

Cortical Columns

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7.1 INTRODUCTION

Modularity is a common organizational principle in all parts of the brain. The cerebral cortex exhibits a laminar and a radial organization. Cortical columns are sometimes regarded as the basic functional units in cerebral cortical processing, development, and evolution. *Cortical column* is a historic term that can refer to a vertically arranged cell constellation, a pattern of connectivity, myelin distribution, metabolic characteristics, staining property, vasculature, magnitude of specific gene expression, embryonic origin, or functional properties. The columnar organization reflects the intermittently recursive mapping of several variables under the two-dimensional surface of the neocortex in a variably independent or combined (e.g., hypercolumn) manner. The term *cortical column* is constantly evolving with the improved understanding of the organization and function of the various radially oriented groups of cells that share certain functional or anatomical properties.

Columns are ubiquitous in the brain but are in no way obligatory, and comprehensive descriptions of the various specific forms of "columns" in the brain are still evolving. To date, comparative studies have failed to identify a specific sensory, motor, or cognitive function that is specifically associated with the presence or absence of a particular form of cortical column. The developing cortex contains numerous radial determinants. Pyramidal neurons are generated in "ontogenetic units" and subsequently disperse radially. It has been shown that sibling cells have a stronger tendency to establish synaptic connections with each other in the cortical plate. However, the link between the embryonic and adult columnar constellations is currently not known.

There are, therefore, several problems related to the term and concept of cortical column. (1) The often loose, general, and uncritical use of the term can be confusing. (2) Related to the lack of a universal presence of certain types of column within some cortical areas, brains, or species undermines the idea that similar building blocks comprise all cortical circuits. (3) The concept that the cortical column (or even just an arbitrary columnar unit along the depth of the cortex) has a universally constant number of neurons associated with it, with only the primate visual cortex showing a difference. (4) The lack of correlation between the absence or presence of particular types of column and specific mode of sensory or cognitive processing capacities (across the same brain or across close or more distant species). (5) Although there is evidence for the overall radial disposition of the pyramidal neuron clones and a higher probability of synapse formation between sibling cells, there is a lack of correlation

between the columnar development of the brain and columns in the adult cortex.

Knowledge of the laminar and columnar organization of the cerebral cortex is continuously advancing, and with this the conceptual details of the columnar organization also is changing. The time may arrive when both the concept and the nomenclature will have to adapt to these changes.

The hypothesis of the column as the fundamental processing unit of the cerebral cortex was formulated by Mountcastle (1957) from studies of cells responding to a single modality of tactile stimuli (cutaneous or deep joint receptors) in the somatosensory cortex of cats. The concept emerged from Mountcastle's work and was developed further over five decades; he claimed that the cerebral cortex can be further subdivided into "complex processing and distributing units that link a number of inputs to a number of outputs via overlapping internal processing chains" (Mountcastle, 1957).

By exploring the physiological, anatomical, genetic, and developmental properties of the cerebral cortex, more details of its organization were revealed, and many of these new entities were referred to as 'columns.' The emerging concept in cerebellar circuits by Eccles et al. (1967) fueled the quest for a fundamental cortical processing unit, an archetypical cortical column, which was intensified in the hope of identifying modules that are general for all cortical areas. There are references to functional columns, minicolumns, hypercolumns, ontogenetic or embryonic columns, ocular dominance (OD) columns, orientation columns, and barrel columns. The only common theme linking these terms is that they refer to a structural, physiological, or developmental organization that transcends the laminar pattern and is perpendicular to it. None of these several types of columns are general to all cortical areas, and several are restricted to the primary sensory areas. Table 7.1 gives three definitions and Table 7.2 gives a list of some of the terms that refer to cortical columnar structures. There are so many varieties of cortical columns defined by different criteria and by different authors that it is difficult to define, relate, or compare these columns. The concept of an archetypical cortical column is no better defined now than when it was first introduced.

In this chapter, the following points are discussed and examined: (1) the problems associated with the current nomenclature; (2) the evidence for and against the idea that columns are the common building blocks of the cortex; (3) the question of how constant the cell numbers are within a column and how homogeneous is the structure of the various columns; (4) the possible functions of the columns; and (5) the current knowledge of the columnar development in the cortex.

TABLE 7.1 Examples for definitions of cortical columns

1. Mountcastle (1997) "The modular organization of nervous systems is a widely documented principle of design for both vertebrate and invertebrate brains of which the columnar organization of the neocortex is an example. The classical cytoarchitectural areas of the neocortex are composed of smaller units, local neural circuits repeated iteratively within each area. Modules may vary in cell type and number, in internal and external connectivity, and in mode of neuronal processing between different large entities; within any single large entity they have a basic similarity of internal design and operation. Modules are most commonly grouped into entities by sets of dominating external connections. This unifying factor is most obvious for the heterotypical sensory and motor areas of the neocortex. Columnar defining factors in homotypical areas are generated, in part, within the cortex itself. The set of all modules composing such an entity may be fractionated into different modular subsets by different extrinsic connections. Linkages between them and subsets in other large entities form distributed systems. The neighborhood relations between connected subsets of modules in different entities result in nested distributed systems that serve distributed functions. A cortical area defined in classical cytoarchitectural terms may belong to more than one and sometimes to several distributed systems. Columns in cytoarchitectural areas located at some distance from one another, but with some common properties, may be linked by long-range, intracortical connections."
2. http://en.wikipedia.org/wiki/Cortical_minicolumn
"A cortical column, also called hypercolumn or sometimes cortical module, [1] is a group of neurons in the brain cortex, which can be successively penetrated by a probe inserted perpendicularly to the cortical surface and which have nearly identical receptive fields. Neurons within a minicolumn encode similar features, whereas a hypercolumn 'denotes a unit containing a full set of values for any given set of receptive field parameters.' [2] A cortical module is defined as either synonymous with a hypercolumn (Mountcastle) or as a tissue block of multiple overlapping hypercolumns (Hubel & Wiesel).
Various estimates suggest there are 50–100 cortical minicolumns in a hypercolumn, each comprising around 80 neurons. An important distinction is that the columnar organization is functional by definition, and reflects the local connectivity of the cerebral cortex. Connections 'up' and 'down' within the thickness of the cortex are much denser than connections that spread from side to side."
3. Boucsein et al. (2011) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3072165/> "This slightly ambiguous term loosely describes the concept of vertically arranged groups of cells that share certain functional and/or anatomical properties and could represent a 'basic functional unit' in cortical processing. They are ubiquitous in the brain but in no way obligatory, and a comprehensive description of the various forms of 'columns' in the brain is still lacking."

[1] Towards cortex sized artificial neural systems, Johansson C and Lansner A (2007) *Neural Networks*, vol. 20(1), pp. 48–61. Elsevier.

[2] The columnar organization of the neocortex, Mountcastle VB (1997) *Brain*, vol. 20(4), pp. 701–722. Oxford University Press.

Boucsein C, Nawrot MP, Schnepel P, Aertsen A (2011) Beyond the cortical column: Abundance and physiology of horizontal connections imply a strong role for inputs from the surround. *Frontiers in Neuroscience* 5: 32.

7.2 THE CORTICAL COLUMN NOMENCLATURE REFLECTS THE HISTORY OF CHANGING CONCEPTS OF CORTICAL ANATOMY, FUNCTIONAL REPRESENTATION, AND DEVELOPMENT

7.2.1 Is the Isocortex Hexalaminar?

The cortex (hereafter referring to the forebrain 'neocortex' as distinct from the olfactory and hippocampal three-layered cortex) is organized horizontally into six laminae and vertically into groups of cells linked synaptically across and along the horizontal layers. The definitions of both laminae and radial modules are a historic convention rather than a biologically or functionally related demonstrable reality. All mammalian cerebral neocortices have a uniform laminar structure (therefore also called the isocortex) that has been historically and arbitrarily divided into six layers (Brodmann, 1909; Lorente de Nô, 1922, 1949; von Economo and Koskinas, 2008). This basic master plan is modified according to variations. These variations expose the problem of fitting the hexalaminar universal model to all mammalian cortices. Subdivisions of layers III, IV, V, and VI in some species, missing layers (IV) in some cortical areas, or fused layers (II/III) in other areas indicate that there is uncertainty and a random element to current laminar nomenclature (Molnár, 2011; Molnár and Belgard, 2012).

The radially oriented apical dendrites and processes and the general radial orientation within the cortex have been widely known since the cerebral cortex was first examined microscopically (see, e.g., Cajal, 1909). Also, the vertical connectivity linking neurons across cortical layers was described by Lorente de Nô (1938) in the primary somatosensory cortex of the mouse. The concept of a column emerged from the functional properties of the cortex and received attention after Vernon Mountcastle discovered that the neurons are arranged vertically (or radially in the convoluted cerebrum) in the form of columns spanning the width of the primate somatosensory cortex with cells in each column responding with distinct receptive field properties (superficial as compared to deep skin receptors) to a single receptive field at the periphery (Mountcastle et al., 1957). Although it is now known that these functionally distinct 'columns' were separate, distinct cortical areas and not functional units within a cortical area (Kaas et al., 2011), these observations drove further discoveries of an array of iterative neuronal groups (also called modules) that extend radially across cellular layers VI to II with layer I at the top. Subsequently, Hubel and Wiesel (1968) revealed the orientation and OD columns in the primary visual cortex, and this was followed by the observations of Abeles and Goldstein (1970) in the primary auditory cortex (Table 7.2). These physiological observations led to the

TABLE 7.2 Examples for terms that refer to columnar structures in the cortex

| Module | Cortical area | Definition | Dimension | References |
|----------------------------|---------------|---|--|--|
| Cortical column/module | S1 | Penetrations parallel to the pial surface and crossing the vertical axis of the cortex pass through 300–500-μm blocks of tissue in each of which neurons with identical properties are encountered. Sharp transitions are observed from a block with one set of properties to the adjacent block with different properties. The defining property for place is the peripheral receptive field, the zone on the body surface within which an adequate stimulus evokes a response of cortical cells | 300–500-μm | Mountcastle (1957), Powell and Mountcastle (1959) |
| Ocular dominance column | V1 | Ocular dominance (OD) columns or OD stripes are regions of neurons in the visual cortex that respond to the stimulation from either the left or right eye, and they can be defined both anatomically and physiologically | Variable | Hubel and Wiesel (1969) |
| Orientation columns | V1 | Form orientation slabs that measure 0.5–1.0 mm in the iso-orientation direction and in which a full 180° rotation of orientation preference is repeated | 560 μm | Hubel and Wiesel (1968) |
| Blobs | V1 | Metabolic activity 2DG or cytochrome oxidase staining Blob cells respond differentially at low spatial frequencies (1.1 cycles per degree), interblob cells at higher frequencies (3.8 cycles per degree) | 150-μm diameter, most prominent in layers II and III. Repeat intervals of 500–550 μm; the parallel rows are 350-μm apart | Hendrickson and Wilson (1979), Wong-Riley (1979), Livingstone and Hubel (1984) |
| Isofrequency bands | A1 | Neurons of similar frequency preference are arranged in isofrequency bands (IFBs) across the primary auditory cortex (AI) of many mammals | No wider than 200 μm and 5–7 mm in length extending across the gyrus | Tunturi (1950), Brugge and Merzenich (1973) |
| Binaural summation columns | A1 | Most neurons arrayed in a column perpendicular to the cortical surface display the same aural dominance and binaural interaction Summation columns occupy about two-thirds of the area sampled; suppression columns, about one-third. Within most suppression columns, the contralateral ear was dominant. Within summation columns, aural dominance varied. Summation columns appear to be composed of smaller columns differing in aural dominance | The sizes of binaural interaction columns vary considerably; some occupy several square millimeters of cortical surface. At least some binaural interaction columns occupy strips of cortex oriented orthogonal to isofrequency contours | Imig and Adrián (1977) |
| Motor columnar aggregates | Motor cortex | Pyramidal and nonpyramidal cells are clustered into columnar aggregates | 300 μm wide, separated by 100-μm cell-sparse zones | Meyer (1987) |
| Motion columns | MT | Neurons in monkey MT with similar axes of motion preference are arranged in vertical columns, and these columns are themselves arranged in slabs in which a full rotation of 180° of axis of motion is represented | 400–500 μm | Albright et al. (1984) |

TABLE 7.2 Examples for terms that refer to columnar structures in the cortex—cont'd

| Module | Cortical area | Definition | Dimension | References |
|------------------------------------|-----------------------------------|--|--|---|
| Shape and face recognition columns | Homotypical inferotemporal cortex | Require moderately complex features (shapes and faces) for their activation | | Gross et al. (1972), Perrett et al. (1992) |
| Microcolumns | All cortical areas | The dendrites of 3–20 large pyramidal cells of layer V form clusters that ascend together through layer IV | These modules are ~30 µm in diameter and occur with center-to-center spacing that varies from 20 to 80 µm; the wider spacing occurs in the larger brains of the macaque monkey and man | Fleischhauer et al. (1972), Peters and Walsh (1972) |
| Barrels | Some rodent S1 | Cytoarchitectonic patterning of the layer IV neurons forming a ring-like structure on tangential sections | Variable 300 µm | Woolsey and van der Loos (1970) |
| Synaptic ZN | Monkey primary visual cortex | Synaptic Zn patches correspond to a subset of corticocortical terminations | | Dyck et al. (2003) |
| VGLUT-2 columns | Rat and mouse barrel field | VGLUT-2 marker for thalamocortical termination | Variable 300 µm | Liguz-Lecznar and Skangiel-Kram ska (2007) |
| Ontogenetic units/columns | Monkey | The progenitor cells that generate the minicolumn | Each proliferative unit in the ventricular zone of the monkey consists of 3–5 stem cells, a number that gradually increases to 10–12 stem cells during development; the units are separated by glial septa (Rakic, 1988) | Rakic (1988) |
| Domains | Early postnatal rat cortex | Domains of spontaneously coactive neurons using optical recordings of brain slices labeled with the fluorescent calcium indicator fura-2 in early postnatal rat cortex | The functional domains were 50–120 µm in diameter on tangential slices; they spanned several cortical layers and resembled columns found in the adult cortex in coronal slices | Yuste et al. (1992) |

concept that “neurons within a given column are stereotypically interconnected in the vertical dimension, share extrinsic connectivity, and hence act as basic functional units subserving a set of common static and dynamic cortical operations that include not only sensory and motor areas but also association areas subserving the highest cognitive functions” (Jones and Rakic, 2010). The inclusion of the highest cognitive functions was, of course, an extrapolation that lacked evidence. The concept that the cortex comprises similarly structured units is an attractive one, but it seems that there are far too many variations and individual units that can be highly specialized and vary within certain cortical areas, or sectors within areas.

7.2.2 The Loose and Uncritical Use of the Term in Ways That Are So Generalized as to Be Unhelpful and Even Confusing

Although the anatomical and functional columnarity of the neocortex has never been in doubt, over time and with more discoveries of radial arrangements in the

cortex, the term ‘cortical column’ became looser as columns were defined by cell constellation, pattern of connectivity, myelin content, staining property, magnitude of gene expression, or functional properties (Rockland, 2010; Table 7.2). Although the term column is used by some to refer only to: ‘interconnected neurons, with common input, common output, and common response properties extending through the thickness of the cortex,’ others do not use these criteria, and the term ‘column’ evolved into a loose and somewhat ambiguous term referring to some aspect of the vertical organization of the cortex (Table 7.1, third definition).

Montcastle’s definition of a column in 1997 is different from the one formulated in 1957, and it includes references to physiological, anatomical, and embryological aspects: “The basic unit of the mature neocortex is the *minicolumn*, a narrow chain of neurons extending vertically across the cellular layers II–VI, perpendicular to the pial surface. Each minicolumn in primates contains 80–100 neurons, except for the striate cortex where the number is 2.5 times larger. Minicolumns contain all the major cortical neural cell phenotypes, interconnected

in the vertical dimension. The minicolumn is produced by the iterative division of a small cluster of progenitor cells, a polyclone, in the neuroepithelium, via the intervening ontogenetic unit in the cortical plate of the developing neocortex" (Mountcastle, 1997).

This excerpt shows how, over the decades, the increasingly protean imagery evoked by the term 'column' now obliges investigators to acknowledge its conceptual and linguistic shortcomings (Rockland, 2010). Structural, functional, and embryological definitions are used loosely, and there is a lack of proper and unequivocal definitions. Therefore, it is difficult to define what constitutes a particular 'cortical column.' Moreover, the use of the terminology is not stringent. Most columns have no definable 'solid' borders; some of the structures referred to as a column do not extend across the entire thickness of the cortex from the pial surface to the white matter (e.g., barrels, microcolumns). The term 'column' has become too general. To convey the complex aspects of cortical organization adequately, additional adjectives are required to specify a particular entity. Mountcastle used the terms column and module interchangeably, but nowadays the term module is used more loosely. Other terms, such as 'patch' or 'domain,' suffer, to varying degrees, from the same problem (Rockland, 2010).

7.3 A LACK OF UNIVERSAL PRESENCE OF CERTAIN COLUMNS WITHIN CORTICAL AREAS, BRAINS, AND SPECIES IS UNDERMINING THE IDEA THAT SIMILAR BUILDING BLOCKS COMPRIZE ALL CORTICAL CIRCUITS

7.3.1 The Use of Physiological Methods to Reveal Columns

Evidence for neocortical columnar organization was initially obtained in electrophysiological studies of single neurons in the somatic sensory cortex in anesthetized cats and monkeys (Mountcastle, 1957; Powell and Mountcastle, 1959). Microelectrode penetrations made normal to the pial surface encounter neurons in each cellular layer with similar properties of place and modality. Penetrations parallel to the pial surface and crossing the vertical axis of the cortex pass through 300–500- μm -sized blocks of tissue in each of which neurons with identical properties are encountered. Sharp transitions are observed from a block with one set of properties to the adjacent block with different properties. The defining property for place is the peripheral receptive field, the zone on the body surface within which an adequate stimulus evokes a response of cortical cells. To reveal the functional modularity in the cortex, 2-deoxyglucose,

optical recordings of intrinsic signals, voltage- and calcium-sensitive dyes, and expression of immediate early genes have also been used in both somatosensory and visual cortical areas (Horton and Adams, 2005).

7.3.2 Columnar Organization of Some Afferent and Efferent Projections

Both intrinsic and extrinsic cortical connections are often patchy and appear columnar in cross sections of the cerebral cortex. Various anterograde tracers injected *in vivo* are often dramatically patterned in cross section, especially in layer IV and adjacent layers. The problem here is that, very commonly, a patchy distribution of label that may involve only one or two laminae at most is interpreted as columnar, whereas the label can be a stripe, area, or spot, and the 'column' is projected to the structure because of the investigator's interpretation (Figure 7.1). By contrast, cortical or thalamic terminations in layer I are, in fact, transcolumnar, typically extending over several millimeters. "Bundles of axons from cells of thalamic modules project to columnar zones of termination in layers IV and IIb of the postcentral cortex, forming clusters separated by zones in which terminals are much less dense. Clustering obtains also for the ipsilateral cortico-cortical and transcallosal systems" (Mountcastle, 1997).

It is widely considered that the effective unit of operation in such a distributed system is not the single neuron and its axon, but groups of cells with similar functional properties and anatomical connections (Jones, 1999, 2010). This modular arrangement might allow a large number of neurons to be connected without a significant increase in cortical volume. Mitchison (1992) estimated that fusing 100 cortical columns would lead to a tenfold increase in cortical volume. The explanation for this surprising estimate is that within a column only restricted subsets of neurons are involved in long-distance connections, whereas the majority is only connected locally within the columns. Consequently, the length of axons that interconnect neurons is shortened, also reducing the cortical volume. The hypothesis requires that nerve cells in the middle layers of the cortex, in which most 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. Experiments in the monkey, however, did not show such homogeneous arrangement and revealed that terminal arbors of individual thalamocortical axons are often smaller than the cross-sectional width of the region that showed a response revealed by optical recording in the so-called activity columns (Blasdel and Lund, 1983; Freund et al., 1989). Thus, 'activity columns' are

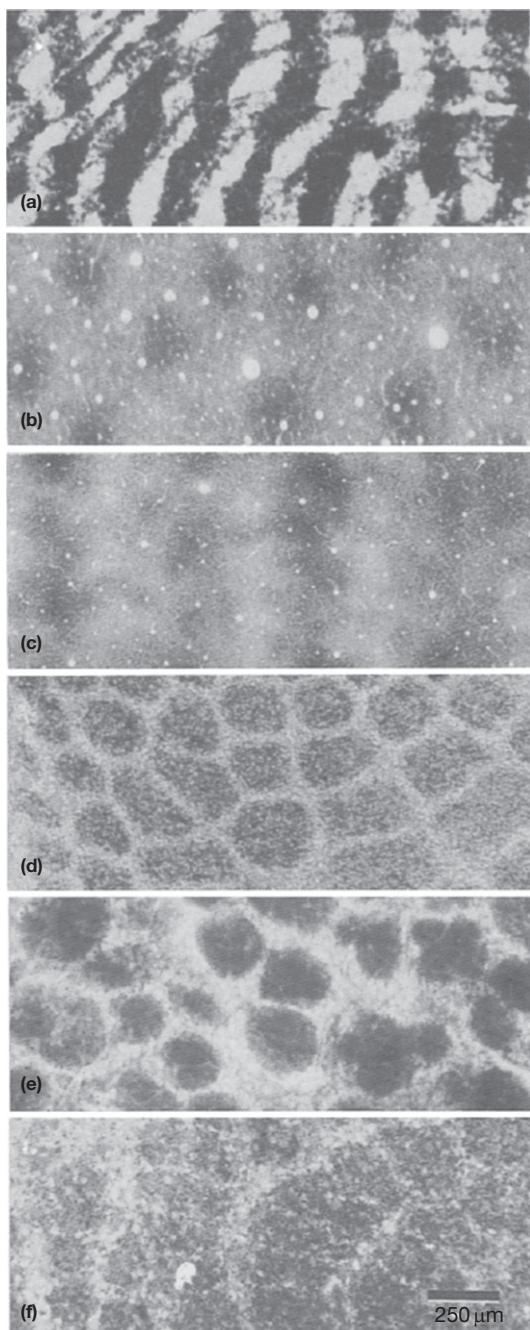


FIGURE 7.1 Examples of modular circuitry in the mammalian brain. (a) Ocular dominance columns in layer IV in primary visual cortex (V1) of a rhesus monkey (autoradiograph after injection of radioactive proline into one eye). (b) Blobs in layers II–III in V1 of a squirrel monkey (cytochrome oxidase (CO) histochemistry). (c) Stripes in layers II–III in V2 of a squirrel monkey (CO histochemistry). (d) Barrels in layer IV in the primary sensory cortex (S1) of a rat (succinic dehydrogenase histochemistry). (e) Barreloids in the ventrobasal nucleus of the thalamus in a rat (succinic dehydrogenase histochemistry). (f) Glomeruli in the olfactory bulb of a mouse (Sudan Black staining). Reproduced from Purves D, Riddle DR, and LaMantia AS (1992) Iterated patterns of brain circuitry (or how the cortex gets its spots). Trends in Neuroscience 15(10): 362–368.

assembled from the convergence of smaller units defined by arbors in a 300–500-μm wide space and not merely by activity-related or molecular factors (Inan and Crair, 2007). Moreover, analysis of a large data set of recordings has revealed that, within a cortical column, connectivity is highly nonuniform (Song et al., 2005).

7.3.3 Modules of the Visual Cortex

The visual cortex processes information concerning form, pattern, and motion within functional maps that reflect the layout of neuronal circuits. The columnar organization in the primate V-1 is defined by the neuronal properties of ocularity and place imposed by geniculocalcarine input and by orientation specificity generated by intracortical processing. The neurons studied in tangential penetrations vary systematically in ocularity (Figure 7.1(a)) and orientation selectivity (Hubel and Wiesel, 1969). As the primary visual cortex has been studied in great detail, this is the area where the cortical columns have been identified most methodically: OD columns, orientation columns, hypercolumns, and alternating callosal and ipsilateral columns (see Table 7.2).

7.3.3.1 OD Columns/Stripes

OD columns or OD stripes are regions of neurons in the visual cortex that respond to stimulation from either the left or right eye, and they can be defined both anatomically and physiologically (Hubel and Wiesel, 1969). Thalamocortical projections carrying signals from one eye or the other synapse mostly within layer IV. In a normally developed visual system, the area of dominance columns for each eye is the same, and each cortical cell responds to visual input predominantly according to its column. OD columns were revealed by single unit recording and transneuronal transport across the lateral geniculate synapse of radioactive amino acids (Hubel and Wiesel, 1969). OD columns are slab-like domains; columnar width is variable as a function of the visual field; that is, they are larger in the foveal representation (Hubel and Wiesel, 1977). In the peripheral visual field representation, the slab-like confirmation breaks up into patches (Adams et al., 2007). Monocular deprivation during early life prevents this balance from developing, and the nondeprived eye assumes control of nearly all cortical cells. These effects were largely identified by Wiesel and Hubel through studies on cats and monkeys (Hubel and Wiesel, 1969).

Similarly, for OD columns of the primate visual cortex, classical anatomical and physiological studies identified core and edge regions functionally distinguished by different degrees of monocular bias (LeVay et al., 1975). More recently, different conditions of visual deprivation have revealed functional subcompartments within OD columns, visualized by either changes in

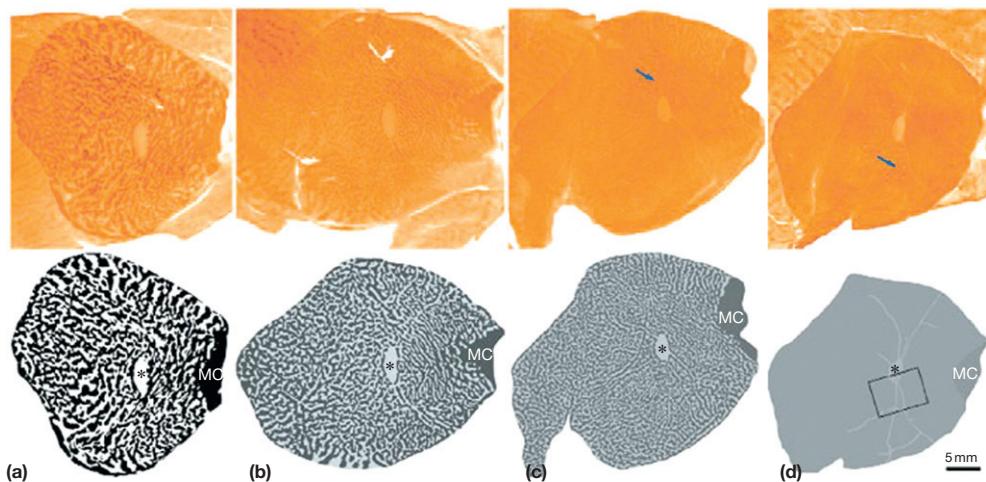


FIGURE 7.2 Variable appearance of ocular dominance columns in normal squirrel monkeys (reproduced from Adams DL and Horton JC (2003). *Capricious expression of cortical columns in the primate brain*. Nature Neuroscience 6: 113–114). Shown are photographic montages of layer 4 C from the left striate cortex of four squirrel monkeys with normal vision 10 days after left eye enucleation. Flatmounts were reacted for CO, and examples for the individual variations are presented: (a) Large, crisply segregated columns; (b) intermediate columns; (c) fine, indistinct columns; (d) rudimentary columns. The columns are essentially absent, although hints were visible in a few peripheral regions of cortex. Note thin profiles (arrows) radiating from the blind spot in (c) and (d), which represent shadows (angioscotomas) from retinal blood vessels. Columns were virtually absent in one-third of the animals (d). MC, monocellular crescent; *, blind spot.

cytochrome oxidase (CO) activity (Horton and Hocking, 1998) or differential expression of immediate early genes (Takahata et al., 2009). Species variation in columnar structure is hard to reconcile with ideas about the fundamental importance of columns. Some members of single species, for example, squirrel monkeys, show enormous variability in the expression of OD columns (Adams and Horton, 2003). Some individuals have normal OD columns throughout the visual cortex; others have them only in parts of the visual cortex, while in some, they are nearly absent (Figure 7.2).

7.3.3.2 Orientation Columns

Within an orientation column, neurons throughout the vertical thickness of the cortex respond to stimuli oriented at the same angle (Hubel and Wiesel, 1968; Hubel et al., 1977, 1978). A neighboring column will then have neurons responding to a slightly different orientation from the one next to it. The functional maps of orientation preference in the ferret, tree shrew, and galago – three species separated since the basal radiation of placental mammals more than 65 Mya ago – share this common organizing principle (Kaschube et al., 2010). Maps of orientation tuning as viewed from the cortical surface (not in sections) contain singularities where orientation columns converge (Blasdel and Salama, 1986), also called pinwheels (Bonhoeffer and Grinvald, 1991).

7.3.3.3 Gene Expression in the Cortex in ‘Columnar’ Fashion

Zones of heightened CO levels can reveal metabolic zones arranged in a modular fashion across the cortex (Livingstone and Hubel, 1984; Figure 7.1(b)), but these

do not extend through all cortical layers. In the monkey, primary visual cortex CO staining reveals metabolic activity in a nonuniform fashion (Wong-Riley, 1979). The patches of CO activity correspond to thalamocortical terminations (Livingstone and Hubel, 1982). Adjacent sections, reactive for synaptic zinc, show patches that correspond to another subset of corticocortical terminations (e.g., Ichinohe and Rockland, 2004). There are numerous other differences that distinguish cortical modules; some of these are associated with thalamic inputs (e.g., Vglut2; 5HTT).

7.3.4 Overlap Between Columnar Entities Within the Same Structures; Combining Physiological and Anatomical Definitions

Individual columns are embedded within distributed networks, and cortical modules are composed of groups of minicolumns. The same column can be part of different networks (e.g., OD and orientation columns or hypercolumns). Despite decades of work, the organization of these modules and their connections, singly or in relation to each other, is only poorly understood. Anatomical observations are often linked to modular patterns of increased metabolic activity, blood flow studies, 2DG uptake, or expression of immediate early genes depending on the stimulus, and may be limited to a single layer, a few layers, or a whole cortical thickness. However, some of these studies revealed no discrete anatomical arrangements that would explain modularity of function, or perceived anatomical arrangements were not in line with detected physiological changes, raising the question: how can an ‘imperfect’ anatomical

arrangement generate functionally distinct modules? At the cellular level, there is growing evidence that cortical columns contain multiple, highly specific, fine-scale subcircuits (Otsuka and Kawaguchi, 2008; Yoshimura et al., 2005) and that within columns, there are locally heterogeneous response properties (Sato et al., 2007).

7.4 NUMBER OF NEURONS IN A CORTICAL COLUMN

The various cortical columns that have been described by different anatomical or physiological methods have very different sizes, shapes, and diameters (examples shown in Figure 7.1). As discussed earlier, the term cortical ‘column’ is ambiguous – it can refer to small-scale minicolumns (diameter 50 µm), to larger scale macrocolumns (diameter – 300–500 µm), or to multiple different structures within both categories (Jones, 2000; Rakic, 2007; Rockland, 2010).

7.4.1 General Concept that the Cortical Column (Even Just an Arbitrary Unit Column that Includes the Full Depth of the Cortex) Has a Universal Constant Number of Neurons Associated with It

Although there is very little quantitative work on the number of neurons in anatomically or physiologically identified cortical columns, it is expected that they are different. It is also generally accepted that the cortical surface areas vary much more than the radial thickness of the cortex. Powell, after returning to Oxford from Mountcastle’s laboratory, was influenced by the concept of the column and set out to quantify parameters within a cortical segment that had roughly the same dimensions as the physiological columns that were estimated (Jones, 1999). After quantification in selected species, it has been proposed that regardless of the thickness of the cortex within an arbitrary (30-µm-wide, 25-µm-deep) vertical ‘column’ between the pial surface and the white matter of the cortex, the number of neurons is 110 in all cytoarchitectonic areas (Rockel et al., 1974, 1980). Under such conditions, the neuronal number was claimed constant in all mammalian species (mouse, rat, cat, Old World monkey, and human) and for all cortical thicknesses, the numbers of cells in these arbitrary columns in prefrontal, primary motor, somatosensory, (posterior) parietal, and temporal neocortex (except the primary visual cortex in primates) all being the same. There was only one area in the cortex that showed a difference from this constant number; in all primates studied (galago, marmoset, squirrel monkey, macaque monkey, baboon, and human), the number per 30-µm-wide, 25-µm-deep column of the visual cortex was increased to about

260–270. This increase is a reflection of the much higher packing density of cells in the true striate cortex. In a later study with Anita Hendrickson, Powell found that the neuronal number remained constant across both the monocular and binocular segments of the macaque visual cortex (Powell and Hendrickson, 1981). The changes in packing density of neurons in the arbitrary unit columns were inversely related to the volume of neuropil.

Using similar methods in marsupials, it has been established that the neuronal numbers are half the ones observed in the mouse in a similar arbitrary unit column (Cheung et al., 2007, 2010; Figure 7.3). Using a more recent ‘unbiased’ stereology method, Herculano-Houzel and her colleagues showed that the density of neurons in the neocortex varies as much as three times even among the highly related primate species (Collins et al., 2010; Herculano-Houzel et al., 2008; Lent et al., 2012). In spite of these observations, it is still true that cortical expansion in evolution is achieved by expanding the cortical surface area, with relatively little change in the thickness. The ratio for the cerebral cortical surface areas in the mouse, macaque, and human is 1:100:1000, whereas for cortical thickness, it is more like 1:1:1 as it is in the range of 2–4 mm in all three species (Rakic, 2009). However, the idea that all mammalian cortices in most areas have a very similar numerical constancy has to be abandoned. In fact, the differences noted earlier might hold a key to understanding cortical specializations for specific functions.

7.5 LACK OF CORRELATION BETWEEN THE ABSENCE OR PRESENCE OF PARTICULAR COLUMNS AND A SPECIFIC SENSORY OR COGNITIVE PROCESSING NETWORK (COMPARISONS ACROSS THE SAME BRAIN AND ACROSS CLOSE AND MORE DISTANT SPECIES)

7.5.1 Microscopic and Macroscopic Cell Patterning Defining Cortical Modules

Most cortical columns can be related to some forms of cellular patterning in the cortex. These can be from subtle microscopic patterns to macroscopically identifiable features. Some distinctive body attachments with characteristic shapes are even recognizable in the somatosensory cortex. Examples include the barrel cortex of the mouse (Woolsey and Van der Loos, 1970), representation of the nasal proboscis of the star-faced mole (Catania and Kaas, 1995), and representation of the raccoon hand (Welker et al., 1964) or primate hand (Jain et al., 1998). These visible columns received special status in neurobiology because they helped investigators to understand questions related to synaptic plasticity and map

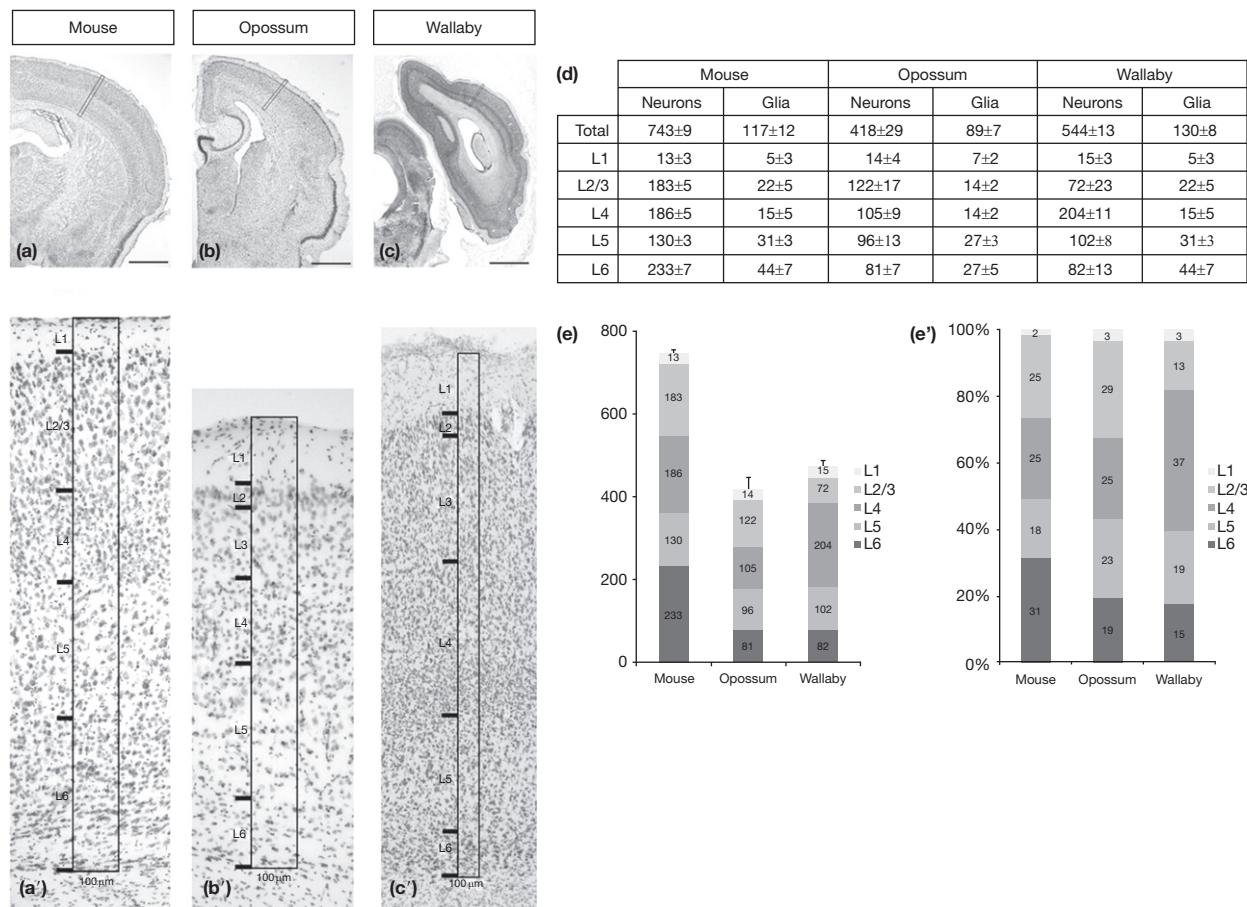


FIGURE 7.3 Quantification of the number of neurons in the mouse, opossum, and wallaby. (a–c) Cresyl violet-stained sections of adult (a) mouse, (b) opossum, and (c) tammar wallaby. An arbitrary 'unit column' (a 100-μm wide) spanning from layer 1 to 6 was marked in the primary somatosensory/visual area (boxed areas in a–c, higher magnification in a'–c'). The number of neurons and glia was quantified in each layer and expressed as mean±SEM in (d). (e) The mean number of neurons present in each cortical layer, showing that the number of neurons in a unit column is not constant between different infraclasses within mammals. (e') The proportion of neurons in each cortical layer. Scale bar: a–b=500 μm, c=1 mm. Reproduced from Cheung AF, Kondo S, Abdel-Mannan O, et al. (2010) The subventricular zone is the developmental milestone of a 6-layered neocortex: comparisons in metatherian and eutherian mammals. *Cerebral Cortex* 20(5): 1071–1081, with permission.

formation. The barrel field is one of the best studied model systems in the mouse cortex; yet, its functional significance has still not been comprehended. Are they structures without any particular function (Horton and Adams, 2005)?

7.5.2 Are Barrels Cortical Columns?

It is puzzling that barrel fields are present in rats, mice, squirrels, rabbits, possums, and porcupines, but not in raccoons, beavers, or cats (Woolsey et al., 1975). The presence or absence of barrels is not related to the presence of actively mobile whiskers (whisking behavior), as guinea pigs do not whisk but nonetheless have a barrel field. The peripheral somatic sensory input is relayed through the brainstem and the ventrobasal complex of the thalamus before it is transmitted to layer IV,

the gateway of the sensory cortical circuitry. Thalamic axons form arbors and establish synapses in a periphery-related pattern in layer IV. This pattern formed by thalamocortical axons can be present in the absence of the cytoarchitectonic pattern that was originally termed barrels by Woolsey and Van der Loos (1970) (see López-Bendito and Molnár, 2003). The individual thalamocortical axon clusters that form periphery-related patterns are first surrounded by densely packed layer IV cells that form the walls of the actual cytoarchitectural 'barrels.' In the middle of each barrel is a plexus of thalamic fibers carrying signals from one corresponding whisker (Figure 7.4). In the barrel field of the rodent somatosensory cortex, dendritic bundles are mostly located in the barrel walls and septa, avoiding the hollows (mouse, Escobar et al., 1986).

In the rodent barrel cortex, dendrites of neurons in layer IV conform to barrel limits (Harris and Woolsey,

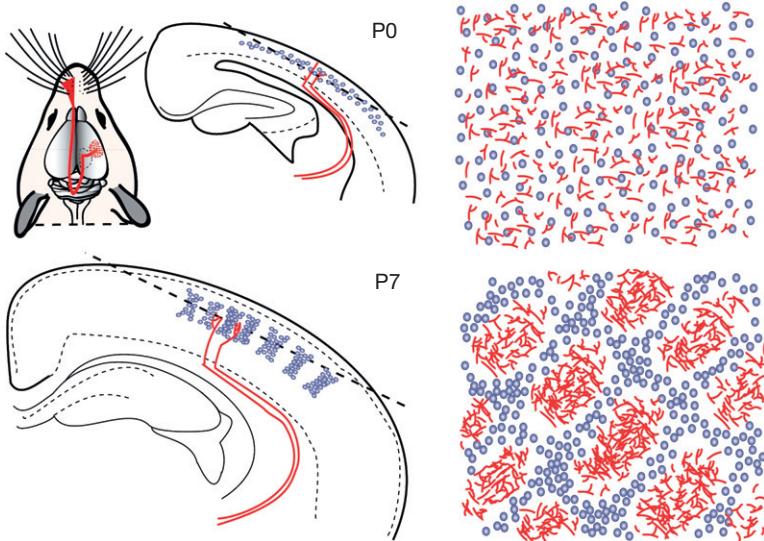


FIGURE 7.4 Schematic overview of the development of the periphery-related thalamocortical patterning and the cytoarchitectonic barrel formation in the mouse. Thalamocortical fiber clusters arise from an initially uniform distribution of thalamocortical arbors (red), and they impose the characteristic patterning of layer IV neurons (blue). Left column represents coronal, right column tangential sections. Reproduced from Molnár Z and Molnár E (2006) Calcium and NeuroD2 control the development of thalamocortical communication. *Neuron* 49(5): 639–642.

1979), but this seems to be an exceptional case. The best documented example of two thalamic systems in the same layer is from rodent barrel cortex (Alloway, 2008). In layer IV, thalamocortical projections from the ventral posterior medial (VPM) and the posterior nuclei target the barrels (lemniscal pathway) and their intervening septa (paralemniscal pathway), respectively. A similar segregation occurs more generally, but with segregation in different layers. The functional significance of the thalamocortical–corticocortical patterning is unknown, but could be related to differential processing by distinct postsynaptic populations. Barrels show variation in size and shape across S1. There have been few quantitative studies of the differences and their relevance.

Sakmann's group has presented a set of papers in which they define a 'standard' column in the rat somatosensory cortex as based on the topographically specific input from the large bundle of thalamocortical axons emanating from a single 'barrelloid' in the VPM nucleus of the thalamus and terminating in one of the 'barrels' in the layer IV aggregations of neurons (Helmstaedter et al., 2007; Meyer et al., 2010; Wimmer et al., 2010). In this case, then, their column is of the kind defined originally by Mountcastle and not a minicolumn, although it may contain minicolumns as defined above. On the basis of measurements of concentrations of thalamocortical axon terminals labeled by green fluorescent protein expressed in their parent cells and extending the width of the periodic densities of terminations (which in layer IV are $\sim 300 \mu\text{m}$ wide) across the depth of the cortex, this column has a cross-sectional area of about 121 000 square microns and a depth of $\sim 1840 \mu\text{m}$ from the pia to white matter. A second kind of column defined by the authors has its basis in the terminations of axons arriving from

the posterior medial (Pom) nucleus of the thalamus and ending deep and superficial to the barrels and especially in the zones of reduced cell density or 'septa' lying between them. This column, as measured from septum to septum and across the intervening barrel, is thus a little wider than the column defined by inputs to the barrels; it has a cross-sectional area of approximately 124 000 square microns, but when projected across the depth of the cortex, it has the same length as the VPM-based column. The measurement of the Pom-based barrel might be rather arbitrary, as the authors describe the axons of Pom neurons as spreading horizontally for seemingly wider extents than those from VPM (Jones and Rakic, 2010).

The barrels in the rodent somatosensory cortex are not stereotyped. Hollow barrels, with cell-sparse cores, are typical of mice, young rats, and the anterolateral subfield of mature rats, but solid columns, with cell-dense cores, are typical of the main posteromedial field in rats (Rice, 1995). Variability is not reported for other columnar systems of connections, but this is likely because many of the systems are harder to visualize globally or require specialized tissue processing.

The function of the barrels in the rodent primary somatosensory cortex is not known. The cortical architecture can be missing or significantly disrupted and yet apparently remain functionally intact. For example, the disrupted barrel cortex in the reeler and in other mutant or transgenic mice is not associated with marked somatosensory deficits (López-Bendito and Molnár, 2003; Rakic and Caviness, 1995).

The degree to which the cortex is modifiable, and by what mechanisms, has been extensively investigated under various environmental manipulations. Although it is not known what the functional relevance (if any) of the

barrel arrangements may be, this system helped the understanding of various aspects of cortical circuit formation and plasticity. Study of the barrel field in various mouse mutants proved to be instrumental in the understanding of the molecular mechanisms of these interactions (Erzurumlu and Kind, 2001). The development of the periphery-related patterning of the thalamocortical projections and the induction of the cytoarchitectonic barrels require both pre- and postsynaptic interactions. During the first days of postnatal development, thalamic projections assume a periphery-related pattern within layer IV precisely mirroring the arrangements of the whiskers. Thalamocortical axon segregation is soon followed by the relocation of layer IV cells from an initially homogeneous distribution to the walls of the barrels surrounding the clustered thalamic projections (Molnár and Molnár, 2006; Figure 7.4).

Van der Loos and Woolsey (1973) provided evidence for the environmental influence on cortical cytoarchitectonic differentiation by demonstrating that changing or blocking the flow of sensory input from specific whiskers during the early stages of development results in a cascade of events that will change the arrangements and somatodendritic morphology of layer IV cells. With the development of finer techniques of clonal analysis and neuronal cell-type specification, one can anticipate a new generation of genetic and molecular manipulations that will help us elucidate the underlying mechanisms of barrel formation. Overexpression of NT3 is reported to result in an enhanced expression of dendritic bundles ('minicolumns') in the rat barrel cortex (Miyashita et al., 2010). However, it is not clear to what extent the barrels represent a general and valid model for cortical columns.

7.5.3 Microcolumns and Apical Dendritic Bundles

There are a number of examples of repeating microarrays of intracortical elements that are interpreted as conforming to a microcolumnar pattern of vertical connections. The observations on patterning of apical dendrites of pyramidal cells with somata located in layers II, III, and V have led, as noted above, to the introduction of the term minicolumns or microcolumns (Fleischhauer et al., 1972; Peters and Walsh, 1972). Innocenti and Vercelli (2010) distinguished minicolumns and bundles, whereas some investigators have used these terms interchangeably. Minicolumns of radially aligned cell bodies can be demonstrated by regular Nissl preparations or other histological methods that reveal cell bodies. Bundles are composed of the apical dendrites of pyramidal neurons whose cell bodies are in different layers and can be seen in material prepared by the Golgi

technique, stained with osmium for electron microscopical analysis, or with markers of somatodendritic morphology (e.g., microtubule-associated protein 2 or SMI32) (Peters and Walsh, 1972; Figure 7.5). Innocenti and Vercelli demonstrated bundles using retrograde transport of lipophilic tracers or intracellular injection of neurons in slice preparations (Innocenti and Vercelli, 2010). Myelinated axons are also organized in bundles; these bundles course close to those of the dendrites, and at least some of them originate from neurons whose apical dendrites are in a bundle (Peters and Sethares, 1996). Depending also on tangential location and depth, the minicolumns and bundles can be more or less sharp.

An average bundle is composed of the dendrites of 3–20 large pyramidal cells of layer V that form clusters that ascend together through layer IV. They are joined in the supragranular layers by the successive addition of the apical dendrites of pyramidal cells of layers II and III, and all ascend further, many sending their terminal arrays to layer I (Figure 7.5). Reconstructions have revealed that individual dendrites change their neighborhood relations along a bundle, superficial dendrites can be added between the dendrites from deeper layers, and individual dendrites can bifurcate to sending branches to neighboring bundles (Massing and Fleischhauer, 1973). In the monkey visual cortex, the microcolumns are estimated to consist of the dendrites of ≈ 142 pyramidal neurons. These modules are 30 μm in diameter and occur with center-to-center spacing that varies from 20 to 80 μm , the wider spacing occurring in the larger brains of the macaque monkey and man. Their estimated density is ≈ 1270 per mm^2 in the monkey visual cortex. In the visual cortex, the mean spacing between modules was found to be 60 μm in the rat, 56 μm in the cat, and 23 μm in the rhesus monkey (Peters, 1997). Not all apical dendrites from layer V enter into the composition of dendritic bundles (Rockland and Ichinohe, 2004). The presence of layer V is not considered the prerequisite to consider a bundle (Innocenti and Vercelli, 2010); however, this issue has not been investigated in mutant mouse cortex that lacks a particular subtype of layer V.

7.5.4 Complex Relationship Relations Between Minicolumns and Dendritic Bundles

Cell bodies of neurons in a minicolumn can be seen to orient obliquely to engage their apical dendrite into the neighboring dendritic bundles already in layer V and more so in layer III (Gabbott, 2003; Peters and Kara, 1987; Peters and Walsh, 1972; Figure 7.5). The progressive addition of dendrites to the bundle from depth to surface in the cortex ('like onions held by their stem';

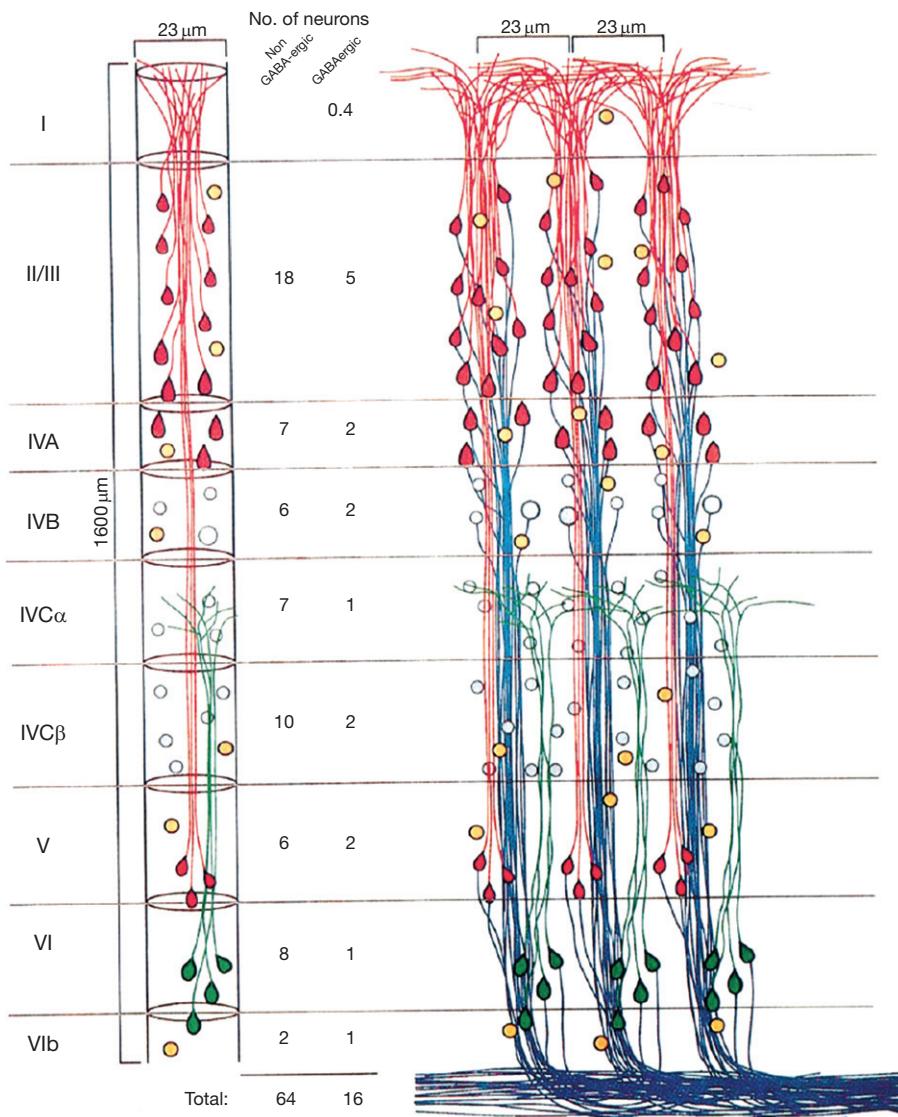


FIGURE 7.5 Bundles and microcolumns in the primary visual cortex of the macaque monkey. (Reproduced from Peters A and Sethares C (1996) Myelinated axons and the pyramidal cell modules in monkey primary visual cortex. *Journal of Comparative Neurology* 365: 232–255). Left panel: Schematic representation of the arrangements of the apical dendrites of pyramidal cells. Layer II/III, IVA, and V pyramidal cells are shown in red, layer VI in green. Gray represents neurons of IVB and IVC without dendrites; azure represents GABAergic neurons. Right panel: Pyramidal minicolumns are represented adjacent to the dendritic bundles. Axons of pyramidal cells are depicted in blue.

(Peters and Kara, 1987) also indicates that the bundles collect dendrites from more than one minicolumn of cell bodies (Massing and Fleischhauer, 1973; Peters and Kara, 1987; Vercelli et al., 2004).

Peters and Sethares (1996) observed that those neurons with apical dendrites in the same bundle also bundle their myelinated axons, indicating that neurons in a dendritic bundle might send their axons to the same target. Subsequently, Lev and White (1997) showed that, in the mouse area MsI, following injection of horseradish peroxidase in the contralateral hemisphere, all dendrites in a labeled bundle belonged to callosally projecting neurons, thus suggesting that dendritic bundles are target specific. This issue has been further investigated by Vercelli et al. (2004) in the visual cortex of the rat for different targets (ipsilateral cortex, superior colliculus (SC), pons, lateral geniculate nucleus, and striatum). This

study strongly supports the concept that dendritic bundles are target specific. Moreover, the composition of dendritic bundles does not seem to depend on the age of the animal and is already established at P3. It is an interesting possibility that some transient elements join the bundles at early developmental stages from the early-generated neurons of the subplate. Thus, it has recently been demonstrated that subplate apical dendrites have a close association with layer V apical dendrites, having the same targets in the early postnatal barrel cortex (Hoerder-Suabedissen and Molnár, 2012). However, it is not known whether dendrodendritic synapses occur in particular dendritic bundles or not.

Unlike what might have been expected, neurons of the same bundle are not more interconnected than neurons of different bundles (Krieger et al., 2007). There

are preferential connections between certain output neurons, interestingly between corticocortical and corticotectal neurons, whose apical dendrites lie in separate dendritic bundles in mouse (Brown and Hestrin, 2009).

Innocenti and Vercelli (2010) proposed that neurons in the different layers of one minicolumn, projecting to different targets, send their apical dendrites to separate dendritic bundles, where they join apical dendrites of neurons from neighboring minicolumns projecting to the same target or combination of targets. They propose that, in a given cortical locale (area or part of an area), an assembly of apical dendritic bundles, which includes each of the outputs to distant cortical or subcortical structures, their parent somata and basal dendrites, and the portion of the neuropil that pertains to them, constitutes a cortical output unit.

Dendritic bundles and microcolumns can be identified in all cortical areas in the cerebral cortex of different mammalian species, such as rodents, carnivores, and primates including humans. The dendritic bundling seems to offer two important advantages. It might minimize the length of the axonal arbors that contact specific neuronal classes, and in development it might simplify the axonal search and recognition of targets. The link, if any, between the minicolumn and apical dendritic bundles and functional cortical units is not yet established. The link between the anatomical organization and the physiological units is not clear.

7.5.5 Columns Outside the Mammalian Isocortex

Columnar arrangements are present in numerous structures in mammals. Iterated circuitry is present in the olfactory bulb glomeruli (Figure 7.1(f)), and in the barreloids (Figure 7.1(e)) and barrelettes in the ventrobasal thalamic nucleus and brainstem, respectively. Columnar structures are also present in the laminated structure of the SC (Harting et al., 1992; Illing and Graybiel, 1986). These are revealed by acetylcholinesterase reactivity as 200–600-μm-wide patches (Harting et al., 1992; Mana and Chevalier, 2001).

Rockland (2010) gives an overview of these patterns: “The periaqueductal gray contains longitudinal columns of afferent inputs, output neurons, and intrinsic interneurons thought to coordinate different strategies for coping with different types of aversive stimuli” (Bandler and Shipley, 1994; Keay and Bandler, 2001). The lateral septal nucleus is reported to have a complex system of chemically and connectionally distinct zones of transverse sheets (Risold and Swanson, 1998). Some thalamic nuclei have distinct domains, which are neurochemically and connectionally distinguishable (Rausell and Jones, 1991). The basal ganglia are organized into

neurochemically and connectionally distinct striosomes and matrix (Graybiel and Ragsdale, 1978).“

In the cerebellar cortex, an elaborate array of modular subdivisions is revealed by histochemical markers, the topography of afferent projections and some efferent projections, and gene expression in subpopulations of Purkinje cells (PCs) (Sillitoe and Joyner, 2007; Voogd and Glickstein, 1998). Zebrin II expression in PC reveals a parasagittal stripe pattern, each stripe consisting of a few hundred to a few thousand PCs, that is highly reproducible, activity independent, and conserved across species. Other molecular and connectivity markers have an orderly relation to zebrin+ or zebrin– stripes (Larouche and Hawkes, 2006). The functional importance of this striking organization remains to be elucidated, but, as compared to the mosaicism of the SC, it has been suggested to subserve a massively parallel architecture with a high number of processing channels (Larouche and Hawkes, 2006). Minicolumn-like dendritic bundles can also be found in numerous noncortical structures (e.g., Roney et al., 1979).

7.5.6 Columns in Nonmammals

The columnar organization of the cerebral cortex is a broadly documented principle of design preserved throughout mammalian evolution (Mountcastle, 1997), and it is often considered unique to mammals. Karten has questioned the assumption of the uniqueness of the neocortical cells and circuits in mammals and has argued for a similar laminar and columnar organization in the avian brain (Wang et al., 2010). Using contemporary methods, Karten and colleagues demonstrated the existence of comparable columnar functional modules in the laminated auditory telencephalon of an avian species (*Gallus gallus*). Tracer placed into individual layers of the telencephalon within the cortical region, which is considered similar to the mammalian auditory cortex by Karten and colleagues, revealed extensive interconnections across layers and between neurons within narrow radial columns perpendicular to the laminae (Wang et al., 2010). This columnar organization was further confirmed by visualization of radially oriented axonal collaterals of individual intracellularly filled neurons. These findings indicate that laminar and columnar properties of the neocortex are not unique to mammals and may have evolved from cells and circuits found in more ancient vertebrates (Shepherd and Grillner, 2010; Montiel et al., 2012).

7.5.7 What Is the Function of a Cortical Column?

The functional rationales for the columnar organization of the cerebral cortex include arguments for ‘augmenting of cortical surface area during speciation;

modular segregation of inputs; and facilitation of computation by enhancing information processing' (Purves et al., 1992). Modular clustering is believed to be important to allow a large number of neurons to be connected without a significant increase in cortical volume (Mitchison, 1992).

However, if modules are essential for information processing, why is it that they are present in some species but not in others without any noticeable perceptual differences (Horton and Adams, 2005; Purves et al., 1992)? Or, if they are essential in enhanced computation, why are they not present in higher motor and association areas (Purves et al., 1992)? The criteria for the identification for modules/columns are so diverse that it is possible that some variables that might define patchy or modular arrangements might be identified in the future.

The experimental paradigms provided by the barrel and the OD column tend to influence the way the cerebral cortex is looked at as a whole, but neither is clearly built up from microcolumnar units of cells or connections. None of these cortical arrangements is associated to a particular cognitive or perceptual ability in species where they are present or absent. Horton and Adams argue that the lack of correlation across species with or without OD columns and vision, and with or without cortical barrel field and whisker function, strongly argues for the 'lack of particular function of these striking but inconstantly expressed anatomical features' (Horton and Adams, 2005).

Dendritic bundles have been found throughout the mammalian brain and are believed to serve fundamental roles in the brain's functioning. However, no physiological experiments to determine their function have been performed on these well-established anatomical units. The function of the anatomical microcolumns as fundamental units of organization is also not clear. Much more comprehensive analysis of the intricacies of intracortical connectivity and the anatomy and physiology of microcolumns in all cortical areas of several species is needed. Combining these approaches could clarify several issues (see Bock et al., 2011). Microcolumns might represent fine-grain functional modularity of the cortex. The radial dispersion of these clusters in some columns is about 400 µm in all species, similar to the spread of some dendritic arbors.

7.5.8 Columns in Neuropathology

Cortical modules have drawn the attention of neuro-pathologists not because their function is known, but because they can be visualized, quantified, and compared between subjects. They might be epiphenomena, but they are detectable entities and therefore can be used as diagnostic signs for abnormal cortical organization.

The periodicities of microcolumnar structures (that contain about 11 neurons and have a periodicity of about 80 µm) were disrupted in two examples of neurodegenerative disease in human (Jones, 2000). Some alterations of the microcolumnar structures have been described in the brains of the more elderly (Peters, 1997).

Currently, it is not known what degree of radial allocation and lateral neuronal dispersion is essential for the proper radial delivery and intermixing of neuronal types in cortical columns. Alterations in the clonal dispersion of neurons have been linked to neuropsychiatric disorders associated with abnormal columnar organization (Torii et al., 2009).

7.6 WHAT IS THE CORRELATION BETWEEN THE COLUMNAR DEVELOPMENT OF THE BRAIN AND FUTURE COLUMNS?

7.6.1 Cortical Columns During Development

Mountcastle emphasized that the mode of generation of the cortex already reflects its basic columnar organization (Mountcastle, 1997). From Golgi preparations and from Nissl-stained material, the radial orientation of neurons within the developing cerebral cortex is apparent from the very beginning (Cajal, 1909). Neurons assume a radial orientation and dendritic polarity shortly after their generation. These observations triggered theories that much of the anatomical substrate for a columnar organization would already be specified at early developmental stages before activity-dependent mechanisms could be activated (Rakic, 1988).

7.6.2 Ontogenic Units/Columns – The Fundamental Building Blocks in the Developing Neocortex

There is strong evidence for the overall radial migration of pyramidal neurons in all mammalian cortices (Rakic, 2009). Clonally related postmitotic pyramidal neurons are initially deployed in a geometrically columnar pattern in the embryonic primate cerebrum. Rakic proposed that the location of the cohorts of cortical neurons from a single neuronal progenitor is not random but is largely predictable (Rakic, 1988). Each neuron in mature cortical 'minicolumns' is derived from one of a small group of progenitors forming a polyclonal group in the ventricular zone (VZ) (Kornack and Rakic, 1995).

The progenitor cells that generate the minicolumn were termed ontogenic columns (Rakic, 1988). Rakic estimated that "each proliferative unit in the ventricular zone of the monkey consists of 3–5 stem cells, a number that gradually increases to 10–12 stem cells during

development; the units are separated by glial septa" (Rakic, 1988). According to this theory the surface area, and thus the size of the neocortex, is determined by the number of ontogenetic units set by the number of symmetric divisions of progenitor cells in the neural epithelium before migration begins (Rakic, 1988, 2009). It has been suggested that one important phenomenon for the increased cerebral complexity during evolution may be the multiplication of neuronal columns throughout the cerebral cortex (Rakic and Caviness, 1995).

According to this theory, functional columns in the adult cerebral cortex must consist of several ontogenetic columns (polyclones). The visual display of these ontogenetic units has not been achieved, and it is still unclear to what extent and how gene expression in the VZ could play a role in the development of discrete functional units, such as minicolumns or columns. Cell lineage experiments using replication-incompetent retroviral vectors have shown that the pyramidal neuronal progeny of a single neuroepithelial/radial glial cell in the dorsal telencephalon is organized into discrete radial clusters of sibling excitatory neurons (Kornack and Rakic, 1995; Noctor et al., 2001). Costa et al. (2009) noted that most neuronal clones derived from E13 progenitors span 150–250 µm in the horizontal axis and contribute to all cortical layers generated after that embryonic stage. The same authors performed mathematical extrapolations for injections at the onset of neurogenesis in the cerebral cortex (E10–11) and suggested that neuronal siblings would not disperse by more than 400–500 µm. Thus, both the radial and horizontal dispersions of excitatory neuronal clones fit well with the possibility that they could help to create a structural basis for the future specification of columns.

How these developmental neural clusters relate to adult anatomical and physiological columns has not been addressed. Neurons from different clones intermix

with the adjacent columns as they migrate across the intermediate zone. In addition to the radial allocation of clonally related neurons, short lateral shifts and transfers from their parental to the neighboring radial glial fibers have been described (Kornack and Rakic, 1995; Noctor et al., 2001; Tan and Breen, 1993). These dispersed neurons intermix with neurons originating from neighboring proliferative units. The molecular mechanisms, their role, and the significance of this lateral dispersion for cortical development are not understood. A recent study revealed that the lateral dispersion depends on the expression levels of Eph receptor As (EphAs) and ephrin-As during neuronal migration. Torii et al. (2009) demonstrated that an EphA and ephrin-A (Efna) signaling-dependent shift in the allocation of clonally related neurons is essential for the proper assembly of cortical columns in the mouse cerebral cortex (Figure 7.6). Currently, it is not known what degree of radial allocation and lateral neuronal dispersion seems to be essential or optimal for the proper radial delivery and intermixing of neuronal types in the cortical columns. The degrees of mixing of derivatives of different progenitors have not been estimated in different species.

7.6.3 Sibling-Neuron Circuits in the Developing Columns

Thus, both the developing cortex and the adult cortical columns have overwhelmingly radial arrangements. In the developing brain, the clonally related neurons have higher chances of being situated within the same radial volume of cortical tissue (Tan and Breen, 1993). It has been proposed that the initial columnar organization may act as a seed to establish the primary information-processing unit in the cortex.

This raises the question as to whether neurons from the same clone develop connectivity preferentially. Are

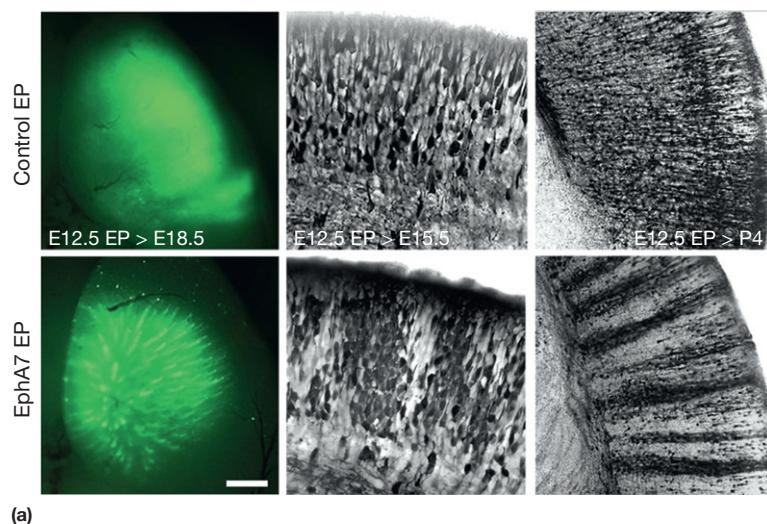


FIGURE 7.6 Eph receptor A (EphA) and ephrin-A (Efna) signaling-dependent shift in the allocation of clonally related neurons changes the level of lateral dispersion in the embryonic brain. Torii and colleagues demonstrated that lateral dispersion depends on the expression levels of EphAs and ephrin-As. Increased EphAs and ephrins during neuronal migration leads to increased tangential sorting of cortical neurons. The figure represents the distribution of EYFP-labeled neurons (green or black) during development in the cortex in which control or EphA7 expression plasmid was delivered using electroporation (EP) with EYFP plasmid. Scale bars, 600 mm (for E18.8), 50 mm (for E15.5), and 200 mm (for P4). Reproduced from Torii M, Hashimoto-Torii K, Levitt P and Rakic P (2009) Integration of neuronal clones in the radial cortical columns by EphA and ephrin-A signalling. *Nature* 461(7263): 524–528.

they more likely to develop chemical synapses with each other rather than with neighboring nonsiblings? Cell lineage or clonal analysis studies have been combined with recording experiments to study the possibility that the cell lineage of single neuroepithelial/radial glia cells could form radial columns of sibling, interconnected neurons. [Yu and colleagues \(2009\)](#) identified individual clones of cortical pyramidal neurons by injecting enhanced green fluorescent protein (EGFP)-expressing retroviruses into the lateral ventricle of mouse embryos at early stages of neurogenesis. They made simultaneous whole-cell recordings on two EGFP-expressing sister neurons and observed that these cells displayed unidirectional synaptic connections in 35% of pairs. In contrast, less than 7% of radially situated nonsister excitatory neurons were connected ([Yu et al., 2009](#)). This experiment provides strong support for the idea that excitatory neurons generated from the same progenitor keep spatial relationships and display (mutual) connectional preferences, but it stops short of relating the clones to adult cortical columns. There is a distinction between the idea that sibling neurons have predictable arrangements and connectivity and the idea that adult columns are ‘preformed’ and prespecified in ontogenetic units in the VZ. More work is needed to clarify these issues.

The potential molecular mechanisms involved in the establishment of sibling-neuron circuits are not known. It has been hypothesized that neurons derived from the same progenitor are more likely to display similar chemical and physical properties because of their genetic inheritance ([Costa and Hedin-Pereira, 2010](#)). Sister neurons might share more of the combinatorial transcription code that has been present in the common cortical progenitors, and therefore the sister neurons might share a similar set of surface molecules that are important for cell–cell recognition or for molecular guidance cues. The molecular determinants of the cell-intrinsic properties for cell–cell recognition between sibling neurons in the cortex remain a largely uncharted territory.

7.6.4 Transient Columnar Domains During Development

The coordinated calcium fluctuation patterns underlying gap junction-mediated communication were suggested as a possible basis for the formation of initial functional cell assemblies in the postnatal cerebral cortex. [Yuste et al. \(1992\)](#) observed distinct domains of spontaneously coactive neurons using optical recordings of brain slices labeled with the fluorescent calcium indicator fura-2 in early postnatal rat cortex. Their observations emphasized the discrete multicellular patterns that are mediated through communication via gap junctions. The functional domains were 50–120 μm in diameter on tangential slices; they spanned several cortical

layers and resembled columns found in the adult cortex in coronal slices. In the developing somatosensory cortex, domains were smaller than, and distinct from, the barrels. Gap junctions coupled the neurons within each domain. Gap junction domains persisted after blockade of sodium- and calcium-dependent action potentials, suggesting that they may promote metabolic rather than activity-related assemblies ([Kandler and Katz, 1998](#)).

There are modules and columns within the developing cortex that are present only transiently during development, but not in the adult. Numerous stains are transient during barrel development ([Erzurumlu et al., 1990](#); [Mitrovic and Schachner, 1996](#)). OD columns are more apparent during development or upon visual deprivation than in normal adults in the marmoset, and the presence or absence of OD columns has been debated in the adult marmoset ([Chappert-Piquemal et al., 2001](#); [Spatz, 1989](#)). There are transient circuits that show a pattern that is transiently related to the (sensory) periphery of the vibrissae in the barrel cortex in the mouse, and this involves the neurites of the early generated and largely transient subplate neurons ([Piñon et al., 2009](#); [Hoerder-Suabedissen and Molnár, 2012](#)). These changes in cortical patterning may reflect the development of synaptic integration that will provide coherent activity among groups of target cells, but it has been questioned whether the observed patterns themselves have any functional relevance ([Purves et al., 1992](#)). Induction of visible and distinguishable barrel patterns or of OD columns has not been linked to a particular sensory or motor capacity ([Horton and Adams, 2005](#); [Purves et al., 1992](#)).

Prior to birth, monocular transduction pathways are already established through a process known as Hebbian learning. Spontaneous retinal activity in one eye of the developing fetus leads to neuronal depolarization ([Galli and Maffei, 1988](#)) that can propagate through the thalamus ([Mooney et al., 1996](#)). Synapses that receive multiple inputs are more likely to propagate the signal, whereas errant connections will not be sufficient to trigger another action potential. If glutamate has been released by the presynaptic axon terminal, postsynaptic neurons that depolarize become permeable to calcium ions. Calcium entry leads to a chemical process that strengthens the synapse, making it more likely to survive than other connections.

Although orientation columns can develop without any externally elicited sensory visual input (before birth), their maintenance relies on postnatal sensory-driven visual activity ([Crair et al., 1998](#)).

7.7 SUMMARY AND THE WAY FORWARD

1. There are several problems associated with the current nomenclature of columns. The concept of a

'universal cortical column' is very captivating in anatomical, physiological, and developmental models of the cerebral cortex, and this is reflected in the current terminology that aims to gloss over differences rather than expose them. There is overwhelming evidence for various forms of radial organization, and some of the modular (columnar) organizations are striking (Douglas and Martin, 2004). However, there are various types of cortical columns, and there is a need to define them more clearly as a better understanding of their properties is gained. The term 'column' might be modified or abandoned altogether when there is more information about the types of cortical circuits and the range of their operations. The term column is still used because of its captivating concept. For the time being, there is no easy alternative to 'column.' It is necessary to establish more specific terminology that will allow specific reference to particular entities. As the cell types of the cerebral cortex become better characterized morphologically, chemically, and physiologically, the details of the types of connections and circuits that they establish with one another within the cortex are becoming understood.

2. It is now known that columns/modules are characteristic of the neocortex, but there is no single structure or function that is *the* common building block of all cortical areas in all mammals. The observations made on the barrels in S1 and the OD columns in V1 have had an enormous influence on the way the cerebral cortex is looked at as a whole; however, it is increasingly apparent that this cannot be generalized to all regions. Horton and Adams write: "At some point, one must abandon the idea that columns are the basic functional entity of the cortex. It now seems doubtful that any single, transcendent principle endows the cerebral cortex with a modular structure. Each individual area is constructed differently, and each will need to be taken apart cell by cell, layer by layer, circuit by circuit, and projection by projection to describe fully the architecture of the cortex" (Horton and Adams, 2005). Under the influence of the new data, the concept will also gradually change and the elusive idea of a 'universal cortical unit' that extends radially as a homogeneous building block in all areas in all mammals may finally have to be rejected.
3. The previous finding of constant cell numbers within an arbitrary unit column and the homogeneous structure of the column is not supported by recent observations. On the contrary, it is apparent that cortical areas exhibit huge differences in cell composition, cell numbers, and connectivity (Lent et al., 2012).
4. The possible functions specifically associated with the presence or absence of a particular column (e.g., OD

columns, barrels) is not clear. Comparative studies have yet to identify a specific sensory, motor, or cognitive function that is specifically associated with a particular form of cortical column. Purves and colleagues postulated that the columnar patterns arise because they are an "incidental consequence of the rules of synapse formation" (Purves et al., 1992).

5. There is overwhelming evidence for early columnar allocation of the developing pyramidal neurons. It is also evident that at early developmental stages an early organization has already been specified before activity-dependent mechanisms could take place. The link between the clonally related neuronal assemblies and future modules of the cortex is not yet clear, but with the current repertoire of methodologies, these issues can now be addressed.

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