Brain (1997), **120,** 701–722

REVIEW ARTICLE

The columnar organization of the neocortex

Vernon B. Mountcastle

The Philip Bard Laboratories of the Department of Neuroscience, and the Krieger Mind-Brain Institute, The Johns Hopkins University, Baltimore, USA

Correspondence to: Vernon B. Mountcastle, The Philip Bard Laboratories of the Department of Neuroscience, and the Krieger Mind-Brain Institute, The Johns Hopkins University, 3400 North Charles Street, Baltimore, MD 21218, USA

Summary

The modular organization of nervous systems is a widely documented principle of design for both vertebrate and invertebrate brains of which the columnar organization of the neocortex is an example. The classical cytoarchitectural areas of the neocortex are composed of smaller units, local neural circuits repeated iteratively within each area. Modules may vary in cell type and number, in internal and external connectivity, and in mode of neuronal processing between different large entities; within any single large entity they have a basic similarity of internal design and operation. Modules are most commonly grouped into entities by sets of dominating external connections. This unifying factor is most obvious for the heterotypical sensory and motor areas of the neocortex. Columnar defining factors in homotypical areas are generated, in part, within the cortex itself. The set of all modules composing such an entity may be fractionated into different modular subsets by different extrinsic connections. Linkages between them and subsets in other large entities form distributed systems. The neighbourhood relations between connected subsets of modules in different entities result in nested distributed systems that serve distributed functions. A cortical area defined in classical cytoarchitectural terms may belong to more than one and sometimes to several distributed systems. Columns in cytoarchitectural areas located at some distance from one another, but with some common properties, may be linked by long-range, intracortical connections.

Keywords: neocortex; columnar organization; modules; distributed systems; primates

Abbreviations: GFAP = glial fibrillary acidic protein; ICMS = intracortical microstimulation; IPSP = inhibitory postsynaptic potential; MT = medial temporal lobe

Definitions and general properties

The neocortex of human is a thin, extended, convoluted sheet of tissue with a surface area of ~2600 cm^2, and thickness 3–4 mm. It contains up to 28×10^9 neurons and approximately the same number of glial cells. Cortical neurons are connected with each other and with cells in other parts of the brain by a vast number of synapses, of the order of 10^{12}. The cortex is organized horizontally into six laminae, and vertically into groups of cells linked synaptically across the horizontal laminae. The basic unit of the mature neocortex is the *minicolumn,* a narrow chain of neurons extending vertically across the cellular layers II–VI, perpendicular to the pial surface (Mountcastle, 1978). Each minicolumn in primates contains ~80–100 neurons, except for the striate cortex where the number is ~2.5 times larger. Minicolumns contain all the major cortical neural cell phenotypes, interconnected in the vertical dimension. The minicolumn is produced by the iterative division of a small cluster of progenitor cells, a polyclone, in the neuroepithelium, via the intervening ontogenetic unit in the cortical plate of the developing neocortex.

Cortical columns are sometimes called modules, and I shall use these terms interchangeably. They are formed by many minicolumns bound together by short-range horizontal connections. Neurons of a column have certain sets of static and physiological dynamic properties in common, upon which other properties may be superimposed. Minicolumns are bound into columns by both cell-autonomous and secondary histogenetic influences. The pattern of growth

into the neocortex of afferent systems in an intermittent distribution is of critical importance. Columns only vary from 300 to 600 μm in diameter, even between species whose brains differ in volume by a factor of 10^3. Cortical expansion in evolution is achieved by expanding cortical surface area, with little change in thickness. This expansion is generated by an increase in the number of cortical columns, not in individual column size (Rakic, 1995*a*). Neuroepithelial proliferation, vertical gliophilic migration, and radial organization occur in all mammalian species. The primitive cortex of reptiles is generated similarly, although its laminar and columnar organization is less pronounced.

Columnar organization allows for intermittently recursive mapping, so that several variables can be mapped to the two dimensional surface of the neocortex. This is clear in the primary sensory receiving areas of the brain, and appears likely to be so for all areas in which systematic maps have been observed (Mountcastle, 1957).

A cortical column is a complex processing and distributing unit that links a number of inputs to a number of outputs via overlapping internal processing chains. Cortical efferent neurons with different extrinsic targets are partially segregated; those of layers II/III project to other cortical areas, those of layers V/VI to subcortical structures. This suggests that the intracolumnar processing operations leading to those different output channels may differ in some fundamental way.

The ontogenesis of the neocortex

Cortical neurons are generated in the pseudostratified, columnar epithelium lining the ventricular and subventricular zones of the developing forebrain. They migrate from their loci of generation to their final positions in the cortex, beginning with the first asymmetric division (Rakic, 1988*b*). Neurons differentiate further after migration, and become arranged in cortical layers where they form efferents and receive extrinsic connections characteristic of the layer. They also develop trans-laminar intrinsic connections that form the network basis of the columns of the mature cortex.

The major phenotypic characteristics of cortical cells are specified early in development. From about embryonic day 40 in the monkey, just before neurogenesis of the cortex begins, both neural [glial fibrillary acidic protein (GFAP) negative] and glial (GFAP positive) precursor cells are present in the ventricular and subventricular zones; they persist throughout the period of active neurogenesis (Levitt, *et al*., 1981).

The earliest event in the formation of the neocortex is the generation of a horizontal layer called the preplate composed of a superficial sublayer of the earliest corticopetal nerve fibres, and the earliest generated neurons. These are the Cajal–Retzius cells and a lower layer of cells that will become the subplate. Subsequent waves of migrating neurons form the cortical plate in an inside to outside temporal sequence creating the future layers VI–II of the mature cortex. The cortical plate is inserted into the preplate, splitting it into an outermost marginal zone, the future layer I, and a lower, thick and partially transient band called the subplate.

Neurons migrating to the neocortex move along radial glial fibres that form palisades linking the neural epithelium and the developing cortical plate (Rakic, 1972). The time of generation of a neuron determines its final laminar (vertical) position in the mature cortex precisely (Rakic, 1974). The tangential (horizontal) spatial position of origin of more than 90% of the neurons in the neural epithelium determines the final tangential position of a cell in the mature neocortex. Neurogenesis begins in the macaque monkey at about E40 and ends at around E100 in the 165 day gestational period (Rakic, 1974). It is probable that humans acquire their full complement of neocortical neurons during the middle trimester. Projection and intrinsic neurons both differentiate in sequence from deep to superficial layers, just as the layers are formed in migration. The pyramidal cells lead the intrinsic interneurons in the emission and growth of axons and dendrites, and in forming synaptic contacts.

Generation of cells in the proliferative ventricular zone neuroepithelium

The neuroepithelium of the cerebral vesicle consists, in its early stages, of a single line of columnar epithelial cells, each of which stretches over the short distance from the ependymal surface of the neural tube to the pia, attached by endfeet to both surfaces (Sidman and Rakic, 1973). The three phases of interphase of the cell cycle (G1, S and G2) occur with the nuclei in the mid-position of the cells. When cells enter the prophase of mitosis they withdraw their processes and assume a globular form, and their nuclei move toward the ventricular surface. After cell division is complete, the nuclei of daughter cells move away from the ventricular surface, and the cells once again extend processes to each surface, and initiate new cycles.

Phenotypic specificity is restricted at this stage, so that just before the onset of asymmetric division and migration the majority of progenitor cells can each generate either pyramidal neurons, nonpyramidal neurons, astrocytes or oligodendrocytes, but only one of these (Parnavelas *et al*., 1991). This conclusion is strengthened by the discovery that cells of the neuroepithelium compose non-overlapping populations with immunoreactivity to either GABA or glutamate, respectively the inhibitory and excitatory synaptic transmitters expressed by cortical neurons. They are therefore committed progenitor cells for the pyramidal (glutaminergic) and nonpyramidal (GABAergic) neurons of the mature cortex.

The radial unit hypothesis and the ontogenetic unit of the neocortex

Angevine and Sidman (1961) discovered the inside to outside sequence of formation of the cortical plate/neocortex using

the ^{3}[H]thymidine labelling method. This general pattern of migration and cortical plate formation has since been observed in a number of mammalian species, and is particularly sharp in primates (Rakic, 1974). The sequence and the settling pattern is prominent in foetal human brains of different ages, suggesting that a similar pattern occurs in man. The pathways followed in migration and the temporal sequence of events in the foetal monkey brain have been defined in an extensive series of experiments by Pasko Rakic (Rakic, 1972, 1974, 1988*a*, *b*, 1990, 1995*a*; Kornack and Rakic, 1995), culminating in the *radial unit hypothesis*. The general idea is illustrated in Fig. 1. Migration of immature neurons from the germinal epithelium to the cortical plate is mainly radial and mainly gliophilic. Following the last mitotic division, immature neurons of the ventricular and sub-ventricular zones attach to an adjacent set of glial guide fibres. Neurons generated serially in time at the same locus in the germinal epithelium migrate sequentially along the same or adjacent sets of glial guide fibres, and settle in the inside to outside pattern in a radial column. Neurons of this radial column form an *ontogenetic unit, the fundamental building block in the developing neocortex* (Rakic, 1988*a*). Thus the basic columnar organization of the cortex reflects its mode of generation (Mountcastle, 1978).

The surface area and thus the size of any neocortex is determined by the number of its ontogenetic units, set by the number of symmetric divisions of progenitor cells in the neural epithelium before migration begins (Rakic, 1988*a*). One extra symmetric division will double the number of ontogenetic units, and thus double the area of the neocortex. The number of cells in each ontogenetic unit is determined by the number of asymmetric divisions of its progenitor cells, beginning with the first at the onset of migration. One additional asymmetric division will add only one cell from each of the several progenitor cells in the relevant polyclone in the neuroepithelium. Expansion of the neocortex in evolution is thought to depend upon mutational change in the number of symmetric divisions in regional zones of the neuroepithelium (Rakic, 1995*b*). An increased number of ontogenetic units interacts with other factors in the creation of new cortical areas, and their evolution through natural selection.

Mosaicism in the ventricular zone

Each proliferative unit in the ventricular zone of the monkey consists of 3–5 stem cells, a number that gradually increases to 10–12 stem cells during development; the units are separated by glial septa (Rakic, 1988*b*). The rate of neuron production varies between adjacent areas of the neuroepithelium, e.g. by >2:1 between the ventricular zone producing area 17 and the adjacent area 18 (Dehay *et al*., 1993). This difference is reflected in the mature cortex by a relatively large number of neurons per unit area of cortical surface in area 17 compared with all other neocortical areas. Cortical parcellation is thus, to a certain degree, set at the level of the ventricular zone, an idea supported also by studies in transgenic mice (Cohen-Tannoudji *et al*., 1994; Soriano *et al*., 1995) and in chimeric mice (Natkatsuji *et al*., 1991). It is also supported by the heterogeneous expression of oncogenes within the ventricular zone. The peptides coded are concentrated in repetitive clusters of radial glial fibres, which form a transient columnar organization within the ventricular zone during the period of maximal neuron production (Johnson and Van der Kooy, 1989). During the early phase of neurogenesis the progenitor cells are coupled together by gap junctions into local clusters (Lo Turco and Kriegstein, 1991). Recent evidence obtained in studies with the retroviral transfer method supports the radial unit hypothesis (Reviewed in Rakic, 1995*b*).

The dual pattern of migration

The migratory course taken by the minority of neurons not following the direct radial pathway to the developing cortical plate has until recently been a matter of some uncertainty. O'Rourke *et al*. (1992) used time-lapse confocal microscopy to observe migration in living slices of developing rodent cortex; 87–90% of the cells observed moved radially along glial guide fibres, as expected. However, the remainder turned aside from this path in the intermediate zone to move tangentially for distances that varied from cell to cell, before resuming radial migration. The problem has been studied further by a number of investigators using as a cell vector a replication-incompetent retrovirus labelled with the reporter gene, *Escherichia coli* B-galactosidase (lac Z) whose product can be identified histochemically (Price *et al*., 1987; Sanes, 1989; Cepko *et al*., 1990; Luskin, 1996). The virus particles are injected into the ventricles of the living rat embryo where they are incorporated into the DNA of dividing cells, and appear undiluted in 50% of their descendants. They can be identified at any later time by histochemical methods. Luskin *et al*. (1993) found in rodents that clonally related neurons were predominantly arranged radially along the migratory pathway and that after migration the neuronal clones remained radially arranged, while cells of glial clones were dispersed tangentially. This is particularly explicit in the convoluted monkey cortex where the majority of clonally related cells, which have migrated from long distances, become arranged in a remarkably radial fashion (Kornack and Rakic, 1995).

Walsh and Cepko (1992, 1993) in similar experiments, injected a library of ~100 genetically identifiable retroviruses, in increasing dilution in different experiments in rats. They observed what they interpreted to be widely dispersed clonal derivatives in the cortical plate. More recently, Walsh and his colleagues have repeated the retroviral library experiment, now combined with a method for identifying cell phenotypes (Reid *et al*., 1995). They have observed that the laterally displaced clones were not produced by tangential migration between the germinal epithelium and the cortical plate, but by a lateral displacement of some progenitor cells within the ventricular zone, an observation made with other methods

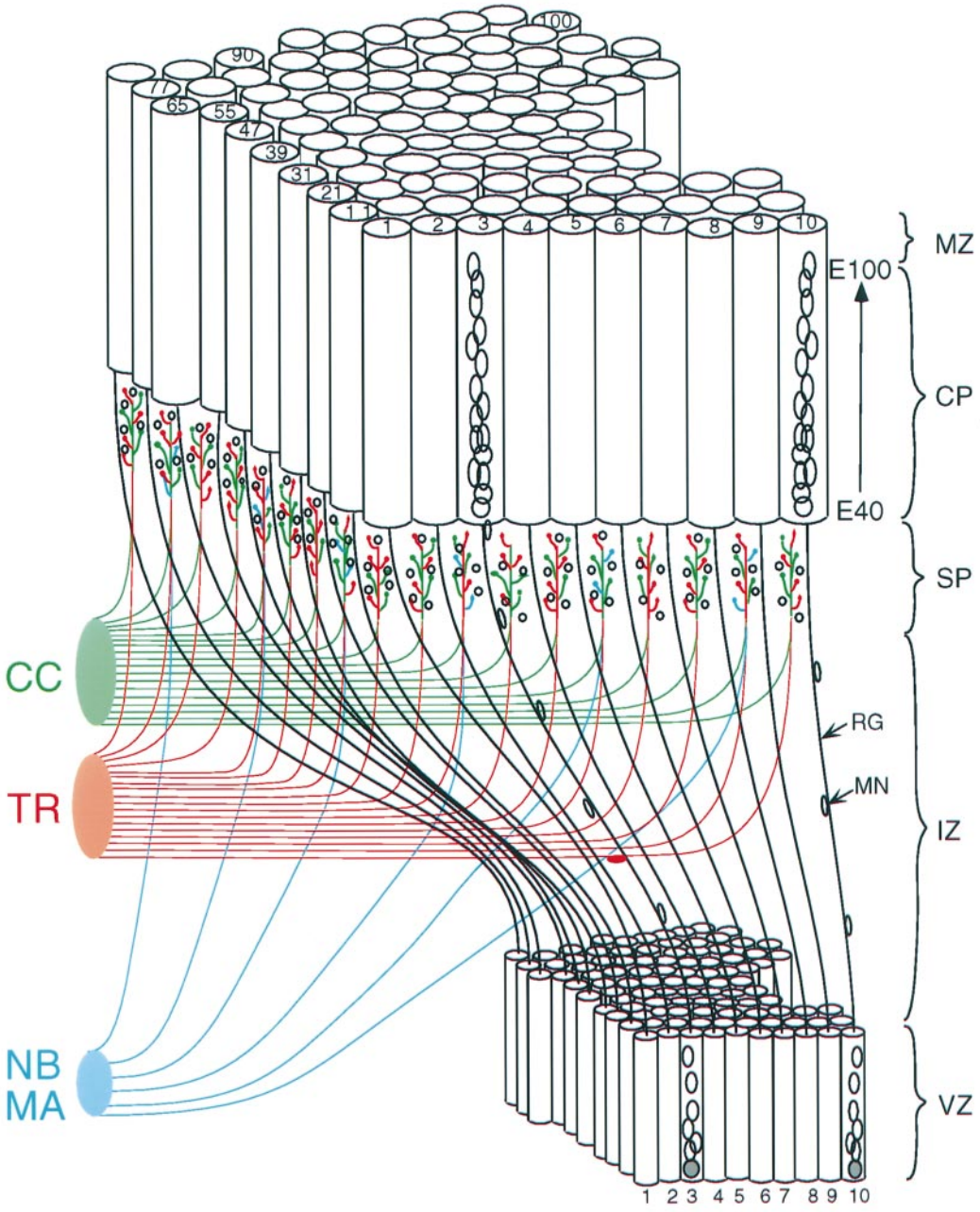

Fig. 1 A three-dimensional illustration of the developmental events occurring during early stages of corticognesis in the monkey. The drawing illustrates radial migration, the predominant mode of neuronal movement, which in primates underlies its columnar organization. After their last division, cohorts of migrating neurons (MN) traverse the intermediate zone (IZ) and the subplate (SP) where they may interact with afferents arriving sequentially from the nucleus basalis (NB), the monamine nuclei of the brainstem (MA), from the thalamic radiation (TR), and from several ipsilateral and contralateral corticocortical bundles (CC). Newly generated neurons bypass those generated earlier, which are situated in the deep cortical layers, and settle at the interface between the developing cortical plate (CP) and the marginal zone (MZ). Eventually they form a radial stack of cells that share a common site of origin but are generated at different times. Although some, presumably neurophilic, cells may detach from the cohort and move laterally, guided by an axonal bundle, most are gliophilic, have affinity for the glial surface, and obey the constraints imposed by transient radial glial (RG) cell scaffolding. This cellular arrangement preserves the relationship between the proliferative mosaic of the ventricular zone (VZ) and the corresponding map within the SP and CP, even though the cortical surface in primates shifts considerably during the massive cerebral growth in the mid-gestational period. The numerals refer to corresponding units in the VZ and CP. (From Rakic, 1995, with permission from Elsevier Siem Publishers.)

by Fishell *et al.* (1993). This lateral migration of progenitor cells within the ventricular zone was followed by the radial migration to the cortical plate of the cells produced by asymmetric division of each progenitor cell at its new location. This mechanism appears to account for the earlier interpretation made by Walsh and Cepko (1992) of a 'widespread' dispersion of neuronal clones in the developing rodent cortex.

Recently this method has been used to follow the fate of clonally related cells in the primate cortex where laminar and columnar organization is more pronounced. Kornack and Rakic (1995) injected into the ventricles of foetal monkeys a mixture of two replication-incompetent, lac-Z labelled retroviruses. One of these preferentially labelled nuclei and the other cytoplasm in 50% of descendent cells. Two modes of neuronal migration were discovered. In the radial pattern, clonal groups of neurons occurred in strict radial alignment extending across several cortical laminae, the number of laminae depending upon the stage of corticogenesis at which injections were made. The results provided further evidence that the several phenotypes observed in mature cortical minicolumns are each derived from one of a small group of progenitors forming a polyclonal group in the ventricular zone. All migrating neurons reach a vertically aligned distribution after migrating along a common glial pathway. Other neuronal clonal groups were arrayed in a horizontal pattern in rows, each row within a stratum of a single cortical layer, parallel to the pial surface. Each neuron in such a row was separated from the next in line by 40–150 μm. The horizontal pattern was spatially limited, and in no instance was a wide tangential dispersion observed. Kornack and Rakic (1995) propose that the radial arrays are produced by successive asymmetric division of progenitor cells; the neurons of the vertical arrays are produced sequentially. Neurons in the horizontal rows are, by contrast, produced from stem cells that, after symmetric division from a single progenitor move laterally for set distances within the ventricular zone, and then produce, by asymmetric divisions, neurons that migrate radially to their common laminar positions. The full implications of this new discovery have not yet evolved. It is certain that the radial arrays compose the ontogenetic units/minicolumns of the mature cortex. It is not yet known which cell types compose the horizontal arrays, nor what their functional significance may be in the adult cortex.

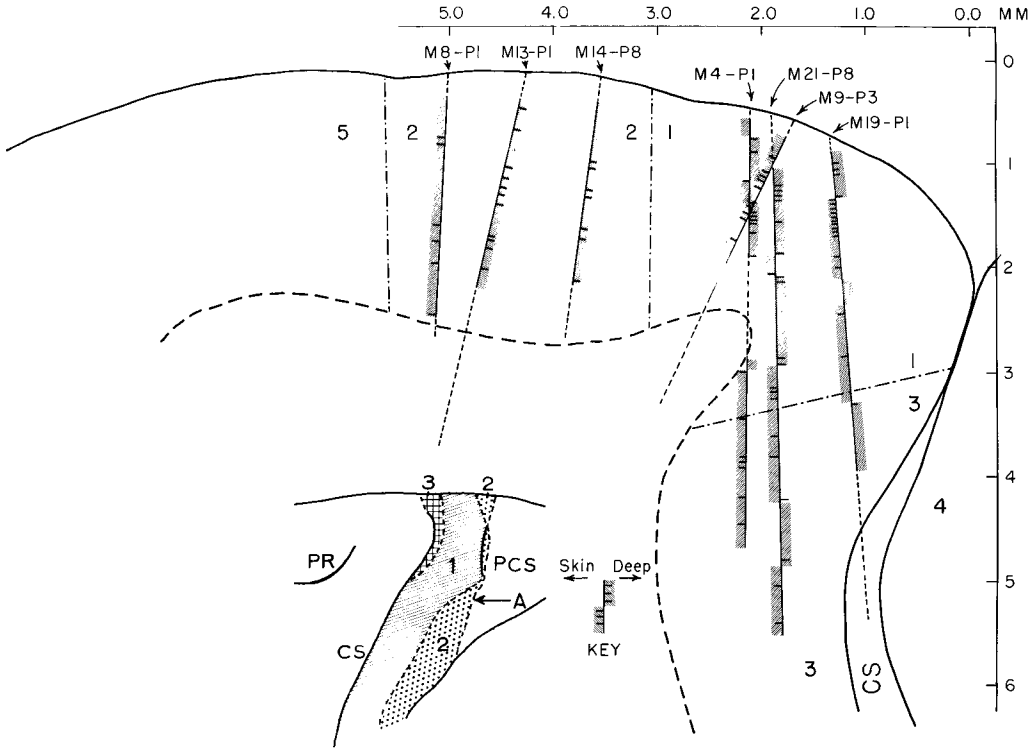

Fig. 2 Reconstructions of the tracks of several microelectrode penetrations made into the postcentral gyrus of anaesthetized monkeys. All were placed within 1 mm of the plane marked A on the inset drawing, which shows the cytoarchitectural areas of the monkey somatic sensory postcentral gyrus (CS = central sulcus; PCS = postcentral sulcus; PR = precentral sulcus). Penetrations made perpendicular to the cortical surface and passing down parallel to its 'vertical' axis encountered neurons which were all of the same modality type. As the sites of penetrations were located more anteriorly in areas 1 and 3 where the vertical axis rolls, alternating groups, or blocks, of neurons with different modality properties were encountered more frequently. In area 3 on the posterior bank of the central sulcus the electrodes passed across the cortical columns. Experiment and penetration numbers are indicated above each track. (From Powell and Mountcastle, 1959.)

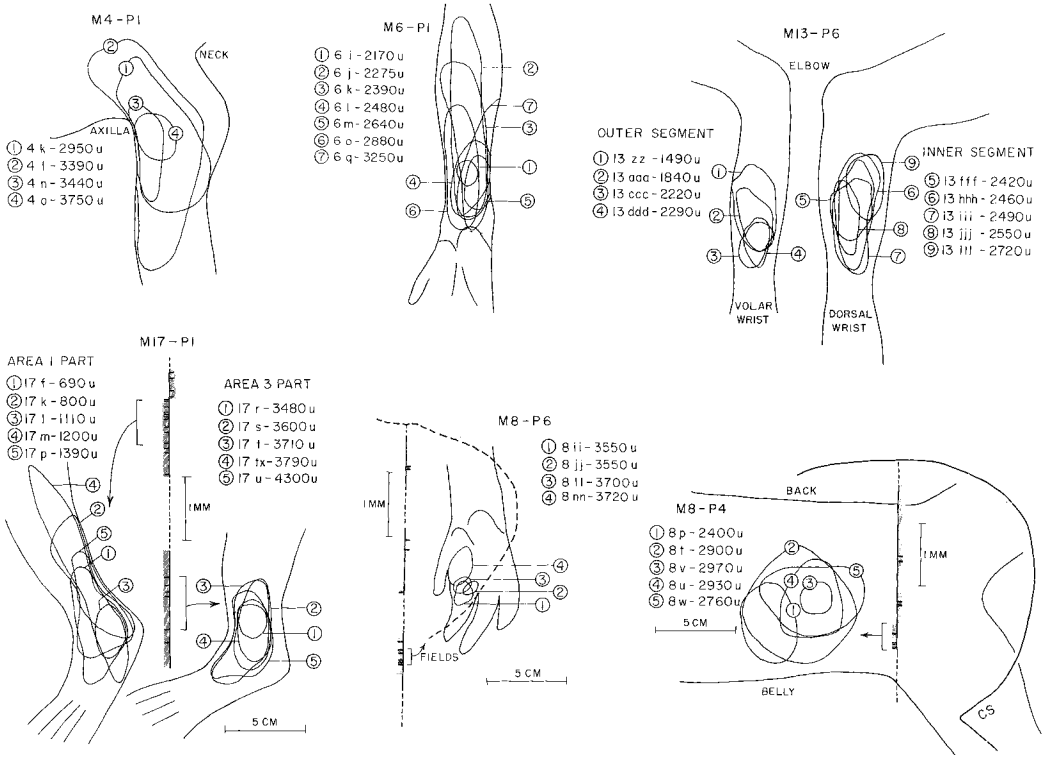

Fig. 3 Drawings of the cutaneous receptive fields of neurons studied in microelectrode penetrations made normal to the pial surface of the postcentral somatic sensory cortex of anaesthetized monkeys. The receptive fields are nearly superimposed, with some variation in total field size and shape. Their central loci of maximal excitability were relatively invariant (not shown). Penetrations are identified as in Fig. 2. Receptive fields are numbered and correlated with cortical depth in microns. (From Powell and Mountcastle, 1959.)

The columnar organization of heterotypical cortical areas

The somatic sensory cortex

Evidence for neocortical columnar organization was obtained in single neuron electrophysiological studies of the somatic sensory cortex in anaesthetized cats and monkeys (Mountcastle, 1957; Powell and Mountcastle, 1959). Microelectrode penetrations made normal to the pial surface encounter neurons in each cellular layer with similar properties of place and modality. Penetrations parallel to the pial surface and crossing the vertical axis of the cortex pass through 300–500 μm sized blocks of tissue in each of which neurons with identical properties are encountered. Sharp transitions are observed from a block with one set of properties to the adjacent block with different properties (Fig. 2). The defining property for place is the peripheral receptive field, the zone on the body surface within which an adequate stimulus evokes a response of the cortical cell (Fig. 3). The word 'modality' is used here in a special sense, to describe the nature of those adequate stimuli and the rate of adaptation to steady stimuli. The modality of a set of cortical neurons can frequently be matched with a particular set of primary afferent fibres, e.g. the quickly adapting cutaneous neurons of the somatic sensory area in the monkey with receptive fields on the glabrous skin of the hand are driven by afferent impulses from the quickly adapting Meissner afferents; the slowly adapting cortical neurons by input from the slowly adapting Merkel afferents, Pacinian cortical neurons by input from Pacinian afferents. Several less precisely defined sets of neurons in the somatic cortex are activated by receptors that lie in the deep tissue beneath the skin.

Columnar organization is maintained, in part, by dynamic physiological mechanisms. In some cortical areas the defining properties for columns are almost wholly set by afferent inflow, like those of place and modality defined above. Properties constructed by intracortical processing predominate in other cases. The degree to which afferent inflow or intracortical constructions set columnar defining properties varies between cortical areas. It is only in a region like the koniocortex of area 3b that the static properties set by inflow predominate. The directionally selective columns of areas 1 and 2, for example, are set by a combination of the static properties of place and mode, combined with a result of intracortical processing, the directional selectivity.

It was a major discovery that there are four separate somatotopic maps of the body form in the postcentral somatic sensory area in primates, one each in areas 3a, 3b, 1 and 2.

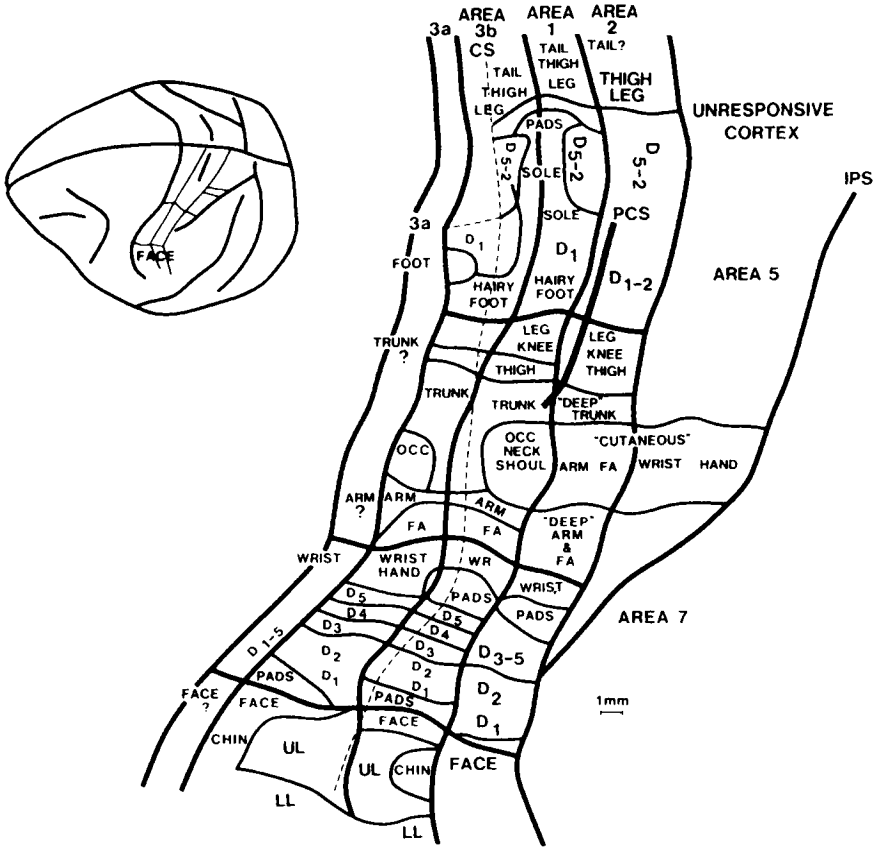

Fig. 4 The somatotopic representation of the contralateral body surface in the four cytoarchitectural areas of the postcentral somatic sensory cortex of the macaque monkey. CS = central sulcus; IPS = intraparietal sulcus; FA = forearm; LL = lower lip; UL = upper lip; D1–D5 = digits of the contralateral hand. (From Kaas and Pons, 1988, with permission from Alan Liss, New York.)

The map shown in Fig. 4 serves to orient the following descriptions of place and modality as columnar defining characteristics. Cortical maps of the body surface are not continuous representations, but collections of regions, each of which is devoted to an afferent inflow from some body part. While the map traces out the general sequence of body parts, some adjacent cortical regions map widely separated body parts, and some adjacent body parts are mapped to separated cortical zones.

Place specificity is a defining characteristic of columns in the somatic sensory cortex

The minicolumn-columnar organization of the somatic sensory cortex for place has been confirmed in microelectrode mapping experiments in cats and monkeys (Favorov and Whitsel, 1988*a, b*; Favorov, 1991). Figure 5A shows the superimposition of the receptive fields determined in a penetration made parallel to the cortical vertical axis, and Fig. 5B gives the result for a penetration slightly off the vertical axis, in which an abrupt shift in receptive field location occurred in mid-course. The spatial shift indicates movement of the electrode from one column to an adjacent one whose neurons are activated from differently located

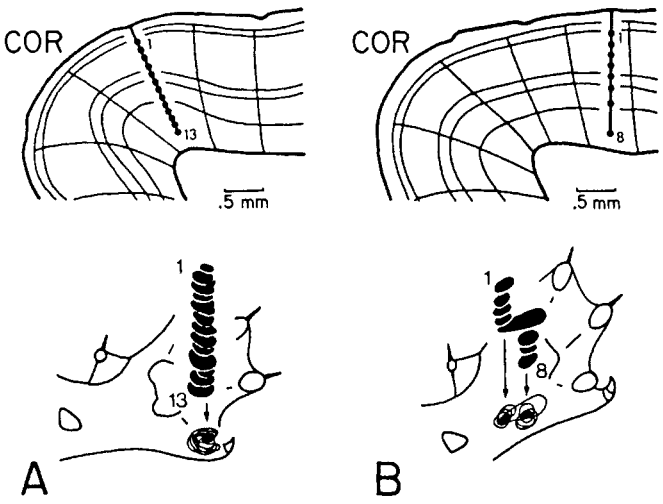

Fig. 5 Location of the peripheral receptive fields of neurons observed in microelectrode penetrations made nearly parallel to the vertical axes of the somatic sensory cortex of the cat. The orientation of the radial cords of cells are indicated by the thin lines. (**A**) The cells observed in this penetration were all related to identical receptive fields. (**B**) This penetration passed from one column to the adjacent one, with a small but abrupt shift in the spatial locations of the neurons encountered. (From Favorow, 1991, with permission from MacMillan.)

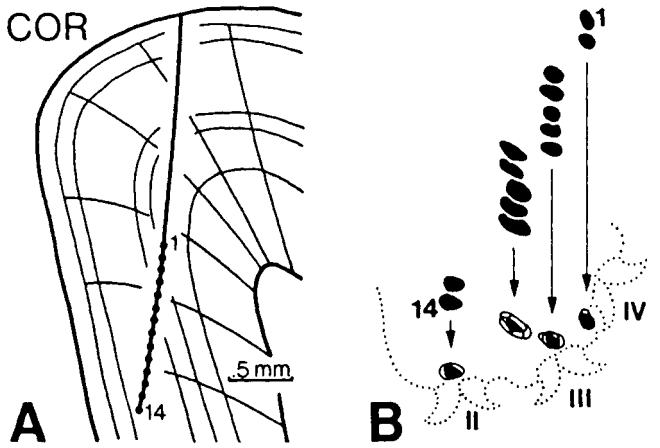

Fig. 6 Location of the peripheral receptive fields of 14 neurons observed in a microelectrode penetration made tangentially through the somatic sensory cortex of the cat. (**A**) The electrode passed nearly parallel to the pial surface. (**B**) There are three abrupt shifts in receptive field locations, as the electrode traversed a series of adjacent columns. (From Favorow, 1991, with permission from MacMillan.)

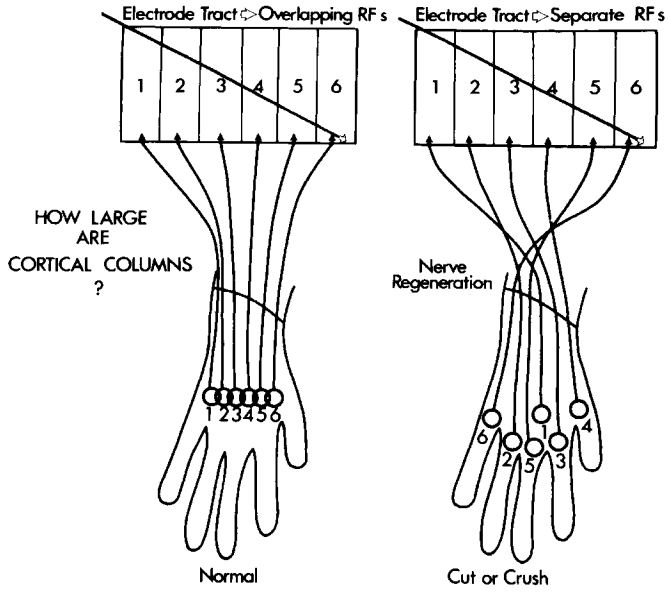

Fig. 7 A nerve-regeneration experiment in the monkey provides evidence for columnar organization of the somatic sensory cortex and an estimate of the smallest identifiable functional element, the cortical minicolumn. *Left*: a recording microelectrode has passed nearly parallel to the pial surface of the cortex, through a region of neurons with the same cutaneous modality property. Adjacent minicolumns are related to adjoining and overlapping peripheral receptive fields, and the transitions between minicolumns then pass unnoticed. *Right*: results obtained in the same animal after section and resuture of the contralateral median nerve, and the mis-direction of the regenerating bundles of nerve fibres now innervating the glabrous skin of the hand. Sudden displacements of the locations of the peripheral receptive fields occur at intervals, within the cortex, of ~40–60 μm, revealing the minicolumns. (From Kaas *et al*., 1981, with permission from MIT Press.)

receptive fields. Such transitions occur with electrode movements of 40–50 μm. Figure 6 shows the three transitions observed in a penetration made across the vertical axis of the cortex; the receptive fields shift abruptly with each transition from one module to another.

Favorov and Diamond (1990) then carried out experiments in which many penetrations were made in closely spaced grids. The results allowed them to define the shape of the cortical column as roughly hexagonal, usually surrounded by six other columns, and doubly convex in the long dimension, with a width of 300–400 μm. Such a column contains ~80 minicolumns of 50–60 μm in diameter. It is discrete and homogeneous; the receptive fields of neurons in the minicolumns of a column shift about the columnar common locus, without topographic progression.

A nerve regeneration experiment in monkeys provides further evidence for the minicolumnar composition of cortical modules (Kaas *et al*., 1981). An initial recording experiment was made with microelectrodes passed tangentially across the hand area of the postcentral somatic cortex. Figure 7 (*left*) shows that over a considerable distance neurons of the same modality type were observed, related to gradually shifting, overlapping receptive fields. The median nerve was then sectioned, resutured, and time allowed for re-innervation of the skin. The recording experiment was then repeated, with the result shown in Fig. 7 (*right*). Now, instead of a smooth progression of overlapping receptive fields, zones of cortex of 40–60 μm dimension were traversed within which receptive fields were identical, but there were sharp shifts in receptive field location between adjacent zones. This was attributed to the misdirection of reinnervating peripheral nerve bundles. A misdirected nerve bundle, innervating a new and abnormal location of skin, then imposed that new receptive field upon the entire minicolumn of neurons to which it projected. This experiment reveals a minicolumn of a dimension comparable to that of the embryologic units, the forerunners of minicolumns in the adult cortex.

Modality specificity is a defining characteristic of columns in the somatic sensory cortex

Each set of modality specific primary afferent fibres entering the dorsal column–medial lemniscal system engages synaptically populations of neurons it thus endows with those same modality properties. Those mode-specific populations are successively linked from the dorsal column nuclei to the ventrobasal complex of the thalamus, and from thence to the somatic sensory area of the cerebral cortex (Mountcastle, 1984). This general conclusion is drawn from many extracellular microelectrode recording experiments in cats and monkeys, made under a variety of experimental conditions. It is unlikely that a subthreshold convergence has been missed, for the modality specificity of somatic cortical neurons is unchanged when they are depolarized to near-threshold levels with the excitatory transmitter glutamate released iontophoretically close to the cell

under observation (Dykes *et al*., 1984; Alloway and Burton, 1986, 1991). Nor is any cross-modal convergence revealed after block of GABA mediated inhibition. Divergence and convergence occur at each level of the system for place but not for modality. Cross-modal convergence occurs in other ascending components of the somatic afferent system, and in their forebrain targets as well. Modality specificity at the postcentral level in primates is expressed in modality pure columns, and modal specificity is the second defining property for columns in this cortical area.

Each of the four postcentral maps of Fig. 4 receives its major input relayed largely from one or two of the modality specific sets of primary afferent fibres. Area 3a neurons are driven from muscle afferents. Areas 3b and 1 each receive inputs from both the rapidly and the slowly adapting sets of cutaneous afferents; area 2 receives inputs largely from joint afferents, although it also contains a complete representation of the cutaneous surface of the hand. If a single area receives input from more than one set of primary afferents, neurons of the different modality properties are segregated within the area. For example, the rapidly and slowly adapting cutaneous neurons of areas 3b and 1 are segregated to different cortical columns. Sur *et al*. (1984) mapped these postcentral areas in several species of monkeys to correlate modality, place and area. The two modality classes were each clustered in bands oriented in the antero-posterior direction, intersecting the medio-lateral line of the representation of the body form. Figure 8 (*left*) shows that the receptive fields of the rapidly and slowly adapting neurons in different modality but identical topographic zones are virtually superimposed. This intermittently recursive mapping of modality onto place is further illustrated in Fig. 8 (*right*). Columnar organization based on place and modality specificity has also been shown for the second somatic area in both anaesthetized and waking monkeys (Whitsel *et al*., 1969).

Metabolic and blood flow studies of the somatic sensory cortex

Local mechanical stimulation of the body surface evokes modular patterns of increased metabolic activity in the contralateral somatic sensory cortex in both cats and monkeys. The pattern consists of many separated elongated regions (0.5×1.5 mm), as if several adjacent columns were activated by the peripheral stimuli, for these metabolically defined modules are larger than those defined electrophysiologically. These linked sets of modules are bordered by zones of decreased uptake due to intracortical inhibition, for the metabolically labelled zones spread and fuse when GABA-mediated intracortical inhibition is blocked with bicuculline. Correlated metabolic and electrophysiological studies show that identical stimuli evoke both the patch of increased metabolic activity and the activity of neurons within it (Juliano and Whitsel, 1987). The increase in metabolism is not uniform within a module; it occurs in narrow, translaminar columns separated by narrow zones of decreased activity, with a spatial period of 18–33 μm (Tommerdahl *et al*., 1993). This result demonstrates active minicolumns in the sensory cortex, and supports the general idea that cortical modules are composed of groups of minicolumns. Such a radially oriented periodic variation of 2-deoxyglucose uptake around the background level was also observed in regions of the somatic cortex not activated by the peripheral stimuli used. The spatial variation was similar to that observed in optical density measurements of Nissl stained sections of the sensory cortex, a reflection of the vertical cording of neuronal cell bodies in this region.

The columnar organization of the visual cortex.

The primary visual cortex of mammals, variously called the striate cortex, area 17, or area V-1, is the most intensively studied structure in the mammalian brain. This tide of research was set in motion in the early 1960s by the work of several investigators, especially by that of David Hubel and Torsten Wiesel, of Peter Bishop and of Otto Creutzfeldt. Hubel and Wiesel established in their first experiments, and elaborated fully in many that followed, that columnar organization in the primate V-1 is defined by the neuronal properties of ocularity and place imposed by geniculate input, and by orientation specificity generated by intracortical processing. Neurons in V-1 are preferentially driven by stimuli delivered to one eye or the other, from a particular locus in the visual field, and they are selectively sensitive to short straight line visual stimuli at particular, limited angles of orientation. These properties are more or less constant from neuron to neuron encountered in microelectrode penetrations made normal to the pial surface. By contrast, these properties change from locus to locus in tangential penetrations made nearly parallel to the pial surface. The neurons studied in such tangential penetrations vary systematically in ocularity and orientation selectivity. This latter property shifts in stepwise fashion with electrode movements as small as 20 μm, and may even change from one vertical chain of cells to the next. A full sequence of 180° is covered in distances that vary from 500–750 μm. A set of such minute orientation columns is termed an orientation hypercolumn.

The property of ocular dominance of these same neurons varies in such a way as to reveal adjacent ocular dominance columns, one for each eye. A pair of such columns contains neurons grading systematically from full dominance by one eye to full dominance by the other, with all gradations in between; such a pair was defined as an ocular dominance hypercolumn. Hubel and Wiesel conjectured from measures of the tangential dimensions of the two classes of hypercolumns, and of the point spread, that double sets of such hypercolumns are sufficient to process all the input from a local region in the visual field, with minimal overlap in regions of the visual field served by adjacent sets of hypercolumns. These findings were summarized in their 1977

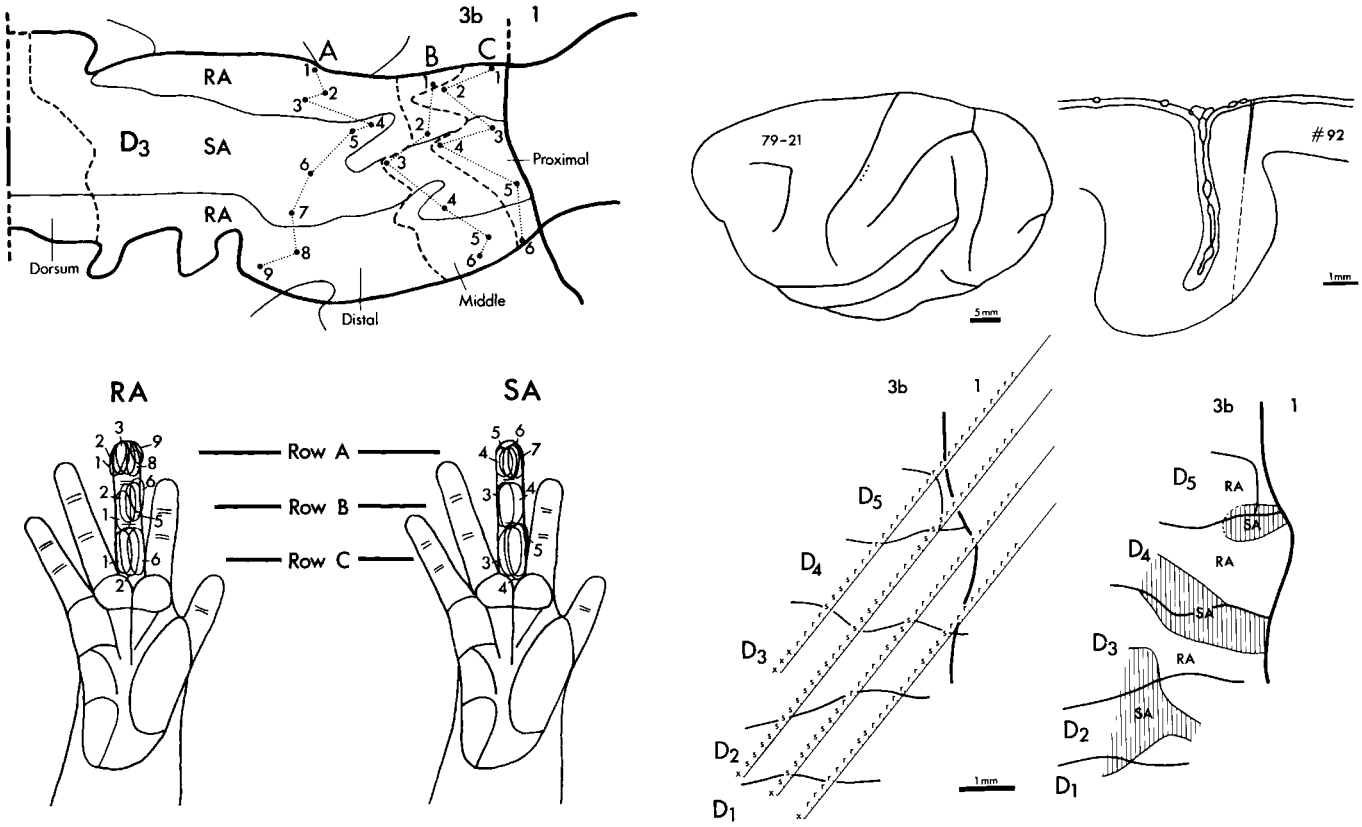

Fig. 8 *Right*. Distribution of recording loci in the postcentral gyrus of a macaque monkey at which slowly adapting (SA) or rapidly adapting (RA) responses were evoked by stimulation of the contralateral fingers, D1–D5. Points of entry of four microelectrode penetrations are shown on the outline drawing of the brain, and a partial reconstruction of one of the electrode tracks on the section drawing. *Left*. Receptive fields for three rows of recording sites across the RA and SA bands in the representation area for the 3rd digit of the contralateral hand in the postcentral gyrus of a macaque monkey. There is overlap of the receptive fields of the two classes of neurons. (From Sur *et al*., 1984, with permission from the American Physiological Society.)

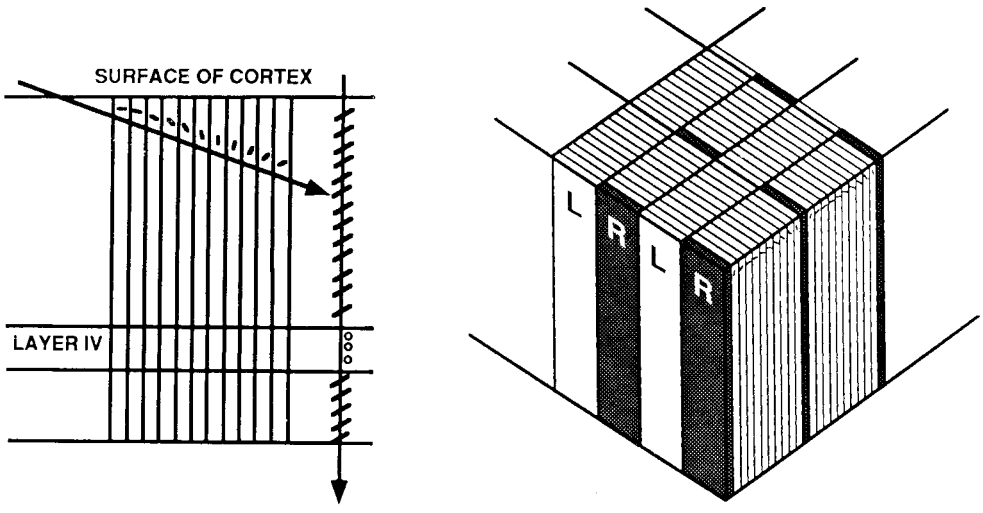

Fig. 9 *Left*. Organization of the striate cortex for orientation preferences, from the work of Hubel and Wiesel. For penetrations made perpendicular to the surface of the cortex the preferred orientation remains almost constant, except for layers IVa and IVc. For penetrations made almost parallel to the cortical surface, the preferred orientation rotates linearly with distance in sequences of 0.5–1.0 mm. Linearity is broken at longer intervals by reversals in the direction of rotation. *Right*. The Hubel and Wiesel model, generated from the inference that slightly rotated orientation preferences may be organized in stacks of parallel slabs, with spacing between slabs of ~700 μm. (From Blasdel, 1992*a*, with permission from Oxford University Press.)

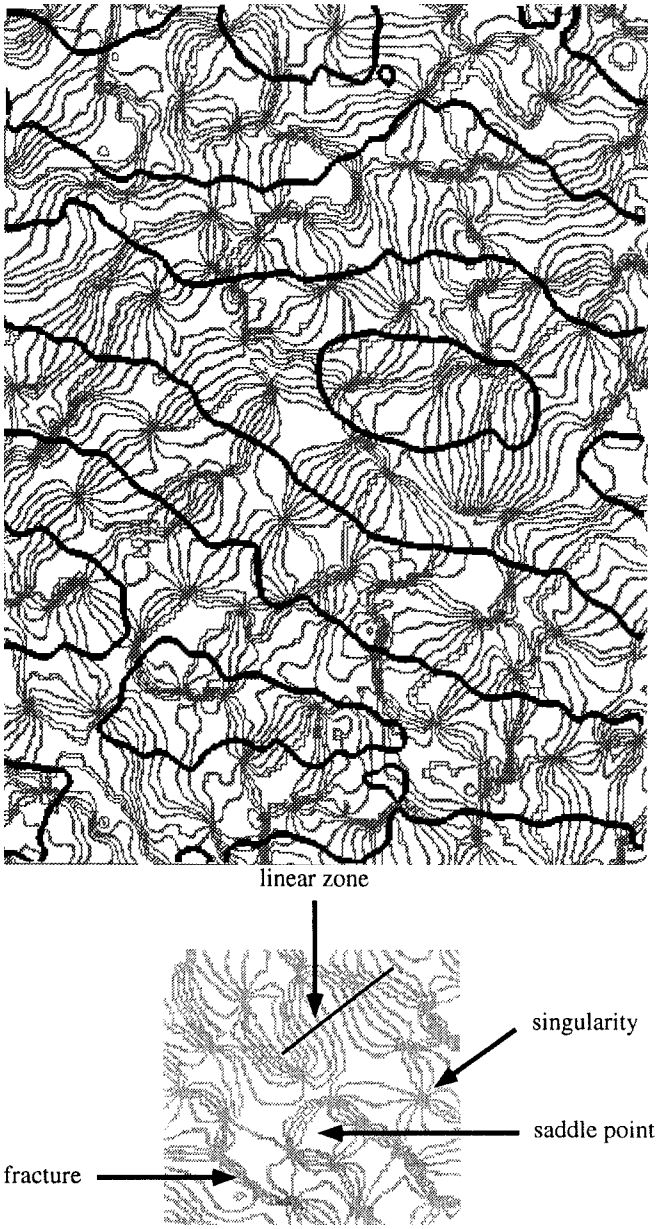

Fig. 10 *Above*. Contour plot of orientation preference and ocular dominance bands in the macaque monkey striate cortex, determined by the method of optical imaging. The iso-orientation lines are shown in grey, and are drawn at intervals of 11.25° in the orientation rotation sequence. The thick black lines indicate the borders between the ocular dominance columns. *Below.* Contour plot showing a part of the results in another monkey. The singularities (*see* text) tend to be at the centre of the ocular dominance columns, the linear zones at the edges of the ocular dominance columns, where the short iso-orientation bands within the linear zone tend to intersect the borders of the ocular dominance columns at right angles, i.e. at ~90°. (From Obermayer and Blasdel, 1993, with permission from Oxford University Press.)

review (Hubel and Wiesel, 1977), and is illustrated by their model shown in Fig. 9.

Since that time the columnar sets in primate V-1 have been studied intensively with optical imaging methods, particularly those in which both the orientation and ocular dominance columns are identified in the same local region of visual cortex (Blasdel, 1992*a*, *b*). It is clear from the map shown in Fig. 10 that in some locations the lateral progression of change in orientation preference occurs in a linear way, while elsewhere the changes are markedly non-linear. The orientation columns form orientation slabs that measure 0.5–1.0 mm in the iso-orientation direction, and in which a full 180° rotation of orientation preference is repeated in ~560 μm. These linear regions occupy ~50% of the cortical surface and are preferentially located at the edges of the ocular dominance columns which they intersect in nearly orthogonal directions. This intersection creates a module in which the several functional properties of V-1 neurons are mapped in an iterative manner, the original 'icecube' model of Hubel and Wiesel.

Three types of non-linear changes in orientation preferences were identified in Blasdel's experiments. *Singularities* are point-like discontinuities created when orientation preferences change continuously through 180° around them. These points tend to be located in the centres of the ocular dominance columns. *Fractures* are local discontinuities at which orientation preferences change abruptly; such sudden local changes were identified by Hubel and Wiesel in their electrophysiological experiments. Finally, *saddle points* are small, patch-like areas within which orientation preferences appear not to change. Saddle points are usually located at the centre of four singularities (Fig. 10). It is still uncertain what role these regions of non-linear orientation change play in the function of the visual cortex.

Understanding of the functional architecture of primate V-1 was complicated by the discovery that local zones of above average metabolic activity occur intermittently along the ocular dominance columns. These dots or blobs were revealed by 2-deoxyglucose or cytochrome oxidase staining (Hendrickson and Wilson, 1979; Wong-Riley 1979; Horton and Hubel, 1981; Horton, 1984). They are local zones of ~150-μm diameter most prominent in layers II and III, arranged along the centre of the ocular dominance columns at a repeat interval of 500–550 μm; the parallel rows are ~350 μm apart. Blob regions receive a direct input from the intercalated layers of the lateral geniculate; the interblob regions receive only intrinsic cortical input. Neurons in the blobs are predominantly sensitive to particular colours and not to stimulus orientations; neurons in the interblobs are the reverse. Blob cells respond differentially at low spatial frequencies (1.1 ± 0.8 cycles per degree, interblob cells at higher frequencies (3.8 ± 0.2 cycles per degree). The blob and interblob regions differ in intrinsic and extrinsic connectivity, and in the differential distribution of a number of molecular markers. Much remains to be learned about the functional organization of primate V-1. The problem has attracted interest from neural modellers; for a critical review, *see* Erwin *et al.* (1995).

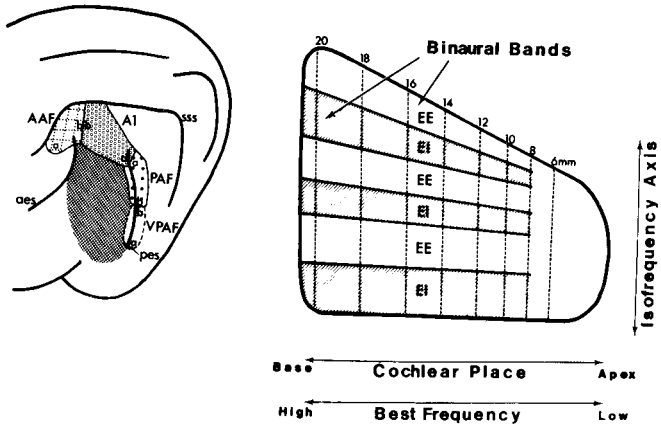

Fig. 11 *Left*. Auditory sensory areas in the neocortex of the cat. AAF = anterior auditory field; A I = primary auditory field; PAF = posterior auditory field; VPAF = ventral posterior auditory field. These four fields are tonotopically organized. The dark cross-hatched field is an auditory responsive area in which no tonotopic organization has been defined; aes = anterior ectosylvian sulcus; pes = postgerior ectosylvian sulcus; sss = suprasylvian sulcus. *Right*. A schema of the internal organization of the primary auditory cortex in the cat. The isofrequency bands run in the vertical direction, and are crossed by the binaural bands in a nearly orthogonal manner. Modes of binocular interaction are indicated: EE = excitatory from both ears; EI = excitatory from the contralateral ear, inhibitory from the ipsilateral ear. (From Merzenich *et al*., 1982, with permission.)

The auditory cortex

The earliest electrophysiological studies of the auditory cortex of carnivores revealed that sound frequencies are mapped in an orderly tonotopic manner to several cortical areas (Woolsey and Walzl, 1942). Tunturi (1950) discovered, in the dog, that the afferent cochlear fibres serving a narrow range of frequencies project to a band of cortical tissue 'no wider than 200 μm, and 5–7 mm in length extending across the gyrus'. This remarkable observation was made using the gross electrode, evoked potential method. Isofrequency bands have since been identified with single neuron methods in the cat, monkey and other mammals (Brugge and Merzenich, 1973; Merzenich and Brugge, 1973; Ahissar *et al*., 1992; Morel *et al*., 1993). These bands are stacked in a linear array to form a sequential representation of sound frequencies that runs, in the cat, in sequence from low to high in the posterior to anterior direction (Fig. 11).

Other functional properties of auditory cortical neurons are not uniform along the isofrequency bands. Neurons with different sensitivities to binaural stimulation, excitatory/excitatory from the two ears, or excitatory/inhibitory, are spatially segregated along each isofrequency band. Each binaural response class forms an antero-posteriorly directed band that crosses the isofrequency bands orthogonally, thus specifying, by that intersection, cortical modules each of which contains neurons with particular combinations of frequency selectivity and binarual response (Fig. 11) (Imig and Adrian, 1977). Neurons in the binaural summation columns send and receive callosal fibres and signal the azimuth location of sound sources in the contralateral half of space.

Every cellular study of the auditory cortex in cat and monkey has provided direct evidence for its columnar organization. Microelectrode penetrations made normal to the pial surface encounter successively neurons from layer II to layer VI that have similar spectral sensitivities and binaural response properties. Penetrations made in the tangential direction, parallel to the pial surface, encounter successive blocks of cells whose properties change abruptly as the electrode passes from one group to the next. These changes occur in step-wise fashion, and the blocks of cells may be as narrow as 100 μm.

A number of other functional properties also vary along the isofrequency bands. The degree of frequency tuning is itself not uniform; it is sharpest in the mid-region of the bands and somewhat broader for neurons located either medial or lateral to the central zone (Heil *et al*., 1992; Schreiner and Sutter, 1992). Auditory cortical neurons are sensitive to frequency modulated stimuli, particularly if the frequency modulation is centred at the best frequency of the cell; they are differentially sensitive to the direction and speed of the modulation. Different auditory cortical neurons respond differently to changes in stimulus intensity and to periodicity pitch (Eggermont, 1991). All these properties appear to be distributed non-randomly (and some periodically) along the isofrequency bands, but how these spatial variations relate to the periodicity of the binaural response columns is still uncertain. It is only the frequency sensitivity of auditory cortical neurons that is determined by the primary afferent input from the cochlea; each of the other functional properties is created by neuronal processing within the several stages of the ascending auditory system and in its cortical targets.

The motor cortex

The layer V neurons, the origins of the pyramidal tract fibres are clustered into groups distributed intermittently in the horizontal dimension. In the human motor cortex pyramidal and non-pyramidal cells are clustered into columnar aggregates ~300 μm wide, separated by 100 μm cell-sparse zones (Meyer, 1987). Forty percent of neurons in such clusters project to a single motoneuron pool in the spinal cord; the remainder project to the motoneuron pools of muscle groups active in similar movements. The recurrent axon collaterals of pyramidal cells project vertically into a 300–500-μm zone that extends through the cellular layers. This provides a strong excitatory drive to adjacent neurons and, via inhibitory interneurons, a columnar surround inhibition (Keller, 1993). The vertical projection of the bundles of pyramidal cell dendrites and of the axons of the double bouquet cells contribute further to the vertical pattern of intrinsic connectivity. Other collaterals of the pyramidal cells of layers III and V project horizontally through the

cortex for 2–3 mm. They end in terminal clusters in columns thought to have spinal cord linkages similar to those of the layer V pyramids of the column of origin (Huntley and Jones, 1991; Aroniadou and Keller, 1993). The projections to the motor cortex from the thalamic ventrolateral nucleus and from other cortical areas terminate in intermittently distributed patches, thus contributing also to the columnar pattern.

The question of the relation of muscles to movements in the motor cortical representations has, until recently, remained unresolved in spite of more than a century of experiments involving electrical stimulations of the motor cortex in many primates, including man. The question was mis-directed, for the problem appears to be not whether muscles or movements are represented, *per se*, but how sets of neurons related to particular muscles are combined in groups that, from time to time, have different compositions, and thus generate the variety of different movements in which any muscle participates. Several lines of study have contributed to the suggested solution, particularly those in which the motor cortex was explored with penetrating microelectrodes. This allows controlled delivery of weak electrical stimuli to local groups of neurons (intracortical microstimulation, ICMS) and recording of the responses of those same cortical cells to sensory stimuli (Asanuma and Rosen, 1972). The main findings are as follows. (i) Threshold ICMS elicits contractions of single muscles at ~40% of stimulation sites; at others, somewhat more intense ICMS is required and it elicits contractions of small groups of muscles. (ii) The cortical area within which ICMS produces a particular local movement is confined to a narrow zone of columnar shape, extending through the cellular layers. Muscle and group specific columns are interspersed in the tangential dimension. Frequently a column overlaps an adjacent one in which ICMS elicits the opposite movement. (iii) Neurons in a column receive afferent input from deep receptors located in the zone of movement, and from cutaneous afferents whose receptive fields are arranged spatially so as to be activated if the evoked movement brings them against an object (Asanuma, 1981). (iv) It is the tangential intermingling of columns related to different single muscles and different small-muscle groups that suggests how movements are represented. They are thought to be driven by the grouping together, from time to time, of active columns related to muscles and muscle groups involved in one particular movement, and in different groups to produce related but different movements. It is not known what mechanism or afferent input selects the particular groups appropriate for a specific movement.

Extensive studies have been made of the motor cortex in waking monkeys as they execute one of a variety of motor tasks, a research program initiated in the 1960s by the late Edward Evarts (Evarts *et al*., 1984). In general the aim of these studies has been to seek correlations between the activity of motor cortical neurons and movement parameters and little attention was paid to the question of columnar organization. However, Georgopoulos *et al*. (1993) have shown that motor cortical neurons active during directed projections of the arm and hand discharge optimally for a particular movement direction of movement. They made an observation important in the present context, that the preferred directions were similar for neurons encountered in microelectrode penetrations made normal to the pial surface and crossing the cortical laminae.

Columnar organization of homotypical cortical areas

A striking feature of homotypical, i.e. 'association', cortical areas is that the defining parameters for columns are neuronal properties constructed within intracortical processing systems. These properties are complex, and rarely, if ever, do the input-linked properties that define modules in sensory areas like 3b or V1 appear unchanged in homotypical areas. The plasticity of cortical synapses suggests that homotypical defining properties may be changed by experience, e.g. with learning and memory, and there is preliminary evidence that this is indeed the case.

Modular organization of homotypical cortex depends, in part, upon the fact that connections between cortical areas are distributed intermittently in the transverse cortical dimension, at both source and target; in homotypical/association cortex they terminate most densely in the supragranular layers, in 200–500 μm wide columns which are separated by zones of equal width in which terminals from that particular source are scarce. The cells of origin in the source area are similarly distributed in intermittent patches in layers II and III.

I consider briefly several areas of homotypical cortex in which modular organization has been documented in electrophysiological experiments in waking monkeys. The first is the posterior parietal cortex (area 7a, now divided into several sub-areas) where neurons with similar properties are arranged in vertical modules extending across the cellular layers, interdigitated with other sets whose neurons have different properties (Mountcastle *et al*., 1975; Mountcastle, 1995). These cortical areas do not reflect any single sensory input, nor are they linked in an unconditional way to peripheral effectors. Neuronal properties in them were discovered in combined electrophysiological and behavioural experiments in monkeys trained to perform acts chosen on the basis of known defects in behaviour produced by lesions of the area, and the connectivity of the area. The properties of the modular sets in the posterior parietal cortex differ greatly, but have one thing in common: they are all related to the animal's actions in immediately surrounding space, or his perception of, and attention to, objects and events within that space. Different neuronal sets are active during (i) the fixation of gaze upon, and attention to, an object of interest, (ii) slow pursuit tracking of such an object, (iii) projection of the arm towards such an object, (iv) manipulation of such an object and (v) to visual stimulation. The last class of neurons possesses constructed visual properties not seen in

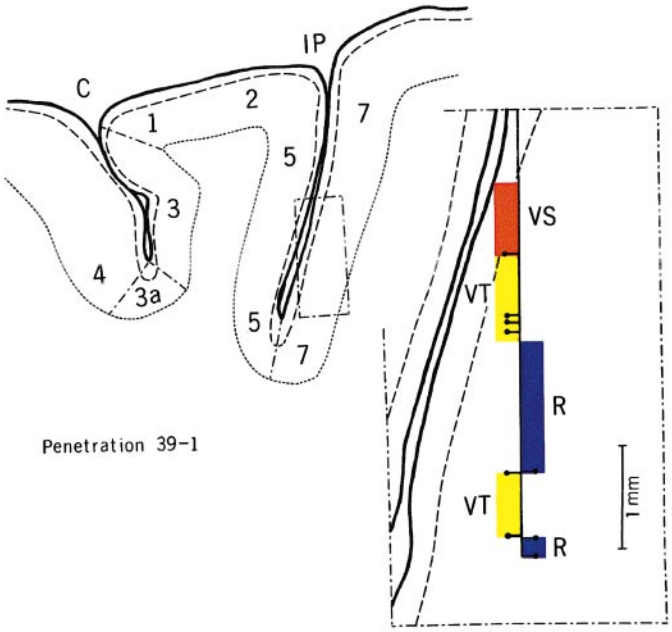

Fig. 12 Results obtained in a microelectrode penetration made into the posterior parietal cortex of a waking, behaving monkey as he executed a series of tasks relevant for parietal lobe function. The electrode passed down the intraparietal sulcus (IP) and then entered area 7 lining the posterior bank of the sulcus. Five blocks of neurons with different functional properties were encountered: visual neurons (VS); visual tracking neurons (VT); reach neurons (R); then VT again and finally R again. The electrode traversed different distances in the columns encountered. (V. B. Mountcastle, unpublished experiment.)

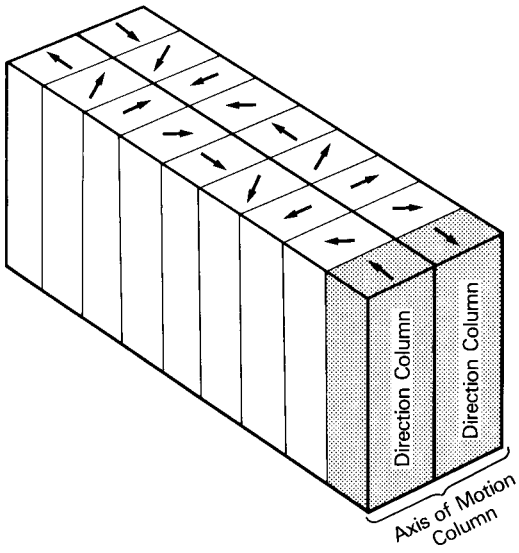

Fig. 13 Three-dimensional model of columnar organization for direction and axis of motion sensitivity of neurons in prestriate area MT in the macaque monkey. Vertical dimension represents depth in the cortex.The long axis of the figure represents two complete revolutions of axis of motion columns; the two directions of motion are represented in adjacent columns. When moving at right angles to the long axis, one encounters frequent 180° reversals in the preferred direction of motion, with no change in the preferred axis of motion. (From Albright *et al*., 1984, with permission from the American Physiological Society.)

any tributary visual areas. They provide a dynamic image of the flow fields in the spatial surround, of the animal's movement through those fields or of the movement of objects through them. Microelectrode penetrations made normal to the surface of the inferior parietal lobule have a high probability of encountering neurons of only one of these classes, as the recording point is moved across the cellular layers. Electrode penetrations made orthogonal to the vertical dimension of the cortex encounter successive blocks of neurons of first one class and then another (Fig. 12). It is not known how these several modular sets are interdigitated in area 7a.

The medial temporal (MT) is a small area of distinctive myeloarchitecture in the posterior bank of the superior temporal sulcus of the monkey. It was discovered by Zeki (1974). It is specialized for processing information about the movement of objects in visual space, and their direction of movement. Zeki labelled it V5, the fifth-order prestriate visual area; it receives input form both V1 and V2. The homologue of monkey V5 has been identified in the human brain using PET (Zeki *et al*., 1991). A patient with bilateral and nearly symmetrical lesions that include this area has been studied in detail (Zihl *et al*., 1983). She has no experience or knowledge of objects in motion, but perceives them accurately when they are stationary. Her defect is specifically selective for visual motion; other aspects of vision and motion perceived through her other senses appear reasonably intact.

Albright *et al*. (1984) found that neurons of monkey MT with similar axes of motion preference are arranged in vertical columns, and that these columns are themselves arranged in slabs in which a full rotation of 180° of axis of motion is represented in 400–500 μm of cortex. The axis of motion columns are intersected by a second set in which the two opposite directions of motion along each axis are represented in two adjacent columns, as shown by the model of Fig. 13. Thus a column in MT is specified by the intersection of two parameter sets, each of which is constructed by intracortical processing.

The homotypical inferotemporal cortex is critical for object vision, since its removal renders a monkey severely handicapped in learning a visual object discrimination or recognition. Gross *et al*. (1972) discovered that many neurons in this area respond selectively to the shapes of objects, and that some cells are best activated by such shapes as the outline of a monkey's hand, or the view of monkey or human faces. This discovery has attracted the interest of many investigators, and we now have a detailed knowledge of this unique set of cortical neurons (Perrett *et al*., 1992). A recent study by Tanaka is of particular interest in the present context (Tanaka *et al*., 1993). They were able to reduce the outlines of complex effective stimuli, like faces, to the features critical for neuronal activation, and confirmed that most of the cells in the anterior portion of the inferotemporal cortex require moderately complex features for their activation. Neurons

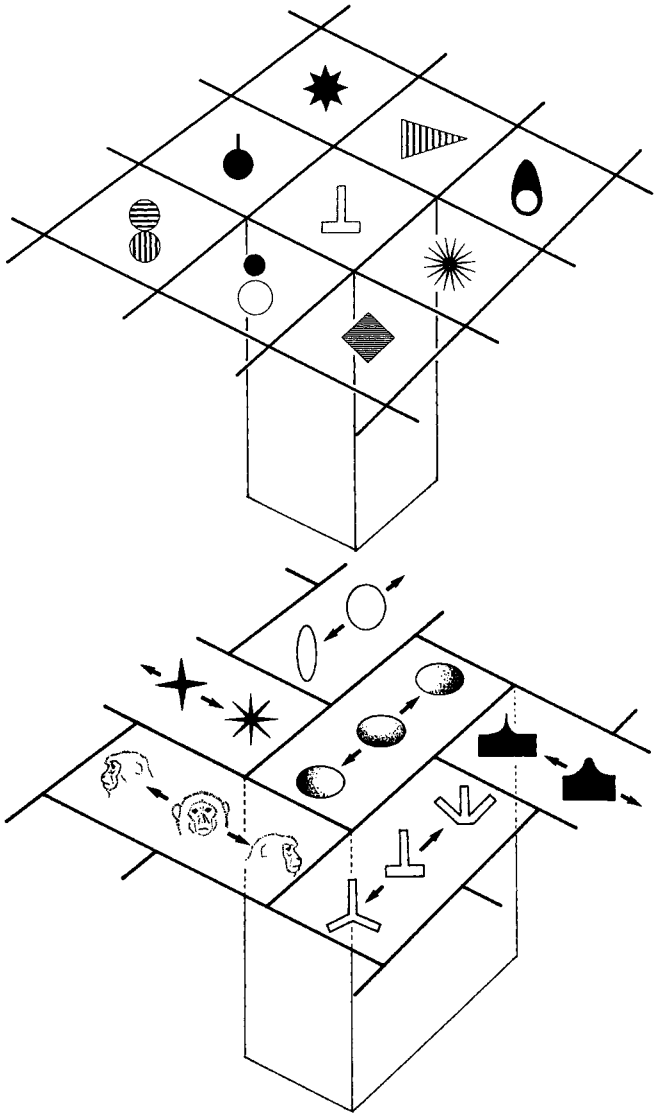

Fig. 14 *Top*. Columnar modules of region TE (anterior inferotemporal cortex) of the temporal neocortex of the macaque monkey. Neurons in each of the modules responded to the critical stimulus features indicated. The modules measure ~400 μm in the horizontal dimension. *Bottom* The neurons in adjacent modules of area TE respond to different but related stimulus features, and on this basis two or three may be linked into larger modules in the manner indicated in the drawing. (From Tanaka, 1996, with permission from the American Physiological Society.)

with similar or closely related selectivities are clustered in columns that extend across the cellular layers, and neurons with different selectivities are arranged in a mosaic like that shown in the model of Fig. 14.

The final example among the homotypical areas is the frontal association cortex, or Walker's areas 46, 9 and 10. These areas, that expand in primates, display clear examples of columnar organization (Goldman and Nauta, 1977). Connections from the ipsilateral and contralateral areas are interdigitated into alternating 500-μm-wide columns that span the full thickness of the cortex (Goldman and Schwartz, 1982). These columns can be individually activated by specific behaviours and are found to serve specific functions (Friedman and Goldman-Rakic, 1994). It is remarkable that the size of columns is preserved in evolution: primitive primates like the tree shrew, with a small prefrontal cortex, have callosal columns that are same width as that of macaque monkeys with a 10 times larger prefrontal surface area. This is compatible with the idea that the cortex expands with the addition of new functional columns of the same size (Bugbee and Goldman-Rakic, 1983).

The anatomical basis of columnar organization

When the general hypothesis of columnar organization was first presented (Mountcastle, 1957) it was met with disbelief by almost all neuroanatomists. This was so, even though the general pattern of vertical connectivity linking neurons across cortical layers had been described by Lorente de Nó nearly two decades earlier, in his (1938) Golgi studies of what we now know is the somatic sensory cortex of the mouse. The classical idea of laminar organization of the cortex was dominant, and suggestions for functional specificity for each of the cellular layers were frequently made, e.g. that the supragranular layers are specialized for 'psychic' functions. In my original description, I included evidence that columnar specificity is dynamic in nature, maintained by pericolumnar inhibition, and might not be revealed by the anatomical methods then in use. This was largely ignored, and perhaps properly so, for the large sets of cortical inhibitory interneurons had yet to be identified.

The use of new methods in neuroanatomical research has now produced compelling evidence for the columnar organization of the neocortex. I review some of it briefly in the following sections.

Columnar organization by afferent projections

The physiological observations that generated the hypothesis of the columnar organization required two sets of anatomical facts then unknown. Firstly, that the terminations of afferent systems to the cortex be disposed in focal clusters of 0.5–1.0 mm dimensions, and that each cluster subtend a bundle of place and mode specific primary afferent fibres feeding the system. Secondly, it was necessary to postulate that this thalamically imposed focus of activity is relayed in the vertical direction in columns limited in the horizontal direction by the input cluster, and that such activity engages neurons in all the cellular layers, including both intrinsic interneurons and efferent pyramidal cells. Moreover, the first physiological observations suggested that intracortical pathways exist over which the activity in one column can suppress that in its immediate neighbors.

Descriptions are now available of the two anatomical arrangements required by the columnar hypothesis (for reviews, *see* Jones, 1981, 1983, 1991). Many correlated anatomical and physiological studies show that the lemniscal afferent system is modularized from the level of the dorsal

root entry to that of the postcentral gyrus. Bundles of axons from cells of thalamic modules project to columnar zones of termination in layers IV and IIIb of the postcentral cortex, forming clusters separated by zones in which terminals are much less dense. Clustering obtains also for the ipsilateral cortico-cortical and trans-callosal systems. The apical zones of the postcentral pattern in which the hands, feet and face are represented are not connected trans-callosally to the other hemisphere. Within the regions of the somatotopic map that are connected, callosal afferents terminate in 0.5–1.0-mm-sized patches. These and the terminal patches of the ipsilateral corticocortical systems overlap to some still undefined degree the clusters of terminals of thalamic afferents in layers IV and IIIb, but extend also into the more superficial layers. In many other cortical areas the terminal zones of these two systems are interdigitated. Convergence does occur; e.g. the pyramidal cells of layer IIIb that emit callosal fibres receive direct synaptic input from thalamic afferents.

The focal zones of terminations of these systems, e.g. the callosal, are arrayed in mediolateral strips that cross in a quasi-orthogonal way the general anterior to posterior representations of each body part across areas 3b, 1 and 2. The intersections specify a module by place, mode and interhemispheric connection, although the meaning of the latter for function is still obscure. The specification of a module by the intersection of such strips appears to be a general property, for it occurs in both the auditory and visual cortices as well as in the postcentral somatic sensory cortex. I emphasize that aligned strips are not functional cortical units.

An important generality can be inferred from these anatomical results and many related physiological observations: that *the effective unit of operation in such a distributed system is not the single neuron and its axon, but groups of cells with similar functional properties and anatomical connections.*

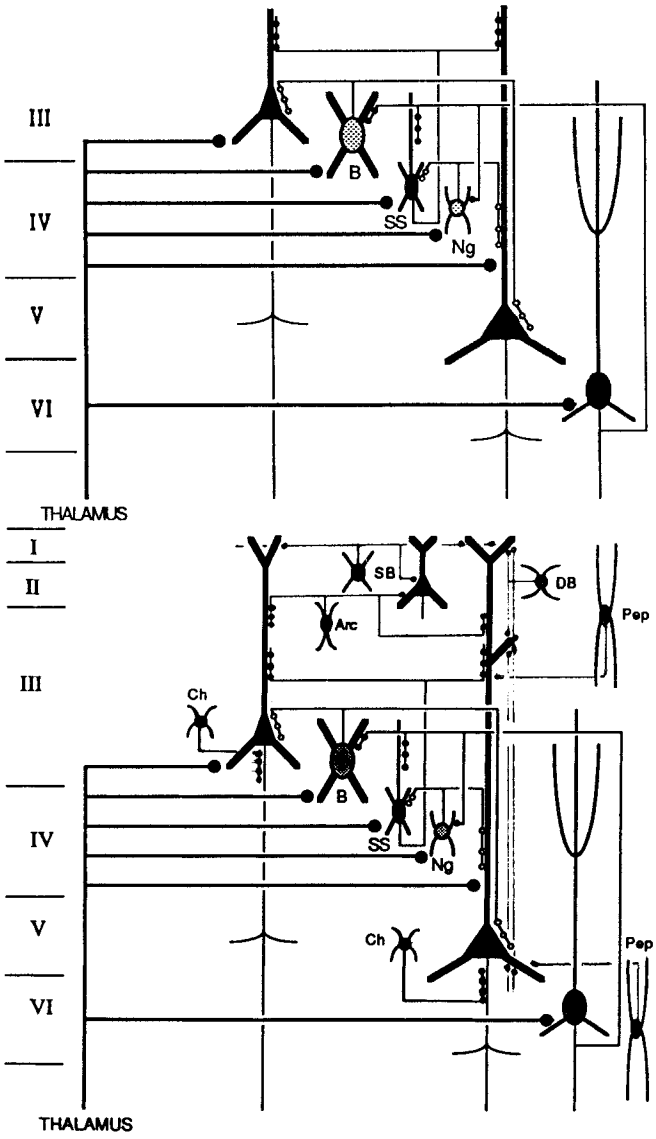

Fig. 15 *Above.* Schematic outline of neuron cell types in the monkey neocortex that receive synapses of thalamocortical fibres. The cells illustrated include the pyramidal cells of layers III, V and VI, and three types of non-pyramidal cells, B = large basket cells, Ng = neuroglioform cells, and SS = non-pyramidal, non-spiny (stellate) cells. *Below.* The scheme from above is repeated, now with the addition of those intrinsic, non-pyramidal cells not known to receive thalamocortical afferents directly: Arc = arcade cells, Ch = chandelier cells, DB = double bouquet cells; Pep = peptidergic cells; and SB = small basket cells. (From Jones, 1991, with permission from MacMillan.)

Columnar organization by intrinsic connectivity

The local excitatory interneurons of layers IV and IIIb (the spiny non-pyramidal or stellate cells) are major postsynaptic targets of afferents from the thalamic ventroposterior nucleus. The axons of the excitatory interneurons project vertically into narrow bundles 100–200 μm wide that run across all the cellular layers, and terminate upon the dendrites and dendritic spines of pyramidal cells, as well as upon inhibitory interneurons. They extend the local patch of thalamic terminals into a translaminar column. As a general rule, all other intrinsic excitatory synaptic actions are imposed via the exuberant recurrent collateral branches of pyramidal cell stem axons. These re-entrant circuits create a bi-directional excitatory system; pyramidal cells of the supra-granular layers innervate pyramidal cells of the infragranular layers in this way, and *vice versa*. The collaterals of any single stem axon avoid its pyramidal cell of origin, but project profusely within the restricted zone of the local columnar population of pyramidal cells, with the exception described below. The recurrent collaterals also terminate upon inhibitory interneurons, providing one mechanism for pericolumnar inhibition (*see* the network diagrams in Fig. 15).

Other recurrent collaterals of the stem axons of pyramidal cells of layers III and V in each of the cytoarchitectural fields of the postcentral cortex project horizontally for long distances within their own area. They generate local, column-like foci of terminal boutons which occur at horizontal intervals of ~800 μm. These projections are linking pathways, either between columns with similar modality properties or for

cross convergence between those with different properties. The functional aspects of this projection are still unknown.

Specific thalamocortical afferents also terminate directly upon the dendrites of pyramidal cells of layers III, V and VI, and provide candidate pathways for monosynaptic transcortical actions through the somatic sensory cortex. The disynaptic IPSPs (inhibitory postsynaptic potentials) evoked in pyramidal cells by thalamocortical volleys indicate that the thalamocortical afferents also terminate directly upon some classes of intrinsic inhibitory interneurons.

The GABAergic, inhibitory double bouquet cells are present in all layers, but are most dense in layers II and III. They project their axons into the vertical bundles of the cortex described below, and terminate upon both pyramidal cells and inhibitory interneurons. They impose a strong vertically directed stream of inhibition, and may also exert a vertically directed disinhibition of those pyramidal cells upon which those other inhibitory interneurons project. The narrow vertical distribution of the double bouquet axons is so specific and restricted that it creates a narrow vertical cylinder of inhibition/dis-inhibition running vertically through the cortex. Other classes of inhibitory interneurons form local control loops. The large and small basket cells and the chandelier cells exert powerful inhibitory controls upon pyramidal cell bodies and initial axons segments, respectively. The horizontal projections of the myelinated axons of the large basket cells extent for 1–2 mm, and provide another pathway for peri-columnar inhibition. The neuroglioform cells project upon the spiny local excitatory interneurons of layers IV and IIIb providing for a tight inhibitory loop at the locus of cortical entry. The peptide cells terminate upon the somata and dendrites of pyramidal cells, but little is known of their function.

The layer I circuits are the least well known of all cortical systems. How they may affect the formation or operation of columns is unknown, and what role they may play in more global cortical function is equally mysterious.

This brief review does little justice to the fund of knowledge that has accumulated concerning the intrinsic organization of the cortex. I review it in greater detail in another place.

Dendritic clusters group cortical neurons into modules of minicolumnar size

The apical dendrites of pyramidal cells that ascend through the cortex are not homogeneously distributed in the tangential dimension. The dendrites of 3–20 large pyramidal cells of layer V form clusters that ascend together through layer IV. They are joined in the supragranular layers by the successive addition of the apical dendrites of pyramidal cells of layers II and III, and all ascend further, many sending their terminal arrays to I (Fleischhauer *et al.*, 1972; Peters and Walsh, 1972). The apical dendrites of pyramidal cells of layer VI are grouped into separate bundles that do not join the clusters, but reach only layer IV where they end within the terminal bushes of thalamocortical fibres. Further knowledge of the clusters has come from quantitative studies on the neocortex of rodents, cats and primates (Peters and Sethares, 1991, 1996; Peters and Yilmaz, 1993). Each dendritic cluster is the centre of a module of pyramidal cells like those of Fig. 16. These modules are ~30 μm in diameter, and occur with centre-to-centre spacing that varies from 20 to 80 μm; the wider spacings occur in the larger brains of the macaque monkey and man. Dendrite clusters appear early in ontogenesis as the cortical plate is forming, and before it receives any afferent axons. The clusters have been described in a wide range of mammalian brains and in every cortical area examined in detail. Dendrites within a cluster are frequently separated by an intercellular cleft. Gap junctions occur between them during cortical ontogenesis, but linkages of this sort are rare in the mature cortex.

The dendritic clusters of pyramidal cells appear to represent one aspect of the mature development of the ontogenetic units of the developing cortex; they fit the observed sizes of minicolumns. Such a minicolumn may not itself be a uniform processor, for it contains pathways that differ in their patterns of synaptic input and in the targets of projecting axons. This assumes that cortical outputs to such diverse targets as the contralateral hemisphere or the thalamus differ in some quality. However, I know of no direct experimental evidence for this assumption.

The transverse diameter of cortical minicolumns has been measured in 15 studies in mice, rats, rabbits, cats and monkeys, with a variety of methods. The overall mean transverse diameter of minicolumns from these studies (mean of means ± SEM) is 56 ± 4 μm.

Columar organization and distributed systems

The remarkable success of neuroanatomical studies of brain connectivity during the last decades has revealed the vast number and diversity of connections that link brain structures to each other. This, together with the results of neurophysiological studies, has led to a new concept of brain function. That is, that brain operations and particularly those of the higher functions are distributed in nature, with some hierarchical and quasi-serial linking operations to the great afferent and efferent systems of the brain. The distributed mode of operation pertains particularly to the homotypical cortex and its reciprocal linkages to subcortical structures, notably to the great re-entrant systems of the forebrain involving thalamus, basal ganglia and cerebellum (Mountcastle, 1978; Goldman-Rakic, 1988).

Several sets of experimental findings lend support to this broad generalization. The first is the discovery of a large number of hitherto unknown, but now clearly specified, cortical areas. The most extensive studies have been made in the macaque monkey, where until now 72 areas have been identified (Van Essen *et al.*, 1990, 1992; Felleman and Van Essen, 1991), and more to come! Their homologues are rapidly being identified in the human neocortex, as well as

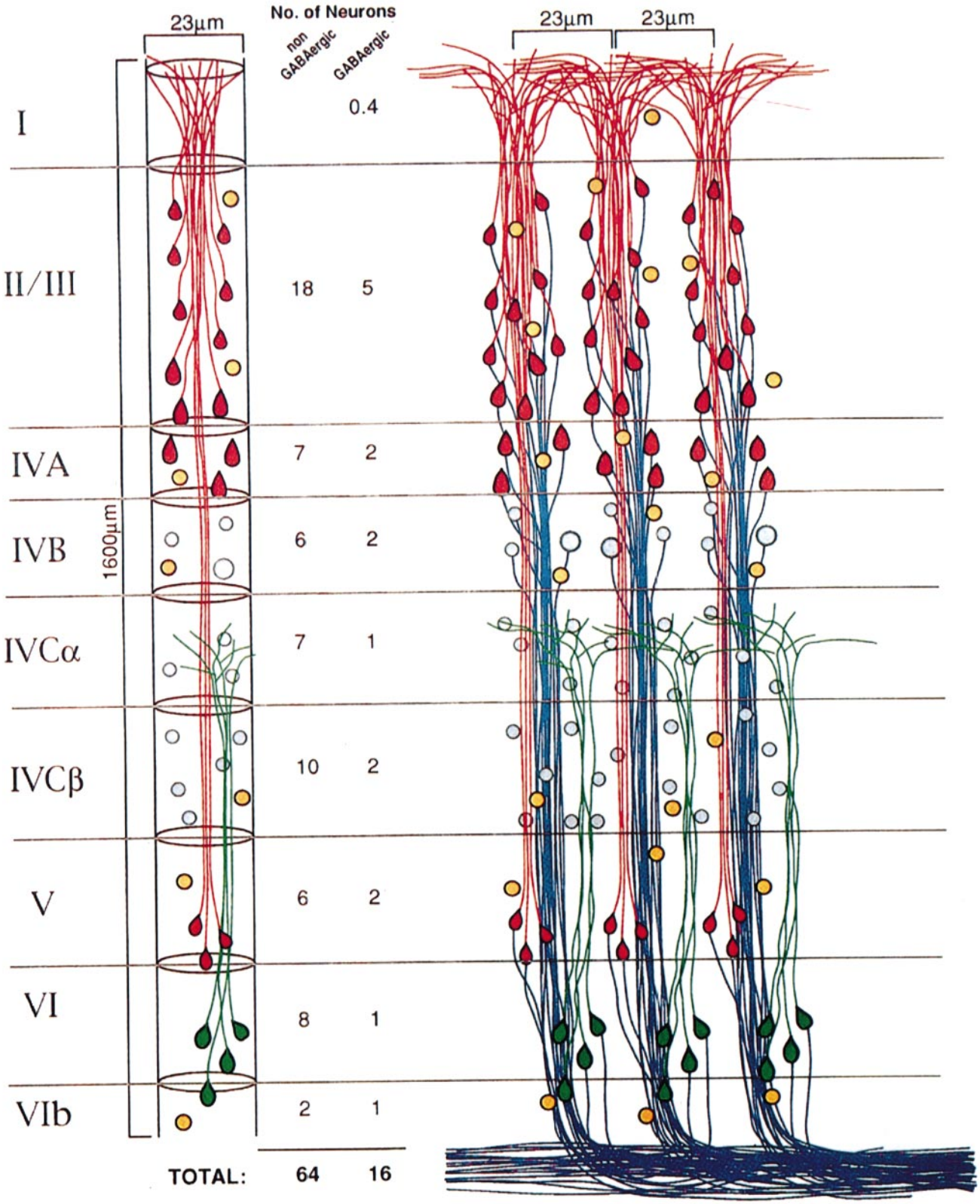

Fig. l6 Diagram of the arrangement of neurons, dendrites and axons in vertical modules of the striate cortex of the macaque monkey. *Left*. A drawing to show the arrangement of the apical dendrites of pyramidal cells; for clarity, only one-half of the neurons present are shown. The pyramidal cells in layers II/III, IVA and V are shown in red, those in layer VI in green. Neurons of IVB and IVC are shown without dendrites, in grey; GABAergic neurons in azure. Total numbers of GABAErgic and non-GABAergic cells are given to the right of the drawing. *Right*. A drawing to represent the pyramidal cell modules (columns) showing the arrangement of dendrites and axons. Colour scheme the same as for the left, pyramidal cell axons are shown in blue. (From Peters and Sethares, 1996, with permission from Wiley-Liss.)

some new areas that appear to be unique to the human. The second set of facts is that alluded to above, i.e. that a large number of distributed connections exists between those cortical areas, e.g. 758 connections have been discovered linking the 72 areas in the macaque monkey, and that list includes only those within the ipsilateral hemisphere. Many of these connections are reciprocal.

The columnar organization of neocortical areas lends further complexity to the concept of distributed systems. This is so because the population of modules of a given cortical area is divided into subsets, each of which entertains only a fraction of all the extrinsic targets of the area. Such an area can thus function as a node in a number of distributed systems. The connectivity patterns of cortical connections are also columnar in nature, since a set of projecting axons terminates in columnar zones of the target area, 200–500 μm wide, separated by zones of equal size in which other systems terminate. When connections are reciprocal, the axon terminals may engage different laminae for what are termed forward and return connections, but the meaning of this for function is unknown. A striking example of the complexity of distributed system interconnections was discovered by Goldman-Rakic and her colleagues (Selemon and Goldman-Rakic, 1988). They discovered that the homotypical cortical areas of the posterior parietal and frontal lobes of the macaque monkey, themselves heavily and reciprocally interconnected, project convergently upon at least 15 other cortical areas. The two convergent projections are arranged differently in different target areas. In some, the convergent projections are interdigitated in adjacent columns, in others the two sets of terminals are interleaved in alternating layers of the same column.

A distributed system is a collection of processing units that are spatially separate and communicate by exchanging messages. A system is distributed if the message-transmission delay is a significant fraction of the time between single events in a processing unit. Given synaptic transmission times in the neocortex (1–5 ms) and the slow conduction velocity in cortico-cortical axons, this seems to fit. Some further and important properties of distributed systems are these. (i) Signal flow through such a system may follow any of a number of pathways in the system. (ii) Action may be initiated at any of a number of nodal loci within a distributed system. (iii) Local lesions within such a system may degrade a function, but not eliminate it completely. Recovery of function after a lesion is a dynamic reorganization of the system, and does not necessarily depend upon a modified structural connectivity. These properties are the everyday experience of the clinical neurologist dealing with patients with brain lesions, particularly if those lesions spare the input and output funnels of the neocortex. (iv) Distributed systems are re-entrant systems; their nodes are open to both externally induced and internally generated signals.

Studies of the dynamic neuronal operations within these distributed systems are now major research programs in neuroscience. How the patterns of neural activity involved in a sensory discrimination or categorization, distributed as they are in wide areas of the brain, are unified into perceptual wholes, and how they flow through to conscious experience, remain among the great enigmas in brain science. Yet confidence is widespread that the persistent application of modern techniques, particularly in studies of waking, behaving primates, monkey and human, will yield steady progress toward their solution. Thus we may hope to approach the ultimate goal of neuroscience, to understand how it is that human brains generate and control human behaviour.

References

Ahissar M, Ahissar E, Bergman H, Vaadia E. Encoding of sound-source location and movement: activity of single neurons and interactions between adjacent neurons in the monkey auditory cortex. J Neurophysiol 1992; 67: 203–15.

Albright TD, Desimone R, Gross CG. Columnar organization of directionally selective cells in visual area MT of the macaque. J Neurophysiol 1984; 51: 16–31.

Alloway KD, Burton H. Bicuculline-induced alterations in neuronal responses to controlled tactile stimuli in the second somatosensory cortex of the cat: a microiontophoretic study. Somatosen Res 1986; 3: 197–211.

Alloway KD, Burton H. Differential effects of GABA and bicuculline on rapidly- and slowly-adapting neurons in primary somatosensory cortex of primates. Exp Brain Res 1991; 85: 598–610.

Angevine JB Jr, Sidman RL. Autoradiographic study of cell migration during histogenesis of cerebral cortex in the mouse. Nature 1961; 192: 766–8.

Aroniadou VA, Keller A. The patterns and synaptic properties of horizontal intracortical connections in the rat motor cortex. J Neurophysiol 1993; 70: 1553–69.

Asanuma H. Functional role of sensory inputs to the motor cortex. [review]. Prog Neurobiol 1981; 16: 241–62.

Asanuma H, Rosen I. Topographical organization of cortical efferent zones projecting to distal forelimb muscles in the monkey. Exp Brain Res 1972; 14: 243–56.

Blasdel GG. Differential imaging of ocular dominance and orientation selectivity in monkey striate cortex. J Neurosci 1992a; 12: 3115–38.

Blasdel GG. Orientation selectivity, preference, and continuity in monkey striate cortex. J Neurosci 1992b; 12: 3139–61.

Brugge JF, Merzenich MM. Responses of neurons in auditory cortex of the macaque monkey to binaural tonal stimulation; effects of varying interaural time and intensity. J Neurophysiol 1973; 36: 1138–58.

Bugbee NM, Goldman-Rakic PS. Columnar organization of cortico-cortical projections in squirrel and rhesus monkeys: similarity of column width in species differing in cortical volume. J Comp Neurol 1983; 220: 355–64.

Cepko CL, Austin CP, Walsh C, Ryder EF, Halliday A, Fields-Berry S. Studies of cortical development using retrovirus vectors. Cold Spring Harb Symp Quant Biol 1990; 55: 265–78.

Cohen-Tannoudji M, Babinet C, Wassel M. Early determination of a mouse somatosensory cortex marker. Nature 1994; 368: 460–3.

Dehay C, Giroud P, Berland M, Smart I, Kennedy H. Modulation of the cell cycle contributes to the parcellation of the primate visual cortex. Nature 1993; 366: 464–6.

Dykes RW, Landry P, Metherate R, Hicks TPY. Functional role of GABA in cat primary somatosensory cortex: shaping receptive fields of cortical neurons. J Neurophysiol 1984; 52: 1066–93.

Eggermont JJ. Rate and synchronization measures of periodicity coding in cat primary auditory cortex. Hear Res 1991; 56: 153–67.

Erwin E, Obermeyer K, Schulten K. Models of orientation and ocular dominance columns in the visual cortex: a critical comparison. Neural Comput 1995; 7: 425–68.

Evarts EV, Shinoda Y, Wise SP. Neurophysiological approaches to higher brain functions. New York: John Wiley, 1984.

Favorov OV. Detection and characterization of the mosaic body representation in SI cortex. In: Franzen O, Westman J, editors. Information processing in the somatosensory system. London: Macmillan Press, 1991: 221–32.

Favorov OV, Diamond ME. Demonstration of discrete place-defined columns – segregates – in the cat SI. J Comp Neurol 1990; 298: 97–112.

Favorov O, Whitsel BL. Spatial organization of the peripheral input to area 1 cell columns. I. The detection of 'segregates'. Brain Res 1988a; 472: 25–42.

Favorov O, Whitsel BL. Spatial organization of the peripheral input to area 1 cell columns. II. The forelimb representation achieved by a mosaic of segregates. Brain Res 1988b; 472: 43–56.

Fishell G, Mason CA, Hatten ME. Dispersion of neural progenitors within the germinal zones of the forebrain [published erratum appears in Nature 1993; 363: 286] [see comments]. Nature 1993; 362: 636–8. Comment in: Nature 1993; 362: 590–1

Fleischhauer K, Petsche H, Wittkowski W. Vertical bundles of dendrites in the neocortex. Z Anat Entwicklungsgesch 1972; 136: 213–23.

Friedman HR, Goldman-Rakic PS. Coactivation of prefrontal cortex and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the rhesus monkey. J Neurosci 1994; 14: 2775–88.

Georgopoulos AP, Taira M, Lukashin A. Cognitive neurophysiology of the motor cortex [see comments]. Science 1993; 260: 47–52. Comment in: Science 1994; 263: 1295–7.

Goldman-Rakic PS. Changing concepts of cortical connectivity: parallel distributed cortical networks. In: Rakic P, Singer W, editors. Neurobiology of neocortex. Chichester: John Wiley, 1988: 177–202.

Goldman PS, Nauta WJH. Columnar organization of association and motor cortex: Autoradiographic evidence for cortico-cortical and commmissural columns in frontal lobe of the newborn rhesus monkey. Brain Res 1977; 122: 369–85.

Goldman PS, Schwartz ML. Interdigitation of contralateral and ipsilateral columnar projections to frontal association cortex in primates. Science 1982; 216: 755–7.

Gross CG, Rocha-Miranda CE, Bender DB. Visual properties of neurons in inferotemporal cortex of the macaque. J Neurophysiol 1972; 35: 96–111.

Heil P, Rajan R, Irvine DR. Sensitivity of neurons in cat primary auditory cortex to tones and frequency-modulated stimuli. II. Organization of response properties along the 'isofrequency' dimension. Hear Res 1992; 63: 135–56.

Hendrickson AE, Wilson JR A difference in [14C]deoxyglucose autoradiographic patterns in striate cortex between Macaca and Saimiri monkeys following monocular stimulation. Brain Res 1979; 170: 353–8.

Horton JC. Cytochrome oxidase patches: a new cytoarchitectonic feature of monkey visual cortex. [Review]. Philos Trans R Soc Lond B biol Sci 1984; 304: 199–253.

Horton JC, Hubel DH. Regular patchy distribution of cytochrome oxidase staining in primary visual cortex of macaque monkey. Nature 1981; 292: 762–4.

Hubel DH, Wiesel TN. Functional architecture of macaque monkey visual cortex. [Review]. Proc R Soc Lond B Biol Sci 1977; 198: 1–59.

Huntley GW, Jones EG. Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. J Neurophysiol 1991; 66: 390–413.

Imig TJ, Adrian HO. Binaural columns in the primary field (A1) of cat auditory cortex. Brain Res 1977; 138: 241–57.

Johnston JG, van der Kooy D. Protooncogene expression identifies a transient columnar organization of the forebrain within the late embryonic ventricular zone. Proc Natl Acad Sci USA 1989; 86:1066–70.

Jones EG. Anatomy of cerebral cortex: columnar input-output organization. In: Schmitt FO, Worden FG, Adelman G, Dennis SG, editors. The organization of the cerebral cortex. Cambridge (MA): MIT Press, 1981: 199–235.

Jones EG. The columnar basis of cortical circuitry. In: Rosenberg RN, editor. The clinical neurosciences, Vol. 5 New York: Churchill Livingstone, 1983: 357–83.

Jones EG. Cellular organization of the primate postcentral gyrus. In: Franzen O, Westman J, editors. Information processing in the somatosensory system. London: Macmillan Press. 1991: 95–107.

Juliano SL, Whitsel BL. A combined 2-deoxyglucose and neurophysiological study of primate somatosensory cortex. J Comp Neurol 1987; 263: 514–25.

Kaas JH, Pons TP. The somatosensory system of primates. In: Steklis HD, Erwin J, editors. Neurosciences. New York: Alan R Liss, 1988: 421–68.

Kaas JH, Nelson RJ, Sur M, Merzenich MM. Organization of somatosensory cortex in primates. In: Schmitt FO,Worden FG, Adelman G, Dennis SG, editors. The organization of the cerebral cortex. Cambridge (MA). MIT Press, 1981: 237–61.

Keller A. Intrinsic synaptic organization of the motor cortex. [Review]. Cerebr Cortex 1993; 3: 430–41.

Kornack DR, Rakic P. Radial and horizontal deployment of clonally

related cells in the primate neocortex: relationship to distinct mitotic lineages. Neuron 1995; 15: 311–21.

Levitt P, Cooper ML, Rakic P. Coexistence of neuronal and glial precursor cells in the cerebral ventricular zone of the fetal monkey: an ultrastructural immunoperoxidase analysis. J Neurosci 1981; 1: 27–39.

Lorente de Nó R. The cerebral cortex: architecture, intracortical connections and motor projections. In: Fulton JF. Physiology of the nervous system. London: Oxford University Press, 1938: 291–339.

Lo Turco JJ, Kriegstein AR. Clusters of coupled neuroblasts in embryonic neocortex. Science 1991; 252: 563–6.

Luskin MB. Neuronal cell lineage in the vertebrate central nervous system. [Review]. FASEB J 1996; 8: 722–30.

Luskin MB, Parnavelas JG, Barfield JA. Neurons, astrocytes, and oligodendrocytes of the rat cerebral cortex originate from separate progenitor cells: an ultrastructural analysis of clonally related cells. J Neurosci 1993; 13: 1730–50.

Merzenich MM, Brugge JF. Representation of the cochlear partition on the superior temporal plane of the macaque monkey. Brain Res 1973; 50: 275–96.

Merzenich MM, Colwell SA, Andersen RA. Auditory forebrain organization. Thalamocortical and corticothalamic connections in the cat. In: Woolsey CN, editor. Cortical sensory organization, Vol. 3: multiple auditory areas. Clifton (NJ): Humana Press, 1982: 43–57.

Meyer G. Forms and spatial arrangement of neurons in the primary motor cortex of man. J Comp Neurol 1987; 262: 402–28.

Morel A, Garraghty PE, Kaas JH. Tonotopic organization, architectonic fields, and connections of auditory cortex in macaque monkeys. J Comp Neurol 1993; 335: 437–59.

Mountcastle VB. Modality and topographic properties of single neurons of cat's somatic sensory cortex. J Neurophysiol 1957; 20: 408–34.

Mountcastle VB. An organizing principle for cerebral function. In: Edelman GM, Mountcastle VB, editors. The mindful brain. Cambridge (MA): MIT Press, 1978: 7–50.

Mountcastle VB. Central nervous mechanisms in mechanoreceptive sensibility. In: Brookhart JM, Mountcastle VB, Darian-Smith I, Geiger SR, editors. Handbook of physiology, Sect. 1, Vol. 3, Pt 2. Bethesda (MD): American Physiological Society, 1984: 789–878.

Mountcastle VB. The parietal system and some higher brain functions. [Review]. Cerebr Cortex 1995; 5: 377–90.

Mountcastle VB, Lynch JC, Georgopoulos A, Sakata H, Acuna C. Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. J Neurophysiol 1975; 38: 871–908.

Nakatsuji N, Kodokawa Y, Suemori H. Radial columnar patches in the chimeric cerebral cortex visualized by use of mouse embryonic stem cells expressing b-galactosidase. Develop Growth Differ 1991; 33: 571–8.

Obermayer K, Blasdel GG. Geometry of orientation and ocular dominance columns in monkey striate cortex. J Neurosci 1993; 13: 4114–29.

O'Rourke NA, Dailey ME, Smith SJ, McConnell SK. Diverse migratory pathways in developing cerebral cortex. Science 1992; 258: 299–302.

Parnavelas JG, Barfield JA, Franke E, Luskin MB. Separate progenitor cells give rise to pyramidal and nonpyramidal neurons in the rat telencephalon. Cerebr Cortex 1991; 1: 463–8.

Perrett DI, Hietanen JK, Oram MW, Benson PJ. Organization and functions of cells responsive to faces in the temporal cortex. Philos Trans R Soc Lond B Biol Sci 1992; 335: 23–30.

Peters A, Sethares C. Organization of pyramidal neurons in area 17 of monkey visual cortex. J Comp Neurol 1991; 306: 1–23.

Peters A, Sethares C. Myelinated axons and the pyramidal cell modules in monkey primary visual cortex. J Comp Neurol 1996; 365: 232–55.

Peters A, Walsh TM. A study of the organization of apical dendrites in the somatic sensory cortex of the rat. J Comp Neurol 1972; 144: 253–68.

Peters A, Yilmaz E. Neuronal organization in area 17 of cat visual cortex. Cerebr Cortex 1993; 3: 49–68.

Powell TPS, Mountcastle VB. Some aspects of the functional organization of the cortex of the postcentral gyrus of the monkey: a correlation of findings obtained in a single unit analysis with cytoarchitecture. Bull Johns Hopkins Hosp 1959; 105: 133–62.

Price J, Turner D, Cepko C. Lineage analysis in the vertebrate nervous system by retrovirus-mediated gene transfer. Proc Natl Acad Sci USA 1987; 84: 156–6.

Rakic P. Mode of cell migration to the superficial layers of fetal monkey neocortex. J Comp Neurol 1972; 145: 61–83.

Rakic P. Neurons in the rhesus monkey visual cortex: systematic relation between time of origin and eventual disposition. Science 1974; 183: 425–7.

Rakic P. Specification of cerebral cortical areas. [Review]. Science 1988a; 241: 170–6.

Rakic P. Intrinsic and extrinsic determinants of neocortical parcellation: a radial unit model. In: Rakic P, Singer W, editors. Neurobiology of neocortex. Chichester: John Wiley, 1988b: 5–27.

Rakic P. Principles of neural cell migration. [Review]. Experientia 1990; 46: 882–91.

Rakic P. Radial versus tangential migration of neuronal clones in the developing cerebral cortex [comment]. [Review]. Proc Natl Acad Sci USA 1995a; 92: 11323–7.

Rakic P. A small step for the cell, a giant leap for mankind: a hypothesis of neocortical expansion during evolution. [Review]. Trends Neurosci 1995b; 18: 383–8.

Reid CB, Liang I, Walsh C. Systematic widespread clonal organization in cerebral cortex. Neuron 1995; 15: 299–310.

Sanes JR. Analysing cell lineage with a recombinant retrovirus. [Review]. Trends Neurosci 1989; 12: 21–8.

Schreiner CE, Sutter ML. Topography of excitatory bandwidth in cat primary auditory cortex: single-neuron versus multiple-neuron recordings. J Neurophysiol 1992; 68: 1487–502.

Selemon LD, Goldman-Rakic PS. Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. J Neurosci 1988; 8: 4049–68.

Sidman RL, Rakic P. Neuronal migration with special reference to developing human brain: a review. [Review]. Brain Res 1973; 62: 1–35.

Soriano E, Dumesnil N, Auladell C, Cohen-Tannoudji M, Sotelo C. Molecular heterogeneity of progenitors and radial migration in the developing cerebral cortex revealed by transgene expression [see comments]. Proc Natl Acad Sci USA 1995; 92: 11676–80. Comment in: Proc Natl Acad Sci USA 1995; 92: 11323–7.

Sur M, Wall JT, Kaas JH. Modular distribution of neurons with slowly adapting and rapidly adapting responses in area 3b of somatosensory cortex in monkeys. J Neurophysiol 1984; 51: 724–44.

Tanaka K. Inferotemporal cortex and object vision. Annu Rev Neurosci 1996; 19: 109–39.

Tanaka K, Fujita I, Kobatake E, Cheng K, Ito M. Serial processing of visual object-features in the posterior and anterior parts of the inferotemporal cortex. In: Ono T, Squire LR, Raichle RE, Perett DI, Fukada M, editors. Brain mechanisms of perception and memory: from neuron to behavior. New York: Oxford University Press, 1993: 34–46.

Tommerdahl M, Favorov O, Whitsel BL, Nakhle B, Gonchar YA. Minicolumnar activation patterns in cat and monkey S1 cortex. Cerebr Cortex 1993; 3: 399–411.

Tunturi AR. Physiological determination of the arrangement of the afferent connections to the middle ectosylvian auditory area in the dog. Am J Physiol 1950; 162: 489–502.

Van Essen DC, Felleman DJ, DeYoe EA, Olavarria J, Knierim J. Modular and hierarchical organization of extrastriate visual cortex in the macaque monkey. Cold Spring Harb Symp Quant Biol 1990; 55: 679–96.

Van Essen DC, Anderson CH, Felleman DJ. Information processing in the primate visual system: an integrated systems perspective. [Review]. Science 1992; 255: 419–23.

Walsh C, Cepko CL. Widespread dispersion of neuronal clones across functional regions of the cerebral cortex [see comments]. Science 1992; 255: 434–40. Comment in: Science 1992; 258: 317–20.

Walsh C, Cepko CL. Clonal dispersion in proliferative layers of developing cerebral cortex [see comments]. Nature 1993; 362: 632–5. Comment in: Nature 1993; 362: 590–1.

Whitsel BL, Petrucelli LM, Werner G. Symmetry and connectivity in the map of the body surface in somatosensory area II of primates. J Neurophysiol 1969; 32: 170–83.

Wong-Riley M. Changes in the visual system in monocularly sutured or enucleated kittens demonstrable with cytochrome oxidase histochemistry. Brain Res 1979; 171: 11–26.

Woolsey CN, Walzl EM. Topical projection of nerve fibers from local regions of the cochlea to the cerebral cortex of the cat. Bull Johns Hopkins Hosp 1942; 71: 315–44.

Zeki SM. Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. J Physiol (Lond) 1974; 236: 549–73.

Zeki S, Watson JDG, Lueck CJ, Friston KJ, Kennard C, Frackowiak RSJ. A direct demonstration of functional specialization in human visual cortex. J Neurosci 1991; 11: 641–9.

Zihl J, Cramon D von, Mai N. Selective disturbance of movement vision after bilateral brain damage. Brain 1983; 106: 313–40.

Received August 30, 1996. Revised November 10, 1996.
Accepted November 25, 1996