Cerebral Cortex

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The mammalian cerebral cortex is an enormous sheet of cells covering in the human brain approximately 250 000 mm^2 and containing 1×10^9 or more nerve cells in a volume of about 300 cm^3. The human cerebral cortex is by no means the largest – it is exceeded in area by that of the whales – but it is probably the most highly differentiated. Differentiation, in this sense, means the subdivision of the cortex into the largest number of histologically distinct subareas each of which has a known or suspected function.

The fundamental divisions of the cerebral cortex in mammals are the hippocampal formation (or archicortex), the olfactory cortex and associated areas such as the entorhinal and periamygdaloid area in the piriform lobule (paleocortex), and the remainder (neocortex). The three parenthetical names indicate the phylogenetic assumptions of past generations of neuroscientists who regarded the neocortex as the hallmark of mammalian evolution. In nonmammalian brains, a hippocampal formation and an olfactory-related cortex can readily be identified, whereas a neocortex is probably absent or if present, is extremely small. The remainder of this article deals only with mammals and only with the neocortex.

The neocortex develops on the surface of the cerebral hemispheres as a series of waves of newly generated cells many of which migrate radially outward from the proliferative ventricular and subventricular zones lining the primitive lateral ventricles while others invade by migration from the region of the developing basal ganglia. The earliest arriving cells form a primordial cortex which is invaded by successive waves of other cells. Each successive wave pushes through its predecessors and comes to lie external to them. In this is the beginnings of one of the overt histological features of the neocortex: lamination. Cells in a particular lamina are born during the same limited time window and aggregate together in the cortex. In all but the most superficial layer of the cortex of a fully developed mammal there are two major neuronal classes (and, of course, neuroglial cells). The two neuronal types are called pyramidal and nonpyramidal. Among the latter are several subtypes. The names of the cells reflect their morphology as seen with stains such as that of Golgi which reveal the morphology of the whole cell. The lamination of the cortex is, at the routine histological level seen with the Nissl stain (which stains only cell somata), a lamination of cell bodies. Stains such as that of Golgi show that processes of the cells can extend across laminae.

In most parts of the mammalian cortex, a six-layered pattern first introduced by the anatomist Brodmann and based upon Nissl staining, has come to be accepted as the standard, though five- and seven-layered patterns have also been in vogue. Layer I is the layer immediately beneath the pia mater and contains very few cell bodies, belonging mainly to neuroglial cells and to a few nonpyramidal neurons – hence its name, 'molecular layer'. Layer II consists of small, tightly packed cell bodies, most of which are small pyramidal neurons, but nevertheless is called the 'external granular layer'. Layer III is a thick layer in which pyramidal cell somata increase progressively in size from superficial to deep. It is referred to as the pyramidal or 'external pyramidal layer'. Layer IV is thin but densely packed with the somata of small pyramidal and nonpyramidal cells. It is called the 'internal granular layer'. Layer V consists primarily of large, loosely dispersed pyramidal cell somata. It is referred to as the ganglionic or 'internal pyramidal layer'. Layer VI is composed of relatively tightly packed, small, round cell somata that belong mostly to a modified form of pyramidal cell. It is called the 'multiform' or 'polymorph layer'. In certain areas, some of these layers can be reduplicated or further subdivided.

The features of the Nissl-stained laminar pattern are superficial. Each layer defined in the terms given, apart from layer I, contains pyramidal and nonpyramidal cells of varying types. All these cells have dendrites and axons that can extend into or through other layers. The majority of the pyramidal cells-with somata in any layer send their apical dendrites through all the supervening layers to end, commonly in a tuft of branched dendrites, in layer I. When stained with the Golgi method, therefore, the lamination of the cortex is far less clear than in a Nissl-stained preparation.

The cerebral cortex is also laminated in terms of the distribution of afferent axons and of some of its intrinsic axonal systems. Traditionally, these layers have been described from myelin-stained preparations, but they can also be discerned in well-stained Golgi and reduced silver preparations which stain axons and dendrites. In these preparations, a tangential fiber plexus is revealed in layer I which is consequently called the plexiform layer. A condensation of fibers in the deepest part of layer I is called the stria of Kaes or Bechterew (Figure 1). Horizontal plexuses of fibers in layer IV and deep in layer V are called

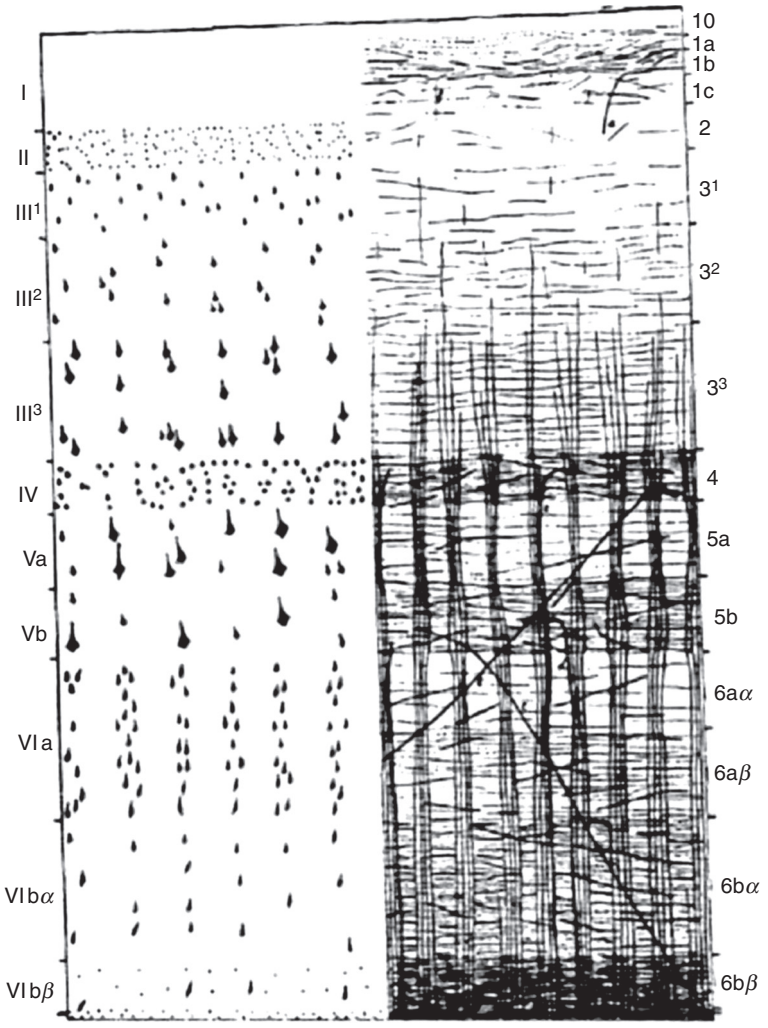

Figure 1 Vogt's scheme of the fundamental plan of cellular (left) and fiber (right) layering in the cerebral cortex. The cellular layers (I through VI) are those given in the text and Vogt divides them into sublayers. Fiber layers 4 and 5b are the bands of Baillarger; the stria of KaesBechterew, when present, is in layer 1c. From Vogt C and Vogt O (1919) Allgemeinere Ergebnisse unserer Hirnforschung. *Journal of Psychology and Neurology* 25: 279–462.

the inner and outer bands of Baillarger. These are probably formed primarily by intrinsic axons of the cortex (i.e., axons of some nonpyramidal cells and collateral branches of axons of pyramidal cells). The outer band of Baillarger is traditionally thought to be formed by the terminal ramifications of thalamocortical axons, but this has been disputed in the visual cortex where the band is referred to as the stria of Gennari and consists mainly of axons arising from intrinsic cortical sources.

Vertical bundles of myelinated axons extend through layers III to VI of the cortex, becoming thicker as they descend and as more axons are added. The bundles are referred to as radial fasciculi and contain axons of pyramidal neurons as they proceed to exit the cortex, and the axons of certain nonpyramidal neurons. Afferent axons coming into the cortex can usually be identified in myelin preparations as thick, obliquely running fibers separate from the radial fasciculi (Figure 1).

The laminar patterns seen in Nissl- and myelin-stained preparations vary from mammal to mammal and across the surface of the cortex of an individual mammalian species. The art of identifying and determining the boundaries of different cortical areas is known as cytoarchitectonics or myeloarchitectonics, depending on whether Nissl or myelin stains are used as the basis for the delineations made. Cortical areas, many with known functional characteristics (visual, auditory, motor, etc.) have cyto- and myeloarchitectonic features and common differences in histochemical staining as well, that enable their borders to be defined and a distinction to be made between them and adjacent areas. The basic types of neocortex are:

'homotypical', found in the frontal, temporal, and parietal lobes; 'heterotypical', divided further into granular and agranular cortex. 'Granular' or 'koniocortex' is found in the sensory areas and in it there is a predominance of small cell bodies in layers II–IV, resulting in a blurring of the borders between the layers; in 'agranular cortex', found in the premotor and motor areas, layer IV disappears during development, and layers III and V form a continuum of increasing pyramidal cell somal size. In conjunction with the changes in the Nissl staining pattern, there are changes in the myelin staining pattern. The homotypical cortex shows all the laminated plexuses, in granular cortex the bands of Baillarger predominate, and in agranular cortex thick radial fasciculi predominate.

With one or two exceptions, mainly in the visual cortex, the pyramidal cells are the output cells of the cerebral cortex, sending their axons to subcortical targets and to other cortical areas on the same and opposite sides of the brain (Figure 2). To a large extent the pyramidal cells with somata in a particular cortical layer send their axons to a defined set of targets, and the laminar localization of cells projecting to the same target(s) does not vary greatly from area to area. The modified pyramidal cells of layer VI send their axons to the principal thalamic nucleus providing the input to the cortical area in which they lie, to the claustrum, and to cortical areas linked functionally with their own. Layer V pyramidal cells provide connections to all other subcortical structures: corticospinal, corticobulbar, corticopontine, corticorubral, corticotectal, corticostriatal, and corticothalamic fibers to nonspecific thalamic nuclei. There are conflicting reports about the extent to which axons to one site arise as branches of those directed to another and there may be species differences in the degree to which this occurs. Pyramidal cells of layers II and III provide most of the axons of the corpus callosum and most of those forming ipsilateral corticocortical connections, though some callosal and ipsilateral corticocortical axons can arise from pyramidal cells with somata in other layers as well. The precise constellation of cortical and subcortical connections emanating from a cortical area varies, with some types of connection and thus the parent cell category being absent from some areas. Corticorubral fibers, for example, arise only in the motor and premotor areas. Others, such as the corticostriatal and corticopontine, probably arise in all areas. It is probably the variation in pyramidal cell size and shape related to these differential connections that helps determine the architectonic characteristics of the individual cortical areas.

Afferent axons entering a cortical area arise from a variety of sites. Every cortical area receives specific afferent fibers from a particular thalamic relay nucleus or nuclei and from a particular set of ipsilateral and contralateral cortical areas. These three sets of fibers release the excitatory amino acid transmitter glutamate. All the inputs to the sensory areas, at least, are highly ordered, topographically organized sets of connections that form an essential element in the mapping of the external world and surface of the

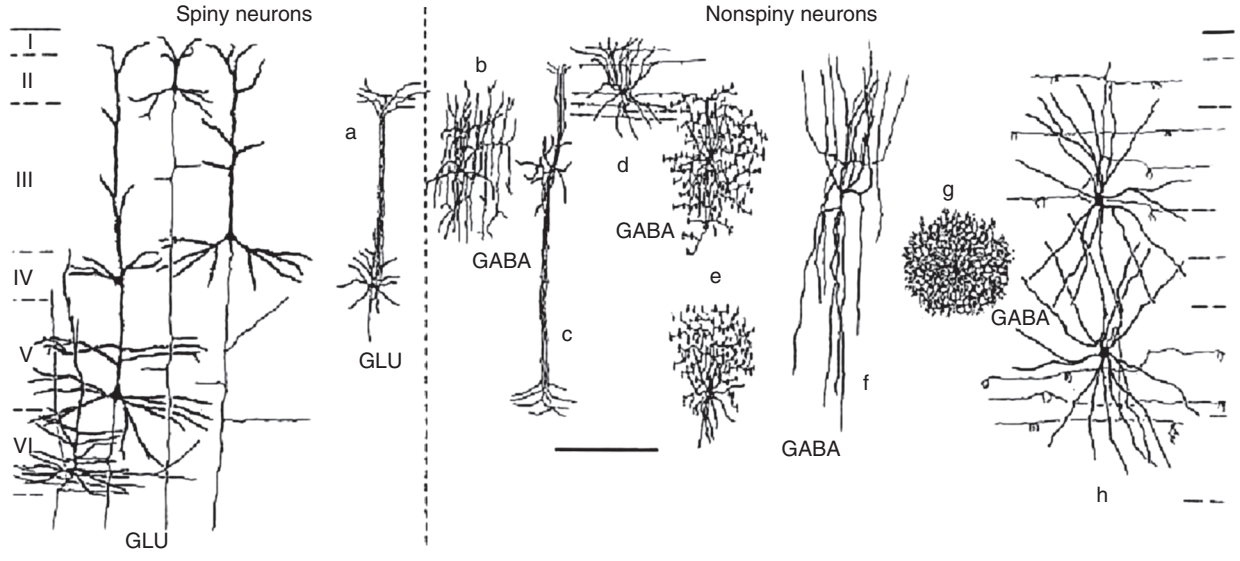

Figure 2 Basic cell types in the monkey cerebral cortex. (Left) Spiny neurons which include pyramidal cells and spiny stellate cells (A), a form of nonpyramidal neuron. Spiny neurons utilize the neurotransmitter, glutamate (Glu). (Right) Nonpyramidal cells all of which use the neurotransmitter, GABA. B, cell with local axon arcades; C, double bouquet cell; D, H, basket cells; E, chandelier cells; F, bi-tufted, usually peptide-containing cell; G, neurogliaform cell. Modified from Jones EG (1981) Anatomy of cerebral cortex: Columnar input-output organization. In: Schmitt FO, Worden FG, and Dennis SG (eds.) *The Cerebral Cortex,* pp. 199–235. Cambridge, MA: MIT Press.

body on to the cortex. Other, more diffusely organized afferent fibers whose cortical distribution does not respect cytoarchitectonic boundaries arise in so-called nonspecific nuclei of the thalamus, in the noradrenergic cells of the locus coeruleus, serotoninergic cells of the midbrain, cholinergic cells of the basal forebrain, and, for many cortical areas, in the dopaminergic cells of the midbrain. It is customarily assumed that some or all of these nonspecific afferent systems are concerned with controlling levels of cortical excitability, arousal and the conscious state. The specific and nonspecific afferent fiber systems terminate in particular cortical layers that tend to vary from area to area and from species to species. In general, specific thalamic fibers end predominantly in the middle layers (III and IV) and corticocortical fibers in layers I–IV. Many nonspecific systems end predominantly in layers I and/or VI.

The three specific afferent fiber systems terminate on both pyramidal and nonpyramidal cells. The further, internal, elaborative circuitry of the cortex is then effected by the axons of nonpyramidal cells and by the intracortical collaterals of pyramidal cell axons. Depending on their morphological types the nonpyramidal cells' axons have rather precise targets, mainly on different levels of the soma-dendritic membranes of other cells. The collaterals of pyramidal cell axons tend to be preferentially distributed to certain layers depending on the target of the principal axon of the pyramidal cell. Most output cells, seem to be affected monosynaptically by specific afferent fibers and polysynaptically by these fibers after relays through one or more other cortical neurons.

Nonpyramidal neurons belong to several morphological categories, each of which has been given a name that usually reflects some aspect of its dendritic or axonal arborization pattern (**Figure 2**). The distributions of their axons are the best determinants of cell type and determine in turn the range of action over which these intrinsic cortical interneurons act. Those with local axons probably serve to modulate local synaptic actions between afferent fibers and efferent cells; those with vertical axons effect interlaminar connections (ascending and descending) and are probably the main determinants of the columnar organization of the cortex such as is manifested in the visual cortex. Those with horizontal axons effect intralaminar and intercolumnar actions. While the division of cortical neurons into pyramidal and nonpyramidal types reflects their division into extrinsically projecting and intrinsic neurons, a further division of equal functional importance is into those which possess substantial populations of dendritic spines and those that are essentially nonspiny. This reflects a division into neurons that produce the excitatory amino acid transmitter glutamate, and those that produce the inhibitory neurotransmitter, γ-aminobutyric acid (GABA). All pyramidal cells are spiny and glutamatergic. Long horizontal collaterals of the axons of layers III and V pyramidal cells are the main sources of horizontally spreading excitation in the cortex. Nonpyramidal cells are divided into spiny and non-spiny types. Spiny nonpyramidal cells (spiny stellate cells) dominate layer IV, are the major recipients of thalamic synapses, are glutamatergic, and their axons provide the main route for information to flow out of layer IV into other layers. The majority of nonpyramidal neurons lack significant populations of dendritic spines, are found in all layers, and use GABA. They account for up to 30% of the total population of cortical neurons. They can be further divided into subpopulations based upon their production of one or other of three calcium-binding proteins: 28KD calbindin, 29KD calretinin, or parvalbumin. The chemical profile of each type of cortical interneuron tends to be associated with the possession of a particular set of membrane conductances that confers different discharge properties upon the cells. A small subpopulation also contains one or more neuropeptides. The combination of inhibitory and excitatory effects mediated by the various types of cortical cell are thought to be critical in shaping the receptive fields of neurons recorded in different layers of the cortex, in maintaining columnar organization in the cortex, and in setting up afferent inhibition between columns.

See also: Brodmann's Areas; Cerebral Cortex: Inhibitory Cells; Hippocampus; Memory Consolidation: Cerebral Cortex; Neocortex: Origins; Olfactory Cortex: Comparative Anatomy; Olfactory Cortex Physiology.

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