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Group Report
Principles of Cortical Self-Organization

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INTRODUCTION

Cortical self-organization refers to the processes that produce the functional and anatomical organization of normal adult neocortex during ontogenetic and phylogenetic development and that maintain or modify this organization over the course of life. Topics of current interest are discussed below under several general headings: (a) parcellation of the neocortex into distinct areas; (b) maps, columns, and modules in the cortex; and (c) plasticity. Finally, the group endeavored to answer the question of whether there is anything distinctive about *neocortical* organization and the processes that give rise to and maintain it, or whether the same mechanisms operate at all levels of the nervous system.

AREAL PARCELLATION

What Constitutes a Cortical Area?

In some sense, cortical areas are still, following the tradition of Gall and Brodman, thought of as "the organs of the brain." Early workers had believed that while some cortical areas were sharply defined, other areas merged gradually into one another. By contrast, modern workers prefer the notion that more or less discrete borders exist between cortical areas; multiple techniques have disclosed more and more borders. Areas are presently recognized on the basis of several criteria: First, *many* areas have a single, more or less continuous *map* of sensory and motor *representation.*

Within an area there are similarities in (a) response characteristics and activity patterns of the neuronal population; (b) input and output connections; (c) neuronal architecture; and (d) neuronal histo- and cytochemical properties. Next, each area is also thought to have a unique physiological function and role in behavior. Finally, it is clear that an area need not be uniform in its properties; these properties may vary gradually and progressively within an area, and an area may contain specialized subareas.

While this list of properties of an area is neither complete nor unique and is not satisfied in every respect by present experimental findings regarding many of the cortical areas we now recognize, it does indicate the types of properties that count in favor of recognizing a region of cortex as a single and distinct area. It was suggested that we recognize two adjacent areas as separate if these properties vary only gradually within either area but change abruptly across their border.

Whatever the difficulty in precisely *defining* the concept of a cortical area, the group agreed about the identifications of most of the particular cortical areas thus far investigated. In the few cases of disagreement, further experimental investigation of the properties enumerated above should produce converging evidence as to the validity of a proposed parcellation.

How Are the Separate Cortical Areas Generated?

The cortical mantle arises from proliferative cells in the ventricular zone. After their final mitoses, these cells migrate along radial glial fibers through the intermediate zone (the future white matter) and cortical subplate to assume positions superficial to the previously generated cells. Early in embryonic life, the cortical cells appear in single file like beads on a string. At this time, cortical columns are distinct anatomical subunits, one cell wide and 80 to 120 cells tall, separated by septa. It is assumed that the height of these columns in a cortical area determines the thickness of the resulting cortex, while the number of columns in a region determines its area.

Observations of the close association between migrating cells and glial fibers led Rakic (this volume) to hypothesize that the cells forming an embryonic cortical column are clonally related—the descendants of a single cell or cells (a "proliferative unit") in the ventricular zone. This view is consistent with the fact that one proliferative ventricular zone cell could give rise to all the cells in a cortical column: the duration of the period during which neurons are generated in the ventricular zone divided by the duration of the cell cycle yields a number of cell divisions large enough to account for the generation of the number of cells in area 17 cortical columns by asymmetric division of stem cells. It is not yet clear, however, whether this number of divisions is large enough for all regions of cortex, particularly

when cell death is taken into account. Definitive experiments to test the clonal identity of cortical columns have not yet been performed. A promising approach to this problem is to attempt to label clones of cells in an embryo by transfection with a retrovirus expression vector that incorporates some functionally neutral, histologically manifest marker, as has recently been achieved in chick retina. The expected result of such an experiment would be that the clonal descendants of labelled ventricular zone cells all express the marker, allowing one to determine whether cells in an embryonic cortical column are clonally related.

While the embryonic cortical columns are distinct at early developmental stages, in later life, with the growth of dentrites and neuropil, these columns lose their discrete appearance. There is not yet any evidence to indicate that the columns visible in embryonic cortex correspond to the functional cortical columns evident from physiological studies in postnatal animals.

When it is first generated, the cortical mantle appears to be uniform, and the borders between future cortical areas are not evident. Two extreme hypotheses and a third compromise between them may be entertained to account for the division of this apparently uniform mantle into separate cortical areas, each with its own patterns of differentiation. First, the ventricular zone is parcelled into distinct groups of proliferative units that produce cells already committed to constituting particular areas by the time of their final mitosis or migration to the cortical plate. Second, the cortical mantle is initially equipotential, and areas become specified as a result of the competition among different thalamic inputs. Third, the cells that give rise to each cortical area are predetermined, but the size of each area can be affected by inputs and outputs.

Evidence in favor of the first hypothesis—of early commitment or prespecification—is the difference among regions of the ventricular zone in the times at which neurons are generated. The part of the ventricular zone in the monkey that gives rise to cortical area 17, which has the largest number of neurons under a unit area of pial surface of any region of cortex, generates neurons between embryonic days 40 (E40) and E100; cortical neurons in the bordering region, area 18, are generated only between E40 and E70. There is no reason to believe that extrinsic factors could affect the duration of such mitotic activity in the proliferative zone. In addition, the first hypothesis is attractive on the ground of simplicity: the ventricular zone appears to offer an ideal environment for types of interaction that might generate morphogenetic fields such as those occurring in the *Drosophila* blastoderm. Finally, several recent experiments demonstrate that some aspects of cell fates, such as pyramidal versus stellate morphology, or lamina of ultimate destination, may already be determined in the ventricular zone or in migrating cells (e.g., McConnell 1985). But definitive experiments on

this point seem likely to require some genetic manipulation or transplantation of small regions of neural tube or ventricular zone, techniques that may not yet be feasible. Molecular markers that distinguish one region of the ventricular zone or cortical mantle from another prior to the arrival of inputs would be useful as well, though their presence would only establish differences, not irreversible commitment. However, none of the presently available markers specific for particular cortical areas are expressed sufficiently early. Findings in Boston-type Siamese cats provide evidence that the definition of the thalamocortical projection map also does not determine the size of cortical areas. This animal has a normal-sized visual cortex and LGN into which is placed an extra map segment that would normally occupy about half of the visual cortex.

The second hypothesis—the parcellation of cortex into cortical areas by an interaction among thalamic or other inputs—is favored by the observation that the presumptive border between areas 17 and 18 is first evident in the boundary between their thalamic inputs, from the lateral geniculate (LGN) and pulvinar nuclei of the thalamus, respectively. This boundary is present while the thalamic afferents ramify in the cortical subplate, before their final target cells have appeared. Have these thalamic axons already sought out distinct cortical territories, or will their partition create the divisions among cortical territories? In the former case, it should be possible to find the molecular markers recognized in the cortical subplate by the ingrowing axons. In the latter case, if the cortical columns are truly uncommitted, then manipulating the size of one of the thalamic inputs might shift the competitive balance in favor of the other input, allowing it to take over more territory in developing cortex and ultimately causing a decrease in the size of one cortical area and a corresponding increase in the other. Rakic has tested this hypothesis in the monkey by measuring the sizes of postnatal visual cortical areas and their thalamic inputs after very early embryonic binocular enucleation. He found that both the LGN and area 17 contained about $^1/_3$ the normal number of neurons. Amazingly, the pattern of sulcation in the occipital lobe of these animals was also grossly different from normal, but consistent among the experimental animals. One finding predicted from this hypothesis was thus confirmed. Another prediction of the hypothesis is that there might be a corresponding enlargement of area 18 (This prediction would not hold if nonthalamic inputs were important for determining the size of cortical areas; in this case, one might even predict that area 18 would be smaller since it receives a major input from area 17). The observation of such an enlargement would crucially support this hypothesis, since it could demonstrate a *change* in the fate of embryonic cortical cells that could not be explained simply by cell death. Unfortunately, for technical reasons, primarily the difficulty in defining the border between areas 18 and 19, measurements have not yet been made to test this. Rakic (this volume)

explores the implications of some of the possible outcomes. Evidence against the second hypothesis are the facts that not all cortical areas have unique thalamic input nuclei and that it is not clear how such a mechanism could give rise to the regularities observed in the orientation and position of cortical areas.

The third (compromise) hypothesis is that the cells that will form a cortical area are committed when they leave the ventricular zone, but that the survival and growth of these cells, and the ultimate size of each cortical area, depend on their thalamic or corticocortical inputs and outputs. This hypothesis implies that only regressive changes in the size of cortical areas could be produced experimentally. It is consistent with experimental findings to date.

How are Cortical Areas Generated Phylogenetically?

Not only does the size of neocortex differ among species, but the *number* of distinct cortical areas dedicated to particular modalities or functions differs greatly as well. In the hedgehog's cortex, for example, we do not find more than one or two of the approximately 24 visual areas of the rhesus monkey, and there is no room for the many additional areas.

Allman advances two alternative mechanisms for producing such changes in the number of cortical areas during phylogeny: (a) that new cortical areas were carved out of previously existing cortex; or (b) that new cortical areas arise by some sort of duplication event, followed by a series of small genetic changes that eventually result in a differentiation of function. The second hypothesis is analogous to current views on the evolution of families of genes. These arise by duplication, followed by selection for mutants in which the product of the duplicated gene has become better able than that of the original gene to carry out a differentiated function. Evidence for hypotheses about phylogeny of the central nervous system has been notoriously difficult to obtain. One of the predictions of the first hypothesis—that new areas arise from colonization of previously existing cortex—is that there should exist intermediate forms in which such colonizing was incomplete. The partial overlap of sensory and motor cortex in marsupials (presumed to arise out of a single ancestral sensory motor cortical area), and the lesser degree of such overlap in the rat, could thus be taken as confirming evidence. However, these forms could as easily be interpreted as arising from a duplication of the ancestral cortical area followed by partial differentiation, and a later merger between portions of each new area. The first hypothesis also fails to explain an overall expansion of cortex in phylogeny.

Evidence in favor of the second—duplication—hypothesis is the fact that cortical areas dedicated to related functions are commonly found in mirror-symmetric pairs, for example areas 17 and 18, 1 and 2, 3a and 3b, and MT

and MST. This hypothesis could also explain how the overall size of cortex could increase with the total number of areas. The duplication of cortical areas could arise simply by a change in the formation of the ventricular zone, according to which a single additional symmetric cell division could double the number of proliferative units, which would then divide asymmetrically through the normal number of cell cycles to give rise to double the number of cortical columns, each of which is the normal size.

Allman has set out to test another prediction of the second hypothesis by generating monoclonal antibodies to specific cortical areas using an immunosuppression technique to eliminate production of lymphocyte clones producing antibodies directed against other cortical areas. The first such specific antibodies produced, to area MT, apparently labelled an extracellular matrix component surrounding efferent fibers from this area (McDonald et al. 1986). This finding raises the possibility that it is the input or output connections which primarily distinguish one cortical area from another, while the intrinsic circuitry may be similar from area to area. Interestingly, monoclonal antibodies generated against chick retinotectal surface markers also bind selectively to fiber systems in the white matter in monkeys (McDonald, Allman, and Dreyer, unpublished observations).

Homologies pose a particular problem for inferring phylogenetic relationships. The present interpretation of the phylogeny of *Cebus* and *Macaque* is that they have no common gyrencephalic ancestor, yet details of their patterns of sulcation are highly similar. The functional and anatomical organizations of their visual systems are similar to each other, and both are similar to the lissencephalic owl monkey. Which of these similarities represent convergent evolution and which are derived from common ancestry is a difficult question. Particularly if the parcellation of cortex is influenced by the periphery, convergent evolution of cortex would be expected to be common in animals occupying similar environments.

Experiments on the "barrel field", the somatosensory cortical representation of rodent vibrissae, may throw light on both phylogenetic and ontogenetic changes (van der Loos 1979; van der Loos and Welker 1985; Welker and van der Loos 1986). In barrel cortex, the array of mystacial and supra- and infraorbital vibrissae are represented by adjacent barrels within layer IV; the intervening skin is represented outside the barrel field (Nussbaumer and van der Loos 1985). By selective inbreeding of mice with supernumerary vibrissae appearing at different sites, van der Loos and coworkers obtained 25 strains, each strain characterized by a different whisker pattern and by a corresponding barrel pattern (i.e., one that was topologically equivalent to the standard or "enriched" whisker pattern, van der Loos et al. 1986). Different strains responded in different ways with respect to the size of their barrel fields: 3 out of the 5 enriched strains had larger fields than the strain bred for the "standard" pattern of vibrissae. Whether the barrel fields of these 3 strains had colonized territory from the

surrounding cortical areas is not yet certain, but van der Loos suggested that these inbreeding experiments may have created "super-mice" with an enlarged telencephalon. The duplication hypothesis of phylogeny appears not to offer an explanation for these findings unless the unit of duplication is the single cortical barrel itself, rather than the entire barrel cortex or S1 cortex as as whole. In ontogeny as well, it seems difficult to conceive how the presence of an extra vibrissa could signal the proliferative cells of the ventricular zone to divide symmetrically to produce a larger area of cortex. The genetic change causing an extra vibrissa to form could, of course, have pleiotropic effects on ventricular zone proliferation as well, but this too seems unlikely. The most attractive possibility is that telencephalic cells that would ordinarily die are saved by the presence of extra input resulting from a cascade of enhanced neuronal survival from periphery to trigeminal ganglion to trigeminal nucleus to ventrobasal thalamus to barrel cortex. It is not yet known whether there is sufficient overproduction of neurons and naturally occurring cell death at each of these stages to account for the observed enlargement of barrel cortex by up to 21% (comparing the strain with the largest to that with the smallest barrel field).

What Is the Functional Significance of Multiple Cortical Areas for Individual Modalities?

Studies of the ontogeny and phylogeny of cortical parcellation naturally give rise to questions regarding its functional significance. The multiple cortical areas present in higher primates, and presumably in humans, constitute an embarrassment of riches. The multitude of visual areas (perhaps 24 in rhesus monkey, for example), outnumber the qualities of visual world for which separate representations had initially been sought. A wealth of cortical areas has been found wherever sought: in auditory, somatosensory, and motor systems and in the prefrontal lobe (Kaas 1987). It is also not clear how or whether multiple representations of a single object contribute to a unique percept, action, or emotion. Finally, it is not known whether it will be possible to test the function of each individual cortical area behaviorally, as some areas may work only in association with others. Allman offered the analogy of hemoglobin, in which the four individual chains, which are the result of gene replications, must interact cooperatively to bind and release oxygen. Nevertheless, the consensus view is that each cortical area is likely to have a particular function, and that multiple cortical areas are important for the following general reasons:

1) Different functions require computation over different inputs; within each cortical area, the inputs required for that area's computation are repetitively rearrayed over the ≤ 1 mm scale of cortical hypercolumns or modules.

2) Different functions may best be served by different systematic representations of output.
3) Successive levels of processing are required to generate higher-order symbolic or categorized representations. For example, language representations must be derived from speech representations which, must be derived from speech-feature representations, which in turn must be derived from sound-feature representations in the auditory system.

The auditory cortex of echolocating bats provides some of the clearest evidence for multiple cortical areas specialized to process different types of acoustic information (Suga, this volume). The distance of a target is represented systematically in one cortical area in terms of the time lag between the bat's vocal sonar output and the receipt of the echo. The target velocity is represented in another area by the Doppler shift of the reflected signal. Another auditory area appears to allow identification of the target by the power spectrum of the reflected signal. Areas of similar function exist in both Old and New World bats; these similarities must be the result of convergent evolution.

In the somatosensory system, behavioral experiments over the years have demonstrated differences in perceptual function among the submodality areas 1, 2, 3a, and 3b. Work of the last three years on motor and other frontal cortex has also revealed multiple parallel systems, the functions of which may be partially dissociated. In the primate visual system, most behavioral functions require area 17. Data from lesions in humans and animals strongly implicate area MT/V5 for some types of visual motion processing and part of V4 for color (reviewed in Andersen, this volume; Zeki, this volume). For example, transient defects in smooth-pursuit eye movements and the perception of moving stimuli follow from lesions confined to area MT. A long-lasting inability to perceive structure from motion has also been found. These phenomena have led Zeki to posit that the function of cortical areas is "to construct categories in an unlabelled world." For example, he explains the apparently scrambled topography of the color area of V4 by noting that the computation of perceived color needs wide-ranging information about the visual surround, but does not need to know the precise disposition of the various parts of the surround.

Do Such Computations Require Multiple Cortical Areas?

It appears that the owl's visual wulst, with many more layers than mammalian neocortex, performs orientation-, length- and disparity-selective functions similar to V1, V2 and V3 in mammals (Pettigrew and Konishi 1976). The owl wulst contains visual field maps stacked in register with a total thickness of more than 10mm, which far exceeds that of the neocortex in any mammal. The owl wulst lacks the pyramidal-type neuron with its long apical dendrite,

which is an ubiquitous feature of mammalian neocortex (Pettigrew 1978). Allman suggested that the apical dendrite might perform a unique computational function in neocortical information processing, in which local interactions occur over the length of the shaft. He further suggested that there might be some biophysical constraint limiting the length of the apical dendrite to less than 2mm. Perhaps once mammals became committed to a neocortical architecture involving interactions along the apical dendrite, they could no longer increase computational complexity by increasing the thickness of the neocortex beyond a few millimeters, and thus expanded horizontally instead, by adding multiple areas.

Some functions carried out within subareas of a single cortical area in some species may be carried out in multiple cortical areas in other species. The *galago,* for example, does not have cytochrome oxidase-rich stripes in V2; instead, V2 is split into dorsal and ventral halves and another area is intercalated between them (Allman, unpublished observations).

CORTICAL MAPS

The notion of cortical maps, however confusing to the philosopher, (Hacker 1987; Blakemore 1988) is central to our understanding of the organization of cortex. It is useful to distinguish three basic forms of maps.

1) *Topographic maps*, in which successive positions on the cortex may be related to successive positions on a sensory receptor surface or motor effector sheet, are common in the more peripheral stages of processing. These maps may be subject to different degrees of metric and even topological distortion. For example, the retinal receptor surface is represented in V1 completely and in exquisite detail. Retinal representations in other visual areas have different metrics and even omissions. The cochlea is represented topographically within at least five cortical areas in the superior temporal cortex of macaques. Cochleotopic representations differ from those in other systems in that there is an isorepresentational (isofrequency) axis extending across them from edge to edge. Cutaneous and deep mechanoreceptors are represented topographically in the multiple subdivisions of SI cortex, including areas 1, 2, 3a, and 3b, and in SII. Area 4 and other cortical areas have, at least on a very coarse scale, topographic maps of motor output.

2) *Computational maps* are the orderly representation of some quality abstracted from the sensory input (or potentially some abstraction of movement). One example of a computational map is the auditory representation of spatial position. The azimuthal component is computed from differences between the two ears in the intensity and phase (or times of arrival) of a sound stimulus; the interpretation of these cues depends

strongly on the sound frequency. The elevational component depends on even more subtle cues about the sound's frequency spectrum (e.g., King and Hutchings 1987; reviewed in Konishi et al. 1987). Other notable examples are the orderly representations of target range and velocity computed in separate auditory cortical areas of echo locating bats (Suga, this volume). The representation of color in monkey V4 has many of the features of a computational map as well (Zeki, this volume).

3) *Intercalated, interdigitated,* or *reiterated maps* exist in areas that may have a topographic or computational map when considered on a coarser scale, but on a fine scale have discontinuities of various forms or repeated reversals of map order. The map of V1 in the monkey is an interdigitated map at the scale of the ocular dominance columns, with a low spatial frequency and color-sensitive map intercalated into the cytochrome oxidase blobs, but on all larger scales it is strictly topographic (Hubel and Wiesel 1974a, b). The map of the visual field in the cat's area LS is a good example of a reiterated map: local neighbor relations are preserved almost everywhere, but the division of the visual field into central, upper peripheral, and lower peripheral pieces, and several reversals in topographic order, allow each part of the visual field to be represented in two to four quite different places (Sherk 1986; Zumbroich et al. 1986). The motor maps in area 4 and elsewhere are reiterated or interdigitated on a scale of several millimeters, so that each muscle is represented at four or more separate points (Strick, personal communication). Multiply reiterated (or possibly even scrambled) maps may be advantageous for compressing into the dimensions of a modular cortical processing unit information that would be represented over a wide region of a strictly topographic or computational map.

Significance of Maps

Cortical maps are thought to be important for the following reasons:

1) Maps allow local interactions. Most cortical connections are short-range. Long distance connections can be achieved only at considerable metabolic cost, and they have the potential of introducing delays and temporal scatter. Maps may bring the significant aspects of each topographical or computational representation together. A map may allow all the information dealt with at each point in the represented continuum to be arrayed within range of the dendrites of single cortical cells.

2) The metric properties of maps may allow them to represent similarity, even in an abstracted computational representation. The local continuity of maps allows the distance on the cortex to serve as a metric for distance in the continuum of representation. In the auditory system, for example, interactions between neighboring frequencies can take place over fixed distances in the cochleotopic map.

3) Maps may allow an intrinsic correlation-sensitive mechanism to make conjunctions and detect related aspects of a representation. The background paper of von der Malsburg and Singer (this volume) gives numerous examples. Computational maps would thus permit new conjunctions to be discovered in feature space rather than in receptor space.
4) Maps allow multiple addressing. In a map laid out in topographic or computational space, any intrinsic inputs that locally activate or consolidate it automatically select similar items.

Maps Without Order?

The visual, visual-motor, and auditory systems provide several examples of sensory representations that do not appear to be ordered on a scale of more than a few hundreds of microns. Inferotemporal (IT) cortex in the monkey contains cells selective for some complex shapes and objects, including views of a face. Receptive fields of single cells are large; they always include the fovea and about half include part of the ipsilateral visual field. They respond independently of visual-field position within the receptive field. They vary in receptive field size, position, and optimal stimulus. While clusters of neighboring neurons are usually similar in their properties, neighboring clusters are as different as distant clusters in terms of the properties studied to date. Gross suggests that we do not yet know the appropriate question to ask or the stimulus dimension to explore to reveal order in the IT representation.

In one of the posterior parietal visual areas (7a), Andersen has found that neuronal responses in relation to vision and eye movement act to transform visual stimuli in retinal space into head-centered coordinates (reviewed in Andersen, this volume). No topographic or computational order is evident in this area. Cells with different visual and head-position responses appear to be scattered throughout the area. Andersen and Zipser have constructed a 3-layer network model that is taught to transform retinal into head coordinates using back-propagation for error correction. The intermediate ("hidden") units in this model come to mimic many aspects of the behavior of the cells in posterior parietal cortex. Interestingly, these hidden units do not form anything like a map. The criticism was raised that in network models, unlike the real brain, everything is connected to everything else. Andersen replied that, for this problem at least, widespread connections must be the case in the brain as well, since an output of position with respect to the head must be generated for each retinal position and each eye position. Andersen proposed that some cortical functions, like the network model, may genuinely lack orderly representations. The network model suggests a mechanism by which such useful but disorderly representations might be established.

Relation of Maps to Cortical Laminae, Columns, and Modules

Cortical maps are defined as if the cortex were two-dimensional; but the cortex consists of multiple laminae, and the continuity of cortical areas is locally disturbed by the existence of columns. The laminar and columnar organization of the visual cortex, for example, allows a great economy of connections over what would be required to produce its receptive fields without such orderly arrangement (Hubel and Wiesel 1962). Within a single cortical area, however, long distance excitatory connections and short-to-moderate distance inhibitory connections have been demonstrated (reviewed in Gilbert et al., this volume). Many of these connections are highly specific, conveying, in visual cortex for example, long distance excitation only to cells in columns selective for similar orientations. Cortical organization on this level is now open to study by a number of exciting new techniques such as optical recordings.

Cortical modules, about 0.5–1 mm on a side, are common to many or all regions of cortex. In visual cortex, such modules (termed hypercolumns) were first described as containing a complete cycle of both orientation and ocular dominance (Hubel and Wiesel 1974a). Work in the visual cortex has disclosed a profound relationship between cortical magnification, receptive field size and scatter, and the modules (Hubel and Wiesel 1974b). As cortical magnification increases, receptive field size and scatter decrease so as to produce about 50% overlap between the retinal areas represented in two adjacent modules. This relation has been shown to hold over more than three orders of magnitude of receptive field size in somatosensory cortex as well (Sur et al. 1980), and it may be a general rule for cortical maps.

How Are Maps Generated and Maintained?

At least coarse maps have been demonstrated to form in every system examined when neuronal electrical activity is disrupted or absent (reviewed in Harris 1981). The best evidence for map formation in the absence of activity comes from fish and amphibian retinotectal systems. Corticothalamic and thalamocortical topography are both evident *in utero* in the visual cortex before photoreceptors mature, at a time when even spontaneous retinal electrical activity is unlikely. Similar thalamocortical topography is evident in the visual system of anophthalmic mice. The laminar specificity of thalamocortical connections appears to be similarly unaffected by neural activity (Jensen and Killackey 1985; Dawson and Killackey 1987). These specificities then require an explanation in terms of selective affinities or markers.

The metrics magnification of different cortical representations of the same modality can be grossly different in a single species, and can differ among

species for a single cortical area (see Kaas, this volume; Allman, this volume). This diversity appears least in the primary sensory cortices, where it may be restricted by the anatomical spread of thalamic inputs, and where relative stability and uniformity may be important for more central representations. The regularities of the different magnifications in the different cortical areas seem unlikely to result from the chance operation of the correlation-sensitive mechansims on a uniform input. Rather, such regularities require either an innate, activity-independent map or the innate specification of the relative amounts of input from different topographic regions.

The detailed order of cortical maps, in contrast to the gross order, appears likely to be created and maintained by correlations in the patterns of discharge of neighboring input neurons (see von der Malsburg and Singer, this volume; Merzenich, this volume). Support for this notion comes from studies in which detailed map order is disrupted by disrupting activity, as in the regenerating retinotectal systems in fish and amphibia (e.g., Boss and Schmidt 1984). The order in both topographic and computational sensory maps is such that real world stimuli will produce simultaneous activation of inputs that should be represented at a single point on the cortical map. For example, a real sound source in two-dimensional space will simultaneously activate just the right combinations of interaural phase shifts and intensity differences at each frequency that are appropriate to code the particular location of the sound source in a cortical representation of acoustic space. As the sound source moves in space, these combinations change. A cortex that adjusts the strengths of initially rather widespread connections so as to maximize the moment-to-moment local correlation of activity will refine its map of auditory space to the optimal one (see von der Malsburg and Singer, this volume). In computational maps based on complex cues, as noted above, the map may not become fixed at an early age, since the appropriate combinations of cues change during normal growth and with aging. Hence, these maps require substantial capacity for refinement throughout life. It is difficult to conceive of any mechanism that might continually refine these maps other than one based on coincident activity. Singer proposed that one may regard the initial, activity-independent, coarse maps as "the frozen wisdom of evolution" in excluding possible input activities not worthwhile to correlate. The activity-dependent processes then operate only over possibilities constrained by these initial anatomical connections.

Andersen pointed out one limitation to the notion of map refinement by simple correlated activity in reference to monkey area MT. Here cells are excited by moving surfaces so that the correlated activities of neighboring points in the visual field are appropriate for map formation. But they are also excited by local *discontinuities* of motion; indeed, detection of such texture–motion borders may be one of the functions of this area. In this

case, activities of neighboring map points are anticorrelated. Palm pointed out that if the parameter mapped is not continuous, then it is also not clear what would be produced by a correlation-sensitive mechanism like that advocated above.

How Are Different Maps Matched to One Another?

Maps in cortical areas provide connections to and receive connections from thalamic and other cortical maps. These very long distance connections can be remarkably precise in connecting matching parts of two maps, but they are sometimes more widespread. Recent work on the projections of single vibrissa columns in the mouse barrel field shows the whole range of specificities: precise point-to-point projections to regions of the brainstem trigeminal complex, two opposite kinds of point-to-line projections (one barrel to the representations of the others in its rostrocaudal row in thalamic reticular and posterior nuclei, versus one barrel to the others in its dorsoventral arc in the thalamic ventrobasal nucleus and the superior colliculus), and five projections of each individual barrel to the entire vibrissal representations of S2 motor cortex, perirhinal cortex, the pons, the caudate putamen, and the contralateral barrel field (Hoogland et al. 1987; Walker et al. 1987).

How does the brain create such well-matched connections when they occur? Findings in the Siamese cat, among others, suggest that *multiple mechanisms* must be involved. In this animal, a retinal pigment defect causes an extra portion of each retina to project contralaterally, where it terminates in the part of the LGN that normally would serve the mirror-image visual field position for the ipsilateral eye. In the "Midwestern" pattern of thalamocortical projections, no adjustment of topographic map position is made to compensate for the abnormal retinogeniculate input. In the "Boston" projection pattern, thalamocortical fibers rearrange the normal map to insert an extra segment of ipsilateral field representation next to the 17/18 border. Some animals show a mixture of the two patterns. The following series of events could account for all of the results as follows: initially, rather widespread thalamocortical connections form a coarse map. Those fibers from abnormal ipsilateral field geniculate representations not extending to the 17/18 border region are fated to follow the Midwestern pattern and remain in cortex devoted to the periphery of the contralateral visual field. The thalamocortical fibers that initially reach the 17/18 border are organized into a representation of the ipsilateral visual field that abuts the representation of the contralateral vertical meridian. This abnormal insertion is regulated by the same activity-dependent correlation process (discussed above) that operates in normal map refinement.

The development of some corticocortical and callosal connections differs from that of the thalamocortical projections in that an initially very widespread "exuberant" projection seems to be the rule, followed by retraction of most of the axons and in some cases, death of the exuberantly projecting cells (Cowan et al. 1984). (Interestingly, the frontal lobe may be an exception to this general rule of exuberancy—true in occipital, temporal, and parietal cortex—for both its callosal and other corticocortical connections; Goldman-Rakic 1987). There is evidence that cell death eliminates projections from the inappropriate layers of area 17 to area 18, while axon elimination selectively removes projections from the upper layers so as to create the patchy pattern of association cells characteristic of the adult (Price and Blakemore 1985). One intriguing feature of the exuberant callosal projections and many of the homolateral corticocortical projections is that they appear never to make improper connections with cells in the cortical grey matter (Killackey and Belford 1979). Instead, while they ramify under extensive regions of cortex, they remain entirely within the subplate zone. In this region, there are many synaptic connections with and among a population of subplate neurons, most of which are destined to die (Chun et al. 1987). These largely transient subplate neurons are generated very early in embryonic development and contain numerous peptide neurotransmitters. It is possible that they may confer specificity on corticocortical (as well as thalamocortical) connections, instructing the afferent fibers which cortical areas are appropriate for growth into the grey matter.

It is widely believed that callosal connections form specific projections to bilaterally symmetric regions of the contralateral hemisphere. While this is certainly true for many projections at a gross level, these connections may not always be refined to precise mirror-symmetry within individual areas. This was fortunate, since the group was unable to devise a mechanism that might produce such a refinement.

PLASTICITY

Significance and Mechanisms of Plasticity in Development

Activity-dependent plasticity in the developing nervous system appears to be widespread as a mechanism for the refinement of connections. Such plasticity could plausibly operate through "Hebbian"-type synapses, in which correlated presynaptic inputs to the same postsynaptic cell mutually strengthen one another. The current state of knowledge about the cellular and molecular bases of such mechanisms has recently been reviewed (Changeux and Konishi 1986). During sensitive periods, such plastic changes

are possible, but they gradually become irreversible by the selective loss of inappropriate connections and the growth and/or strengthening of appropriate ones. The correlated activity needed to drive such mechanisms need not result from natural (or adequate) stimulation, since spontaneous discharges are highly correlated among neighboring cells in many systems (e.g., Mastronarde 1983). Indeed, Stryker presents evidence that spontaneous activity in the developing visual system is what normally drives the formation of ocular dominance columns in visual cortex (Stryker 1986).

Numerous phenomena in development appear likely to proceed by such a process. Examples are compensation for growth in the owl's auditory map of two-dimensional space (Knudsen and Knudsen 1985) and in the *Xenopus* tectal representation of the ipsilateral eye (Udin and Keating 1981), and the matching of independent maps, for example the visual and auditory representations in tectum. The present view of the way in which this mechanism operates is: (1) that the mechanism operates on multiple inputs to a common postsynaptic cell or group of cells; (2) that the statistical properties or patterns of activity are important; (3) that the response of the postsynaptic cell to its inputs is crucial; but that (4) the significant postsynaptic response may not be the classical Na^+-dependent action potential; (5) that the postsynaptic activation required for plasticity may have a threshold, and this threshold may involve local Ca^{2+} entry through NMDA-receptor channels; (6) that modulatory systems may also contribute to presynaptic or postsynaptic responses or their modification; and (7) that the plasticity evident in development may use mechanisms similar to those of long term potentiation demonstrated in adult hippocampus and cortex; but (8) that, during the sensitive period, unlike or to a greater extent than in the adult, the ineffective connections may be removed and the potentiated ones consolidated by selective growth (for review, see Singer 1987).

Stryker presented some of his laboratory's recent findings on mechanisms of plasticity in developing visual cortex of the cat (Reiter and Stryker 1987). Reiter and Stryker chronically inhibited neurons in a region of visual cortex by infusing the $GABA_A$ agonist muscimol; this treatment left afferent discharges unaffected. They then deprived muscimol-treated animals of vision in one eye for a week, producing the expected ocular dominance shift in favor of the open eye in untreated control regions. When the muscimol blockade was allowed to wear off, however, they found a consistent shift in favor of the less active *closed* eye in regions in which all spike discharge had previously been inhibited. Plasticity in opposite directions produced by identical afferent activity confirms the crucial role of the postsynaptic cell in this process. Furthermore, this experiment shows that the direction of plasticity—whether the more active eye is made relatively stronger or weaker—must depend on the postsynaptic membrane voltage or conductance. Finally, the plasticity in the blocked area clearly did not

require postsynaptic action potentials, since these had been blocked throughout the deprivation period. The mechanism revealed by this experiment would act in concert with the normal excitatory notion of "Hebbian" synapses to produce similar effects.

Van Essen presented some recent findings with Calloway (1987) that inactive motoneurons connecting to active muscle have an advantage over the active inputs. This is very different from a "Hebbian"-type mechanism, but it would be teleologically useful in matching motor unit size to recruitment order.

The mechanisms noted above have been studied and analyzed for relatively strong excitatory inputs. It is not yet clear how they would work to refine inhibitory inputs or very weak excitatory inputs. Some connections in the nervous system, such as the relatively weak 1A afferent to motoneuron synapses in the frog, appear to make highly specific connections without ever making widespread incorrect connections that must later be eliminated (Sah and Frank 1984).

Comparison of Plasticity in the Adult Nervous System to Plasticity in Development

Merzenich argued that it is probably erroneous to believe that adult and developmental plasticity are fundamentally different. He compared the plasticity of sound localization ability in owls to that in humans. An owl can compensate for a unilateral earplug during that period of its life when the head is growing (Knudsen and Knudsen 1986). By the end of this time, relatively late in life, the anatomical projection sustaining this plasticity has been refined to its adult state, and the latitude over which adjustments can take place is reduced from 20° to no more than a few degrees. In the human, plasticity in sound-localization ability, similar to that in young owls, persists throughout adult life. Does this phenomenon represent developmental or adult plasticity? We can think of only a single mechanism —based on detection of correlation or coincidence—to explain either plasticity. Therefore, the distinction between the two forms may lie only in the fact that in developmental plasticity, physiological changes are eventually followed up by the loss of relatively ineffective anatomical connections. These anatomical changes then restrict the latitude for further physiological change.

While this hypothesis has many attractive features, it has been difficult to verify with present experimental techniques. Its central notion is that the logic and some of the phenomena of developmental and adult plasticity are similar. Future work identifying the cellular and molecular mechanisms of one form of plasticity will allow a test of whether those mechanisms mediate the other form.

Merzenich reviewed the work presented in his background paper (Merzenich, this volume) that demonstrates: (a) that extreme differential use of a skin surface can cause its representation in somatosensory areas 1 and 3b to expand, causing neighboring areas to shift their cortical loci as well; and (b) that the shift in the cortical locus representing a given skin surface appears to be limited to about ± 700 μm (about $\frac{1}{2}$ to $\frac{1}{3}$ of the hand representation) in these areas. The distance limit for translocation of representations was sometimes greater, however, in the case of cortical lesions. In nearly all cases, altered maps continued to follow the normal rule relating receptive field size, scatter, and magnification, so that an expanded representation was arrayed in finer detail as well. This finding suggests that the altered maps are produced by the same mechanism that refines normal maps. The expansion of map representations by use may be viewed as a mechanism for adjusting cortical magnification in relation to the *activity* of afferent fibers as well as in relation to their number, which had been the traditional assumption.

Plastic changes in somatosensory map territories have previously been noted at subcortical levels, in the spinal cord, dorsal column nuclei, and in the thalamus. Nevertheless, several lines of evidence (reviewed in Merzenich, this volume) suggest that a major component of plasticity takes place at the thalamocortical level:

1) There is thought to be greater convergence and divergence of anatomical connections at this level than at some lower levels of the nervous system, so that thalamocortical axonal arbors may span 1–4 mm in monkey area 3b.

2) There are sometimes changes of up to 600 μm in the physiologically defined border between the adjacent hand and face representations in cortex, whereas the hand and face representations are absolutely segregated at thalamic and lower levels.

3) Plasticity appears to be powerfully affected by behavioral state, as indicated particularly by classical conditioning experiments; these phenomena are thought to be fundamentally cortical.

4) Cortical lesions of the monkey S1 hand area can cause loss of the hand representation in S2; this large cortical zone comes to be excited principally from the foot due to filling in by adjacent S2 representations, apparently as a consequence of a change in the effectiveness of the corticocortical projection from S1 to S2.

5) Cortical representations reorganize locally around a restricted cortical lesion. Taking all the evidence into account, the consensus was that we cannot yet conclude that the kind of plasticity evident in cortical maps does not also reflect various degrees of subcortical plasticity. However, in cases where subcortical plasticity is likely not involved, such as in shifts of the hand/face border, cortical plasticity may be nearly as great as in the questionable cases.

In these plasticity experiments, maps have been defined in the granular and sometimes in the supragranular layers. Less is known about the receptive fields of infragranular neurons or about lateral interconnections within the altered cortex. It would be unprecedented, however, for the extragranular representation to fail to overlap the granular layer receptive fields.

To date, work on these phenomena has concentrated on defining the conditions that produce plasticity and devising likely explanations for the logic of such plastic changes. A major challenge for the future of plasticity studies will be to define their precise locus, and cellular and molecular mechanisms. It is intriguing in this respect that GABA and its synthetic enzyme GAD, along with other molecules important to the function of the nervous system, are rapidly regulated up and down in adult monkey visual cortex by visual stimulation or deprivation, while similar changes do not take place in the LGN. A Ca^{2+}-calmodulin-dependent protein kinase, for example, shows increased activity in regions of cortex dominated by a deprived eye (Hendry and Kennedy 1986).

Is There Anything Distinctive About Cortical Organization?

It is taken as an article of faith that there is an information processing algorithm unique to cortex that is a product of the regularities in its architecture. Additional hypotheses have also been advanced:

1) Perhaps neocortex has no single function that could not be performed subcortically, but its advantage over other, more specialized areas is that it can process any set of neural data with a single format. Therefore, it can bring multiple convergent systems into a position in which they can interact by common principles.

2) Neocortex works by a cascade of information from area to area; in this respect, it is unlike thalamic relay nuclei, which do not communicate with one another.

3) Neocortex has expanded rapidly in phylogeny by creating multiple new areas. While mammals with very small cortices have behavioral capacities no more impressive than noncorticate animals, the capacity for rapid phylogenetic change may be the most important feature of cortex.

4) Neocortex appears to be necessary for representational memory, so that stored information no longer in evidence can affect behavior. While there is a capacity for plastic change at subcortical levels, most such changes resemble the parametric gain adjustment of, e.g., the vestibulo-ocular reflex more than they resemble representational memory.

5) Neocortex is the only part of the brain having output connections to nearly the entire neuraxis (with the possible exception of the vestibular system).

6) Neocortex matures very slowly in terms of synaptogenesis and even more slowly in terms of myelination. Species with greater amounts of neocortex exhibit greater neoteny. Perhaps this most human trait of extended childhood, with the opportunity for greater neural plasticity in adapting to the environment, is the most important neurobehavioral capacity made possible by neocortex.

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