, where the last neocortical neurons are produced close to or shortly after birth (Angevine and Sidman 1961; Berry and Rogers 1965; Smart and Smart 1982), primates including man acquire their full complement of neurons by midgestation.

The high proportion of mitotic figures at the ventricular surface suggested to the early neuroanatomists that most cortical neurons might be produced there (His 1904; Ramon y Cajal 1911). Again, the direct evidence for this conclusion came from ^{3}H-thymidine autoradiographic analysis. A series of monkey embryos sacrificed within two hours after injection of isotope showed that all neurons of the neocortex are produced in the proliferative zone near the cerebral ventricle (Rakic 1978; Rakic and Goldman-Rakic 1982). Therefore, cortical neurons must migrate to the cortex after their last mitotic division. Golgi, electron microscopic, autoradiographic, and immunocytochemical analyses have revealed that both neuronal and glial cells coexist in the proliferative zone from the onset of corticogenesis (Levitt et al. 1983; Rakic 1972b; Schmechel and Rakic 1979). The point relevant to the proposed radial unit model of cortical development is that interaction between glial fibers and postmitotic neurons has to be taken into account when considering mechanisms of neuronal migration and cortical parcellation (Rakic 1972b).

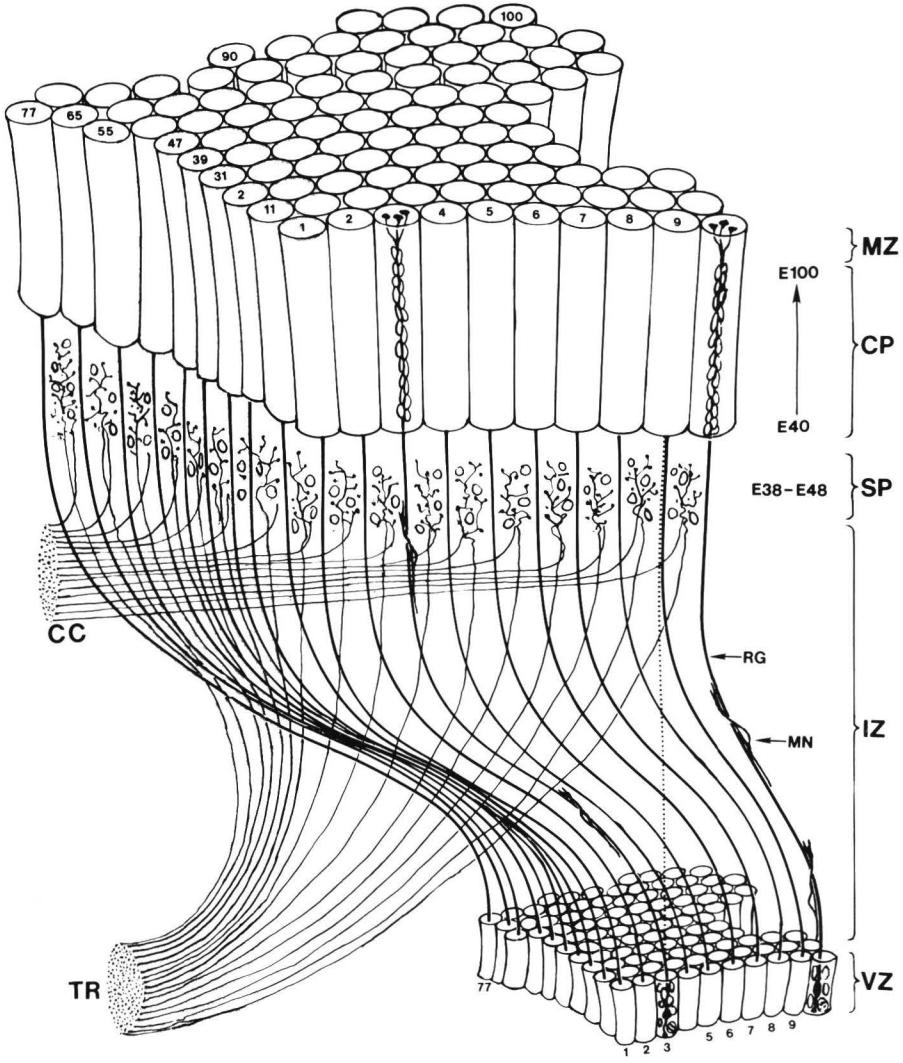

Fig. 1—The relationship between a small patch of the proliferative, ventricular zone (VZ) and its corresponding area within the cortical plate (CP) in the developing cerebrum. Although the cerebral surface in primates expands during prenatal development, resulting in a shift between the VZ and CP, ontogenetic columns (outlined by cylinders) remain attached to the corresponding proliferative units by the grid of radial glial fibers. All cortical neurons produced between E40 and E100 by a given proliferative unit migrate in succession along the same radial glial guides (RG) and form a single ontogenetic column. Each migrating neuron (MN) traverses the intermediate (IZ) and subplate (SP) zones that contain "waiting" terminals of

NEURONS MIGRATE ALONG RADIAL GLIAL GRIDS

Although the most massive migration of neurons in primates occurs during the rapid and differential growth of the cerebral wall that causes buckling of its surface, postmitotic neurons nevertheless find their way through the intricate cellular lattice of the intermediate and subplate zones. Electron microscopic studies revealed that the pathways of migrating cells are established by a guidance mechanism that depends on interaction with the shafts of radial glial cells that stretch across the developing telencephalic wall (Rakic 1972b). Therefore, the migrational pattern of these neurons is imposed by the shape and nature of non-neuronal scaffolding, which is provided by the fascicles of radial glial fibers. This scaffolding is particularly prominent during a period of about two months when most radial glial cells do not divide (Schmechel and Rakic 1979). Possible cellular and molecular mechanisms underlying the translocation of migrating cells and their guidance to the cortex have been reviewed elsewhere, and several candidate molecules have been tested *in vitro* (Edelman 1983; Hatten and Mason 1986; Lindner et al. 1983). Here, I will focus only on the significance of the glial scaffolding for columnar compartmentalization of the neocortex as it relates to the radial unit hypothesis.

Migrating neurons in the large primate cerebrum have to pass through a long and often tortuous pathway across the intermediate zone and, at later stages, across the subplate zone before arriving at their proper destination (Fig. 1). The intermediate zone increases in thickness by the addition of axonal fascicles of various origins. After most of these axons acquire their myelin sheet, this zone is transformed into the subcortical white matter. The transient subplate zone, which is situated below the developing cortical plate, consists of early generated interstitial neurons dispersed among incoming thalamic afferents (Kostovic and Rakic 1980; Rakic 1977; Rakic and Goldman-Rakic 1982; Shatz and Luskin 1986) and, at later stages, among corticocortical afferents as well (Goldman-Rakic 1981; Rakic and Goldman-Rakic 1982). It has been suggested that the subplate zone might

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thalamic radiation (TR) and corticocortical afferents (CC). After entering the cortical plate, each MN bypasses deeper-lying earlier generated neurons and assumes the most superficial position at the interphase between the CP and marginal zone (MZ). As a result, the set of proliferative units 1–100 produce a set of ontogenetic columns 1–100 in the same relative position to each other. Glial scaffolding prevents a mismatch between proliferative unit 3 and ontogenetic column 9 (dashed line). According to the radial unit model, the tangential coordinates of cortical neurons are determined by the position of their ancestors at the ventricle, while their radial positions are determined by the time of genesis and rate of neuronal migration. Thus, the basic topography and/or modality is specified by the spatial distribution of proliferative units, while the neuronal phenotypes within units are specified by time. Modified from Rakic (1978, 1982).

be a waiting compartment where afferent fibers make temporary contacts with interstitial cells and migrating neurons before their entry into the cortex (Rakic 1977). We do not yet understand the nature of these contacts or their significance, although the presence of synapses, neurotransmitters, and neuromodulators indicates neuronal interaction (Chun et al. 1987; Kostovic and Rakic 1980).

The proliferative zone can be regarded as a mosaic of proliferative units, each of which provides about one hundred generations of neurons that follow the same radial glial pathway (Fig. 1). The cohorts of genealogically related cells finally end up in the cortical plate stacked one above the other in the form of ontogenetic columns (Rakic 1974, 1978; Rakic and Goldman-Rakic 1982). Confinement of several generations of postmitotic cells to a common glial guide may serve to divide the cerebral wall into radial units that extend from the proliferative units across the migratory intermediate zone to the ontogenetic columns in the cortex (Fig. 1). The number of proliferative units, therefore, determines the number of ontogenetic columns (Rakic 1978). A set of regulatory genes analogous to the homeotic genes, which govern segmental differentiation in drosophila (Lewis 1978; Morata and Lawrence 1977; Scott 1984), may parcellate proliferative units within the ventricular zone into a proto map of basic cytoarchitectonic areas. The radial glial scaffolding simply enables translation of such a map from the ventricular zone to the expanding cortical plate. The use of the term "proto map" in this context implies that a given site (proliferative unit) of the ventricular zone generates neurons that form area-specific ontogenetic columns. After the number of proliferative units is established, homeotic genes may turn on another set of genes that determine individual phenotypes of cells produced in each proliferative unit. Therefore, this hypothesis is based on the assumption that (a) within the ventricular zone some proliferative cells have been committed to differentiate into a particular cortical area; and (b) cells produced within an ontogenetic column are genealogically related (Rakic 1972b, 1978, 1988; Rakic and Goldman-Rakic 1982). Thus, the complex three-dimensional organization of the adult cortex can be explained by genetic specification as well as spatial and temporal gradients originating from the two-dimensional map of the proliferative zone (Fig. 1).

LAMINAR POSITION AND PHENOTYPE OF NEURONS ARE TIME-SPECIFIC

As suspected from the examination of Golgi impregnated tissue (Koelliker 1896; Ramon y Cajal 1911; Vignal 1888) and proven by ^{3}H-thymidine autoradiography in a variety of species (Angevine and Sidman 1961; Berry

and Rogers 1965; Luskin and Shatz 1985; Rakic 1974; Smart and Smart 1982), neurons destined for deeper cortical layers are generated earliest and are bypassed by those of the more superficial layers. The relationship between the time of neuronal origin and their laminar position, referred to as an "inside-out" gradient of neurogenesis, is particularly sharp in primates where each injection of ^{3}H-thymidine labels a highly selective sample of cortical neurons (Rakic 1974). This gradient is present throughout the entire cortex, although simultaneously generated neurons destined for various areas display small differences in their laminar position (Rakic 1974, 1978; Rakic and Goldman-Rakic 1982; Sidman and Rakic 1973; Smart and Smart 1982). The inside-out gradient is characteristic of the mammalian telencephalon, since in reptiles telencephalic neurons settle in an opposite (outside-in) gradient (Goffinet et al. 1986).

On a given day, one area may receive pyramidal cells of layer V, while on the next day it may receive stellate neurons of layer IV. On the other hand, both types of neurons within one layer can be generated simultaneously. It remains possible that different phenotypes of the same ontogenetic column may originate from two or more clones situated in the single proliferative unit (Rakic 1978; Rakic and Goldman-Rakic 1982). At present, we are not able to follow the lineage of cortical neurons as has been done for neurons in some simple invertebrates, but we can determine when they become committed to their phenotypes.

Several lines of evidence suggest that a neuron's fate may be determined before the cell assumes its final position. First, in reeler mutant mice, cells that acquire inappropriate laminar positions within the cortex nevertheless differentiate into neuronal types corresponding to the time of their origin rather than the types expected in their new location (Caviness and Rakic 1978). Second, neurons that remain close to their origin near the ventricular surface due to X-irradiation, which prevents their migration, assume their appropriate phenotype and also establish appropriate efferent connections (Jensen and Killackey 1984). Third, ventricular cells transplanted into a host's proliferative zone migrate to the positions and assume morphological characteristics similar to those of normal cortical neurons with the same birthdates (McConnell 1985, 1987). Finally, a subset of callosal neurons destined for layer III in the monkey fetus sends its axons to the opposite hemisphere before entering the cortical plate (Schwartz and Goldman-Rakic 1986). These findings collectively suggest that the basic properties of neurons such as their morphology and/or prospective synaptic contacts may be specified early, i.e., determined before cells reach their final positions. A similar conclusion has been draw for the neuronal classes of the cerebellar cortex (granule cells, interneurons of the molecular layer, and Purkinje cells), which originate from different precursors (Rakic 1972a). More recently, it has been suggested that all Purkinje cells arise from a few clones

established early in the proliferative zones (Herrup 1986). It should be emphasized, however, that determination of the basic types of neurons (e.g., pyramidal versus stellate) does not address the larger issue of their areal specificity (e.g., area 17 versus area 18), or modal specificity (e.g., visual versus auditory). Knowing how and when neurons differentiate into certain types does not tell us how they find their areal and laminar positions, what controls their number, or how they become an integral part of the cortex as a whole.

FETAL CORTEX CONSISTS OF ONTOGENETIC COLUMNS

According to the radial unit hypothesis, proliferative units should have corresponding ontogenetic columns in the cortex (Rakic 1978). In monkey embryos at midgestation, each ontogenetic column may contain between 80 and 120 neurons stacked on top of one another, separated by intercolumnar spaces. In some areas like the cingulate cortex, where neurogenesis lasts about one month, ontogenetic columns have fewer neurons, whereas the visual cortex, which is produced over almost two months, has columns with a higher number of neurons (Rakic, submitted). However, final numbers of neurons within the columns may be subsequently modified by differential cell death (Finlay and Slattery 1983).

The total number of proliferative units and the number of units subserving specific cytoarchitectonic areas vary between species and among individuals of the same species. We estimate that in the fetal monkey, the number of proliferative units in the cerebral ventricular zone and the number of ontogenetic columns in the cortical plate may be in the vicinity of 15 to 20 million. In humans, the number is probably ten times higher, while in the rat, probably ten times smaller. The number of ontogenetic columns comprising various areas has not been precisely determined in any species, but it is likely that the average striate cortex in a rhesus monkey contains between 2.5 to 3 million (Rakic, unpublished). These numbers are rough approximations complicated by large individual variations. Subsequent neuronal growth, elaboration of dendrites, ingrowth of afferents, formation of synapses, and proliferation of glial cells distort the initially simple radial organization. Although in most areas the fetal type of radial organization disappears by the time the cortical plate acquires its horizontal lamination, its vestiges can still be discerned in some areas, even in an adult.

Columnar deployment of neurons in the adult neocortex was recognized almost fifty years ago (Lorente de No 1938), but most subsequent research focused on its laminar organization. It was Mountcastle (1957) who established the functional significance of radial organization in the cerebral cortex by discovering that all neurons within a single column respond to the same stimulus. His work revealed that the cortex can be conceived of as a

mosaic of interrelated cellular columns concerned with one specific modality (touch, pressure, joint movement, etc.) and with a single point (receptive field) at the periphery (Mountcastle 1957, 1979). Projections from a given thalamic nucleus or from its parts may terminate in the form of stripes that innervate arrays of ontogenetic columns arranged as "colonnades", or parallel rows of columns (Eccles 1984; Mountcastle 1979; Szentagothai 1978). Similar functional or anatomical columns have been observed in other sensory areas (Hubel and Wiesel 1977; Jones et al. 1975; Jones 1981) as well as in associaton cortex (Goldman and Nauta 1977; Goldman-Rakic and Schwartz 1982). However, the present article is not concerned with the columnar terminal fields of thalamic or corticocortical connections. Rather, it is focused on the cohorts of genealogically related neurons that may provide the developmental basis for the columnar organization of neurons and their function in the adult cortex (Rakic 1978).

CORTEX EXPANDS MAINLY BY ADDITION OF RADIAL UNITS

There is little doubt that the neocortical mantle enlarges during evolution by unequal growth of existing cytoarchitectonic areas and by the addition of new ones (e.g., Brodmann 1909; Ebbesson 1980; Kaas 1987; Sanides 1972). This is accomplished by the addition of ontogenetic columns, which in turn are produced by the proliferative units in the ventricular zone. The hypothesis consistent with our findings is that cells of the proliferative units arise mainly by symmetrical cell divisions, while later they produce cortical cells mainly by asymmetrical divisions. The number of units in each individual, therefore, must be determined early, before the onset of neurogenesis. A single additional round of symmetrical cell divisions at the stage of unit formation would double their number as well as the number of ontogenetic columns that they subsequently produce. Conversely, the number of neurons within the ontogenetic columns depends on the rate of cell production by asymmetrical division in the proliferative units. An additional cell division would increase the numer of neurons within a given ontogenetic column by only one. Indeed, the number of cells in ontogenetic columns, reflected in the thickness of the cortex, changes relatively little during evolution (Rockel et al. 1980). It may not be coincidental that the size of the columnated afferent terminal fields in the cortex is relatively constant, even in species with large differences in the cerebral surface (Bugbee and Goldman-Rakic 1983). Although an increase in the number of ontogenetic columns explains the expansion of the cortical surface as a whole, it does not address the issue of a differential increase in the surface of various cytoarchitectonic areas.

Two basic cellular mechanisms, or their combination, could account for differential expansion of cytoarchitectonic fields. According to one

hypothesis, the areal specificity of cortical neurons is rigidly determined within the ventricular zone (i.e., the number of proliferative units devoted to each area is fixed). The differential increase in the number of units producing area-specific columns can be regulated at early embryonic stages by homeosis, meaning the "assumption of one member of a metric series of the form to another member of the series" (Bateson 1894). More recently, genes that regulate such developmental changes, the so-called homeotic genes, have been demonstrated in a variety of species (Gehring 1985; Lewis 1978; Scott 1984). It is likely that such master genes, at later stages, control production of neuronal phenotypes within the proliferative units, thereby generating variations on the common neural pattern in ontogenetic columns subserving individual cytoarchitectonic areas. Therefore, regulatory genes may preserve an evolutionary component and provide instruction both for duplication and for changes in the mosaic of proliferative units at the ventricular surface.

An alternative possibility is that the areal positions and modal specificity of neurons are not determined in the proliferative units, and that their phenotype and function are decided later by the type of input they receive from the periphery via the thalamus (Creutzfeldt 1977; Mountcastle 1957). Although this hypothesis provides a logical and attractive explanation for the diversification of cytoarchitectonic areas, it is difficult to reconcile it with a variety of evidence indicating that the information from the receptors of the periphery cannot be the sole determinant of cortical areas. For example, the basic pattern of geniculocortical connections is present not only before the formation of contacts with the retinal receptors (Nishimura and Rakic 1986), but they develop appropriate topography and are maintained in the absence of both eyes (Olivaria and van Sluyters 1984; Rakic 1988; Rakic and Williams 1986). Results of these and other studies, some of which are reviewed in preceding sections, indicate that certain areal markers must be present in the cortical plate independently of input from the periphery.

There is a third possibility which combines features from both above-mentioned hypotheses and is compatible with most of the available information. According to the radial unit model, proliferation units produce area-specific ontogenetic columns, but their final number devoted to a given area can be adjusted downward by a complex input/output relationship. This model would be in general accord with the theories of selective stabilization (Changeux and Danchin 1976), neuronal group selection (Edelman and Finkel 1984), and competitive elimination (Rakic 1986), which were proposed to explain the fine tuning of synaptic connections within a given system. We are now at a point where the various hypothesis proposed for cortical parcellation can be experimentally tested.

EXPERIMENTAL MANIPULATION OF CYTOARCHITECTONIC AREAS

To distinguish between mechanisms of cortical parcellation discussed in the preceding section, a number of axons in a specific thalamocortical or corticocortical system should be altered at early embryonic stages and the effect on cortical areas examined. We have recently found that binocular enucleation performed on monkey embryos in the first half of gestation provides a useful test of the role thalamic afferents may play in the regulation of cytoarchitectonic fields. When enucleation is performed around E60, after all neurons of the lateral geniculate nucleus have been generated, but prior to ingrowth of their axons into the developing cortical plate (Rakic 1977), this thalamic nucleus comes to contain less than one-half of the neurons present in the age-matched controls (Rakic, submitted; Rakic and Williams 1986; Rakic, unpublished). The occipital lobe in enucleated animals displays dramatic changes in the pattern of convolutions but has topographically well-defined residual connections with the diminished lateral geniculate nucleus. Since geniculocortical axons project to the striate cortex in a predictable manner (Fig. 2A), the presence of fewer fibers during corticogenesis could affect the size of the primary visual cortex in at least three ways: (a) the number and height of the ontogenetic columns may remain the same as in controls, resulting in dilution of geniculocortical afferents (Fig. 2B); (b) the number of columns devoted to area 17 could remain the same, but their height may be diminished by the process of second order transneuronal degeneration (Fig. 2C); (c) the number of ontogenetic columns can be reduced, while their height (i.e., the number of cells in each column) remains the same (Fig. 2D).

The results support the model illustrated in Fig. 2D. The striate cortex in enucleates was well-defined by a sharp border with the adjacent area, indicating that a morphological distinction between them develops in the absence of any information from the retina. Most unexpectedly, the thickness of the striate cortex and its characteristic complement of layers and sublayers was within the normal range (Rakic 1988; Rakic and Williams 1986). However, most importantly, the area of the striate cortex in enucleates was less than half the size it was in the age-matched controls. Thus, despite the absence of retinal input to the lateral geniculate nucleus and the severely reduced number of geniculocortical afferents, the striate cortex had the normal number of neurons per layer and per ontogenetic column, while the total number of neurons in the area and its surface was diminished in proportion to the loss of geniculate neurons (Rakic 1988; Rakic and Williams 1986; Rakic, unpublished). The method of this reduction is not understood, and our working hypotheses are illustrated in Fig. 3: the striate cortex (area

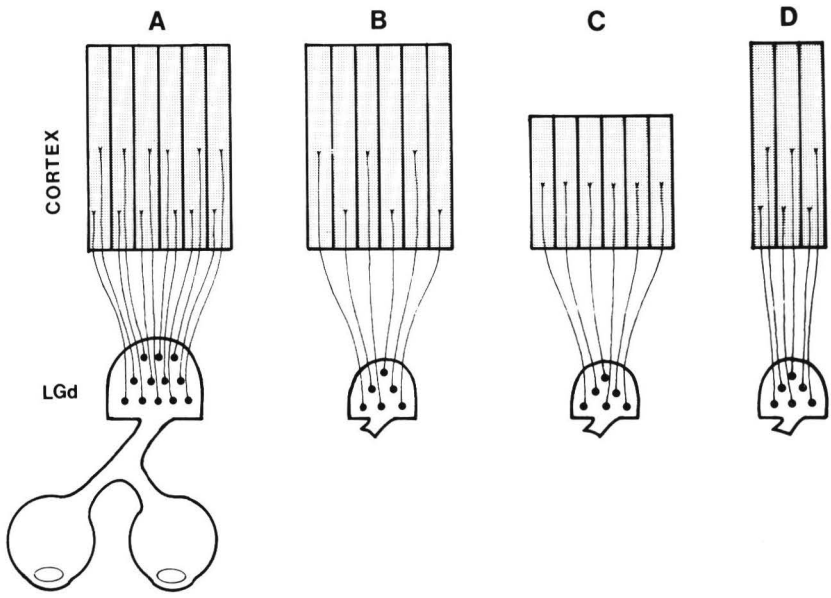

Fig. 2—Schematic of the possible consequences of diminished afferent input to the visual cortex from the dorsal lateral geniculate nucleus (LGd) in animals binocularly enucleated at early embryonic stages. The normal numerical relationship between geniculocortical projections and ontogenetic columns in the cortex schematically illustrated in A can be altered in three basic ways (B,C,D), discussed in the text.

17) can simply lose a number of ontogenetic columns, diminishing the total size of the cortex (Fig. 3B). Alternatively, the prestriate cortex (area 18), which normally receives input from the adjacent thalamic nucleus (pulvinar) and from the other parietal and temporal cortices, could take over some of the territory from area 17 (Fig. 3C). Finally, a number of columns that were specified for area 17 (X in Fig. 3D) could, in the absence of normal afferents, receive input from the pulvinar and other cortical areas, thus becoming a new cytoarchitectonic area that is genetically striate (area 17) and connectionally prestriate (area 18). Our preliminary data favor the last hypothesis (Fig. 3D), but additional experiments need to be done.

So far, results obtained from our experiments are in harmony with the observation that the human left cerebral hemisphere with a larger auditory cortex also has a larger medial geniculate nucleus (Eidelberg and Galaburda 1982). Finally, it may be relevant to mention that the laminar distribution of major neurotransmitter receptors within the striate area in early enucleated monkeys retains the appropriate pattern (Rakic et al. 1987), and that synaptic density within each layer, as revealed by quantitative electron

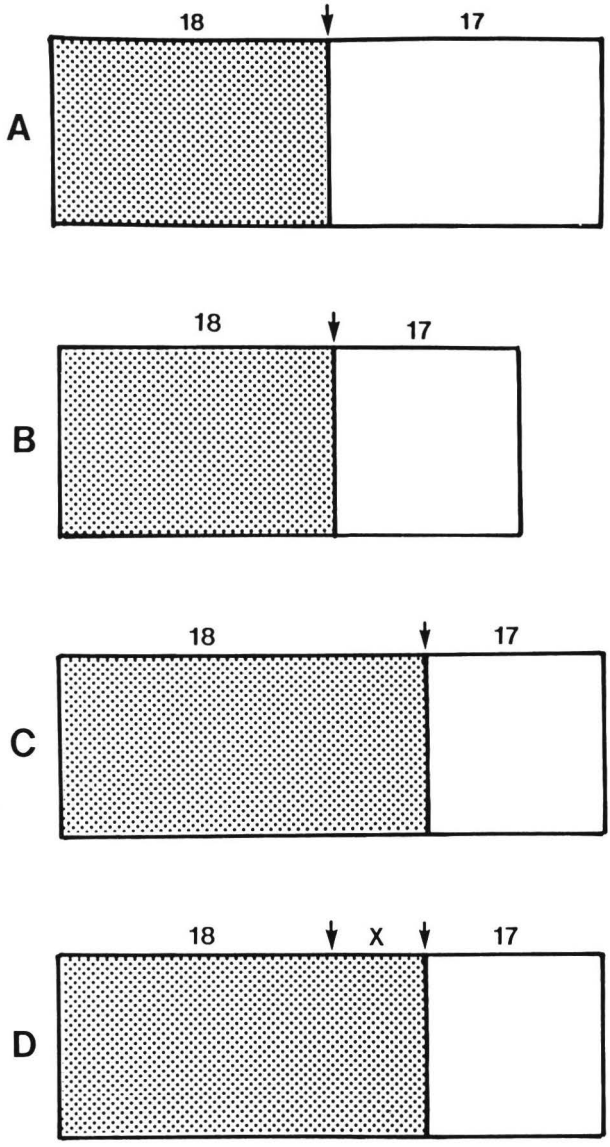

Fig. 3—Schematic of the relationship between the striate (area 17) and prestriate (area 18) cortex in a normal animal **(A)** and the possible mechanisms responsible for the reduction of area 17 in binocular enucleates **(B–D)**: the striate cortex can be diminished by differential cell death due to diminished input **(B)**; encroachment of area 18 into its territory **(C)**; or by formation of a new area **(X)**, which is genetically striate but receives input characteristic for area 18 **(D)**. Further explanation in the text.

microscopy, develops within the normal range (Bourgeois and Rakic 1987). Thus, our data demonstrate that the number of specific thalamic afferents affects the final number of ontogenetic columns in the corresponding cortical area, but does not alter the number of neurons within each ontogenetic column or their phenotype.

Thalamic regulation may be only part of a more complex interactive process that occurs during development and parcellation of the neocortex.Prenatal resection of the fetal cortex, which eliminates or decreases specific corticocortical input to the subplate at early stages, has a profound effect on the gyral pattern and anatomy of the other, unoperated areas on both sides (Goldman-Rakic 1980; Goldman-Rakic and Rakic 1984; Rakic 1988). On the basis of experiments in other systems, one can predict that multiple inputs to a given cytoarchitectonic area could have an effect on its final size. For example, we have found that initially overproduced retinogeniculate axons compete for their territory and for their survival (Rakic 1981; Rakic and Riley 1983). This can be demonstrated by early monocular enucleation, as graphically presented in Fig. 4A-C. In this series of experiments we found that by midgestation, about 3 million axons originating from each eye terminate in an overlapping manner in the lateral geniculate nucleus, but that their number diminished during the period of segregation to about 1.2 million. However, if one eye is removed at the stage of retinogeniculate overlap, the remaining eye retains a larger number of ganglion cells and their axons than it otherwise would, but this number is still smaller than the sum of two normal eyes (Rakic and Riley 1983).

Our preliminary data indicate that the same general principle of competitive elimination may apply for cortical areas that share some common synaptic targets during development (Fig. 4D, E). For example, unilateral resection of the occipital cortex at midgestational periods results in an enlarged inferior parietal lobule on the side of the lesion (Goldman-Rakic and Rakic 1984; Rakic, unpublished). One hypothesis to explain this dramatic result is that supernumerary cells in the parietal lobe may survive in the absence of competition with projections from the occipital lobe in the subcortical structures, or in the other cortical areas with which they share common synaptic targets (Fig. 4D, E). Another hypothesis is that input from the remaining areas spreads to the territories normally occupied by the removed region. In cortical ablation experiments and in thalamic reduction experiments (described above), ontogenetic columns genetically specified for one area receive afferents characteristic of another area. As a result, we may have experimentally created a new cytoarchitectonic area that could contain different synaptoarchitecture. This is an important goal of future research as it may hold a key to understanding how new cytoarchitectonic areas may be introduced during evolution.

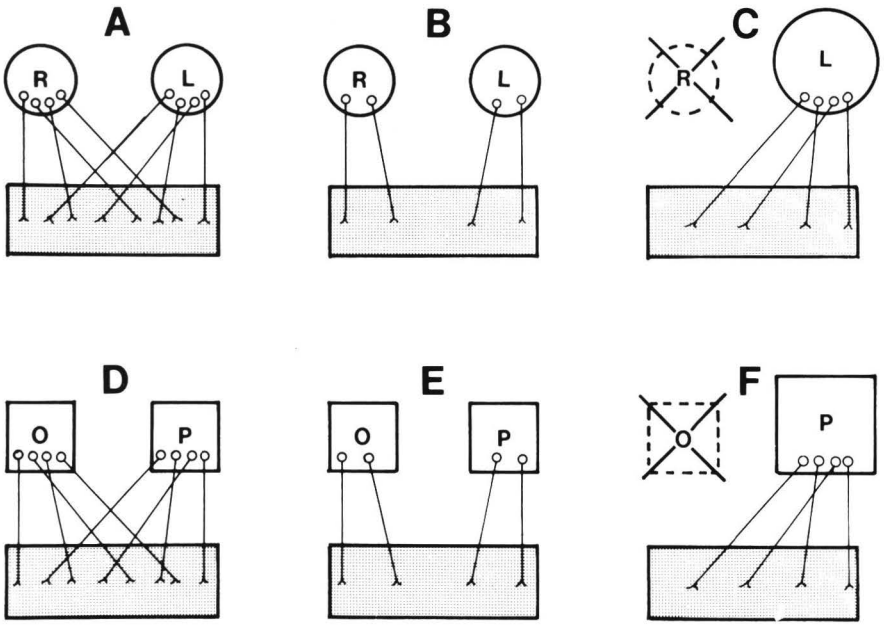

Fig. 4—Diagrammatic representation of the model of competitive interaction between structures with supernumerary projections that share common synaptic targets (shaded boxes). **A**: Projections from the right (R) and left (L) eye to the brain are initially overproduced and intermixed. **B**: These projections become segregated by competitive elimination during normal development. **C**: Removal of the competition from one eye at the critical period results in retention of a larger number of neurons and axons in the remaining eye. Views **D–F** are diagrammatic representations of the similar type of competitive interaction that may occur between neurons of the occipital (O) and parietal cortex (P) which share a common synaptic target during embryogenesis. Further explanation in the text.

REORGANIZATION OF CORTICAL REPRESENTATION WITHIN AREAS

Development and modifiability of the cortical representation is related, but is a somewhat different issue since it involves the intraareal changes in maps (within a single area), rather than interareal changes (between different areas). Nevertheless, the results of intercortical manipulation in nonhuman primates are in general agreement with the "intracortical principles of magnification", according to which more densely innervated parts of the periphery have a larger representation in the somatosensory (Woolsey et al. 1942), visual (Daniel and Whitteridge 1961), and auditory (Suga and Jen 1976) areas. For example, in the trigeminal system in rodents, the number of sensory axons innervating a given vibrissal follicle and the size of the

corresponding barrel in the cortex are closely correlated (Lee and Woolsey 1975; van der Loos 1979). Manipulation of the size of trigeminal innervation by a neonatal lesion in neighboring follicles or by selective inbreeding of mice with an "extra" whisker indicate that the "size of the somatory map and of its parts, while relating to the number of nerve fibers innervating the corresponding sensory periphery, is not an invariable function of it" (Welker and van der Loos 1986). Recently, it has been shown that the forepaw and hindpaw representations in the somatosensory map also can be changed by damage to the periphery in newborn rodents (Dawson and Killackey 1987; Seo and Ito 1987). Likewise, peripheral nerve injury in developing rats changes the representational pattern in the motor cortex (Danoghue and Sanes 1987).

Physiologically defined shifts in the borders of somatosensory representations have also been demonstrated in adult monkeys and cats. For example, peripheral nerve transection or digit amputation in adult primates (Merzenich et al. 1983, and this volume) alters the borders between areas representing these digits. Likewise, in adult cats elimination of thalamic input to the motor cortex results in the reorganization of corticocortical projections (Asanuma et al. 1985). Although no anatomical substrate has thus far been demonstrated for these changes, they indicate considerable competitive interaction among various cortical connections in the adult cortex. Data from such a heterogenous set of experimental results obtained by different methods in various species are not easily comparable and are still far from being conclusive. Nevertheless, they support the notion that, although areal specificity and representation of the periphery may be already indicated at the time of cell production within the proliferative zone, the final number of ontogenetic columns devoted to a given receptive field or area may be to some extent regulated by competive interaction among participating neurons.

RADIAL UNIT MODEL CAN EXPLAIN THE PATTERN OF SOME HUMAN CORTICAL MALFORMATIONS

Another source of evidence supporting the radial unit hypothesis comes from the pattern of major cortical malformations in humans. Among abnormalities of the cortical mantle caused by defective proliferation and/or migration of cortical neurons, lissencephaly and polymicrogyria are the most prominent (reviewed in Volpe 1981). There are several variations of these two basic types of malformations but in general, lissencephalic brains have a smooth cerebral surface, diminished total area, and approximately normal cortical thickness, whereas polymicrogyria is characterized by a highly convoluted cerebrum with nearly normal surface area, and thin cortex (Richman et al. 1974; Volpe 1981). Since the etiology of these two

malformations is a mystery, their classification in the past has been based on the appearance of the cortex at the time of death.

These types of cortical malformation can now be classified into two major categories on the basis of developmental mechanisms outlined by the radial unit hypothesis. The first category consists of malformations in which the number of ontogenetic columns in the cortex is diminished, while the number of neurons within each ontogenetic column remains relatively normal. The second category consists of malformations in which the number of ontogenetic columns in the cortex remains normal, while the number of neurons within each column is diminshed. Although most malformations predominantly display features of one or the other of these two categories, some are a mixture of both types.

It can be expected that the first category is the result of an early defect that occurs at the time when proliferative units are being formed within the cerebral ventricular zone. The defect in this case should precede the onset of neurogenesis and therefore probably occurs in humans within the first 7 weeks of gestation. Once the number of proliferative units in the ventricular zone has been established, each unit produces the usual number of neurons that form ontogenetic columns of normal height. As a result, the cortex has normal thickness but a smaller surface.

The defect in the second category of malformations begins after the normal number of proliferative units have been established. This defect should, therefore, occur after the 7th week of gestation, and should not greatly affect the number of ontogenetic columns. However, it can be expected that it affects the number of neurons produced within each proliferative unit. As a result, ontogenetic columns should have fewer neurons and consequently a thinner cortex. It should be emphasized that a smaller number of cells in the ontogenetic columns could be the result of low production in the proliferative unit, subsequent cell death, or a failure of their migration. In the latter case, some cortical neurons may survive in ectopic positions within the white matter, as frequently occurs in polymicrogyric brains (Volpe 1981). Although the proposed classification of cortical malformations does not address the issue of their primary etiology, it suggests possible developmental mechanisms and delineates the timing and sequence of cellular events. The pattern of cortical malformations, on the other hand, supports the radial unit hypothesis by exposing the possible consequences of defects occurring during the stages when proliferative units or columns are forming.

UNSOLVED QUESTIONS AND FUTURE PROSPECTS

The *radial unit model* can explain how the immense cellular mass of the neocortex disperses so that postmitotic cells generated near the cerebral

ventricle find their final laminar and regional positions in appropriate cytoarchitectonic areas with species-specific and individual-specific differences in their size. This model assumes that cortical areas are the end product of genetic information that can be modified by epigenetic variables. Advances in genetic and experimental manipulation of cortical development provide an opportunity to examine the validity of the radial unit model of cortical parcellation, and to determine the role of intrinsic and extrinsic factors in regulating the size of cytoarchitectonic areas. Furthermore, the fact that the radial unit model is consistent with the observed pattern of cortical abnormalities in major cortical malformations allows its validation at the genetic level.

Although the proposed model and its experimental testing has settled some issues, it has also led to a new set of questions. For example, we have learned that the number of radial columns devoted to the striate area can be altered by manipulation of the input it receives, but we do not understand the mechanisms involved in this regulatory process (Fig. 3). We do not even have some rather basic facts. For example, is the area of the striate cortex in early enucleates diminished by differential neuronal elimination, or by a shifting of the adjacent peristriate area into the territory normally occupied by the striate columns? If the latter possibility is the case, should this region be considered an enlarged area 18, or a new type of cortex which has input appropriate for area 18, but ontogenetic columns appropriate for area 17? What is the pattern of connectivity and what is the function of this artificially formed cortical area? What is the best research strategy to mark the embryonic site of the prospective areal borders before afferents invade the cortical plate and cytoarchitectonic characteristics emerge? Modern methods and research strategies using a combination of prenatal neurosurgery, transgenetic animals, cDNA and mRNA probes, or retrovirus-mediated gene transfer to label and to follow the progeny of neuronal clones from the site of their origin in the proliferative units to their final positions in the ontogenetic columns promise to provide further testing of the radial unit model of cortical development.

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