Brain (2002), **125,** 935–951

REVIEW ARTICLE

The minicolumn hypothesis in neuroscience

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Summary

The minicolumn is a continuing source of research and debate more than half a century after it was identified as a component of brain organization. The minicolumn is a sophisticated local network that contains within it the elements for redundancy and plasticity. Although it is sometimes compared to subcortical nuclei, the design of the minicolumn is a distinctive form of module that has evolved specifically in the neocortex. It unites the horizontal and vertical components of cortex within the same cortical space. Minicolumns are often considered highly repetitive, even clone-like, units. However, they display considerable heterogeneity between areas and species, perhaps even within a given macrocolumn. Despite a growing recognition of the anatomical basis of the cortical minicolumn, as well as its physiological properties, the potential of the minicolumn has not been exploited in fields such as comparative neuroanatomy, abnormalities of the brain and mind, and evolution.

Keywords: columnar organization; minicolumns; modules

Abbreviations: 2DG = 2-deoxy glucose; IOS = intrinsic optical signal

Introduction

The vertical cell column of the neocortex has been a model for cortical organization as well as a topic of debate since its discovery (Mountcastle, 1957; Hubel and Wiesel, 1963; Slimp and Towe, 1990; Swindale, 1990; Jones, 2000). Though not its discoverer, Mountcastle pioneered the columnar hypothesis (Mountcastle, 1957, 1978). While many outstanding scientists helped unveil the role of the adult column, Rakic and colleagues provided evidence for the embryological origin of vertical units (Rakic, 1972, 1988*a*, *b*, 1995). Robust experimental and anatomical work on the anatomy and physiology of the cortical minicolumn has been especially productive. Mountcastle's comprehensive and much needed review brought together the anatomical and physiological evidence accrued over the last few decades (Mountcastle, 1997). In the last decade in particular, new discoveries have validated the legitimacy of the minicolumn as an anatomical and functional unit, raising new questions regarding the minicolumn's structure and organization. The minicolumn (sometimes referred to as the microcolumn), with its 80–100 neurones, is the smallest level of vertical organization in the cortex, and is the focus of this paper. The 'macrocolumn' is a larger unit that consists of many minicolumns, estimated by some to contain between 60 and 80 (Favorov and Kelly, 1994*a*, *b*, *c*; Mountcastle, 1997; Calvin, 1998). The 'segregate' is a specific form of macrocolumn in the somatosensory cortex (Favorov and Diamond, 1990). The 'hypercolumn' is a form of macrocolumn specific to the visual cortex (Hubel and Wiesel, 1977). Confusion arises when these terms are interchanged without distinction. In this discussion, the term 'column' refers to the minicolumn unless otherwise stated.

The minicolumn, and columnar organization in general, is a perspective, a way of classifying and organizing the cortex. Its study is more holistic than focusing on single cells, and less ambitious than comprehending millions of them in diverse networks. In topics such as brain evolution, neurology, and comparative anatomy, the minicolumn represents a potential way of integrating disparate elements of anatomy, physiology and chemistry. In addition, its study deserves respect as a means of understanding cognition and disorders of the mind (Johannisson, 1993, 1997; Johannisson and Nilsson, 1996; Gustafsson, 1997; Buldyrev *et al*., 2000; Buxhoeveden *et al*., 2001*a*; Casanova *et al*., 2001*a*, *b*, *c*, *d*). This paper will review the columnar organization of neurones

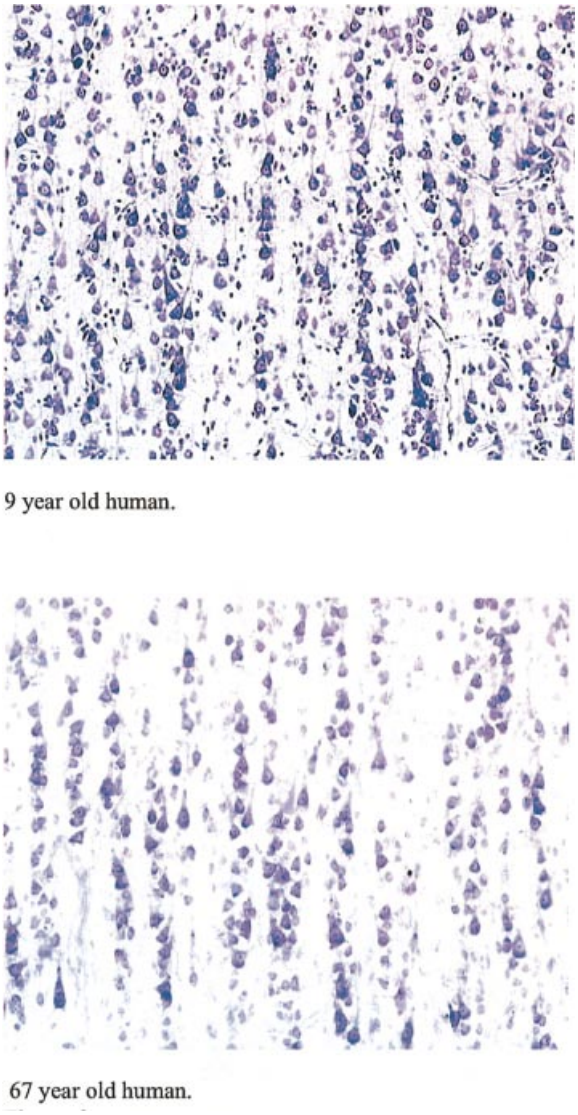

Fig. 1 Minicolumns according to cell soma arrays in planum temporale at various ages. Lamina III, 35-μm thick Nissl-stained slides, celloidin embedded. Yakovlev–Haleem collection. 100× total magnification.

in the cortex, discuss criticisms of the model, differentiate its organization from other forms of brain nuclei and ganglia, and explore its potential role in neurobiology.

Basic anatomy and physiology of the cortical minicolumn

Lorente de Nó (1938) first described the 'vertical cylinders' of cells (Fig. 1), and was perhaps the first to assign them a basic physiological role: 'All the elements of the cortex are represented in it, and therefore it may be called an elementary unit, in which, theoretically, the whole process of transmission of impulses from the afferent fibre to the efferent axon may be accomplished.' The minicolumn generally consists of 80–100 neurones that vertically traverse lamina II–VI; researchers consider it to be a basic anatomical and physiological unit of the cortex (Mountcastle, 1957, 1997; Jones, 1981, 1984, 2000; Kaas *et al*., 1981; Favorov and Whitsel, 1988*a*, *b*; Favorov and Diamond, 1990; Lee and Whitsel, 1992; Lee *et al*., 1992; Favorov and Kelly, 1994*a*, *b*, *c*; Calvin, 1998). Jones (2000) describes the minicolumn as a unit in which 'nerve cells in the middle of layers of the cortex, in which thalamic afferents terminate, should be joined by narrow vertical connections to cells in layers lying superficial and deep to them, so that all cells in the column are excited by incoming stimuli with only small latency differences.'

Because minicolumns have been found in many diverse forms of cortical tissue (Mountcastle, 1997), they are probably not limited to specific regions. Computerized image analysis of adult, Nissl-stained tissue reveals vertically aligned cells, with each column separated by vertically defined cell-poor spaces. The ontogenetic radial cell columns seen during the formation of the cortex (Rakic, 1972) are probably the precursors of adult minicolumns. This vertical organization is overlaid upon a later horizontal organization that becomes noticeable at ~24–28 weeks (Table 1). While each minicolumn receives portions of terminations from the major thalamo-cortical bundle, no specific anatomical pathways demarcate the structure and shape of minicolumns. Because minicolumns exist anatomically on the basis of cell nuclei and fibre bundles, their physiology may be influenced as much by intrinsic (especially inhibitory interneurones) as by extrinsic circuitry. This structure is more pronounced in some areas of cortex than others.

Researchers have discovered an anatomically based size between 20–60 μm in many different species including mice, rats, cats, rabbits, monkeys and humans (Escobar *et al*., 1986; Fleischhauer *et al*., 1972; Peters and Walsh, 1972; Feldman and Peters, 1974; Schmolke and Viebahn, 1986; Peters and Kara, 1987; Schmolke, 1989, 1987; Peters and Sethares, 1991, 1996; Schlaug *et al*., 1995; Buxhoeveden *et al*., 1996). A metabolic [2-deoxy glucose (2DG)] examination of macrocolumns in somatosensory cortex of cat and monkey revealed within module patterns equivalent to between 30 and 50 μm (Tommerdahl *et al*., 1993). The size of macrocolumns is generally linked to the termination width of the thalamic input (Jones, 1981; Jones *et al*., 1982). *In vivo* physiological studies have determined the size of minicolumns, primarily in the somatosensory cortex. It seems to range between 40 and 60 μm (Kaas *et al*., 1981; Favorov and Whitsel, 1988*a*; Favorov and Diamond, 1990; Peters and Yilmaz, 1993). Computerized image analysis reveals a fairly consistent range for minicolumn size in humans, between 35 and ~60 μm, depending on the area examined (Schlaug *et al*., 1995; Buxhoeveden *et al*., 1996; Buxhoeveden *et al*., 2000; Buxhoeveden and Casanova, 2001*b*). A recent study utilizing a novel approach provided a mean value of 80 μm for 'intercolumnar distance' and a 50 μm width for columns (Buldyrev *et al*., 2000). Our most recent studies of Nissl-stained tissue of area Tpt reveal mean *in vitro* sizes for humans approximating

Table 1 *Vertical components of a minicolumn*

Vertical bundles

Axons

1. Layer IV stellate cell axons (100–200 μm in width, suggesting that they engage multiple cell columns below the usual macrocolumn size). Excitatory.
2. Double bouquet cell axons. Form tight bundles with centre-to-centre spacing that ranges from 15 to 30 μm. Inhibitory. DeFelipe (1990).
3. Myelinated axons (suspected efferents in VI) centre-to-centre spacing of 34 μm (SD ± 13) (Peters and Sethares, 1997). Excitatory.

Dendrites

1. Layer V apical dendrite bundles: rat V1 55–60 μm with an estimated 335 neurones (Peters and Kara, 1987). Rat somatosensory 50 μm (Peters and Walsh, 1972). Rabbit VI 40–45 μm (Fleischhauer *et al*., 1972; Schmolke and Fleischhauer, 1984; Schmolke, 1987). Cat V1, 56 μm, SS, auditory 50–70 μm (Feldman and Peters, 1974). Monkey V1, 30 μm with 142 cells (Peters and Sethares, 1991).
2. Vertical branching collaterals off horizontal dendrites (Calvin, 1998)
3. Dendrites of non-pyramidal neocortical neurones have vertical bias (Jin *et al*., 2001)

Cell soma

1. Basket cells in human motor cortex (Marin-Padilla, 1970)
2. Pyramidal cells
3. GABAergic interneurones (DeFelipe and Jones, 1985) in VI, S1, M1

40–50 μm (Buxhoeveden *et al*., 2000, 2001*a*, *b*; Buxhoeveden and Casanova, 2001*a*).

Experiments have determined the physiological basis of the minicolumn by using microelectrodes, 2DG metabolic labelling, evoked potentials and nerve regeneration (Mountcastle, 1957, 1978, 1997; Kaas *et al*., 1981; Favorov and Whitsel, 1988*a*, *b*; Favorov and Diamond, 1990; Lee and Whitsel, 1992; Shamma *et al*., 1993; Tommerdahl *et al*., 1993; Favorov and Kelly, 1994*a*, *b*; Sugimoto *et al*., 1997). These experiments demonstrated that peripheral receptive fields corresponded to specific activation of neurones located in a vertical dimension ~40–50 μm wide. Each of these minicolumns was responsible for a particular receptive field. Kaas *et al*. (1981) used a nerve regeneration experiment to establish the cortical minicolumn as the smallest identifiable unit of function. They also determined their size, which ranged from 40 to 60 μm in the rhesus monkey. Finally, studies have examined the response of microelectrode recordings of neurones to sound. They found evidence for columnar organization of the primary auditory cortex (Shamma *et al*., 1993; Sugimoto *et al*., 1997).

While this paper focuses upon the minicolumn, it is intricately intertwined with the macrocolumn. Mountcastle (1997) defines a macrocolumn as: 'Many minicolumns bound together by short-range horizontal connections. Neurones within a column share certain static and dynamic physiological properties, upon which other properties may be superimposed. Minicolumns are bound into columns by both cell-autonomous and secondary histogenetic influences.' This definition, which is supported by experimental data, views the larger unit as a continuum of many minicolumns. Juliano and Whitsel (1987) used electrophysiology to demonstrate that the metabolic activity seen in 2DG blobs activated neurones. Their research showed that the metabolic response and evoked potentials are measuring the same response in larger macrocolumn-size units. A later study showed that larger 2DG blobs are not uniform in their composition, but consist of smaller zones that correspond to minicolumns (Tommerdahl *et al*., 1993). McCasland and Woolsey (1988) reported a similar finding for macrocolumns in barrel field cortex of rodents: they are comprised of smaller vertical units comparable to a single minicolumn, or possibly a group of minicolumns. Favorov and Kelly (1994*a*, *b*) demonstrated that macrocolumns are not homogenous units, but exist on the basis of individual minicolumns. The output of a macrocolumn results from tightly knit interactions between the smaller individual units within it. Therefore, columns function by interfacing between the minicolumn and macrocolumn (or mini–macro column interface) rather than as anatomically static and physiologically rigid homogenous units. No research has yet determined the capacity of minicolumns for independent activity outside the macrocolumn that they belong to.

The visibility of cell columns in Nissl-stained tissue depends on the linear arrangement of pyramidal cells and the existence of non-cell space enclosing both sides of the column core. The core area of the column contains the majority of the neurones, apical dendrites, myelinated fibres of the thalamus, cortical efferents and corticocortical fibres, as well as unmyelinated axons and synapses (Seldon, 1981*a*, 1982, 1985; Ong and Carey, 1990; Peters and Payne, 1993; Peters and Sethares, 1996; Mountcastle, 1997). Myelinated axon bundles are presumably cortical efferents originating in pyramidal cells in layer II/III. They descend towards the white matter in bundles that lie within or adjacent to the cellular core of the column (Peters and Sethares, 1996). In general, a vertical organization is more discernable in layers III, V and VI than in the granule cell layers of II and IV. Apical dendrites originating in layer V pyrimidal cells ascend in bundles through or adjacent to the cell column core (Fleischhauer *et al*., 1972; Schmolke, 1989; Peters and Payne, 1993). Thus, the compartments of a minicolumn contain

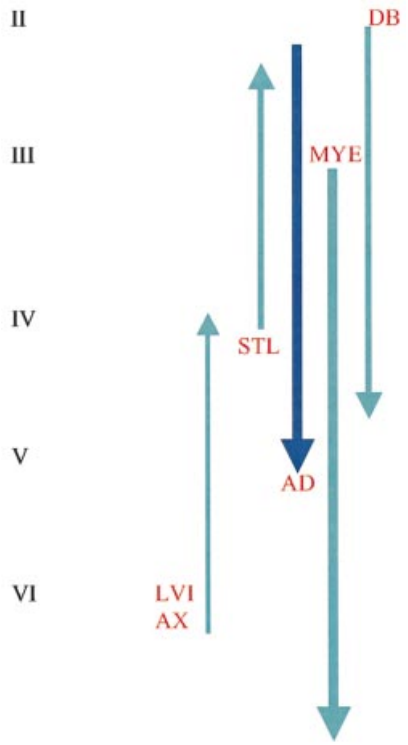

Fig. 2 The major fibre pathways shown in this figure are intrinsic, except for the myelinated bundles. They may contribute to the linear placement of cell soma and the overall vertical appearance of minicolumns. DB = Double Bouquet Cell; STL = Layer IV Stellate Cell; AD = Layer V Apical Dendrite; LVI = Layer VI Axon; MYE = Myelinated axon (efferent). Arrows indicate direction of signals. Green = arrows; blue = dendrite.

many different kinds of fibres and neurones (Fig. 2) The visibility of minicolumns also varies widely between cortical areas, presumably reflecting organizational differences. A cell-poor area surrounds both sides, noticeable in a cell body stain. This area, called the peripheral neuropil space, is rich in unmyelinated axon fibres, dendritic arborizations and synapses (Jones and Burton, 1974; Szentagothai, 1983; Seldon, 1985; Ong and Carey, 1990).

To ensure accurate data comparisons, researchers using light microscopy to locate and measure minicolumns in *in vitro* tissue must consider certain caveats. They must control for shrinkage, thickness of the tissue slice, magnification, resolution of image, plane of cut and staining artefacts. Since brain tissue can undergo significant shrinkage during processing, researchers must consider it to ensure accurate data. Studies by Pakkenberg (1966) and Robins *et al*. (1956) reveal an average tissue linear shrinkage of 36%, which is equivalent to 74–83% volume reduction during processing. Most tissue used for morphometric studies has been treated by paraffin or celloidin as an embedding medium. Paraffin has a much greater propensity for shrinkage than does celloidin, leading to more closely packed cell columns. Thus, comparisons between differently treated brain tissues must account for shrinkage factors carefully. Since shrinkage varies between brains, this procedure is appropriate for all studies.

Table 1 briefly summarizes the structures that constitute the vertical anatomy of the minicolumn. The minicolumn contains all the essential neuronal elements found within the cortex and arguably within a given cortical region. Thus, descriptions of cortical cells and pathways found within the cortex hold true for the architecture of the mini- and macrocolumn. An overview of this architecture and its relationship to the minicolumn is described below.

Cell types

Two basic cell types appear in the neocortex (and hence minicolumn): spiny and non-spiny (DeFelipe and Farinas, 1992). Spiny cells include pyramidal and non-pyramidal (stellate) cells; their dendritic branches display spines. The pyramidal cells that constitute ~75–80% of all neurones are the only projection neurones of the cortex (Jones, 1984). A second group of neurones includes the smooth or non-spiny cells, which consist of interneurones (DeFelipe and Farinas, 1992). Local interneurones constituting the remainder of cells do not send processes outside the cortex. Most of these are inhibitory, although layer IV stellate cells are excitatory. Inhibitory interneurones may constitute anywhere from 10 to 25% of the cells in the cortex (Houser *et al*., 1983; Fitzpatrick *et al*., 1987; Hendry *et al*., 1987). The three best known types of inhibitory cells include the basket (large and small) cells, the chandelier cell and the double bouquet cell.

Local inhibitory circuits

Understanding how columns work depends on knowledge of the functioning of local inhibitory circuits. In addition to the basic types of feedforward and feedback inhibition found in subcortical nuclei (Kandel, 2000), these circuits include an array of cortical inhibitory interneurones that are not yet understood (Miles, 2000). Given the plenitude of types and morphologies, they 'endanger the notion of cell types in the central nervous system' (Miles, 2000). Specific synaptic sites for each of the three major types of recognized inhibitory interneurones promote a different effect on its target neurones (usually pyramidal cells). One type of inhibitory action is described as perisomatic (basket and chandelier cell); i.e. synapses are made onto cell soma, initial segments and axon hillocks (DeFelipe *et al*., 1986, 1990). This type of synapse strongly diminishes the action potential. In the second kind of synaptic pattern, typical of the double bouquet cell, interneurones synapse onto the branches and distal segments of the dendritic trees. This action results in 'synaptic integration' (a much weaker and less direct form of inhibition). Many inhibitory and excitatory connections may cancel each other out before being passed down the dendritic tree. By comparison, the axon hillock of a pyramidal cell typically reveals about five chandelier cell synapses with no competing excitatory ones (DeFelipe and Jones, 1985; DeFelipe *et al*.,

1990; DeFelipe and Farinas, 1992). Researchers have grouped the highly complex inhibitory interneurones according to their discharge patterns, the number and (spatial) distribution of target signals, and changing kinetic patterns (Gupta *et al*., 2000; Martina *et al*., 2000). Slight alterations in any phase can significantly affect the quality of information processing. So important is inhibition in the functioning of the mini–macro column that researchers have linked certain diseases of the mind to disturbances at this level (Childs and Blair, 1997; Gustafsson, 1997; Jambaque *et al*., 2000; Casanova *et al*., 2002). DeFelipe and others are examining the role of the chandelier cell in epilepsy, which points to the potential importance of these intrinsic circuits in disease (Marco *et al*., 1996; Marco and DeFelipe, 1997; DeFelipe, 1999; Hirsch *et al*., 1999).

A recent study on feedforward inhibition in mouse barrel cortex closely links excitation and inhibition to the function of a column (Porter *et al*., 2001). After an initial volley of excitation, input from the thalamus excites inhibitory interneurones, which then fire on short latency. This detailed experiment also found that thalamocortical excitation and inhibition work in synchrony, utilizing the most important sensory information while suppressing weaker or distracting inputs. The axons of layer IV interneurones are aligned vertically. This orientation suggests that after thalamic volley, inhibition flows upward to the supragranular layers, as do excitation from the stellate and star pyramidal cells. Porter *et al*. (2001) also noted that only a subset of interneurones in each barrel responded to thalamocortical stimulation. A recent study found that dendritic trees of non-pyramidal GABAergic cells have a strong vertical bias (Jin *et al*., 2001).

Columns evidently utilize lateral inhibition to sharpen their borders and increase definition (Marin-Padilla, 1970; Szentagothai, 1978; DeFelipe *et al*., 1990; Favorov and Kelly, 1994*a*, *b*; DeFelipe, 1999). The primary source for this inhibitory effect is probably derived from axon bundles of double bouquet cells. They arrange themselves in essentially repeatable patterns between 15–30 μm wide, depending on the cortical area examined (DeFelipe *et al*., 1990; DeFelipe, 1999). Without this vital part of the mini–macro column interface, a given minicolumn would cease to function as an individual unit. Recently, Budd and Kisvarday (2001) found that layer IV clutch cell axons (a form of basket cell) tended to have isotropic connections within 50 μm of their cell body, and anisotropic lateral connectivity beyond that. They found the estimated peak connection probability for the clutch axons to be within a 30–45 μm radius that coincided with the 50 μm lateral isotropic connectivity. Other authors have proposed more than one source of columnar lateral inhibition than the large basket cells provided (Marin-Padilla, 1970). Lund *et al*. (1993) describe a model based on a study of intrinsic circuitry. In their model, simultaneously activated basket cells could create distinctive domains by cancelling out pyramidal cell excitation.

Researchers have created computer models based on physiological studies of somatosensory cortex in cat and monkey cortex. These models have critically tied the fundamental shaping of the macrocolumn during development to the correct balance of excitation and inhibition of individual minicolumns (Favorov and Kelly, 1994*a*, *b*). One computer model links decreased inhibition for minicolumns within a macrocolumn to a 10-fold change in the timing sequence of neighbouring minicolumns (Buxhoeveden and Casanova, 2001*a*). Because neighbouring columns remain active long after they would normally have shut down, they cannot respond to new inputs.

Laminae

The laminae provide neuronal differentiation and specialization within the homogeneity of the vertical array. Some authors have even described layers II and III as associational cortex, layer IV as sensory cortex or the 'inbox' of the column, and layers V and VI as the 'outbox' or motor cortex (Diamond, 1979; Calvin, 1998). Afferent input derives from three sources: thalamic, callosal and ipsilateral cortico-cortical. Input from the thalamus goes predominately to cells in layer IV, but some go to layer IIIb and even layer V. In visual cortex, lateral geniculate nucleus input is further divided into subdivisions of layer IV. From layer IV, input is sent 'upstairs' to layers III and II. These cells in turn send the connections to layers V and VI. Thalamic input also goes to interneurones. Callosal input is received in layers IV, IIIb, III and II (Mountcastle, 1997; Herschkowitz *et al*., 1999). Corticocortical afferents go to layers IV, IIIb, III and II. Although corticocortical and callosal afferents overlap to some degree with thalamic input, they also extend to more superficial layers (Mountcastle, 1997).

All this transferring of information inevitably causes a time delay that may significantly affect brain function. Output pathways are derived only from pyramidal cells. In monkey cortex, cells in layer VI send connections to the thalamus, claustrum and other cortical regions (Jones, 1984). Layer V sends projections to the spinal cord, pons, medulla, tectum, thalamus, red nucleus and striatum (Jones, 1984). Layer III neurones go to ipsilateral cortex and the corpus callosum, while layer II are corticocortical only (Jones, 1984). In addition, layer III pyramidal cells send axons laterally to other minicolumns in the area, which form connections with neighbouring minicolumns (Calvin, 1998; Yabuta and Callaway, 1998).

One can envision the cortical column as a unit constructed of specialized horizontal layers. Each of them contains a diffuse set of local inhibitory circuits, gradients of receptor types, and at least three major types of extrinsic input and output pathways. It is doubtful that a column utilizes all its input and output pathways at the same time. The capacity to selectively inhibit individual laminae adds flexibility and complexity to the vertical organization. Seen in this way, a

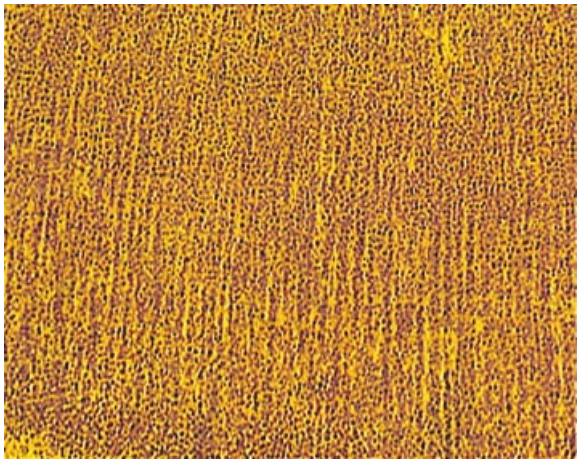

Fig. 3 Human foetal columns at ~26 gestational weeks.

vertical column can be dissected into horizontal components and reconstructed into new formations.

Developmental anatomy of minicolumns

Rakic showed that the earliest organization in the cortex is the vertical array of cells (Fig. 3) (Rakic, 1972, 1990). Once they migrate from the ventricular zone to the cortical mantle, they form ontogenetic radial cell columns. It was known that ~87–90% of cells migrated along the direct radial pathways that Rakic described (Rakic, 1972, 1988*a*, *b*). Later discoveries showed that some cells did not follow this pathway, creating a discrepancy regarding the nature of migrating neurone patterns in developing cortex (Walsh and Cepko, 1988; O'Rourke *et al*., 1992, 1995; Walsh, 1993). It now appears that the horizontally displaced clones resulted not from tangential migration between germinal epithelium and the cortical plate, but from certain progenitor cells in the ventricular zone. Kornack and Rakic (1995) used retrovirally labelled clones in the germinal cell layer to label cells at different gestational times with the marker gene *lacZ*. The distribution of labelled cells suggests two different modes of cell division. Thus, in primates the first phase of cell division symmetrically doubles the number of progenitor cells of future cortical minicolumns. A second phase then intertwines with the first to provide progenitor cells that divide asymmetrically. This mode of reproduction provides for cells that leave the ventricular zone and form a scaffold along the cortex in inside (grey–white matter junction) to outside (pia) fashion. The Kornack–Rakic experiment suggests the number of symmetrical divisions early in gestation dictate the size of the cortex and total number of minicolumns (Kornack and Rakic, 1995). Later asymmetrical divisions provide for the neuronal density within individual minicolumns.

Despite the lack of conclusive evidence, most researchers believe that ontogenetic cell columns develop into adult minicolumns (Swindale, 1990; Mountcastle, 1997). A qualitative anatomical study of development in human auditory cortex concluded that ontogenetic radial cell columns were the same vertical minicolumns found in the adult brain (Krmpotic-Nemanic *et al*., 1984). Yuste and colleagues traced physiological activity that was columnar and radial during the development of the rat neocortex. They concluded that: 'The shape of the coronal domains strongly suggests the columnar units of visual and somatosensory cortex and the proposed radial units associated with radial glial fibers' (Yuste *et al*., 1992).

Very few studies have examined the maturation process from the ontogenetic radial column to the adult minicolumn (Krmpotic-Nemanic *et al*., 1984). Buxhoeveden and colleagues attempted a limited examination of the structure of the cell column in the human foetal cortex (Buxhoeveden *et al*., 1996; unpublished data). In general, morphological features of minicolumns such as linearity, cell density and neuropil space developed at a different rate in each lamina. Changes leading to lamination appeared at 24 weeks, while more pronounced lamination began at ~29 weeks (Krmpotic-Nemanic *et al*., 1984; Buxhoeveden *et al*., 1996). Before the onset of lamination, the columns are highly linear throughout the cortical mantle. Between 14 and 29 weeks, the centre-to-centre spacing distance of the minicolumns in our sample doubled from 4.6 to 9.6 μm. From 29 to 42 weeks, a period of 13 weeks, this distance increased only 4.5 μm. At the end of gestation the mean width of a minicolumn was ~13 μm, approximately one-third adult size.

Columns and modules

Generally, a column organizes a myriad number of neurones with various specializations into a coherent functional unit (Szentagothai, 1978, 1979, 1983). As such, it shares properties with the concept of the module. Modules have been defined as a group of cells with similar response properties (Leise, 1990), or the repetitive use of basically similar units (Szentagothai, 1983). Krubitzer (1995) defines them simply as 'structural and physiological discontinuities within the limits of classically defined cortical field.' Leise (1990) refers to modules as larger organizing units, extending beyond cortical units to include subcortical nuclei and neuropils (spherical lobes of tissue visible without specialized staining methods) found in invertebrate brains. These definitions do not limit a module to the neocortex. Leise argues that the nuclei and structures found in invertebrates such as neuropils and ganglia can be defined as modules fitting Mountcastle's criteria for columns. Modular construction of nervous tissue is considered a common feature of nervous systems, not just of mammals, and may either be an organizing principle or a remarkable convergence.

In her examination of six aspects of Mountcastle's criteria for minicolumns, Leise (1990) concluded that invertebrate neuropils satisfy at least five of them. However, they mostly fail to meet Mountcastle's criterion that topographial representations can shift across a field of modules. She describes modules in various subcortical regions, based on mosaic

regions of alternating acytecholinesterase activity within the striatum of mammals including humans, the basal ganglia and superior collicus. Similarly, the dorsolateral and ventromedial nucleus of motor nuclei in the spinal cord is viewed as two cylinders (Szentagothai, 1983), and the anterior and posterior grey matter are referred to as 'columns' (Carpenter, 1983). Although they are vertical and share similar tasks, they have little else in common with the cortical minicolumn. It is probably a mistake to equate these subcortical modules too closely with cortical minicolumns. Minicolumns differ from other modules by virtue of their local circuitry, small size and sheer number, dual migration, the horizontal and vertical overlay, and multifunctional capacities, as well as the amount of distant and local networking done by minicolumns. The ability of the cortex to utilize functionally distinct columns within the same cortical space is well established in visual cortex where multiple columnar systems are present (Hubener *et al*., 1997).

Patterns of organization seem to repeat themselves in the CNS. Similar circuit themes like recurrent and reciprocal inhibition and feedforward–feedback pathways appear throughout the brain. Because the brain is a product of evolution, nothing appears in a vacuum but is a modification of what preceded it. The CNS clearly exemplifies the addition of one structure to another. From this perspective, columnar organization emerges from existing cortical anatomy and function, not as a radically new structure. Even primitive brains network and cluster cells of similar function into localized regions. Thus, similarities between phylogenetically ancient subcortical structures and the neocortex are easy to construe. These similarities provide an evolutionary rationale for the existence of the cell column, because it does not appear abruptly or in isolation. Nonetheless, despite these general similarities, the cortical column is a substantial modification of any other structure in the brain, and not merely a copy of subcortical organization.

Minicolumns as superimposed dual organizational themes

Cortical columns seem to be uniquely composed of two distinctive types of anatomical organization that share the same cortical space. Evidence exists for a dual phylogenetic origin in the cerebral cortex, one for the radial configuration and one for the horizontal lamina (see above, 'Developmental anatomy of minicolumns') (Nauta and Karten, 1970; Kuan *et al*., 1997). This dual organization may enhance the efficiency of cortical tissue by incorporating two somewhat distinct anatomies (themes) within the same spatial domain. For example, in columnar neocortex, a particular stellate cell plays a role not only as part of sensory nuclei known as lamina IV, but also as part of a vertical unit of ~100 cells. Because of the latter, its axons project to a very select group of neurones located immediately above it. The messages sent by this cell to the supragranular layers are also transmitted vertically to the infragranular layers, so that the activity of this lamina IV neurone merges with that of the entire vertical unit.

Because the tasks of columns are also distributed (Mountcastle, 1997), each particular region may process diffuse types of information. Were this a subcortical region, processing of very different kinds of information might be performed by a different group of more specialized neurones.

Cortical homogeneity

While the neocortex is subdivided in cytoarchitectonic regions, it is still strikingly homogenous in its overall anatomical appearance. As evidence for this, researchers have historically encountered difficulties in their attempts to subdivide the cortex. The development of the cortex reveals anatomical homogeneity from its inception in the form of ontogenetic cell columns, which is the first order of organization in the neocortex. An examination of the columnar organization of fetal tissue strikingly reveals a basic uniformity that extends throughout the cortical mantle. The changes that will later make the cortex distinctive build upon this initial anatomical template. As the cortex matures this uniformity decreases. Nonetheless, the basic vertical and horizontal configuration remains the dominant outline of organization subject to regional variation. However, the specialization of columns in different regions of the brain is not well understood. Very little work has elucidated such differences, a difficult task considering the range of techniques used to examine mini- and macrocolumns.

A recent study of mouse brains reveals highly specified locations of cells and microcircuits in the cortex (Kozloski *et al*., 2001). The study reported that specific connections (targets of layer V cortical tectal neurones) are organized anatomically in a stereotyped fashion, with specific patterns differing between animals. The distribution of four types of neurones with connections to this pyramidal neurone was distinctive and stereotyped in each case. Fusiform interneurones were located within a range of 30–65 μm of the trigger cell and always below it. Another class of large triangular interneurones were all positioned above the trigger neurone, and almost as close. The most distant neurones were called 'dangling' pyramidal cells, though one appears immediately below the layer V pyramidal cell. The study ruled out the possibility of probabilistic or random connections and confirmed the precise organization of neuronal microcircuits. Cortical connections for these trigger neurones were heavily localized. Their proximity appeared to be the equivalent of minicolumn space with some horizontal dispersal to neighbours. The study also showed a variation of patterns among animals of the same species. The implication is that column organization predictably varies between individuals as well as species.

Most striking about the relative homogeneity of the cortex, cortical cell columns must integrate information as diverse as auditory, visual, touch, movement, emotion, memory,

language and more into a unified whole. Despite this diversification of function and the immense size of the cortex, all minicolumns look quite similar. Thus, they differ from subcortical areas, whose very distinctive nuclei perform specialized tasks. Subcortical structures arrange cells anatomically into nuclei and ganglia that are both specific to a region and highly divergent from each other. For example, the spinal cord involves a central grey area with external white-matter fibre bundles. The medulla is remarkable for its highly distinguishable mass called the inferior olive, with an array of diverse looking nuclei and fibre tracts. The pons contains yet a different assortment of nuclei and fibres, as do the mesencephalon, thalamus and basal ganglia. This disparate assembly of cell clusters makes subcortical regions generally much easier to identify than cortical ones. The cerebellum, like the neocortex, has a more homogeneous organization that differs uniquely from the rest of the CNS, but it does not involve the same levels of diversification as the neocortex.

Heterogeneity within homogeneity: columns are specialized

Although homogeneous in their outline, minicolumns are also highly irregular. It is probably a mistake, and the basis for some confusion, to describe them as repetitive, almost clone-like reiterations (Rockel *et al*., 1980). Their apparent homogeneity probably arises from the model of anatomical organization in which similar inputs, outputs and local circuitry form a basic template for cortical organization. Columnar theory postulates a fundamental strategy for cortical organization. However, it does not require identical units. Despite their similar outlines, columns reveal quite diverse separate configurations. A developing minicolumn can build a highly specific set of synaptic contacts that differs from those of its immediate neighbours. Thus, essential differences may appear between minicolumns in different areas of cortex, or even within the same region (Swindale, 1990). Moreover, they can attract different numbers of afferent fibres while projecting a slightly dissimilar set of efferent pathways. Change between minicolumns may depend on the role of environmental influences on minicolumn configuration, as well as possible differences in the distribution of cells and fibres. Minicolumns appear to be heavily dependent on environmental input (Rakic, 1988*a*, *b*, 1995; Favorov and Kelly, 1994*a*, *b*), which promotes variability among individuals. This variability could account for some of the 'gross' morphological differences that have been observed between minicolumns. These include aspects such as the amount of neuropil space in the periphery, cell density within a column, the vertical linearity of the perikarya, the width of a column and the ratio of width to amount of peripheral neuropil space (Buxhoeveden *et al*., 1996; 2001*a*, *b*).

Columnar heterogeneity involves differences in architectonic appearance, response properties, connectivity, immunocytochemistry, metabolism and stimulus preference (Krubitzer, 1995). Species differences appear in area 17, where primates have acquired specific modules to process colour, form and motion; these modules differ from those of rodents or cats (Livingstone and Hubel, 1984). In addition, projections from area 17 to extrastriate cortex primate brains differ from those of rodents, and these interconnections arise from the modules within the two fields. Specific comparisons reveal that the visual systems of monkeys display better colour and visual acuity than those of cats (Orban, 1984). While the rhesus monkey has a larger brain, their minicolumns (in this region) are much smaller: ~31 μm compared with 56 μm in the two-dimensional plane (Peters and Sethares, 1991; Peters and Yilmaz, 1993). When extrapolated to three dimensions, the columns in the cat visual cortex are actually three times larger than those of monkeys (Peters and Yilmaz, 1993). The monkey's cell columns are smaller and appear more 'complex', because they have relatively more cells, providing more detailed specification of information than the cat's. Recently, it was demonstrated that cells in layer IVa of primary visual cortex differ between human and ape, a surprising finding considering the assumed similarity of this region (Preuss *et al*., 1999). Cell densities in layer IV may vary between prosimians and anthropoids (Preuss and Goldman-Rakic, 1991). They may also vary in posterior cingulate cortex layer IV, where packing density is less dense in prosimians than in anthropoids (Zilles *et al*., 1986). Minicolumns based on layer V apical dendrites are significantly larger and contain more neurones in cat V1 than in monkey (Peters and Yilmaz, 1993; Peters and Sethares, 1996).

Homologous regions of temporal cortex in closely related human and non-human primate species reveal differences in size, relationships between cells within a column and variations in the amount of peripheral neuropil space within their borders (Buxhoeveden *et al*., 1996, 2001*a*). Buxhoeveden and colleagues and Seldon found minicolumn lateralization (wider columns with more peripheral neuropil space in the left hemisphere) in some areas of the auditory association cortex (Seldon, 1981*a*, *b*; Buxhoeveden *et al*., 2000; Buxhoeveden and Casanova, 2001*b*). This finding was absent from homologous regions in the brains of the common chimpanzee (*Pan troglodytes*) and rhesus (*Macaca mulatta*) monkey. This species specificity in minicolumn lateralization and morphology, in selected regions of the brain, separates human brains from those of non-human primates. Asymmetry of minicolumns may signify variations in neuropil and the thickness of myelinated axons in the left hemisphere (Anderson *et al*., 1999). The lateralization of minicolumns in human brain may represent an evolutionary alteration in circuitry in what had previously been identical regions of brain (Seldon, 1981*a*, *b*). Lateralization of columns in certain regions of the cortex may also be a major source of columnar homogeneity within a species.

Rodents reveal a unique, very specialized macrocolumn called the barrel cortex (Woolsey and Van Der Loos, 1970;

Welker and Van der Loos, 1986). Barrel field cortex is a module that is species specific (rodents only), area specific (somatosensory cortex) and lamina specific (mostly lamina IV) (Woolsey and Van der Loos, 1970; Welker and Woolsey, 1974; Keller, 1995). Evidence exists that barrel field columns, like macrocolumns in cat and monkey somatosensory cortex, are comprised of smaller vertical units comparable to a single minicolumn, or even a group of minicolumns (McCasland and Woolsey, 1988). The same authors also found considerable individual variation in the radial labelling distribution of corresponding columns in different cerebral hemispheres.

Different species reveal different types of columns in different regions of the brain. The visual cortex contains highly specific types of columns called orientation and ocular dominance columns, as well as hypercolumns, the merging of more than one macrocolumn. In fact, the visual system reveals a columnar organization for an array of tasks, in what is referred to as 'multiple columnar systems' (Hubener *et al*., 1997). Hubener *et al*. (1997) state that rather than envisioning the visual cortex as containing identical modules, it should be viewed as being composed of mosaics of functional domains with different properties arranged non-randomly. Within the macaque monkey, basal dendrite arbors of pyramidal cells in supragranular layers (III) of temporal and parietal regions are larger and contain more branching and spines than in the occipital lobe. Those in the frontal lobe are even larger (Lund *et al*., 1993; Elston and Rosa, 1997; Elston, 2000). Layer V basal dendrites for these same features also vary in areas TEO, TE and the superior polysensory area (Elston and Rosa, 2000). Elston and Rosa (2000) conclude that intrinsic circuitry differs across cortical areas. Interestingly, the peak complexity attained by the dendritic field of a layer V pyramidal cell was 50–70 μm from the cell body, after which the number of branches decreased. This is well within minicolumn range. Likewise, spine density also varied as a function of distance and peaked at ~70–130 μm from cell soma.

The vertical appearance of cortex is known to vary within a brain. Some regions tend to be more columnar than others, although no one has specifically analysed the precise linear variation of the cortex. Studies also show that cell columns in different cortical areas contain distinctive patterns of NADPH-diaphorase expression (Csillik *et al*., 1998; Barone and Kennedy, 2000) and GABA neurones (Beaulieu, 1993). Finally, the number of neurones found in different cortical areas reveals no basic uniformity (Beaulieu, 1993; Skoglund *et al*., 1996).

Variation in the size of minicolumns, as well as the distribution of neuropil space, is markedly present in very small regions of interest that fall within macrocolumn size (Buxhoeveden *et al*., 1996). The amount of variation described in measures of column width or centre-to-centre spacing tends to be large (Schlaug *et al*., 1995; Buxhoeveden *et al*., 1996; Peters and Sethares, 1996; Buxhoeveden *et al*., 2000). A coefficient of variation ranges typically between 0.18 and 0.30 (Buxhoeveden *et al*., 1996). No research has yet shown whether this variation is real rather than the result of *z*-axis artefact (see above, 'Columns and modules'). If this is not artefact, minicolumns lack a homogenous configuration, even within a single macrocolumn.

The 'decline' of the single cell and the rise of plasticity

A networking concept of the brain has slowly replaced views singling out the neurone as the functional unit of the brain (Douglas and Martin, 1991*a*, *b*). Arguably, the loss of single cell autonomy is more evident in the neocortex than anywhere else, contributing to the theory of a distributed function system (Mountcastle, 1997). The output of a minicolumn may resemble that of a single, very complex (usually projection) neurone, or that of a tightly knit group of neurones in phylogenetically older parts of the nervous system. The column contains concentrated circuitry in highly localized units, diminishing the autonomy of single cells within it. In the cortex, more cells do the job that fewer do in other regions. This, in turn, creates more variation, complexity and subtlety. Subcortical nuclei achieve complexity by networking, often over long distances between other nuclei. Although the cortex also networks, the initial outputs from each column have already undergone extensive localized processing. As brain evolution paralleled the increase in cell number, a reduction occurred in the sovereignty of individual neurones; fewer of them occupy critical positions. As a consequence, plasticity and redundancy have increased. In nervous systems containing only a few hundred thousand neurones, each cell plays a more essential role in the function of the organism than systems containing billions of neurones.

Another argument favouring columnar organization of single neurones holds that the cortex lacks enough myelinated bundles to connect every neurone reciprocally in each hemisphere (Cook, 1984). Estimates of the number of callosal fibres range from 200 to 500 million (Cook, 1984; Houzel and Milleret, 1999). Quite possibly, each minicolumn both receives and sends a myelinated fibre to a counterpart in the other hemisphere (Cook, 1984). In the visual cortex, callosal axon terminations seem to correspond to orientation columns (Innocenti, 1994). Houzel and Milleret (1999) found only a minority of callosal axons performing a strict point-to-point mapping of retinotopically corresponding sites in the visual cortex of cats. Many of them have widespread arbors, demonstrating that a single callosal fibre can influence several cortical columns in the opposite hemisphere. Based on the comparatively small number of myelinated axonal fibres in the corpus callosum, minicolumns and not individual cells establish contact with each other. The same can be said of projection fibres. Notably, a 'striking feature of the pallial structure is the relatively small number of projection fibres compared with the enormous number of cortical neurones' (Carpenter, 1983). Development of callosal axons in cat visual cortex (17 and 18) reveals that from the earliest stages

they grow into the grey matter in columnar-like bundles. Boutons are then distributed in radial columns whose diameter increases with age (Aggoun-Aouaoui *et al*., 1996).

The retinal ganglion cells might exemplify ways that non-cortical neurones may function with greater autonomy than cortical ones. The dendritic trees of these cells may contain as many as 20–30 electronic subunits. They can electronically decouple sections of the dendritic tree, suggesting a high degree of local activity. Local inhibitory and excitatory input could be processed in a small region of the dendrite before being passed further on. This was found to be rare, if present at all, in cortical neurones, where subunit processing on dendritic spines in the cortex may constitute <10% of them (Douglas and Martin, 1991*b*). In the neocortex, most signals are transferred to the shaft of the dendrite without further processing. In a minicolumn, information is both compartmentalized and shared. This gathers all the cells of a column into a conglomerate of inputs. Thus, not all of the neurones need direct connections with the thalamus or the opposite hemisphere. Rather, certain ones are dedicated to passing the information on.

Cortical neurones probably exert less individual autonomy than subcortical ones, revealing great cortical plasticity. Neurones in regions like the spinal cord, for example, depend intricately on each other, with functional output more directly related to single cells. When individual projection neurones are more directly tied to specific outcomes, their loss results in more pronounced consequences. The loss of only a few alpha motor neurones results in deficits in muscle control. An equivalent effect seems less plausible in the cortex due to the design of the minicolumn. With so many cells located within a minicolumn, the loss of a few would not result in the kind of deficits incurred by the spinal cord motor unit, though the loss of certain cells (such as a chandelier cell) may be more significant than others (DeFelipe, 1999). Furthermore, even if a minicolumn is damaged, it is unlikely to noticeably disrupt the action of an entire macrocolumn. Arguably, column design builds in cortical redundancy.

The ‘temporal column’

All biological processes operate within the dimension of time. This temporal component affects the column as much as it does cells, pathways and synapses. Without the correct sequencing of neural activity, the nervous system would degenerate into chaos, and the mini–macro column interface would disintegrate. It may be argued that time sequencing affects the functioning of the vertical organization more critically than it does the horizontal. While many ‘hard’ anatomical components arrange themselves vertically (Table 1), vertical function is less ‘fixed’ than the horizontal one. The horizontal layers are present in all temporal phases of the neuronal activity. In other words, as a definable anatomical feature of the cortex, they always carry out generalized tasks, regardless of the time element. On the other hand, precise combinations of inhibition and excitation ‘create’ columns of different size and function (according to the limitations of a basic anatomical outline). Based on the research done to date, columnar units may potentially exist in various ‘states’. A physiological macrocolumn may consist of different vertical subunits at any given moment, depending on the function it serves. An anatomically distinct 50 μm radial unit can merge its physiological boundaries to become part of something that moments ago was three individual minicolumns. At any given instant, it may consist of 60 activated minicolumns, a moment later 10, and so forth. Furthermore, the lamina within a column may undergo selective inhibition or excitation, thereby temporally ‘fragmenting’ the vertical unity of the column, as may be the case with barrel cortex in rodents. On a larger level, the activation patterns seen in PET scans or blood oxygenation level dependent (BOLD) fMRI are suggestive of fleeting activations of columns in time (Duong *et al*., 2000; Kim *et al*., 2000).

Cell columns and medical anomalies

The expansion of the neocortex is a critical issue in the study of primate brain evolution. It may be due to an increase in the number of minicolumns, so that cortical area increases rather than cortical thickness (Rakic, 1978, 1990, 1995; Bugbee and Goldman-Rakic, 1983). A recent study found that the duration of cell cycles in monkeys is five times longer than in rodents, and that monkey cortex had an accelerated cell division during neurogenesis (Kornack and Rakic, 1998). The authors conclude that the evolutionary modification of the duration and number of progenitor cell divisions contributed to enlargement of the cortex (Kornack and Rakic, 1998). Sawaguchi and Kubota (1986) focus on the multiplication of cortical macrocolumns as the basis for cortical enlargement and evolution (the column multiplication hypothesis). This view envisions macrocolumns as genetically based and susceptible to genetic mutation and variation. These scientists hypothesize that in higher primates pre-existing columns in some areas have multiplied. Rakic’s model makes the radial ontogenetic cell column the basis for this sort of selection (Rakic, 1995). Since both types of column are intimately intertwined, these postulates are not mutually exclusive.

However, examples in the medical literature raise challenging questions about cortical organization and brain size. They closely relate the outcome of a brain injury to its organization. In some cases, when fluid or cysts replace very substantial amounts of cortex, the patient has retained normal cognitive abilities (Bigler, 1988; Lebeer, 1998). Similar instances have been reported for hydrocephalic, Dandy–Walker syndrome, porencephalic cysts and others (Suarez *et al*., 1984; Zhang and Yi, 1984). In some cases, only a small part of a neural system must function (motor, visual, etc.) to allow operation of the whole brain. Furthermore, when more tissue is damaged, the patient suffers less functional loss than if only part of a region is involved. The ‘mass action effect’ and surround inhibition may be possible reasons why removal of larger regions affects patients less than partial damage

(Mealey *et al*., 1973). According to Lebeer (1998): 'The relation between extent of damage and functional loss is not linear but follows a U-shaped curve.' Lebeer cites three individuals who, despite devastating brain loss, are 'ortho-functioning' (capable of participating in school or work in a reasonably independent way). It should be noted that a dysfunction is usually associated with these pathologies. Yet this is not always the case, even when fluid replaced as much as 95% of the cortex (Lebeer, 1998). A mathematician was found to be functioning with an IQ of 126, with normal social skills, with only one-twentieth of a normal cortex, which was estimated to be about one-third the size of that of a chimpanzee (Lewin, 1980). Caution, however, is required when interpreting the actual amount of cortex loss to megalencephaly; brain scans can be deceptive, with more tissue present than film reveals.

Perhaps more definitive examples involve cases of children with an entire hemisphere, or large parts of it, removed due to intractable seizures disorders (hemispherectomy). In many cases the results are surprisingly good (Bogen, 1997; Stark and McGregor, 1997; Boatman *et al*., 1999; Menard *et al*., 2000). In one case, removal of the left hemisphere in an 8.5-year-old actually resulted in improved language skills (Vargha-Khadem *et al*., 1997). In other cases, left hemispherectomized patients developed good language skills despite removal of the entire left hemisphere, indicating remarkable plasticity of the right hemisphere for language (de Bode and Curtiss, 2000).

These cases suggest that the type of cortical damage, rather than the amount, is the critical determinant. In cats with induced hydroencephaly most of the cells in the cortex were found to be undamaged, even though the thickness of the cortical mantle was severely compressed (Rubin *et al*., 1975, 1976). Because the basic processing units (columns) were intact, they had time to adapt to the slow loss of myelinated axons. In Alzheimer's disease, severe cognitive dysfunction occurs though less of the total brain tissue is involved than in some the examples reported above. Alzheimer's disease may involve the disruption of closely integrated pathways, beginning in the hippocampus, that follow axonal pathways (Ritchie and Touchon, 1992; De Lacoste and White, 1993). Since efferent information enters minicolumns via axonal pathways, disruption of specific columnar communication could occur. In megalencephaly or cortical transection, the damage occurs more randomly with regards to specific columnar pathways. This may result in a different sort of impairment with a better opportunity for plasticity to operate. This contrast is analogous to the difference between systemic destruction of tissue throughout the body and the loss of an entire limb. In the former case, the body gradually fails to adjust to erosion, although in the latter, the body can rely on intact limbs to make adjustments.

Some new studies reveal potential differences in the columnar organization of brains in patients with autism, Down's syndrome and schizophrenia (Buxhoeveden and Casanova, 2000, 2001*b*; Buxhoeveden *et al*., 2000; Casanova *et al*., 2000, 2001*a*, *b*, *c*, *d*). These studies seem to implicate columns in disorders of the brain, and provide a new way in which to approach these kinds of disorders. Further research must determine whether abnormalities in cell columns are primary causes or secondary effects.

Questions about the nature of columnar organization

Some authors have regarded claims about mini- and macrocolumns with scepticism (Slimp and Towe, 1990; Swindale, 1990). It has been argued that the origin of the vertical striations seen in Nissl-stained minicolumn tissue is unclear. Furthermore, it is difficult to determine whether these striations define single groups of cells that extend from the white matter to pial surface (Swindale, 1990). However, the use of optical density measurements by objective and quantitative computerized imaging has revealed the presence of repeatable densities of cells of minicolumn size from layer II–VI (Tommerdahl *et al*., 1993; Schlaug, 1995; Buxhoeveden *et al*., 1996; Buldyrev *et al*., 2000). The use of very different methods has yielded similar results. The generally small differences in size between these studies can be accounted for by biological variation, areal and species differentiation, methods used, tissue thickness and variations in shrinkage factors. In a limited comparison of myelinated bundles with cell soma in serial sections, we found a correlation between the two (D. P. Buxhoeveden, unpublished data). Results from this and future studies may definitely correlate cell soma minicolumns with those defined by myelinated bundles (Fig. 4) (Peters and Sethares, 1996).

Another avenue of research supports the validity of the minicolumn as an anatomical and physiological reality. Studies have correlated optical density arrays seen in Nissl stained slides with optical measures of brain activity (MacVicar and Hochman, 1991; Haglund *et al*., 1992). For example, the intrinsic optical signal (IOS) measures the change in optical properties that results from the ionic properties of cell activation (Holthoff *et al*., 1994; Dodt *et al*., 1996; Holthoff and Witte, 1996). These experiments have analysed the spatial distribution of neuronal activity by electrical stimulation of axons in the white matter immediately below layer VI (Holthoff and Witte, 1996; Kohn *et al*., 1997). They confirm the presence of a regular spatial variation in the intensity of the optical signal that corresponded to the size of minicolumns. Kohn *et al*. (1997) correlated the IOS 'minicolumns' with those in serially sectioned Nissl slides. Another study examined periodic variations within 2DG blobs in somatosensory cortex in monkey brain. It found minicolumn size periodicity matching that of optical densities in serially stained Nissl slides (Tommerdahl *et al*., 1993). The direct comparison of serial images obtained in Nissl tissue with metabolic activation conclusively demonstrated that cell soma and metabolic columns are one and the same at the minicolumn level.

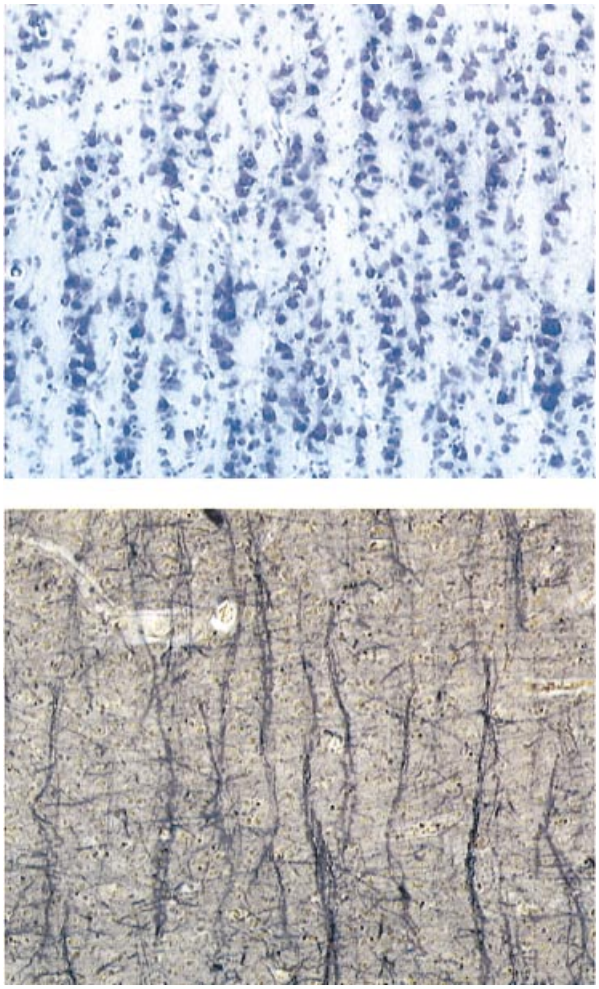

Fig. 4 Myelinated fibre bundles and cell soma columns in the same region (planum temporale) of a 16-year-old male cortex. Although these are not serial sections, the correlation between myelin bundles and cell arrays is clear.

Swindale (1990) has claimed that aside from the work of Hubel and Wiesel (1977) in visual cortex, no physiological evidence has been found that minicolumns are capable of discrete functional activity. However, microelectrode studies in cat and monkey have provided evidence for discrete minicolumn functionality in somatosensory cortex (Kaas, 1981; Favorov *et al*., 1987; Favorov and Whitsel, 1988*a*, *b*; Favorov and Diamond, 1990). It has been argued that the interpretation of receptive field studies may be difficult (Slimp and Towe, 1990). Nonetheless, the evidence obtained by IOS and the 2DG studies is no less significant in defining minicolumns as functioning units (Holthoff and Witte, 1996; Kohn *et al*., 1997).

Studies of oscillatory responses in the cortex provide yet more evidence for columnar organization, where it was found that neurones in separate columns are capable of synchronizing their oscillatory responses. The anatomical substrate for this is based on tangential or reciprocal projections from columns in other cortical areas (Gray *et al*., 1989; Llinas *et al*., 1990; Freiwald *et al*., 1995). Shamma *et al*. (1993) studied response properties in auditory cortex of ferret brain and found a columnar organization for the responses. Most cells in a local region shared similar response features as to frequency-modulated tone. Sugimoto *et al*. (1997) found evidence for partial minicolumnar organization based on stimulus amplitude in auditory cortex of gerbil brains (penetrations were in 100 μm steps). Because the anatomical level of these oscillators is unclear, they may involve everything from minicolumns to hypercolumns.

Some leading questions concerning columnar organization were summarized at a recent symposium focused on the cortical cell column (Computation in the cortical column, 2000), including the following.

(i) Does the diversity in the different forms of columns according to morphology, electrophysiological properties, molecular and connectivity patterns mean that columns are multidimensional and extremely complex? Or are they relatively simple computation machines that share similarity in their principles of operation?

(ii) To what extent are columns genetically determined? Is the genetic basis for columns merely an outline while the adult column is an emergent property?

(iii) To what extent are specialized columns such as those in barrel field cortex representative of the operations of columns in primate cortex? That is, are columns highly specialized according to species and regions?

(iv) What is the precise functional significance of the various anatomical features that represent vertical organization? In addition to these questions, we may ask how columns are affected by, and contribute to, disease processes.

Conclusions

Based on evidence for the minicolumn from so many diverse sources involving distinctive premises and procedures, the minicolumn must be considered a strong model for cortical organization. However, it may be a mistake to view minicolumns as clone-like repetitive units. They reveal patterns of vertical organization, as well as similar, but not necessarily identical, inputs and outputs. The evidence seems to favour variation within a basic outline, even among minicolumns in very small regions of interest. Differences can exist in regard to pathways, neuropil, intrinsic circuits and even neurones (such as the Meynert cell, which is known to be present over distances exceeding minicolumn size). Nonetheless, the minicolumn seems to be the most basic and consistent template by which the neocortex organizes its neurones, pathways and intrinsic circuits.

Acknowledgements

This work was completed with the help of Emil Roy. This material is based upon work supported by the Theodore and Vada Stanley Foundation, the Office of Research and

Development (R&D), Department of Veterans Affairs (VA) and NIMH grant MH61606.

References

Aggoun-Aouaoui D, Kiper DC, Innocenti GM. Growth of callosal terminal arbors in primary visual areas of the cat. Eur J Neurosci 1996; 8: 1132–48.

Anderson B, Southern BD, Powers RE. Anatomic asymmetries of the posterior superior temporal lobes: a postmortem study. Neuropsychiatry Neuropsychol Behav Neurol 1999; 12: 247–54.

Barone P, Kennedy H. Non-uniformity of neocortex: areal heterogeneity of NADPH-diaphorase reactive neurons in adult macaque monkeys. Cereb Cortex 2000; 10: 160–74.

Beaulieu C. Numerical data on neocortical neurons in adult rat, with special reference to the GABA population. Brain Res 1993; 609: 284–92.

Bigler ED. Good outcome associated with cerebral reconstitution in hydrocephalus. J Child Neurol 1988; 3: 297–8.

Boatman D, Freeman J, Vining E, Pulsifer M, Miglioretti D, Minahan R, et al. Language recovery after left hemispherectomy in children with late-onset seizures. Ann Neurol 1999; 46: 579–86.

Bogen JE. Does cognition in the disconnected right hemisphere require right hemisphere possession of language? [Review]. Brain Lang 1997; 57: 12–21.

Budd JM, Kisvarday ZF. Local lateral connectivity of inhibitory clutch cells in layer 4 of cat visual cortex (area 17). Exp Brain Res 2001; 140: 245–50.

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

Buldyrev SV, Cruz L, Gomez-Isla T, Gomez-Tortosa E, Havlin S, Le R, et al. Description of microcolumnar ensembles in association cortex and their disruption in Alzheimer and Lewy body dementias. Proc Natl Acad Sci USA 2000; 97: 5039–43.

Buxhoeveden D, Casanova MF. Comparative lateralization patterns in the language area of human, chimpanzee, and rhesus monkey brains. Laterality 2000; 5: 315–30.

Buxhoeveden D, Casanova MF. Computer modeling of excitation-inhibition defects in autism. In: Proceedings Summary of the American Psychiatric Association Annual Meeting; 2001a. p. NR 728.

Buxhoeveden D, Casanova, MF. A quantitative comparison of radial cell columns in Tpt cortex of Down's syndrome and normal subjects. J Intel Disabil Res. In press 2001b.

Buxhoeveden D, Lefkowitz W, Loats P, Armstrong E. The linear organization of cell columns in human and nonhuman anthropoid Tpt cortex. Anat Embryol (Berlin) 1996; 194: 23–36.

Buxhoeveden D, Roy E, Switala A, Casanova MF. Reduced interneuronal space in schizophrenia [letter]. Biol Psychiatry 2000; 47: 681–82.

Buxhoeveden D, Switala AE, Litaker M, Roy E, Casanova MF. Lateralization in human planum temporale is absent in nonhuman primates. Brain Behav Evol 2001a; 57: 349–58.

Buxhoeveden DP, Switala AE, Roy E, Litaker M, Casanova MF. Morphological differences between minicolumns in human and non-human primate cortex. Am J Phys Anthropol 2001b; 115: 361–71.

Calvin WH. Competing for consciousness: how subconscious thoughts cook on the back burner. [Online]. 1998, April 30; Available from: http://williamcalvin.com/1990s/1998JConsc Studies.htm last updated April 30, 2001.

Carpenter MB. Human neuroanatomy. 8th ed. Baltimore: Williams and Wilkins; 1983.

Casanova MF, Buxhoeveden D, Sohol G. Brain development and evolution. In: Ernst M, Rumsey J, editors. Functional neuroimaging in child psychiatry. Cambridge (UK): Cambridge University Press; 2000. p. 113–36.

Casanova MF, Buxhoeveden D, Switala AE, Roy E. Minicolumn pathology in Asperger's syndrome [abstract]. Biol Psychiatry 2001a; 49 (8S): 158S.

Casanova MF, Buxhoeveden D, Switala AE, Roy E. Anomalies in the cortical processing units of the autistic brain [abstract]. Biol Psychiatry 2001b; 49 (8S): 98S.

Casanova MF, Pathiraja A, Buxhoeveden D, Switala A, Roy E. Comparative lateralization of minicolumns in normal human and schizophrenic brains [abstract]. Schizophrenia Res 2001c; 49 (1–2 Suppl): 60.

Casanova MF, Buxhoeveden D, Switala A, Roy E. Gray level index abnormalities in the brains of autistic children. In: Proceedings Summary of the American Psychiatric Association Annual Meeting; 2001d. p. NR 726.

Casanova MF, Buxhoeveden D, Switala A, Roy E. Minicolumn pathology in autism. Neurology 2002; 58: 428–32.

Childs JA, Blair JL.Valproic acid treatment of epilepsy in autistic twins. J Neurosci Nurs 1997; 29: 244–8.

Cook ND. Homotopic callosal inhibition. Brain Lang 1984; 23: 116–25.

Computation in the cortical column. A NIPS 2000 Workshop. Available from: http://www.keck.ucsf.edu/~linden/ColumnWorkshop/abstract.html

Csillik B, Nemcsok J, Bonczl I, Knyihar-Csillik E. Nitric oxide synthase and the acetyl choline receptor in the prefrontal cortex: metasynaptic organization of the brain. Neurobiology 1998; 6: 383–404.

de Bode S, Curtiss S. Language after hemispherectomy. Brain Cogn 2000; 43: 135–8.

DeFelipe J. Chandelier cells and epilepsy. [Review]. Brain 1999; 122: 1807–22.

DeFelipe J, Farinas I. The pyramidal neuron of the cerebral cortex morphological and chemical characteristics of the synaptic inputs. [Review]. Prog Neurobiol 1992; 39: 563–607.

DeFelipe J, Jones EG. Vertical organization of γ-aminobutyric acid-accumulating intrinsic neuronal systems in monkey cerebral cortex. J Neurosci 1985; 5: 3246–60.

DeFelipe J, Hendry SHC, Jones EG. A correlative electron microscopic study of basket cells and large GABAergic neurons in the monkey sensory-motor cortex. Neuroscience 1986; 17: 991–1009.

DeFelipe J, Hendry SH, Hashikawa T, Molinari M, Jones EG. A microcolumnar structure of monkey cerebral cortex revealed by immunocytochemical studies of double bouquet cell axons. Neuroscience 1990; 37: 655–73.

De Lacoste MC, White CL 3rd. The role of cortical connectivity in Alzheimer's disease pathogenesis: a review and model system. [Review]. Neurobiol Aging 1993; 14: 1–16.

Diamond IT. The subdivisions of neocortex: a proposal to revise the traditional view of sensory, motor, and association areas. In: Sprague JM, Epstein AN, editors. Progress in psychobiology and physiological psychology, Vol. 8. New York: Academic Press; 1979. p. 1–43.

Dodt HU, D'Arcangelo G, Pestel E, Zieglgansberger W. The spread of excitation in neocortical columns visualized with infrared-darkfield videomicroscopy. Neuroreport 1996; 7: 1553–8.

Douglas RJ, Martin KA. Opening the grey box. [Review]. Trends Neurosci 1991a; 14: 286–93.

Douglas RJ, Martin KA. A functional microcircuit for cat visual cortex. J Physiol (Lond) 1991b; 440: 735–69.

Duong TQ, Kim DS, Ugurbil K, Kim SG. Spatiotemporal dynamics of the BOLD fMRI signals: toward mapping submillimeter cortical columns using the early negative response. Magn Reson Med 2000; 44: 231–42.

Elston GN. Pyramidal cells of the frontal lobe: all the more spinous to think with. J Neurosci. 2000; 20 (RC95): 1–4. Available from: http://www.jneurosci.org

Elston GN, Rosa MG. The occipitoparietal pathway of the macaque monkey: comparison of pyramidal cell morphology in layer III of functionally related cortical visual areas. Cereb Cortex 1997; 7: 432–52.

Elston GN, Rosa MG. Pyramidal cells, patches, and cortical columns: a comparative study of infragranular neurons in TEO, TE, and the superior temporal polysensory areas of the macaque monkey. J Neurosci 2000; 20 (RC117): 1–5. Available from: http://www.jneurosci.org

Escobar MI, Pimienta H, Caviness VS, Jacobson M, Crandall JE, Kosik KS. Architecture of apical dendrites in the murine neocortex: dual apical dendritic systems. Neuroscience 1986; 17: 975–89.

Favorov OV, 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 OV, 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.

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

Favorov OV, Kelly DG. Minicolumnar organization within somatosensory cortical segregates. I. Development of afferent connections. Cereb Cortex 1994a; 4: 408–27.

Favorov OV, Kelly DG. Minicolumnar organization within somatosensory cortical segregates. II. Emergent functional properties. Cereb Cortex 1994b; 4: 428–42.

Favorov OV, Kelly DG. Stimulus-response in local neuronal populations of the cerebral cortex. Neuroreport 1996; 7: 2293–301.

Favorov OV, Diamond ME, Whitsel BL. Evidence for a mosaic representation of the body surface in area 3b of the somatic cortex of cat. Proc Natl Acad Sci USA 1987; 84: 6606–10.

Feldman ML, Peters A. A study of barrels and pyramidal dendritic clusters in the cerebral cortex. Brain Res 1974; 77: 55–76.

Fitzpatrick D, Lund JS, Schmechel DE, Towles AC. Distribution of GABAergic neurons and axon terminals in the macaque striate cortex. J Comp Neurol 1987; 264: 73–91.

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

Freiwald WA, Kreiter AK, Singer W. Stimulus dependent intercolumnar synchronization of single unit responses in cat area 17. Neuroreport 1995; 6: 2348–52.

Gray CM, Konig P, Engel AK, Singer W. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. Nature 1989; 338: 334–7.

Gupta A, Wang Y, Markram H. Organizing principles for a diversity of GABAergic interneurons and synapses in the neocortex. Science 2000; 287: 273–8.

Gustafsson L. Inadequate cortical feature maps: a neural circuit theory of autism. [Review]. Biol Psychiatry 1997; 42: 1138–47.

Haglund MM, Ojemann GA, Hochman DW. Optical imaging of epileptiform and functional activity in human cerebral cortex. Nature 1992; 358: 668–71.

Hendry SH, Schwark HD, Jones EG, Yan J. Numbers and proportions of GABA-immunoreactive neurons in different areas of monkey cerebral cortex. J Neurosci 1987; 7: 1503–19.

Herschkowitz N, Kagan J, Zilles K. Neurobiological bases of behavioral development in the second year. [Review]. Neuropediatrics 1999; 30: 221–30.

Hirsch JC, Agassandian C, Merchan-Perez A, Ben-Ari Y, DeFelipe J, Esclapez M, et al. Deficit of quantal release of GABA in experimental models of temporal lobe epilepsy. Nat Neurosci 1999; 2: 499–500.

Holthoff K, Witte OW. Intrinsic optical signals in rat neocortical slices measured with near-infrared dark-field microscopy reveal changes in extracellular space. J Neurosci 1996; 16: 2740–9.

Holthoff K, Dodt HU, Witte OW. Changes in intrinsic optical signal of rat neocortical slices following afferent stimulation. Neurosci Lett 1994; 180: 227–30.

Houser CR, Hendry SH, Jones EG, Vaughn JE. Morphological diversity of immunocytochemically identified GABA neurons in the monkey sensory-motor cortex. J Neurocytol 1983; 12: 617–38.

Houzel JC, Milleret C. Visual inter-hemispheric processing:

constraints and potentialities set by axonal morphology. [Review]. J Physiol Paris 1999; 93: 271–84.

Hubel DH, Wiesel TN. Shape and arrangement of columns in the cat's striate cortex. J Physiol (Lond) 1963; 165: 559–68.

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

Hubener M, Shoham D, Grinvald A, Bonhoeffer T. Spatial relationships among three columnar systems in cat area 17. J Neurosci 1997; 17: 9270–84.

Innocenti GM. Some new trends in the study of the corpus callosum. [Review]. Behav Brain Res 1994; 64: 1–8.

Jambaque I, Chiron C, Dumas C, Mumford J, Dulac O. Mental and behavioural outcome of infantile epilepsy treated by vigabatrin in tuberous sclerosis patients. Epilepsy Res 2000; 38: 151–60.

Jin X, Mathers PH, Szabo G, Katarova Z, Agmon A. Vertical bias in dendritic trees of non-pyramidal neocortical neurons expressing GAD67-GFP in vitro. Cereb Cortex 2001; 11: 666–78.

Johannisson T. Schizophrenic symptoms: a theory based on a neurophysiological model. Med Hypotheses 1993; 41: 329–31.

Johannisson T. Columnar analysis of sleep electroencephalogram. Med Hypotheses 1997; 49: 187–9.

Johannisson T, Nilsson H. The alpha rhythm in the electroencephalogram: a theory based on a neurophysiological model. Med Hypotheses 1996; 46: 557–61.

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. p. 199–235.

Jones EG. Laminar distribution of cortical efferent cells. In: Peters A, Jones EG, editors. Cerebral cortex: cellular components of the cerebral cortex. New York: Plenum Press; 1984. p. 521–53.

Jones EG. Microcolumns in the cerebral cortex [letter]. Proc Natl Acad Sci USA 2000; 97: 5019–21.

Jones EG, Burton H. Cytoarchitecture and somatic sensory connectivity of thalamic nuclei other than the ventrobasal complex in the cat. J Comp Neurol 1974; 154: 395–432.

Jones EG, Friedman DP, Hendry SH. Thalamic basis of place- and modality-specific columns in monkey somatosensory cortex: a correlative anatomical and physiological study. J Neurophysiol 1982; 48: 545–68.

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

Juliano S, Hand PJ, Whitsel BL. Patterns of increased metabolic activity in somatosensory cortex of monkeys Macaca fascicularis, subjected to controlled cutaneous stimulation: a 2-deoxyglucose study. J Neurophysiol 1981; 46: 1260–82.

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. p. 237–61.

Kandel ER. Nerve cells and behavior. In: Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science, 4th ed. New York: McGraw-Hill; 2000. p. 19–35.

Keller A. Synaptic organization of the barrel cortex. In: Jones EG, Diamond IT, editors. Cerebral cortex, Vol. 11: the barrel cortex of rodents. New York: Plenum Press; 1995. p. 221–62.

Kim DS, Duong TQ, Kim SG. High-resolution mapping of iso-orientation columns by fMRI. Nat Neurosci 2000; 3: 164–9.

Kohn A, Pinheiro A, Tommerdahl MA, Whitsel BL. Optical imaging in vitro provides evidence for the minicolumnar nature of cortical response. Neuroreport 1997; 8: 3513–8.

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.

Kornack DR, Rakic P. Changes in cell-cycle kinetics during the development and evolution of primate neocortex. Proc Natl Acad Sci USA 1998; 95: 1242–6.

Kozloski J, Hamzei-Sichani F, Yuste R. Stereotyped position of local synaptic targets in neocortex. Science 2001; 293: 868–72.

Krmpotic-Nemanic J, Kostovic I, Nemanic D. Prenatal and perinatal development of radial cell columns in the human auditory cortex. Acta Otolaryngol (Stockh) 1984; 97: 489–95.

Krubitzer L. The organization of neocortex in mammals: are species differences really so different? [Review]. Trends Neurosci 1995; 18: 408–17.

Kuan CY, Elliott EA, Flavell RA, Rakic P. Restrictive clonal allocation in the chimeric mouse brain. Proc Natl Acad Sci USA 1997; 94: 3374–9.

Lebeer J. How much brain does a mind need? Scientific, clinical, and educational implications of ecological plasticity. [Review]. Dev Med Child Neurol 1998; 40: 352–7.

Lee CJ, Whitsel BL. Mechanisms underlying somatosensory cortical dynamics: 1. In vivo studies. Cereb Cortex 1992; 2: 81–106.

Lee CJ, Whitsel BL, Tommerdahl M. Mechanisms underlying somatosensory cortical dynamics: II. In vitro studies. Cereb Cortex 1992; 2: 107–33.

Lewin R. Is your brain really necessary? Science 1980; 210: 1232–4.

Leise EM. Modular construction of nervous systems: a basic principle of design for invertebrates and vertebrates. [Review]. Brain Res Brain Res Rev 1990; 15: 1–23.

Livingstone MS, Hubel DH. Specificity of intrinsic connections in primate primary visual cortex. J Neurosci 1984; 4: 2830–5.

Llinas R. Intrinsic electrical properties of nerve cells and their role in network oscillation. [Review]. Cold Spring Harb Symp Quant Biol 1990; 55: 933–8.

Lorente de Nó R. The cerebral cortex: architecture, intracortical connections, motor projections. In: Fulton JF, editor. Physiology of the nervous system. London: Oxford University Press; 1938. p. 274–301.

Lund JS, Yoshioka T, Levitt JB. Comparison of intrinsic

connectivity in different areas of macaque monkey cerebral cortex. Cereb Cortex 1993; 3: 148–62.

MacVicar BA, Hochman D. Imaging of synaptically evoked intrinsic optical signals in hippocampal slices. J Neurosci 1991; 11: 1458–69.

Marco P, DeFelipe J. Altered synaptic activity in the human temporal neocortex removed from epileptic patients. Exp Brain Res 1997; 114: 1–10.

Marco P, Sola RG, Pulido P, Alijarde MT, Sanchez A, Ramon y Cajal S, et al. Inhibitory neurons in the human epileptogenic temporal neocortex. An immunocytochemical study. Brain 1996; 119: 1327–47.

Marin-Padilla M. Prenatal and early postnatal ontogenesis of the human motor cortex: a golgi study. II. The basket-pyramidal system. Brain Res 1970; 23: 185–91.

Martina M, Vida I, Jonas P. Distal initiation and active propagation of action potentials in interneuron dendrites. Science 2000; 287: 295–300.

McCasland JS, Woolsey TA. High-resolution 2-deoxyglucose mapping of functional cortical columns in mouse barrel cortex. J Comp Neurol 1988; 278: 555–69.

Mealey J, Gilmor RL, Bubb MP. The prognosis of hydrocephalus overt at birth. J Neurosurg 1973; 39: 348–55.

Menard A, Le Normand MT, Rigoard MT, Cohen H. Language development in a child with left hemispherectomy. Brain Cogn 2000; 43: 332–40.

Miles R. Diversity in inhibition [letter]. Science 2000; 287: 244–6.

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: the unit module and the distributed system. In: Edelman GM, Mountcastle VB, editors. The mindful brain: cortical organization and the group-selective theory of higher brain function. Cambridge (MA): MIT Press; 1978. p. 7–51.

Mountcastle VB. The columnar organization of the neocortex. [Review]. Brain 1997; 120: 701–22.

Nauta WJH, Karten HJ. A general profile of the vertebrate brain, with sidelights on the ancestry of cerebral cortex. In: Schmitt FO, editor. The neurosciences: second study program. New York: Rockefeller University Press; 1970. p. 7–26.

Ong WY, Garey LJ. Neuronal architecture of the human temporal cortex. Anat Embryol (Berl) 1990; 181: 351–64.

Orban GA, Neuronal operations in the visual cortex. Studies in brain function, Vol. II. Berlin: Springer-Verlag; 1984.

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

O'Rourke NA, Sullivan DP, Kaznowski CE, Jacobs AA, McConnell SK. Tangential migration of neurons in the developing cerebral cortex. Development 1995; 121: 2165–76.

Pakkenberg H. The number of nerve cells in the cerebral cortex of man. J Comp Neurol 1966; 128: 17–20.

Peters A, Kara DA. The neuronal composition of area 17 of rat visual cortex. IV. The organization of pyramidal cells. J Comp Neurol 1987; 260: 573–90.

Peters A, Payne BR. Numerical relationships between geniculocortical afferents and pyramidal cell modules in cat primary visual cortex. [Review]. Cereb Cortex 1993; 3: 69–78.

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. Cereb Cortex 1993; 3: 49–68.

Porter JT, Johnson CK, Agmon A. Diverse types of interneurons generate thalamus-evoked feedforward inhibition in the mouse barrel cortex. J Neurosci 2001; 21: 2699–710.

Preuss TM, Goldman-Rakic PS. Myelo- and cytoarchitecture of the granular frontal cortex and surrounding regions in the strepsirhine primate Galago and the anthropoid primate Macaca. J Comp Neurol 1991; 310: 429–74.

Preuss TM, Qi H, Kaas JH. Distinctive compartmental organization of human primary visual cortex. Proc Natl Acad Sci USA 1999; 96: 11601–6.

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

Rakic P. Neuronal migration and contact guidance in the primate telencephalon. [Review]. Postgrad Med J 1978; 54, Suppl 1: 25–40.

Rakic P. The specification of cerebral cortical areas: the radial unit hypothesis. [Review]. Science 1988a; 241: 170–6.

Rakic P. Defects of neuronal migration and the pathogenesis of cortical malformations. [Review]. Prog Brain Res 1988b; 73: 15–37.

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

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

Ritchie K, Touchon J. Heterogeneity in senile dementia of the Alzheimer type: individual differences, progressive deterioration or clinical sub-types? [Review]. J Clin Epidemiol 1992; 45: 1391–8.

Robins E, Smith DE, Eydt KM. The quantitative histochemistry of the cerebral cortex—I. J Neurochem 1956; 1: 54–67.

Rockel AJ, Hiorns RW, Powell TP. The basic uniformity of structure of the neocortex. Brain 1980; 103: 221–44.

Rubin RC, Hochwald G, Tiell M, Liwnicz B, Epstein F.

Reconstitution of the cerebral cortical mantle in shunt-corrected hydrocephalus. Dev Med Child Neurol Suppl 1975; 35: 151–6.

Rubin RC, Hochwald GM, Tiell M, Epstein F, Ghatak N, Wisniewski H. Hydrocephalus: III. Reconstitution of the cerebral cortical mantle following ventricular shunting. Surg Neurol 1976; 5: 179–83.

Sawaguchi T, Kubota K. A hypothesis on the primate neocortex evolution: column-multiplication hypothesis. [Review]. Int J Neurosci 1986; 30: 57–64.

Schlaug G, Schleicher A, Zilles K. Quantitative analysis of the columnar arrangement of neurons in the human cingulate cortex. J Comp Neurol 1995; 351: 441–52.

Schmolke C. Morphological organization of the neuropil in laminae II-V of rabbit visual cortex. Anat Embryol (Berl) 1987; 176: 203–12.

Schmolke C. The ontogeny of dendrite bundles in rabbit visual cortex. Anat Embryol (Berl) 1989; 180: 371–81.

Schmolke C, Viebahn C. Dendrite bundles in lamina II/III of the rabbit neocortex. Anat Embryol (Berl) 1986; 173: 343–8.

Seldon HL. Structure of human auditory cortex. I. Cytoarchitectonics and dendritic distributions. Brain Res 1981a; 229: 277–94.

Seldon HL. Structure of human auditory cortex. II. axon distributions and morphological correlates of speech perception. Brain Res 1981b; 229: 295–310.

Seldon HL. Structure of human auditory cortex. III. statistical analysis of dendritic trees. Brain Res 1982; 249: 211–21.

Seldon HL. The anatomy of speech perception. In: Jones EG, Peters A, editors. Cerebral cortex, Vol. 4: association and auditory cortices. New York: Plenum Press; 1985. p. 273–327.

Shamma SA, Fleshman JW, Wiser PR, Versnel H. Organization of response areas in ferret primary auditory cortex. J Neurophysiol 1993; 69: 367–83.

Skoglund TS, Pascher R, Berthold CH. Heterogeneity in the columnar number of neurons in different neocortical areas in the rat. Neurosci Lett 1996; 208: 97–100.

Slimp JC, Towe AL. Spatial distribution of modalities and receptive fields in sensorimotor cortex of awake cats. Exp Neurol 1990; 107: 78–96.

Stark RE, McGregor KK. Follow-up study of a right- and a left-hemispherectomized child: implications for localization and impairment of language in children. Brain Lang 1997; 60: 222–4.

Suarez JC, Sfaello ZM, Albarenque M, Viano JC. Porencephalic congenital cysts with hydrocephalus. Childs Brain 1984; 11: 77–86.

Sugimoto S, Sakurada M, Horikawa J, Taniguchi I. The columnar and layer-specific response properties of neurons in the primary auditory cortex of Mongolian gerbils. Hear Res 1997; 112: 175–85.

Swindale NV. Is the cerebral cortex modular? [Review]. Trends Neurosci 1990; 13: 487–92.

Szentagothai J. The neuron network of the cerebral cortex: a functional interpretation. The Ferrier Lecture 1977. Proc R Soc Lond B Biol Sci 1978; 201: 219–48.

Szentagothai J. Local neuron circuits of the neocortex. In: Schmitt FO, Worden FG, editors. The neurosciences: fourth study program. Cambridge (MA): MIT Press; 1979. p. 399–415.

Szentagothai J. The modular architectonic principle of neural centers. [Review]. Rev Physiol Biochem Pharmacol 1983; 98: 11–61.

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

Vargha-Khadem F, Carr LJ, Isaacs E, Brett E, Adams C, Mishkin M. Onset of speech after left hemispherectomy in a nine-year-old boy. Brain 1997; 120: 159–82.

Walsh C. Cell lineage and regional specification in the mammalian neocortex. [Review]. Perspect Dev Neurobiol 1993; 1: 75–80.

Walsh C, Cepko CL. Clonally related cortical cells show several migration patterns. Science 1988; 241: 1342–5.

Welker E, Van der Loos H. Quantitative correlation between barrel-field size and the sensory innervation of the whiskerpad: a comparative study in six strains of mice bred for different patterns of mystacial vibrissae. J Neurosci 1986; 6: 3355–73.

Welker E, Woolsey TA. Structure of layer IV in the somatosensory neocortex of the rat: description and comparison with the mouse. J Comp Neurol 1974; 158: 437–53.

Woolsey TA, Van der Loos H. The structural organization of layer IV in the somatosensory region (S1) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitectonic units. Brain Res 1970; 17: 205–42.

Yabuta NH, Callaway EM. Cytochrome-oxidase blobs and intrinsic horizontal connections of layer 2/3 pyramidal neurons in primate V1. Vis Neurosci 1998; 15: 1007–27.

Yuste R, Peinado A, Katz LC. Neuronal domains in developing neocortex. Science 1992; 257: 665–8.

Zhang X, Yi SY. Report of ten cases of porencephaly. Chin Med J 1984; 97: 786–8.

Zilles K, Armstrong E, Schlaug G, Schleicher A. Quantitative cytoarchitectonics of the posterior cingulate cortex in primates. J Comp Neurol 1986; 253: 514–24.

Received October 19, 2001.
Accepted December 6, 2001