15 Telencephalon: Neocortex

Introduction

The neocortex is an ultracomplex, six-layered structure that develops from the dorsal pallial sector of the telencephalic hemispheres (Figs. 2.24, 2.25, 11.1). All mammals, including monotremes and marsupials, possess a neocortex, but in reptiles, i.e. the ancestors of mammals, only a three-layered neocortical primordium is present [509, 511]. The term neocortex refers to its late phylogenetic appearance, in comparison to the "palaeocortical" olfactory cortex and the "archicortical" hippocampal cortex, both of which are present in all amniotes [509].

The size of the neocortex varies greatly among the various mammalian groups. In some insectivores, such as the hedgehog, its

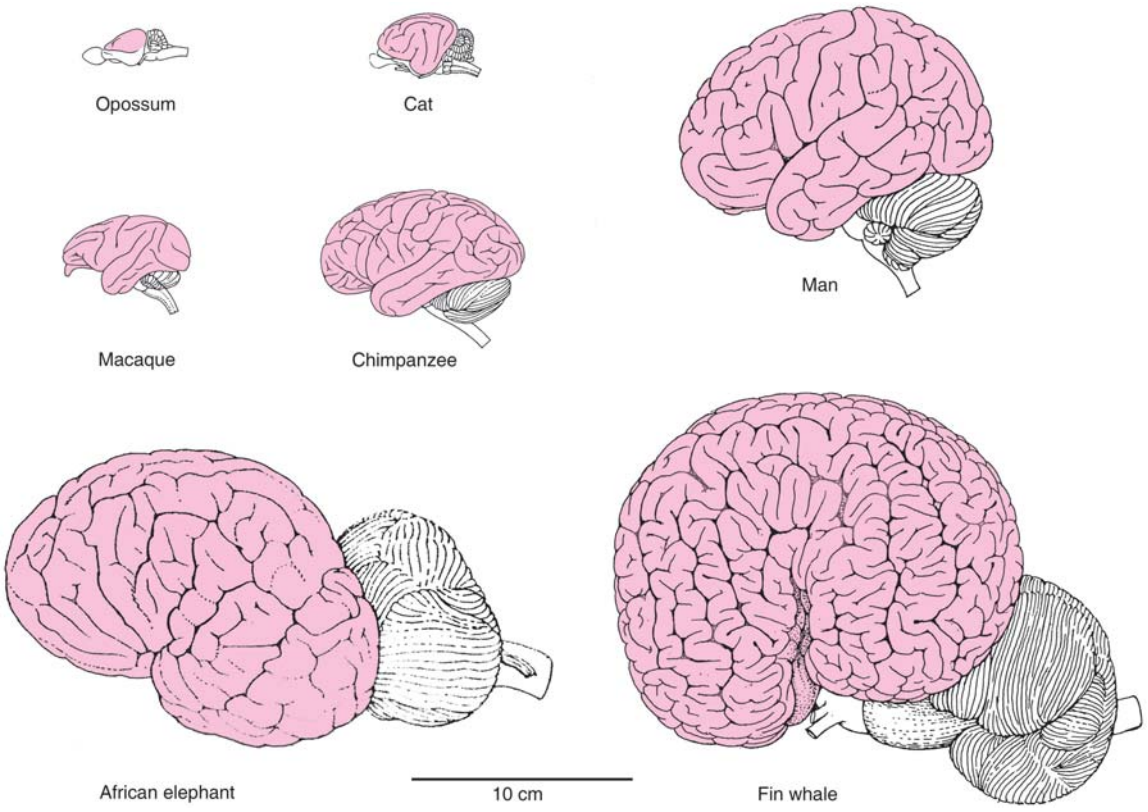


Fig. 15.1. Brains of some mammals drawn on the same scale. The neocortex is shown in *red*

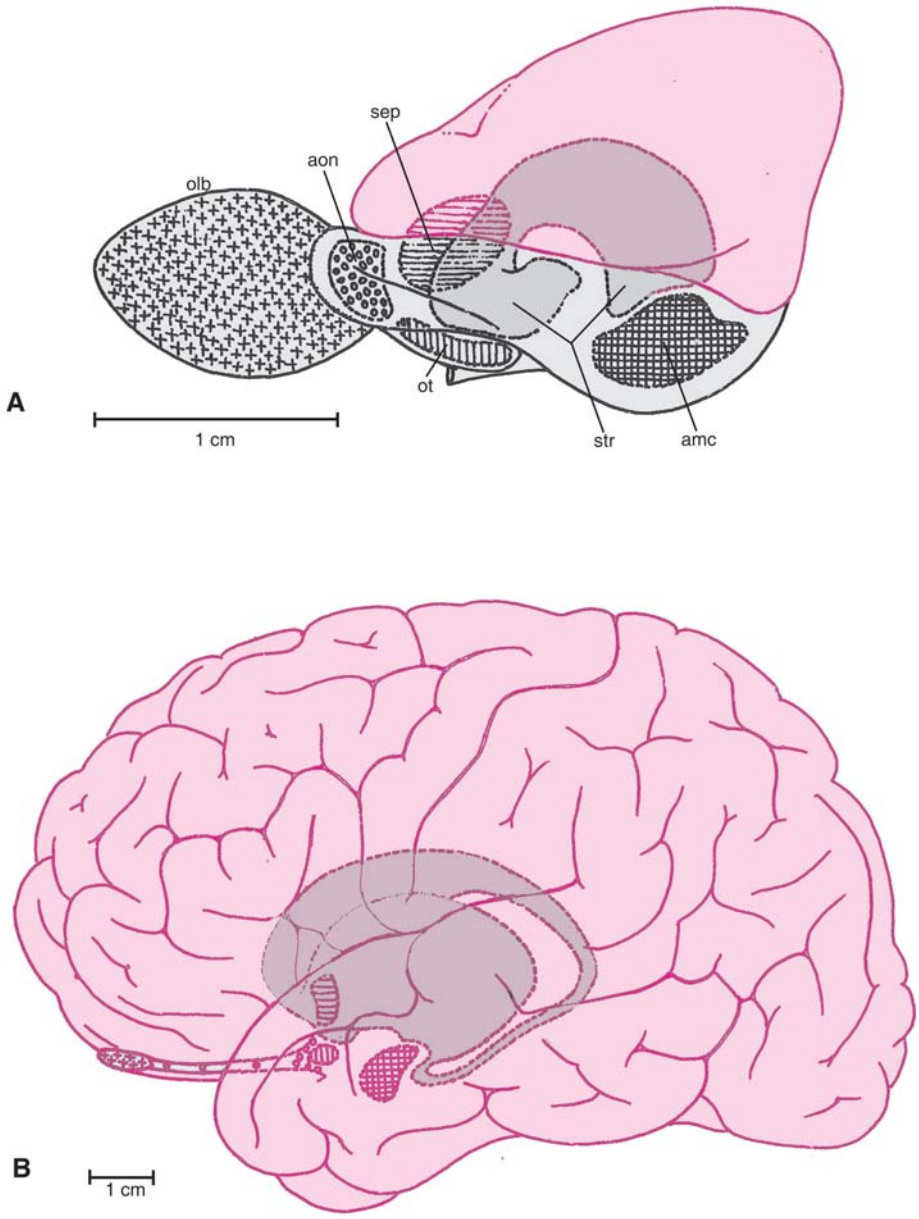


Fig. 15.2. The telencephalon of the opossum (**A**) and human (**B**). The position and extent of the neocortex (shown in *red*) and of a number of subcortical centres (marked in **A** and **B** by the same *hatchings/symbols*) are indicated. In the opossum, the neocortex covers the remaining parts of the telencephalic hemispheres like a cap. In humans, the enormously expanded neocortex almost completely surrounds all subcortical centres. *amc*, amygdaloid complex; *aon*, anterior olfactory nucleus; *olb*, olfactory bulb; *ot*, olfactory tubercle; *sep*, precommissural septum; *str*, corpus striatum

size does not exceed that of the "older" parts of the cortex, but in primates and cetaceans it attains remarkable proportions, becoming by far the largest centre in the brain (Figs. 15.1, 15.2). Stephan and Andy [709] determined the average index of progression for the neocortex (and for many other brain structures) in a number of insectivores, prosimians and simians, including humans. These indices express how many times larger the neocortex is in a particular group of species than in that of a typical basal insectivore of the same size. It was found that in prosimians the neocortex is on average 14.5 times, and in the simians 45.5 times larger than in basal insectivores. In humans, the neocortex appeared to be 156 times larger than that of basal insectivores.

As regards the functional differentiation of the neocortex, in many "primitive" mammals (marsupials, insectivores and rodents) much of the neocortex is occupied by projection areas which either receive, via the thalamus, impulses directly related to the various special senses, or are concerned with the steering of motor activity. The sensory fields comprise the somatosensory cortex, receiving impulses from sense organs situated in the skin, the muscles and the joints, then the primary visual cortex and finally the primary auditory cortex.

There is evidence suggesting that already in primitive mammals the various projection areas just mentioned are separated from each other by narrow strips of non-projection cortex (see Cajal [84], p. 830 and figure 531). What we now see is that these strips expand enormously to form a large area known as the parietotemporal association cortex. Another area of association cortex develops in front of the motor cortical areas (Fig. 15.3). This region is known as the prefrontal association cortex. All cortical areas maintain afferent and efferent connections with subcortical centres. However, these various association cortical areas are primarily connected with other cortical fields.

The neocortex shows a laminated structure throughout its extent. Whereas in the piriform and hippocampal parts of the mammalian cortex three layers can be distinguished, in the neocortex six layers are usually recognized (Fig. 15.4 B). The characterization and determination of these layers is generally based on Nissl-stained material. Although the study of such material, in which the dendritic and axonal processes of the neurons remain largely unstained, yields in itself very little insight into the structural and functional organization of the cortex, the results of such *cytoarchitectonic analyses* are important because they provide a very useful general framework for studies employing other, more critical techniques.

Beginning at the surface, the six neocortical layers are as follows: (I) lamina molecularis, (II) lamina granularis externa, (III) lamina pyramidalis externa, (IV) lamina granularis interna, (V) lamina pyramidalis interna and (VI) lamina multiformis.

I. The *lamina molecularis* or *lamina zonalis* contains only very few cell bodies.
II. The *lamina granularis externa* is composed of small, densely packed cell bodies. The name of this layer is misleading because most of its constituent somata belong to small pyramidal neurons which, like all typical cortical pyramids, direct their apices toward the surface.
III. The *lamina pyramidalis externa* is a thick layer in which pyramidal somata prevail. These somata increase progressively in size from superficial to deep.
IV. The *lamina granularis interna* consists of small, densely packed, pyramidal and non-pyramidal somata.
V. The *lamina pyramidalis interna* consists mainly of medium-sized and large, loosely arranged pyramidal somata.
VI. The *lamina multiformis* is composed of relatively tightly packed, spindle-shaped somata. Golgi material reveals that most of these somata belong to modified pyramidal cells.

The neocortex is frequently also designated as *isocortex* [784, 791] or *homogenetic cortex*. Brodmann [70, 71] used the latter term to indicate that, even though some cortical areas in the adult brain may have more or less than six layers, the entire neocortex has passed through a basic, six-layered stage during ontogeny (Fig. 15.4 A).

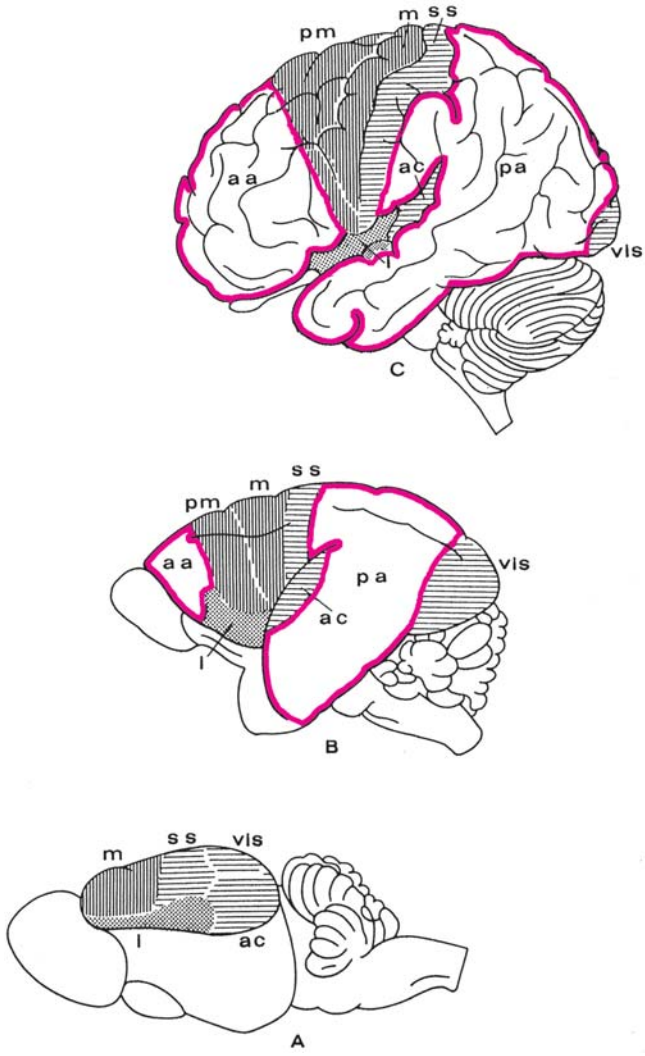


Fig. 15.3. Lateral views of the brains of the hedgehog (**A**), the prosimian *Galago* (**B**) and human (**C**) to show the evolutionary differentiation of the neocortex. In the hedgehog almost the entire neocortex is occupied by sensory (ss, vis, ac) and motor (m) areas. In the prosimian *Galago* the sensory cortical areas are separated by an area occupied by association cortex (pa). A second area of association cortex (aa) is found in front of the premotor cortex (pm). In the human the association areas are strongly developed. *aa*, anterior association area; *ac*, auditory cortex; *i*, insular cortex; *m*, motor cortex; *pa*, posterior association area; *pm*, premotor cortex; *ss*, somatosensory cortex; *vis*, visual cortex

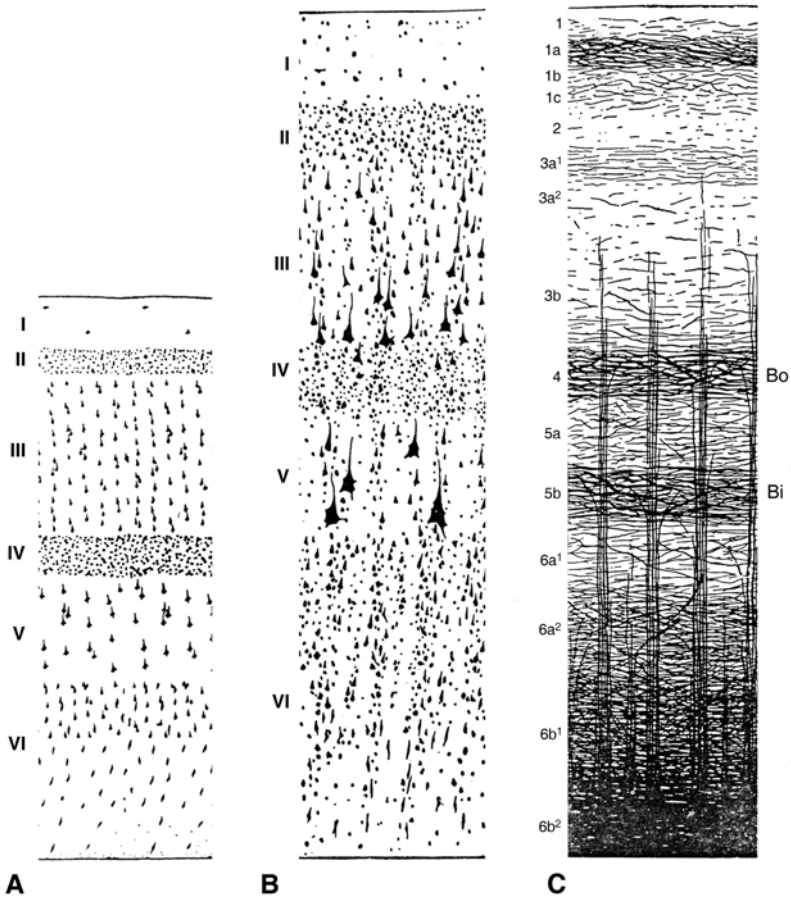


Fig. 15.4. The laminar pattern of the human neocortex: **A** in a newborn, diagrammatic; **B** Nissl preparation, adult; **C** myelin sheath preparation, adult. After Vogt and Vogt [786] and Rose [637]. *Bi, Bo*, inner and outer stripes of Baillarger

Apart from the neuronal perikarya, several other structural elements in the cortex show a more or less distinct laminar arrangement. Myelin-stained and reduced silver preparations reveal the presence of tangentially oriented fibre concentrations at several levels, and Golgi material shows that these fibres and their terminal ramifications may contribute to plexiform zones, which are likewise tangentially arranged. Thus, lamina I contains a dense plexus of horizontally running extrinsic and intrinsic fibres that contact the apical dendritic bouquets of pyramidal neurons situated in the deeper layers. Tangential plexuses of fibres in layer IV and deep in layer V are known as the outer and inner striae of Baillarger. These striae are probably formed primarily by intrinsic cortical axons, i.e. axons of local circuit neurons and collateral branches of pyramidal cell axons [340]. The outer stria of Baillarger is particularly well developed in the visual cortex, where it is referred to as Gennari's (or Vicq d'Azyr's) line (Fig. 5.13 C).

Although tangential lamination is a prominent feature of the neocortex, many of its constituent elements show an evident radial orientation. Prominent among these are the pyramidal cells. The apical dendritic shafts of these ubiquitous elements extend peripherally, and many of them reach the most superficial layers before forming their terminal tufts. The axons of the pyramidal cells are also radially oriented. They emerge from the basis of the cell bodies and descend toward the white matter.

The pyramidal cell axons acquire a myelin sheath at a short distance from the soma and assemble in bundles that increase in size as they descend and as more axons are added. These bundles are known as radial fasciculi. The apical dendrites of the pyramidal cells are also arranged in bundles [194, 196, 565, 568]. These axonal and dendritic bundles impose upon the neuronal cell bodies an arrangement in slender radially oriented columns that extend throughout the thickness of the cortex. Not only the main axons of the pyramidal cells, but also their collateral branches often show a radial orientation, and the same holds true for the axonal systems of many intrinsic cortical neurons. Many extrinsic afferents also take a radial course after having entered the cortex from the deep white matter.

The systematic study of the disposition of myelinated fibres in brain structures is known as *myeloarchitectonics*. Detailed myeloarchitectonic analyses of the human cerebral cortex have been carried out by C. and O. Vogt [784, 786, 789–791]. So far as the neocortex is concerned, the layers distinguished in these analyses correspond to the cytoarchitectonic layers of Brodmann and others (Fig. 15.4 B); however, they are designated with arabic, rather than with roman numerals (Fig. 15.4 C).

Lorente de Nó [416] concluded on the basis of the study of extensive Golgi material that the main pattern of connections between cortical neurons is in a vertical direction. He advanced the idea that the cerebral cortex essentially consists of small, radially arranged sets of neurons having a thalamic afferent fibre as their axis. According to Lorente de Nó, these column-like elementary units contain all types of cortical cells and within their confines the whole process of the transmission of impulses from the afferent fibre to the efferent axon is accomplished. Electrophysiological studies of the somaesthetic [494] and the visual cortex [308] have provided powerful evidence for the presence of functionally discrete radial columns or modules in these sensory areas. Later, morphological studies [242] showed that in other areas the cortical modules are organized around cortico-cortical afferents rather than thalamic inputs. The cortical columns will be further discussed in a later section of the present chapter.

Some quantitative data on the cerebral cortex are presented in Table 15.1.

Table 15.1. Quantitative data on the human cerebral cortex

Volume (both hemispheres)	517 cm^3 (males) 440 cm^3 (females)	Pakkenberg and Gundersen [525]
Surface (both hemispheres)	1470–2275 cm^2	Blinkov and Glezer [56] Elias and Schwartz [173] Pakkenberg and Gundersen [525]
Depth of neocortex	1.5–5 mm	von Economo and Koskinas [796]
Total number of neurons (both hemispheres)	22.8×10^9	Pakkenberg and Gundersen [525]

Sulcal Pattern

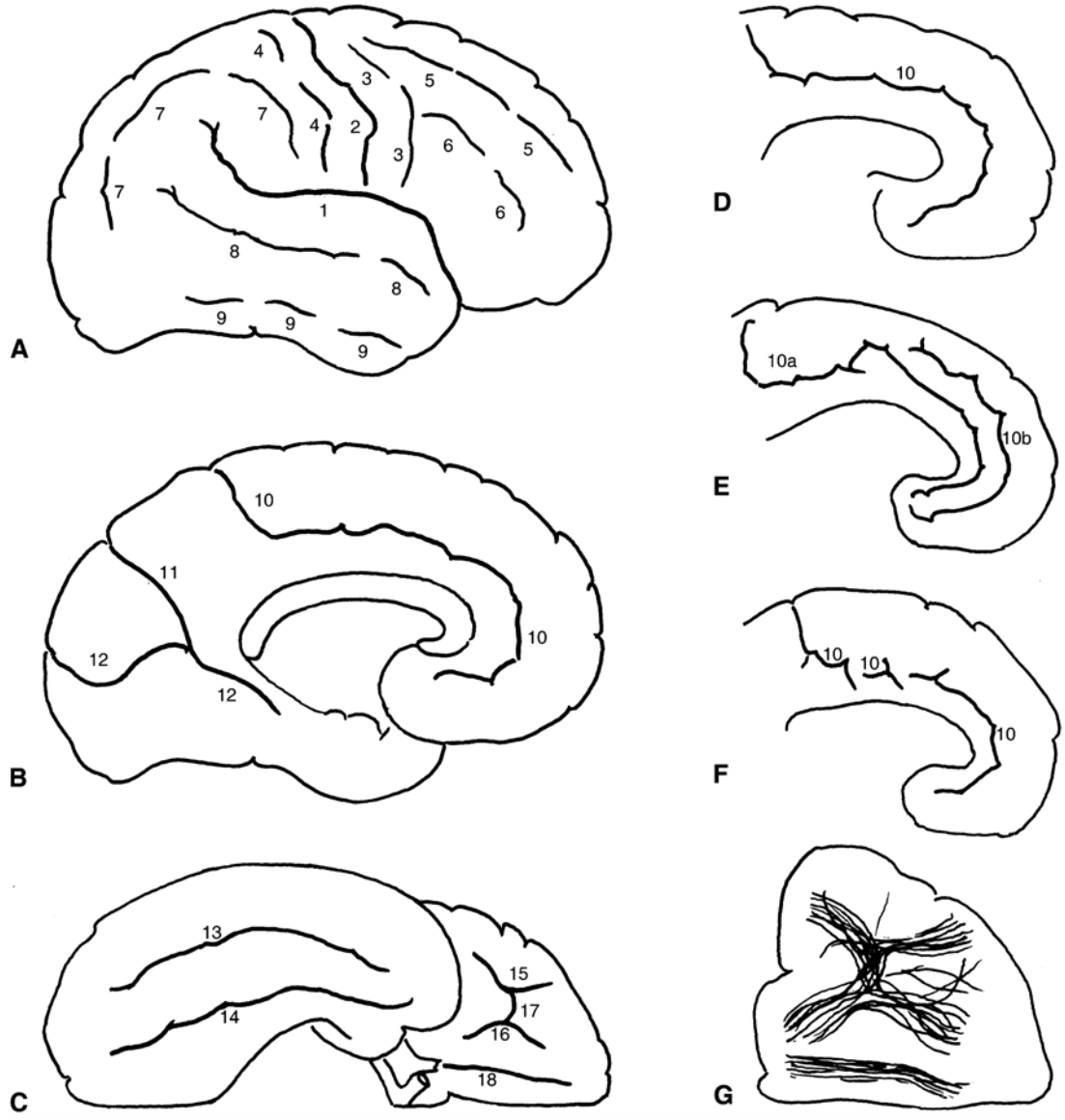
The human cerebral cortex, as that of other large mammals, is strongly folded (Fig. 15.1) [31]. Convolutions or gyri are separated by fissures or sulci. In humans, almost two thirds of the neocortex is hidden away in the depth of the sulci [64]. The sulcal pattern of the human cerebral hemispheres has been the subject of numerous studies, as for instance those of Retzius [615], Bailey and von Bonin [30] and Ono et al. [519]. These studies have shown that the overall sulcal pattern on the telencephalic surface is highly characteristic for humans (Fig. 15.5 A–C) and that the same holds true for other mammalian species. However, the individual sulci show a considerable intersubject variability. They may vary in position and course (Fig. 15.5 G). Many sulci may show one or several interruptions (Fig. 15.5 A, F) and some may be doubled over a certain part of their trajectory (Fig. 15.5 E). The sulcal pattern not only varies among individuals but also varies between the two hemispheres in the same individual. Some sulci, including the lateral and central sulci and the parieto/occipital and cingulate sulci, mark the boundaries between cerebral lobes (Fig. 1.4).

Structural and Functional Subdivision of Neocortex

Structural Subdivision 1: Cytoarchitecture

Although the laminar basic pattern is recognizable throughout the neocortex, this structure is not homogeneous. Differences in the relative thickness and cell density of the various layers, and in the size, shape and arrangement of the neuronal perikarya, are present (Figs. 15.6, 15.7) and have been used to divide the neocortex into cytoarchitectural areas. Similarly, differences in the pattern of myelinated fibres (local development and distinctness of the striae of Baillarger, length of the radial fasciculi) have been used in myeloarchitectonic parcellations of the cortex (see below).

During the first half of the twentieth century, several (groups of) investigators, namely Campbell [85], Brodmann [70, 71], von Economo and Koskinas [796], Bailey and von Bonin [30] and Sarkissov et al. [649], have produced cytoarchitectonic maps of the human cerebral cortex (Table 15.2). In all of these maps, the cortex is parcellated into a number of juxtaposed areas or fields. Brodmann's map, which is by far the most widely used, is shown in Fig. 15.8. Brodmann distinguished 44 sharply delineated areas, each of which he designated with a different figure. He emphasized that the boundaries between these areas generally do not coincide with the sulci on the cerebral surface. Von Economo and Koskinas [796] and Sarkissov et al. [649] subdivided several of Brodmann's areas into smaller units; hence, their total number of fields is somewhat larger



1 Lateral sulcus (Sylvian fissure)
2 Central sulcus (of Rolando)
3 Precentral sulcus
4 Postcentral sulcus
5 Superior frontal sulcus
6 Inferior frontal sulcus
7 Intraparietal sulcus
8 Superior temporal sulcus
9 Inferior temporal sulcus
10 Cingulate sulcus
11 Parieto-occipital sulcus
12 Calcarine sulcus
13 Occipitotemporal sulcus
14 Collateral sulcus
15 Lateral orbital sulcus
16 Medial orbital sulcus
17 Arcuate orbital sulcus
18 Olfactory sulcus

Fig. 15.5 A–G. Synopsis of cerebral sulci. **A–C** Lateral, medial and ventral aspect of a cerebral hemisphere, showing the most important sulci. **D–F** Three variations in the course of the cingulate sulcus, as depicted by Retzius [615]. In **D** there is a single, continuous cingulate sulcus; in **E** the sulcus is doubled (*10a,b*) and in **F** it is interrupted twice. **G** Ten variants in the course of the sulci on the orbitofrontal cortex, derived from Kanai [358], have been transferred to a standard outline of this region

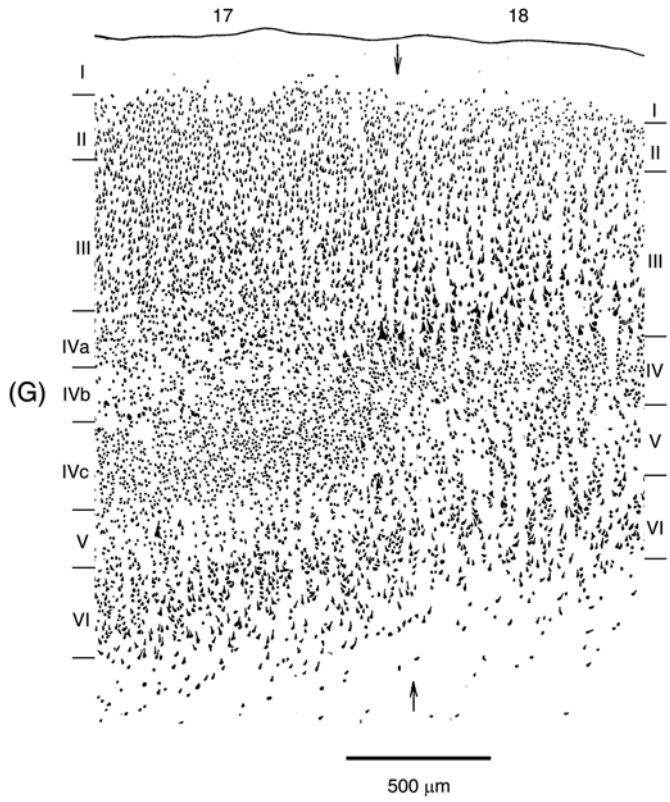


Fig. 15.6. Areas 17 and 18 and their border zone in the human brain. Reproduced from Vogt and Vogt [786]. The position of the line of Gennari (*G*) corresponds with that of the cell-poor layer IVb

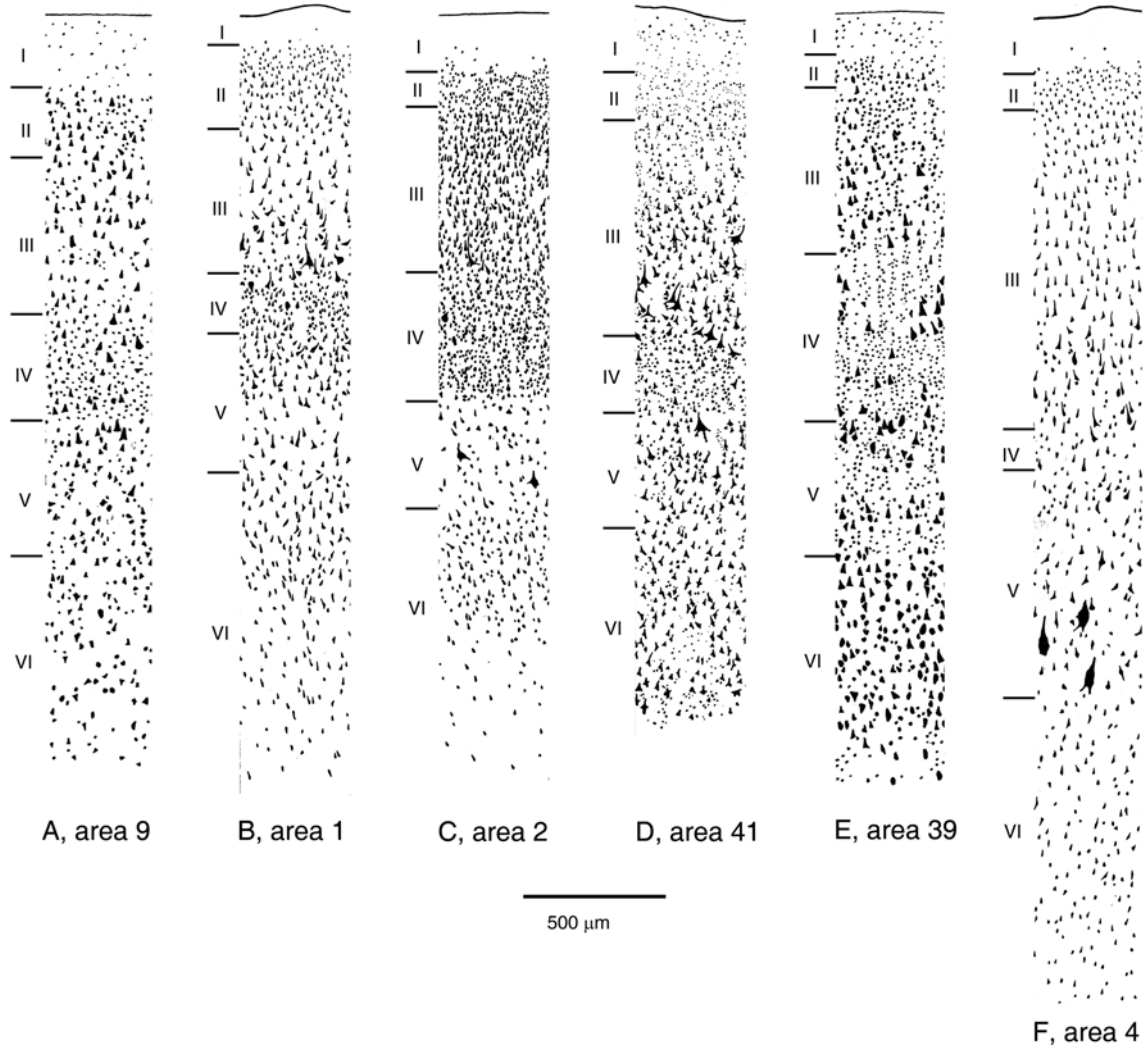


Fig. 15.7. Cytoarchitecture of several neocortical areas, designated with Brodmann's [70, 71] numbers

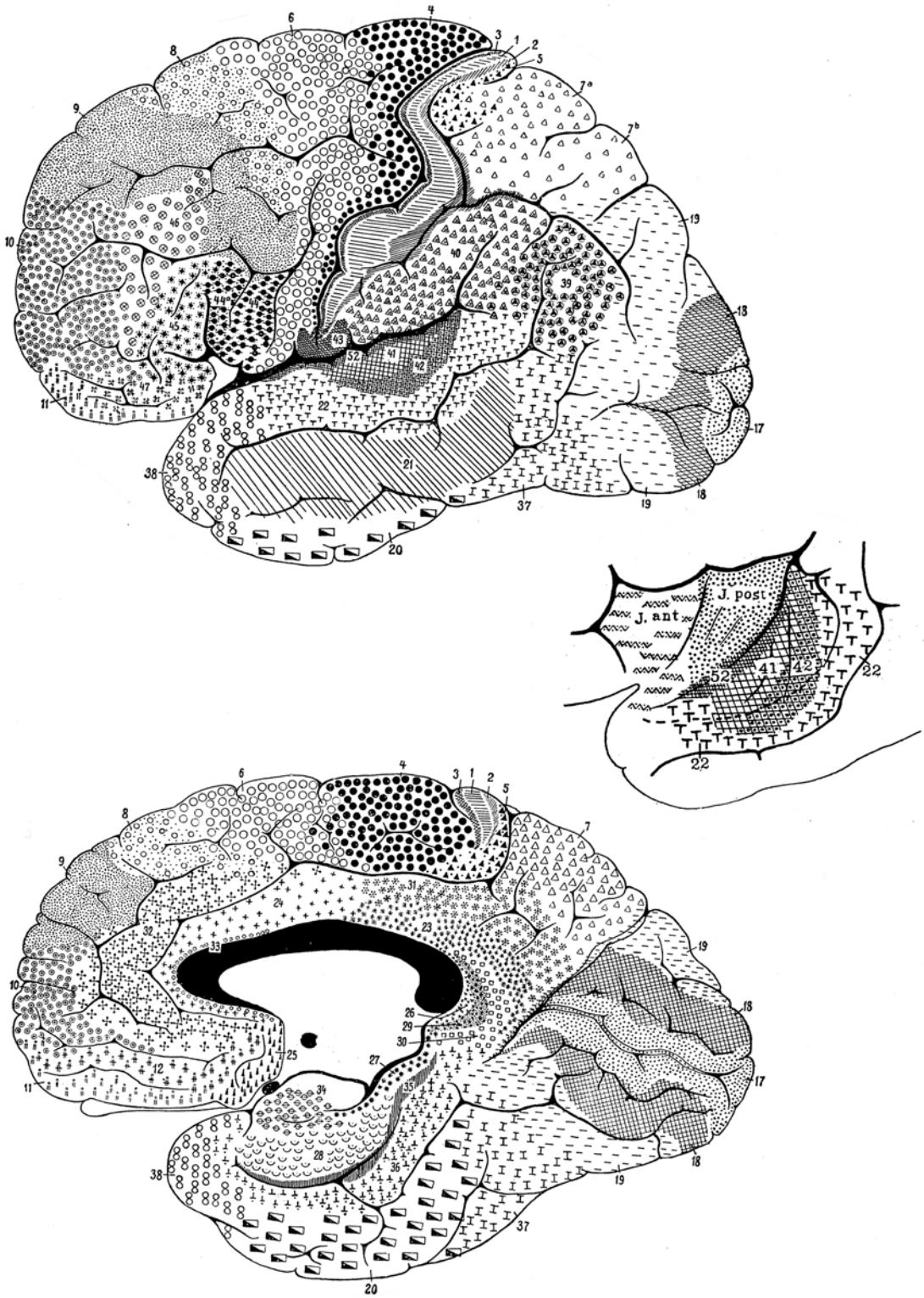


Fig. 15.8. Brodmann's famous map of the cytoarchitecture of the human cerebral cortex. The latest (1914) version is shown here [71]. In the pericentral and retrosplenial regions some (parts of) cytoarchitectonic areas have been transferred to the free surface of the hemisphere. The small auxiliary chart shows the cytoarchitecture of the insula and the upper surface of the superior temporal gyrus

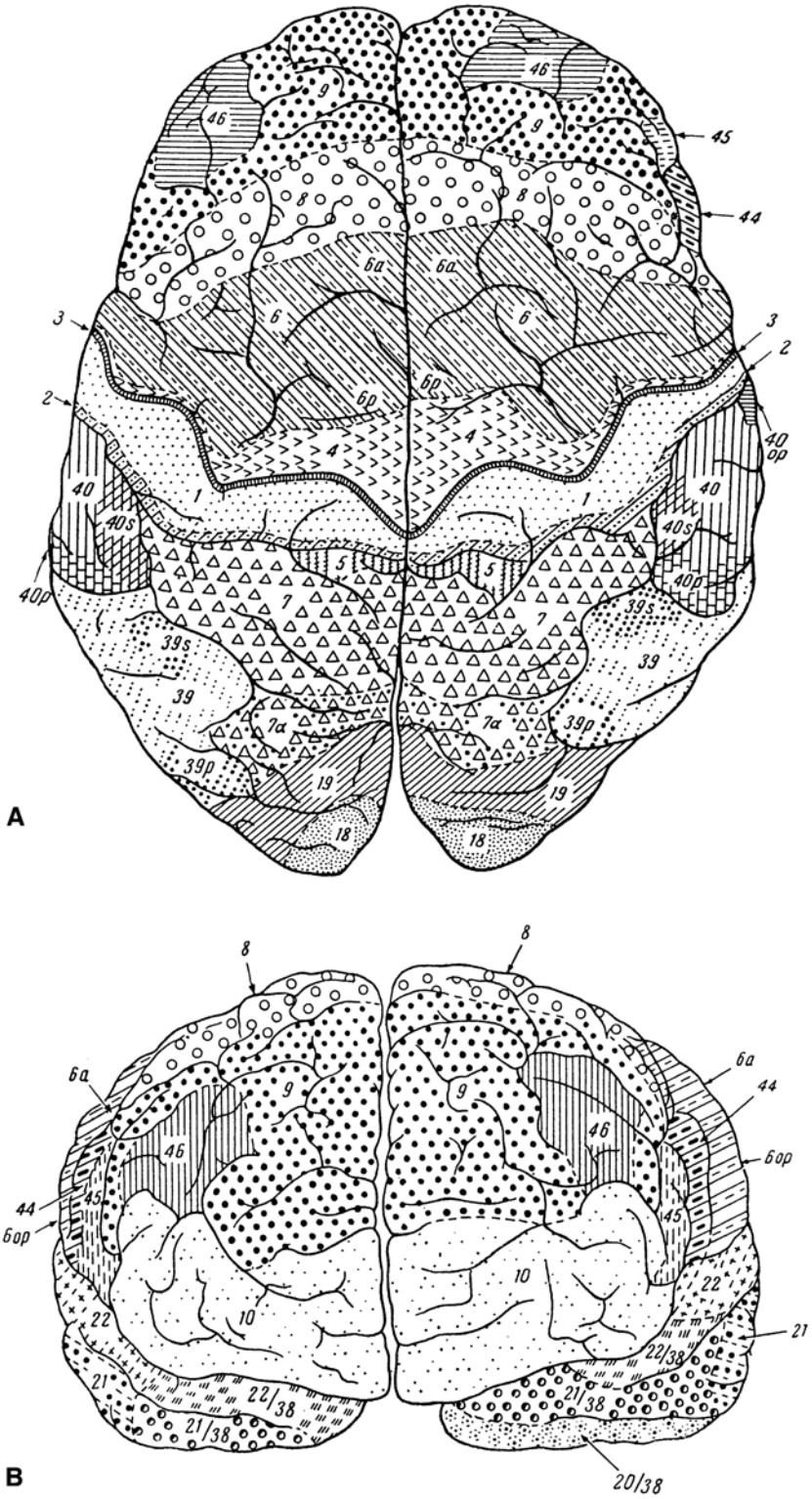


Fig. 15.9 A, B. Cytoarchitectonic analysis of the human cerebral cortex, according to Sarkissov et al. [649]. These authors mapped the results of their analysis not only on lateral and medial views (not reproduced here), but also on upper (**A**) and frontopolar views (**B**) of the hemispheres. They followed Brodmann's numbering scheme and introduced self-explanatory symbols for subareas and transitional zones

Table 15.2. Architectonic subdivisions of the human neocortex

Author(s)	Type of analysis	No. of fields	Judgement of borders
Campbell (1905) [85]	Cyto- (myelo-)	14	Sharp
Brodmann (1909, 1914) [70, 71]	Cyto-	44 [a]	Sharp
von Economo and Koskinas (1925) [796]	Cyto-	54	Generally not sharp
Vogt and Vogt (1919, 1926) [784, 791]	Myelo-	> 200	Very sharp
Bailey and von Bonin (1951) [30]	Cyto-	8	Generally not sharp
Sarkissov et al. (1955) [649]	Cyto-	52	Many transition zones

[a] The highest numbered area in Brodmann's map is area 52; however, because areas numbered 13–16 and 48–51 are lacking the total number of areas in his map amounts to 44

than that of Brodmann. According to von Economo and Koskinas, who designated the various cytoarchitectonic areas with combinations of letters and figures (PA1, TE2 etc.), the interareal boundaries are generally not sharp. The map of Sarkissov and colleagues (Fig. 15.9) is patterned after that of Brodmann. Their nomenclature followed Brodmann's numbering scheme. However, they intercalated transition zones between several of the areas that Brodmann had distinguished.

Several authors have attempted to allocate the various cytoarchitectonic areas to a smaller number of variant types. It is worthy of note in this context that as early as 1874, Betz [51] pointed out that the human cerebral cortex is divided by the central sulcus of Rolando into an anterior part in which pyramidal cells predominate and a posterior part where granular cells prevail. In the anterior part he described the giant pyramidal cells that bear his name. Von Economo [795], who also focussed on the distribution of pyramidal and granular cells, recognized five fundamental cytoarchitectural types in the human neocortex, which he labelled 1–5 (Fig. 15.10). The cortical types labelled 2, 3 and 4 contain the six typical neocortical layers described above, although not all of these are developed to the same degree in the different types. Von Economo designated these areas as *homotypical,* thus contrasting them to the *heterotypical* cortical types 1 and 5, in which, at least in the fully developed cortex, the six layers cannot be clearly discerned.

The cortex of fundamental type 1 is distinguished by its lack of distinct granular layers II and IV, whereas the pyramidal layers III and V are strongly developed. Reference to Fig. 15.10 B,C shows that this *agranular cortex* occupies a region situated directly in front of the central sulcus, which corresponds to the areas 4 and 6 of Brodmann, and that this type of cortex is also found in the paracentral lobule on the medial surface of the hemisphere and in the rostral part of the cingulate gyrus. Within this region, area 4 is characterized by the presence of the giant pyramidal cells of Betz in its fifth layer (Fig. 15.7 F). Because the agranular cortex gives rise to prominent corticobulbar and corticospinal projections, it may be considered the prototype of *"motor" cortex*.

The other type of heterotypical cortex (labelled 5) is characterized by its richness in small, granular cells and the strongly developed layers II and IV. Layers III and V, on the other hand, are poorly developed. Areas belonging to this type of cortex are found in the anterior part of the postcentral gyrus, along the calcarine fissure and in a limited part of the upper surface of the superior temporal gyrus. The type 5 cortex is called *granular cortex* or *koniocortex* (in Greek *konios* = dust). It is characteristic of those cortical areas that receive the great afferent systems, i.e. the somatosensory projection, the acoustic projection and the optic radiation. A particularly well-differentiated granular cortex is found in the area striata (area 17 of Brodmann). As shown in

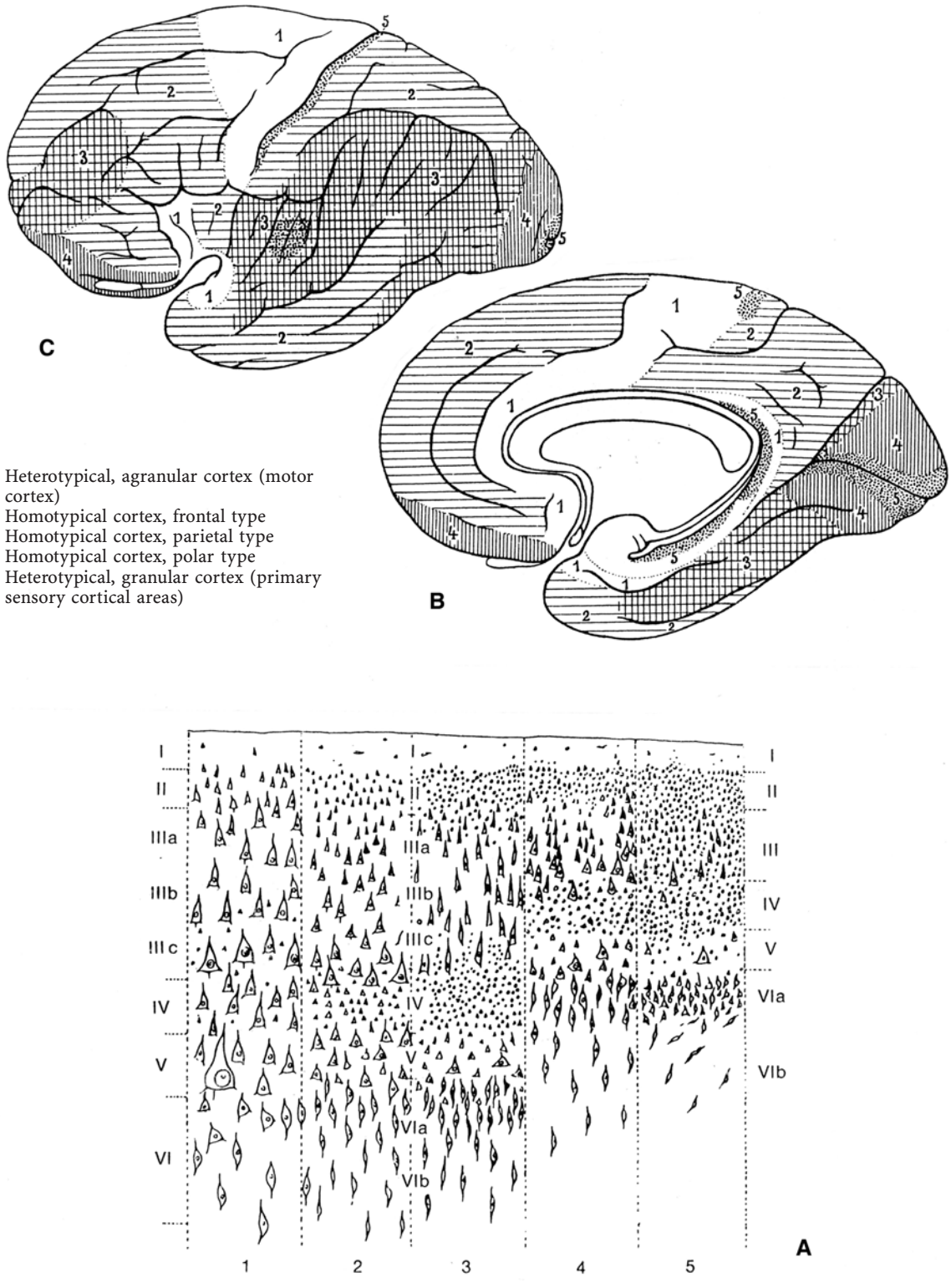


Fig. 15.10. The five principal types of neocortex (**A**), as distinguished by von Economo [795] and their distribution over the medial (**B**) and lateral surfaces (**C**) of the cerebral hemispheres

Fig. 15.6, the number of granular cells is exceedingly high here and the inner granular layer is clearly subdivided into three sublayers, IVa, b and c. The middle of these, which is relatively poor in cells, coincides with the layer of myelinated fibres known as the line of Gennari or Vic d'Azyr.

The three types of homotypical cortex (2, 3 and 4; Fig. 15.10) occupy an intermediate position between the agranular (1) and granular (5) types. They are named according to their main, but not exclusive localization: frontal type (2), parietal type (3) and polar type (4). Types 2 and 3 both contain numerous small and medium-sized pyramidal cells, but in type 3, granular cells are more prominent than in type 2 (Fig. 15.7 A, E). The polar type (4) occupies small areas near the frontal and occipital poles, hence its name. It is characterized by its thinness and high content of granular cells. In both the parietal (3) and polar (4) types of cortex, the multiform layer (VI) is particularly well developed (Fig. 15.7 E). The homotypical cortical types (2, 3 and 4) occupy much of what Flechsig [191, 192] and many later investigators have provisionally designated as *association cortex.*

If we consider the cytoarchitectonic analyses of Campbell [85], Brodmann [70, 71], von Economo and Koskinas [796], Bailey and von Bonin [30] and Sarkissov et al. [649] in light of the classification of cortical types just discussed, the following conclusions can be drawn:

1. The heterotypical agranular and granular areas, i.e. the primary motor and primary sensory fields, have been recognized and delineated in all of these analyses.
2. The homotypical cortex was left largely undivided by Campbell and by Bailey and von Bonin; hence, the number of areas distinguished by these authors is considerably smaller than that recognized by the others (Table 15.2).
3. With regard to the location and subdivision of the three types of homotypical cortex, the results of Brodmann, von Economo and Koskinas and Sarkissov et al. are in general closely comparable. Exceptions should be made, however, for the medial temporal lobe and the orbitofrontal cortex. In both of these regions the analyses of the "classical" cytoarchitectonists, as well as those of later investigators, have led to widely diverging results (Fig. 15.11) [518, 718].

In his notable monograph of 1909, Brodmann [70] did not confine himself to the human brain, but also presented cytoarchitectonic analyses of the cortex of a considerable number of other mammalian species, among them two primates, a prosimian, a carnivore and an insectivore. The number of areas identified in these animals was smaller than that in the human. Thus, he delineated 24 areas in the macaque *Cercopithecus,* 26 in the marmoset *Callithrix,* 14 in the prosimian *Lemur* and 12 in the insectivore *Erinaceus*. In the monkeys studied, homologues of the human primary motor areas 4 and 6 and the primary sensory areas 3, 1, 2 and 17 could be identified, and the same holds true for several of the human "association" areas, such as the frontal areas 9 and 12, the parietal areas 5 and 7 and the temporal areas 20–22 (Fig. 15.12). Brodmann's comparative cytoarchitectonic explorations laid the foundation for later electrical stimulation studies as well as for experimental analyses of cortical fibre connections (see below).

Structural Subdivision 2: Myeloarchitecture

It has already been mentioned that C. and O. Vogt [784, 786, 789–791] subjected the human cerebral cortex to a detailed myeloarchitectonic analysis. The myelinated fibres in the cortex show two principal orientations, tangential and radial. The tangential fibres tend to form laminae, which in general can be readily identified in conjunction with the corresponding layers observed in Nissl preparations (Fig. 15.4 B, C). The radially oriented fibres are arranged in bundles, termed radii, which ascend from and descend to the subcortical white matter. The Vogts noticed that the number and distinctness of the tangential fibre layers show considerable local differences in the cortex, and that the same holds true for the extent to which the radii penetrate into the cortex. Focussing on

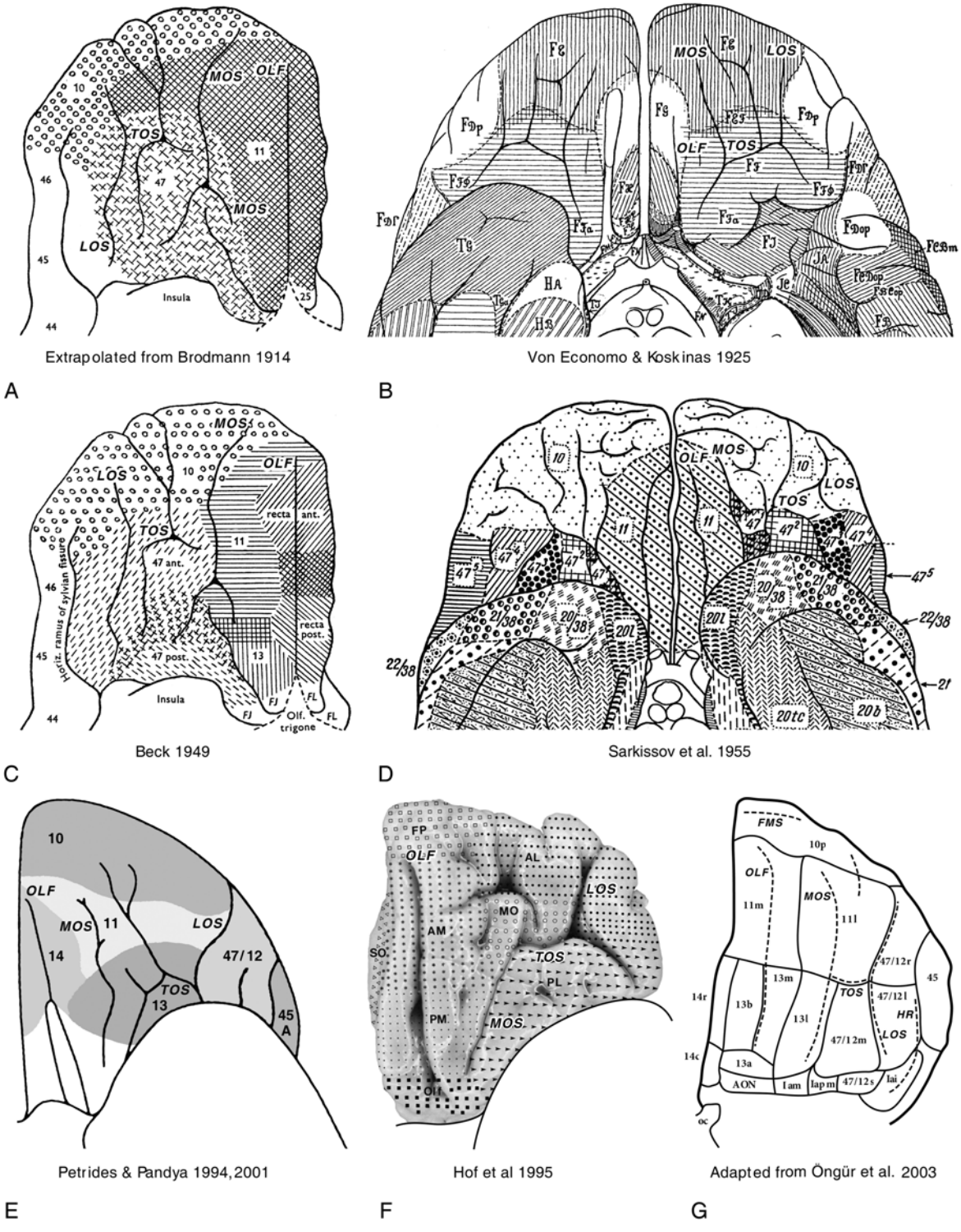


Fig. 15.11 A–G. Cytoarchitectonic parcellations of the human orbitofrontal cortex. Note that the analyses of the seven (groups of) authors have led to widely diverging results. Courtesy of Drs. H. Uylings and G. Rajkowska. *LOS*, lateral orbital sulcus; *MOS*, medial orbital sulcus; *OLF*, olfactory sulcus; *TOS*, transverse orbital sulcus. References cited: Brodmann [71], von Economo and Koskinas [796], Beck [44], Sarkissov et al. [649], Petrides and Pandya [577], Hof et al. [301], Öngür et al. [518]

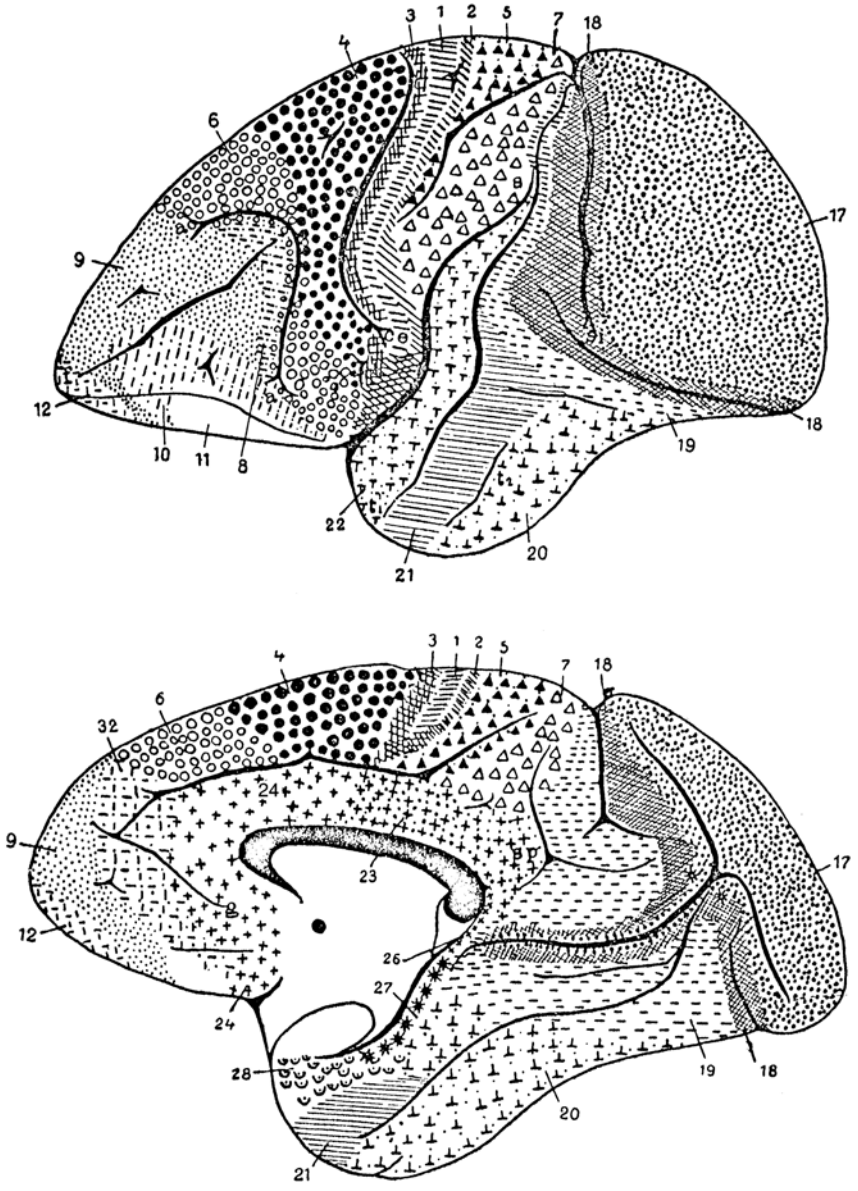


Fig. 15.12. Cytoarchitectonic map of the cerebral cortex of the macaque *Cercopithecus*, according to Brodmann [70]

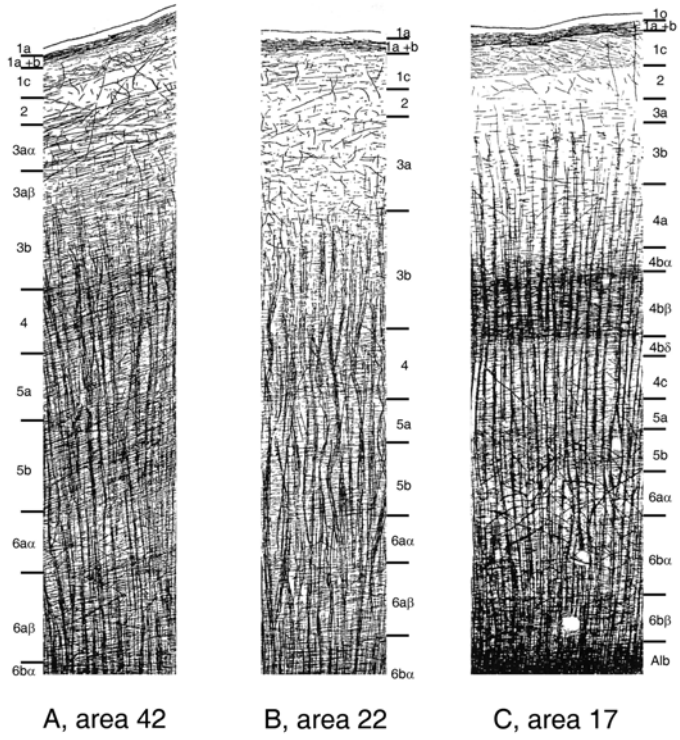


Fig. 15.13 A–C. Myeloarchitecture of some cortical areas, according to the Vogts. The *numbers* have been added according to the Brodmann scheme. Reproduced from Rose [637]

these differences, they were able to delineate a large number of areas whose boundaries were found to coincide with those of Brodmann's cytoarchitectonic fields (Fig. 15.13) [787]. They emphasized that the areal boundaries are very sharp and omnilaminar, i.e. characterized by changes in all layers. In their parcellation of the cortex, the Vogts went much further than Brodmann. Many of the areas distinguished by the latter were subdivided into several subareas, which in turn were claimed to be subdivisible into still smaller units, termed campuli [787].

The Vogts did not investigate the temporal and occipital lobes; hence, their myeloarchitectonic map of the human cortex remained incomplete [64].

Structural Subdivision 3: Myelogenesis

Myelinated fibres also took a central position in the investigations of Flechsig [191–193]. However, this author did not study the disposition of the myelinated fibres in the mature cortex, but rather the temporal order in which the fibres of the white matter immediately underneath the different parts of the cortex become myelinated during development. Flechsig distinguished 45 myelogenetic areas, which he numbered according to their sequences of myelination during foetal and early postnatal life (Fig. 15.14). He classed these areas in three categories, *primordial areas* (1–16), which show signs of myelination before birth, *intermediate areas* (17–36), which become myelinated between birth and the second postnatal month and *terminal areas* (37–45), which myelinate after the second postnatal month.

Flechsig observed that the prenatally myelinating fibres belong to the large sensory and motor projections. For this reason he characterized the primordial areas as *projection areas*. According to Flechsig, the postnatally maturing fibres form associative links between different parts of the cortex; hence, he designated the intermediate and terminal areas as *association areas*. He speculated that these areas subserve higher cognitive and mental functions. In his view, clusters of late-maturing areas form three association centres in the human brain: a large *posterior association centre,* occupying much of the parietal, occipital and temporal lobes; an *anterior association centre,* expanding in front of the motor projection areas; and a small *insular association centre* (Fig. 15.14).

Structural Subdivision 4: Connectivity

Cytoarchitectonic studies form an indispensable first step in the analysis of any part of the central nervous system. They should logically be followed by exploration of the fibre connections of the delineated grisea. The fibre connections may be used as auxiliary criteria in the detection and homologization of morphological entities, but secondly and more importantly, they may give salient clues as to the functional significance of their targets. Experimental studies on two sets of connections, thalamocortical and cortico-cortical, have led to very useful functional subdivisions of the neocortex. It is important to note that, because humans, for obvious reasons, cannot be subjected to interventional techniques, our knowledge of the fibre connections mentioned is almost entirely based on studies in non-human primates, particularly the rhesus macaque.

The thalamic nuclei and their connections have been extensively discussed in Chap. 8. Let it suffice to recall here that the four groups of specific thalamic nuclei, sensory relay nuclei, motor relay nuclei, limbic nuclei and association nuclei, project to specific areas or regions of the cortex and together innervate the entire cortex (Fig. 8.4).

The *sensory relay nuclei,* i.e. the lateral posterior nucleus, the lateral geniculate body and the medial geniculate body, project to and functionally define the primary sensory cortices. The ventral posterior nucleus receives afferents from the somatosensory pathways and projects to the areas 3, 1 and 2, which collectively form the primary somatosensory area, S1. The lateral geniculate body receives afferents from the retina and projects to the primary visual cortex, V1, which corresponds to

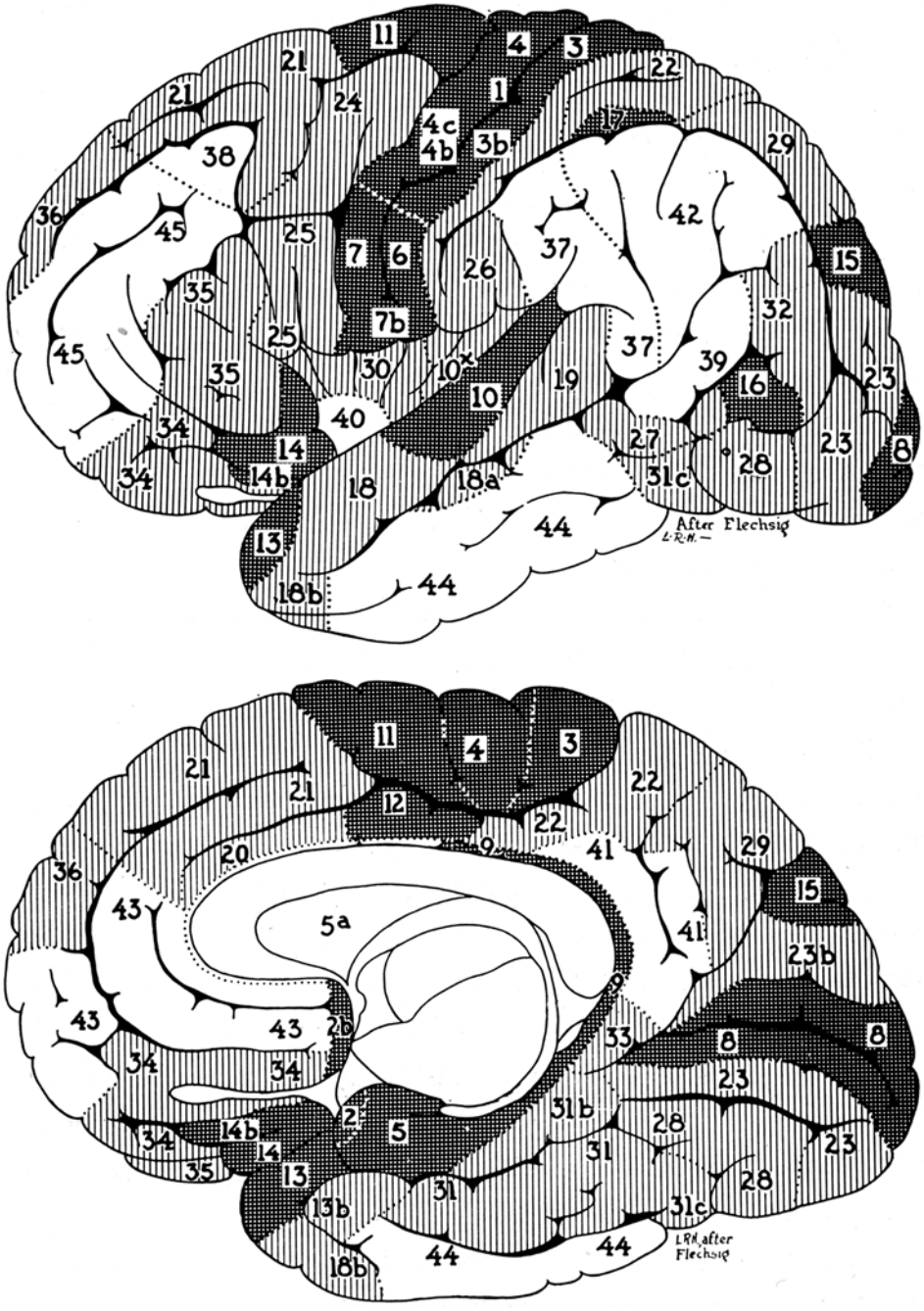


Fig. 15.14. Myelogenetic subdivision of the human cerebral cortex, according to Flechsig [193]. The *numbers* of the areas indicate the sequence of myelination during fetal and early postnatal life: *1–16* (*cross-hatched*), early myelinating, primordial areas; *17–36* (*vertical lines*), intermediate areas; *37–45* (*white*), terminal or "association" areas. Reproduced from von Bonin [793]

area 17. This area is also known as the striate area, because of the presence of the line of Gennari, or the calcarine cortex, because it surrounds the calcarine sulcus. The medial geniculate body, which represents the thalamic processing station in the auditory pathway, sends its efferents to the primary auditory cortex, A1, which consists of the areas 41 and 42.

The *motor relay nuclei* comprise the ventral anterior nucleus (VA) and the anterior and posterior divisions of the ventral lateral nucleus (VLa, VLp). VA is the principal target of fibres ascending from the pars reticulata of the substantia nigra and projects to the frontal eye field (area 8) and adjacent parts of the prefrontal cortex. VLa is the terminus of afferents from the internal segment of the globus pallidus and projects to the premotor cortex (area 6). VLp, finally, receives a massive input from the cerebellar nuclei and sends its efferents to the primary motor cortex, M1 (area 4). It should be mentioned that the efferent projections from the three motor relay nuclei, VA, VLa and VLp, are focussed on the cortical areas mentioned but that their terminal fields overlap to some extent.

The *limbic nuclei* comprise the anterior nuclear complex and the lateral dorsal nucleus. These structures are linked by being the targets of hippocampal fibres arising from the subicular complex, reaching the thalamus via the fornix, the mamillary nuclei and the mamillothalamic tract (Fig. 12.13). They are the source of thalamic fibres to the cingulate gyrus (areas 23, 24, 32), including the retrosplenial areas 29 and 30, this projection extending as far posteriorly and inferiorly as the presubiculum and parasubiculum and the entorhinal cortex (area 28) [712]. The sources of the afferents to the anterior nuclear complex and the lateral dorsal nucleus, as well as the targets of their efferents, all form part of the limbic system.

The *association nuclei* include the mediodorsal nucleus and the pulvinar, two cell masses that are particularly well developed in primates. The pulvinar involves more than one half of the whole thalamic volume in humans [550]. Both cell masses actually represent cell complexes. They can be subdivided into several subsidiary nuclei, each with receiving afferents from one or more specific subcortical source and sending efferents to a specific cortical area or region. However, the distinguishing feature of these two cell masses as a whole is that their subcortical afferents are rather weakly developed and that they receive their principal, *driving* afferents from the cortex. They function primarily as links in cortico-thalamo-cortical association paths, hence their name [680, 681]. The mediodorsal nucleus projects to the prefrontal cortex, which corresponds to Flechsig's anterior association centre (Fig. 15.14). The cortical output of the pulvinar is to the areas of parieto-temporo-occipital cortex, intercalated between the primary somatosensory, auditory and visual areas, i.e. to Flechsig's posterior association centre. However, these projections are less specific than was previously thought. Thus, the mediodorsal nuclei send axons to several cortical regions other than the prefrontal, among them the cingulate, insular and parietal regions, as well as the premotor and motor accessory areas, while the pulvinar has additional connections with the frontal eye field and with the anterior and posterior cingulate, retrosplenial, insular and parahippocampal areas.

The question of whether a cortical area that receives projection fibres from a specific thalamic element possesses structural characteristics that permit its morphological delimitation was specifically addressed by Rose and Woolsey [634] in a study on the structure and thalamic connections of the cingulate gyrus in rabbit and cat. They found that the cingulate cortex in these animals can be subdivided into three cytoarchitectonic areas, and that each of these areas co-extends the distribution field of a particular nucleus within the anterior nuclear group. Such close correlations between cytoarchitecture and the projection fields of individual thalamic nuclei were later also found in many other regions of the cerebral cortex [342, 401, 636, 670].

Experimental studies on the cortico-cortical connections in the rhesus monkey have considerably increased our insights into the functional organization of the association cortices. The fol-

lowing summary of the results of these studies is principally based on review articles by Pandya and colleagues [526, 529, 532, 579], Van Hoesen [773] and Mesulam [463–465]. The latter made a constructive effort to integrate cytoarchitectural and clinical findings in humans with experimental evidence obtained from the non-human primate to form a working model of the human cerebral cortex (Fig. 15.15).

1. The association areas can be subdivided into two main types: modality-specific (unimodal) and high-order (heteromodal). Each primary sensory area is adjoined by a modality-specific sensory association area. These unimodal sensory association areas can be further subdivided into proximal or upstream and distal or downstream components. Proximal areas are only one synapse away from the corresponding primary sensory area, whereas distal areas are at a distance of two or more synapses from the relevant primary area.
2. The unimodal sensory association areas together occupy most of the post-Rolandic neocortex.

   The *somatosensory unimodal association cortex* (SA) is situated in the parietal lobe, directly behind the primary somatosensory areas 3, 1 and 2, which are collectively designated as S1. It is supposed to occupy parts of areas 5 and 7 in the superior parietal lobule and may also include parts of area 40 in the anterior portion of the inferior parietal lobule. The subdivision of the somatosensory association cortex into proximal and distal areas in the human remains to be elucidated.

   The *visual unimodal association cortex* (VA) occupies much of the occipital lobe and extends far anteriorly into the lower parts of the temporal lobe. Its proximal zone consists of the areas 18 and 19 which, together forming the circumstriate belt, surround the primary visual of striate cortex (V1). The distal zone of the unimodal visual association cortex includes areas 20, 21 and 37.

   The *unimodal auditory association cortex* (AA) covers the superior temporal gyrus (area 22). It flanks the primary auditory cortex, A1 (areas 41 and 42), which is located in Heschl's gyrus on the posterior aspect of the temporal plane. The connectivity found in the monkey brain suggests that the posterior part of the superior temporal cortex (area 22) displays the projections of the proximal auditory association cortex, whereas the more anterior part of this gyrus may represent the distal auditory association cortex.

   Unimodal association areas for taste and vestibular sensation have not been identified so far. Some areas in the posterior orbitolateral cortex and anterior insula (13 a, I am) may represent unimodal olfactory association areas (see Figs. 11.7, 11.8).
3. Mesulam [463, 464] considers the premotor cortex anterior to the primary motor area, M1, as a motor analogue of the modality-specific sensory association areas, chiefly because it provides the principal cortical input to M1. According to Mesulam, this *motor association area* (MA) is composed of area 6, including the supplementary motor region (M2), posterior area 8 and area 44. It has reciprocal connections with the unimodal sensory association areas [526, 532].
4. The high-order heteromodal association areas, which are sometimes also designated as polymodal or supramodal areas, receive their principal cortical afferents from (1) unimodal areas, particularly their distal zones, (2) other heteromodal areas and (3) paralimbic areas. In the primate brain, three heteromodal association areas, parietotemporal, medial temporal and prefrontal, have been identified.

The *parietotemporal heteromodal association area* is situated at the juncture of the unimodal sensory association cortices, from which it receives convergent bimodal and trimodal afferents. This area includes the caudal part of the superior parietal lobule (area 7), most of the inferior parietal lobule (areas 39 and 40) and a forwardly extending strip, formed by lateral temporal cortex within the banks of the superior temporal sulcus at the juncture of areas 21 and 22 (Fig. 15.15).

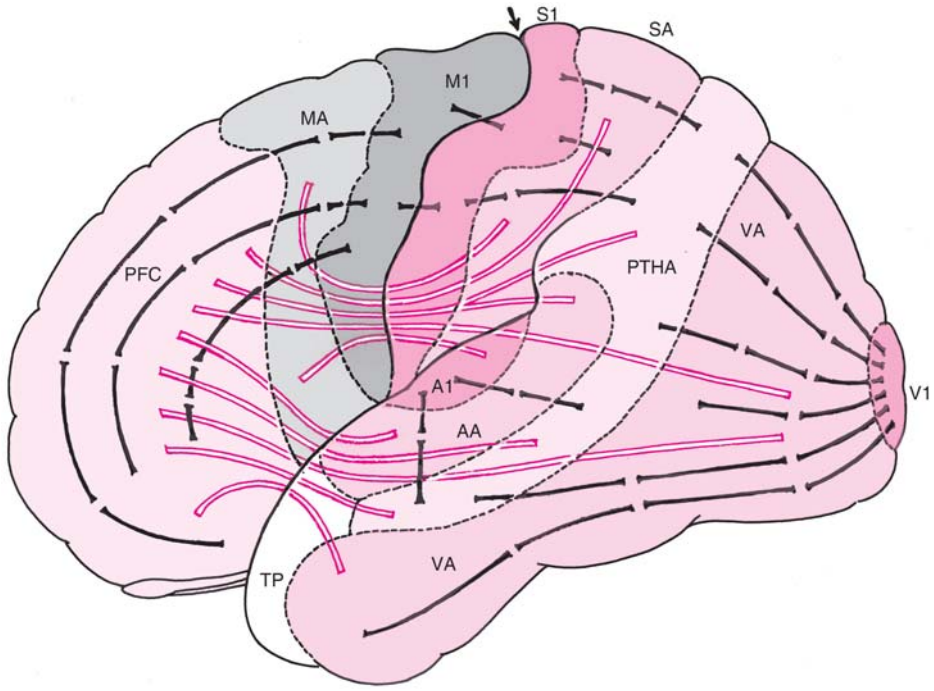


Fig. 15.15. Subdivision of the human neocortex into functional zones. This subdivision is largely based on experimental studies of cortico-cortical connections in monkeys. The primary somatosensory (*S1*), visual (*V1*) and auditory (*A1*) cortical areas (in *dark red*) project via short connections to the adjacent unimodal somatosensory (*SA*), visual (*VA*) and auditory (*AA*) association areas (in *medium red*). These unimodal sensory association areas in turn project to an elongated parietotemporal heteromodal association area (*PTHA*, in *light red*). The unimodal and heteromodal sensory association areas project massively to the prefrontal cortex (*PFC*, in *light red*). These long associational projections are diagrammatically indicated by *red-outlined*, white fibres. Sequences of short connections successively link the various parts of the PFC with the motor association area (*MA*, in *light grey*) and the primary motor area (*M1*, in *dark gray*) (based on Mesulam [463, 465]). *TP*, temporopolar cortex

The *medial temporal heteromodal association area* is formed by the perirhinal areas 35 and 36, which are interposed between the entorhinal area 28 and the visual association areas 19, 37 and 20.

The *prefrontal heteromodal association area* is situated in front of the motor association cortex and includes areas 9 and 10, 45–47 and the anterior parts of areas 8, 11 and 12. It receives afferents from the unimodal sensory association areas, particularly from their distal parts and from the parietotemporal and medial temporal heteromodal association areas. An important output system of the prefrontal heteromodal association area is formed by sequences of short association fibres that successively link the anterior orbitofrontal cortex, the polar and lateral prefrontal areas 9, 10 and 46, the motor association cortex and the primary motor cortex.

If we survey the data just discussed, it may be concluded that most of the human neocortex is occupied by association areas of various kinds and that the boundaries between these areas do not closely correspond to those of the cytoarchitectonic fields, as delineated by Brodmann and others.

Combining connectional data with the results of functional studies has revealed some basic features of the flow of information through the cortex. These features, which may be designated as hierarchical processing, feedback and parallel processing, will now be briefly discussed.

Hierarchical Processing. We have seen that multisynaptic feed-forward systems can be traced from the various primary sensory cortices via successive association areas to the premotor and motor cortices. In light of the results of physiological experiments on the visual system [308, 309], it is assumed that the sequential processing of information within these feed-forward systems becomes progressively more complex and may be characterized on this account as hierarchical [180, 770]. These feed-forward systems arise largely from pyramidal neurons in layer III and terminate in and around layer IV of the cortical area they send axons to [623].

Feed-back. The great majority (75% or more) of the cortical feed-forward connections are reciprocated by descending systems projecting back to areas from which an input was received. The fibres forming these feed-back systems originate nearly always from the infragranular layers V and VI and terminate largely in layers I and VI [623].

Parallel Processing. Extensive anatomical and physiological studies on the visual system of the rhesus monkey have shown that different features of the visual image remain segregated in the striate cortex and in their further projection to the extrastriate visual areas (see Chap. 19 for references and details). These extrastriate visual areas are organized into two hierarchically organized and functionally specialized processing pathways: an occipitoparietal pathway or "dorsal stream", concerned with spatial vision and movement, and an occipitotemporal pathway or "ventral stream" for object identification (Fig. 19.6). Areas along both pathways are organized hierarchically, such that the initial, low-level inputs are transformed into more complex and specific representations through successive stages of processing. Both pathways project separately to different parts of the prefrontal cortex. There is evidence suggesting that parallel processing channels are also present in the central somatosensory and auditory systems.

It should be emphasized that the various processing streams do not operate in isolation. There is substantial intermixing and cross-talk between them at successive levels of processing. Association fibres forming lateral connections between areas at the same processing level differ from ascending and descending fibres in that they terminate in a columnar pattern involving all cortical layers. It is assumed that via these interlinking fibres the information processed within the individual channels is combined into behaviourally relevant percepts. Together, the processing streams and their interconnections form *distributed hierarchical networks* subserving a *distributed hierarchical processing of information* [180, 770].

Functional Subdivision

The first systematic attempt to localize different functions in different regions of the cerebral cortex was made by Franz Joseph Gall (1758–1828) and his collaborator Johann Spurzheim (1758–1832), the founders of *phrenology* [187, 256]. Gall and Spurzheim maintained that the cerebral cortex is composed of discrete organs or regions that represent different mental faculties ("*seelische Kräfte*"), and that there are as many such organs as there are mental faculties. They distinguished 35 such faculties, including arithmetic, hope, speech, causality, destructiveness and parental love (Fig. 15.16). Gall and Spurzheim, moreover, suggested that the organs subserving these faculties correspond to prominences of the overlying skull. On that account, they asserted to be able to disclose a person's intellectual and moral abilities by palpating the bumps of his/her skull.

Gall and Spurzheim's doctrine was strongly contested by Marie-Jean-Pierre Flourens (1794–1867), who stated on the basis of extensive ablation experiments that the crucial factor determining how an animal organism is affected by brain damage is the amount of tissue removed and not its location. In short: only the *size* and not the *site* of the lesion matters.

In spite of its empirical weakness, phrenology has had a positive and lasting influence on modern neuroscience because it stimulated the discussion of whether specific functions and qualities of the mind could be localized within the convolution of the brain. During the second half of the nineteenth century a number of clinical, anatomical and experimental landmark studies appeared that seemed to favour localization.

In 1865, Paul Broca (1824–1880) described several patients in whom circumscript lesions at the basis of the third convolution of the left frontal lobe had led to a *motor aphasia*, i.e. the inability to produce articulated speech [67]. A few years later, Carl Wernicke (1848–1905) reported on a second type of language disorder, namely the inability to comprehend speech while having speech production relatively unaffected. He associated this *sensory aphasia* with damage to the posterior part of the left hemisphere, in the region where the occipital, parietal and temporal regions meet [811]. It is important to note that Wernicke in his remarkable 1874 monograph, and in a later textbook [812], did not confine himself to attributing the different forms of aphasia to particular areas or centres. He designed circuit diagrams for reading, writing and speech and postulated that certain disorders of communication could result from damage to the connections between the various processing centres included in these diagrams.

During the last decade of the nineteenth century, and the first decade of the twentieth century, several authors, including Hugo Liepmann (1863–1925) and Joseph Jules Déjerine (1849–1917), extended and substantiated Wernicke's idea that the interruption of cortico-cortical fibre connections ("disconnection") may cause various kinds of behavioural impairment. Liepmann [410, 411] published several studies on apraxias, the higher-order disorders in the execution of skilled movements. He showed that several sites of damage, including the corpus callosum and the white matter deep to the supramarginal gyrus, could produce apraxia by disconnecting pathways joining selected sensory, motor and language areas. Déjerine [143, 144] analysed the various types of acquired reading disorders (alexias). He found, inter alia, that pure alexia, the inability to read with a preserved ability to write, may be caused by a lesion in the left occipital lobe, which disconnects the calcarine cortex from the angular gyrus.

In 1868, John Harlow (1819–1907) reported on the case of Phineas Gage, who exhibited profound changes in personality, social conduct and emotional stability, following an accident in which an explosion drove an iron bar – more than a meter in length and weighing about 6 kg – through the anterior part of his brain, destroying the prefrontal cortex bilaterally [278]. Harlow's case study was followed by several other publications, reporting profound character changes following lesions of the frontal lobes [187].

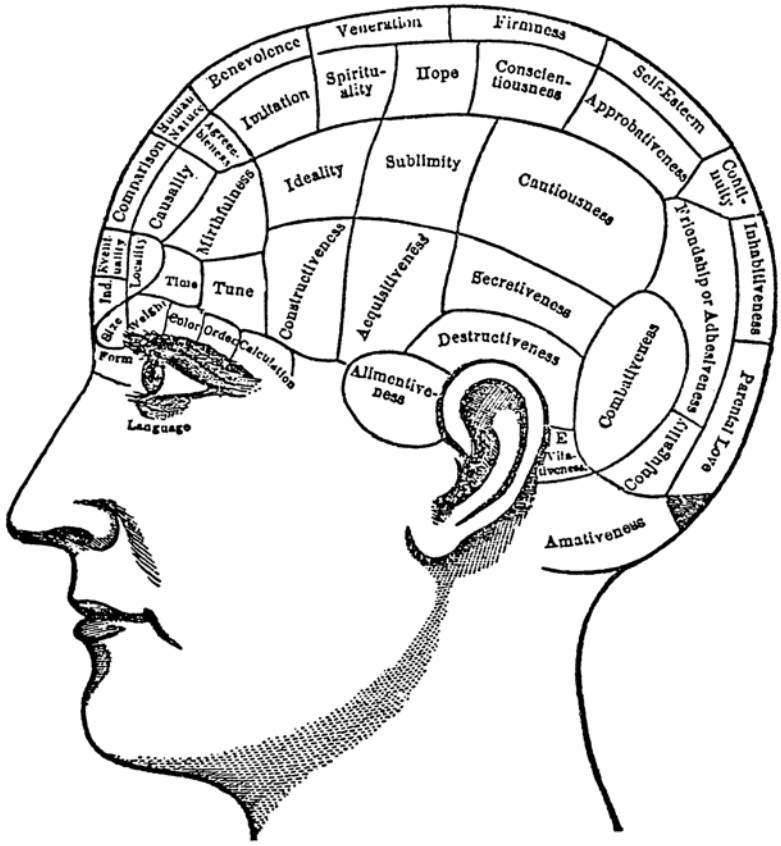


Fig. 15.16. Gall and Spurzheim's "phrenological head", showing 35 mental faculties, residing in specific organs of the cerebral cortex, projected upon the surface of the skull

The landmark experiments in 1870 of Gustav Theodor Fritsch (1838–1927) and Eduard Hitzig (1838–1907) led to the discovery of a motor zone in the cortex. They found that electrical stimulation of the anterior part of the cerebral cortex in dogs produces distinct motor reactions on the contralateral side and presented evidence suggesting a topographical arrangement of muscle groups in the area that was stimulated [212]. Their experiments were confirmed by David Ferrier (1843–1928) for various mammals, including monkeys [182]. Ferrier also induced lesions in the precentral cortex of monkeys. He noted that the lesions were associated with paralysis and weakness of muscles on the opposite side. The experiments of Fritsch and Hitzig [212] and Ferrier [182] confirmed the inferences on the existence of somatotopically arranged motor centres in the brain made by John Hughlings Jackson (1835–1911) from observations on patients suffering from a certain type of epileptic seizure, now commonly designated as Jacksonian fits. This kind of convulsion starts locally in a group of muscles and then spreads in an orderly fashion to other muscles [326]. For example, the contractions may begin in the lower part of the face and spread to the ipsilateral arm and, in turn, to the corresponding leg or vice versa.

During the last quarter of the nineteenth century, there was an extensive search for the localization of sensory centres in the cortex (see Finger [187] for a detailed account). As regards audition, Ferrier [182] and Ferrier and Yeo [183] reported on the effects of lesions of the superior temporal gyrus in monkeys. It was found that animals with bilateral lesions were totally irresponsive to hearing and that animals with unilateral lesions were deaf in the contralateral ear. In 1891, Charles K. Mills (1845–1931) presented two cases of totally deaf patients, one with a marked atrophy of both superior temporal convolutions, the other with severely damaged superior temporal gyri, due to successive strokes [471]. These findings were considered to be highly supportive of Ferrier's experimental findings with monkeys.

In 1881, Hermann Munk (1839–1912) reported that lesions of the occipital lobes in dogs and monkeys lead to blindness [499] and during the 1880s, several clinicians identified blindness with damage to the occipital cortex [256]. Salomon Henschen (1847–1930) collected over 160 clinical cases of blindness and hemianopsia after cortical lesions from the literature [288]. This vast amount of material led him to identify the "centre of vision" or "cortical retina" with the striate cortex [256].

The fact that lesions in the region of the central sulcus can cause somatosensory disturbances in human patients was recognized in 1884 by Moses Allen Starr (1854–1932). He noticed that in the majority of cases of such disturbances, the lesion was posterior to the central sulcus in the postcentral gyrus or the adjacent parietal region [705]. In the 1890s, Frederick Mott (1853–1926) [493] and Hermann Munk [500] reported that, in monkeys, lesions in the region of the central sulcus cause loss of touch and pressure sensations as well as paralysis. Neither Mott nor Munk produced or analysed lesions confined to the postcentral gyrus. Due to their studies, the prevailing view at the end of the nineteenth century was that the somatosensory and motor areas overlap [187].

During the period just discussed, several investigators rejected the idea of cortical localization. Prominent among them were Charles-Edouard Brown-Séquard (1817–1894) and Friedrich Goltz (1834–1902). Brown-Séquard [73] rejected Broca's idea that speech can be localized in the cortex. He presented evidence showing that lesions outside Broca's region can affect speech and he cited patients with damage to Broca's area who did not exhibit speech defects [187]. Brown-Séquard proposed that cells subserving speech and other functions are distributed over many parts of the brain. Goltz [248, 249] mistrusted both the results obtained from electrical stimulation of the cortex and the observations made on animals with local cortical ablations after short survival times. Goltz performed large and bilateral ablations of the cerebral cortex in dogs and kept these animals alive for a long time. He observed that in these animals permanent deficits were limited to higher psychic functions such as intelligence and memory. Like Flourens,

Goltz stated that it was the size and not the location of the lesion that determined the severity of its effects on such higher functions [257].

In spite of the objections just briefly outlined, it may be stated that at the beginning of the twentieth century, i.e. at the time that the architectonists began their mapping studies, the idea that at least certain functions can be localized to particular areas of the cerebral cortex prevailed. The monograph in which Campbell [85] presented the first cytoarchitectonic map of the human cerebral cortex was entitled: "Histological studies on the localization of cerebral function". Brodmann [70, 71] and von Economo [795] also emphasized that the cytoarchitectonic fields shown in their maps actually represent functional entities. Brodmann stated that the cerebral cortex should not be considered as a single organ, but rather a complex of organs, and that each of the different organs (i.e. the separate cytoarchitectonic fields) subserves a particular set of functions. He pointed out that many of these fields coincide with well-known physiological centres, specifying that his area 17 co-extends with the "clinical visual area of Henschen" and that his precentral region (area 4) corresponds to the "electromotor zone". However, Brodmann took issue with the idea of the phrenologists that complex mental functions such as memory, will or fantasy could be localized in circumscribed cortical areas. Rather, he believed that these functions result from the conjoint activities of a large number of areas distributed more or less widely over the cortical surface.

During the twentieth century, the study of the effects of brain lesions in human patients continued to play a prominent role in the localization-anti-localization debate. That the outcome of such studies could differ considerably is illustrated by the work of Constantin von Monakow (1853–1930) and Karl Kleist (1879–1960), two clinical neurologists who both had a vast amount of clinical material at their disposal.

Von Monakow [329, 797, 798] admitted that there was some sort of localization of elementary sensory and motor functions, but he emphasized that the answer to the question of what is actually localized remains obscure. He believed that "*Leistungen*", i.e. purposeful accomplishments, are not the product of single cortical areas, but rather involve the whole brain, which functions as a dynamic organizing entity. Von Monakow introduced the concept of *diaschizis of collaboration,* which implies that a breakdown in the widely correlated structures of the brain would result in a gross corresponding defect syndrome instead of the loss of function in the circumscribed area actually hit by the lesion. As regards central visual disturbances, he maintained that many of these are due to interruptions of pathways rather than to the lesion as such. We will see that many of the ideas of von Monakow reemerged and became dominant in the second half of the twentieth century.

The material of Kleist [373, 374] included, apart from numerous regular clinical cases, 300 persons who had sustained local brain injuries during World War I. He summarized his findings concerning the localization of functions in the cerebral cortex in a famous map, shown here in Fig. 15.17. It will be seen that Kleist subdivided the cortex according to Brodmann (see Fig. 15.8), and that he provided almost all of the cytoarchitectonic areas distinguished by the latter with a functional label. The overall functions of the primary sensory and motor areas, which were well known by the end of World War I, were correctly indicated. However, Kleist went far beyond that by attributing all sorts of higher cognitive and mental functions and faculties to many other areas. Thus, he associated temporal area 21 with acoustic awareness ("*akustische Aufmerksamkeit*"), prefrontal area 10 with motor skill ("*motorische Handlungsfolgen*") and orbitofrontal area 11 with personal and social ego ("*Selbst- und Gemeinschafts-Ich*"). It was particularly because of this detailed localization of psychic functions that many of his colleagues disposed of Kleist's map as "brain mythology" [119]. Uttal [744] recently characterized this map as a modern manifestation of phrenological thinking.

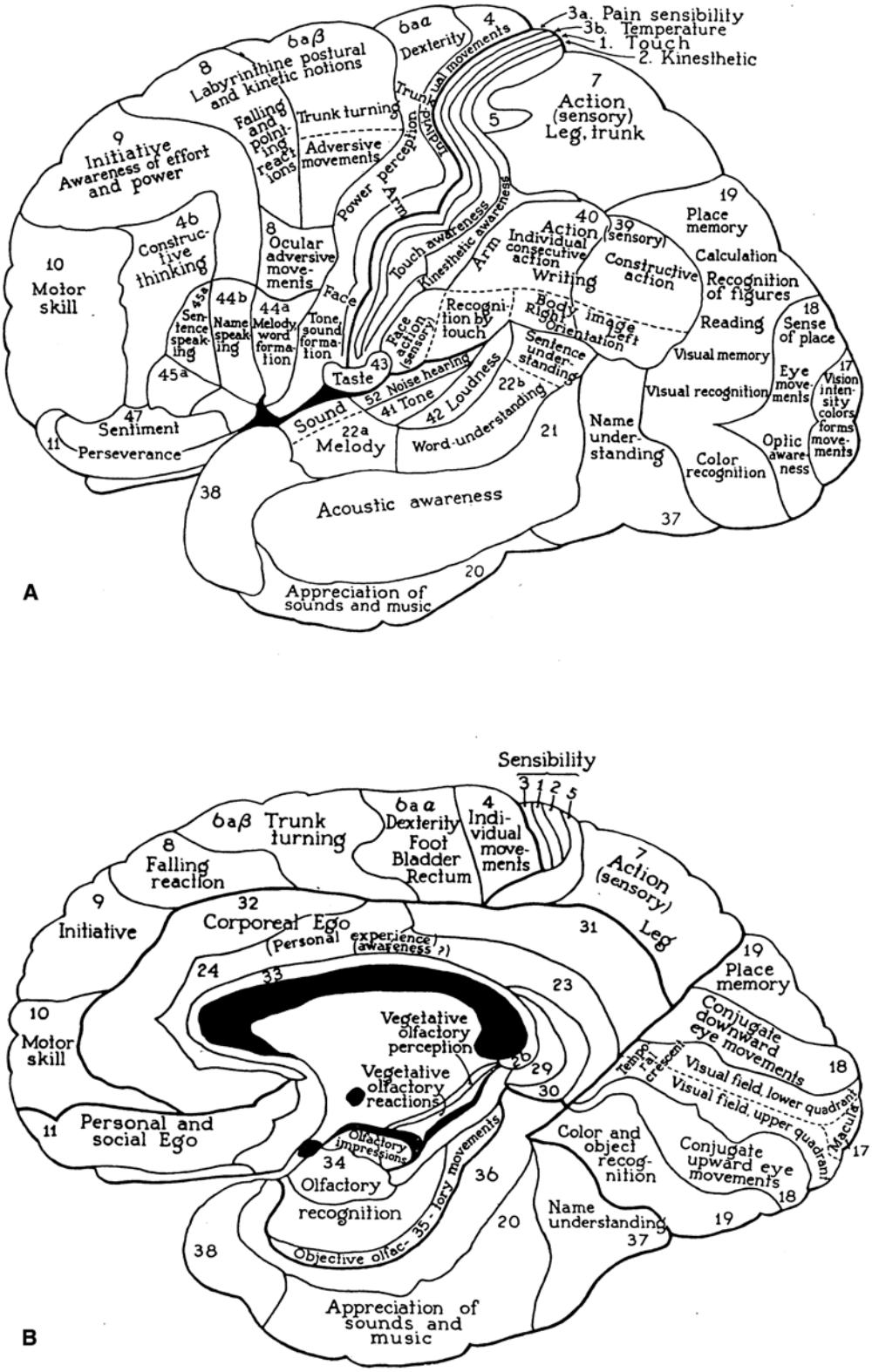


Fig. 15.17 A, B. Localization of functions in the cerebral cortex, according to Kleist [373]. The *numbers* indicate Brodmann's cytoarchitectonic areas

The most ardent anti-localizationist of the twentieth century was, beyond any doubt, Karl Lashley (1890–1954). He subjected animals, mostly rats, to complex maze-learning tests and analysed their performance before and after damaging various parts of the cerebral cortex [392, 393]. He found that their performance in the maze after operation was entirely independent of the location of the cortical lesion and only depended on its size. On the basis of his experimental results, Lashley formulated two general principles of brain organization, equipotentiality and mass action. With the term *equipotentiality* he designated the apparent capacity of any intact part of a functional area to carry out the functions lost by destruction of the whole. He considered it likely that this capacity holds only for associative parts of the cortex and for functions more complex than simple sensory or motor co-ordination. Lashley pointed out that the equipotentiality is not absolute but subject to the principle of *mass action,* whereby the efficiency of performance of a complex function may be reduced in proportion to the extent of brain injury within an equipotential area. Overall, Lashleys ideas about functional localization had much in common with those of Flourens and Goltz, but contrary to these authors, he accepted the general concepts of specialized sensory and motor areas in the cortex [187].

Lashley not only challenged the functional but also the structural subdivision of the cerebral cortex. He and his collaborator Clark [394] independently studied the brains of two spider monkeys *(Ateles geoffroyi),* both producing a cytoarchitectonic map. The two maps showed little agreement. They then compared their two specimens and found that most of the differences were not observer-dependent. They noticed that there was considerable variation in size and appearance of corresponding areas from brain to brain and that some areas could be seen in the one brain, but not in the other. Furthermore, they remained unable to locate the majority of the neocortical areas recognized by other investigators in this monkey and in the rhesus macaque. Lashley and Clark concluded that standard architectonic maps are of little value for the planning of experimental work, because the areal subdivisions are in large part anatomically meaningless, and because individual variation is too great to make the map significant for a single specimen. They emphasized that the preparation of maps representing functional units required that objective criteria and standards be developed and that other methods of confirmation be used, particularly the study of fibre connections.

Difficulties with the cytoarchitectonic method, somewhat similar to those of Lashley and Clark, were experienced by Bailey and von Bonin in their cytoarchitectonic studies of the cortex of the rhesus macaque [794], chimpanzee [29] and human [30]. With regard to the human cortex, they stated that vast areas are so closely similar in structure that any attempt at subdividing them would be unprofitable, if not impossible. It has already been mentioned that the total number of areas distinguished by Bailey and von Bonin [30] is much lower than that of other cytoarchitectonists (Table 15.2). Braak [64] criticized the results of these authors. He stated that they missed or neglected obvious cytoarchitectonic boundaries and suspected that they were content with superficial observations.

Several authors have attempted to localize functional areas in the cortex by electrical stimulation. Vogt and Vogt [784, 785, 787, 788] stimulated the cortex in monkeys *(Cercopithecus)* under general anaesthesia, and Foerster [197] did the same in patients who underwent brain operations under local anaesthesia. They found that, although the classical motor cortex on stimulation at low strength typically reacted with isolated contractions of small muscle groups, quite characteristic, more complex motor effects could be evoked from many other cortical areas. Thus, eye and head movements to the contralateral side could be elicited from areas 8 and 19, and stimulation of the parietal cortex produced synergic flexion of the contralateral arm and leg (Fig. 15.18 C). Their procedure of identifying functionally equivalent areas involved three steps: (1) They plotted the results of the stimulation experiments in the *Cercopithecus* monkeys on a cytoarchitectonic

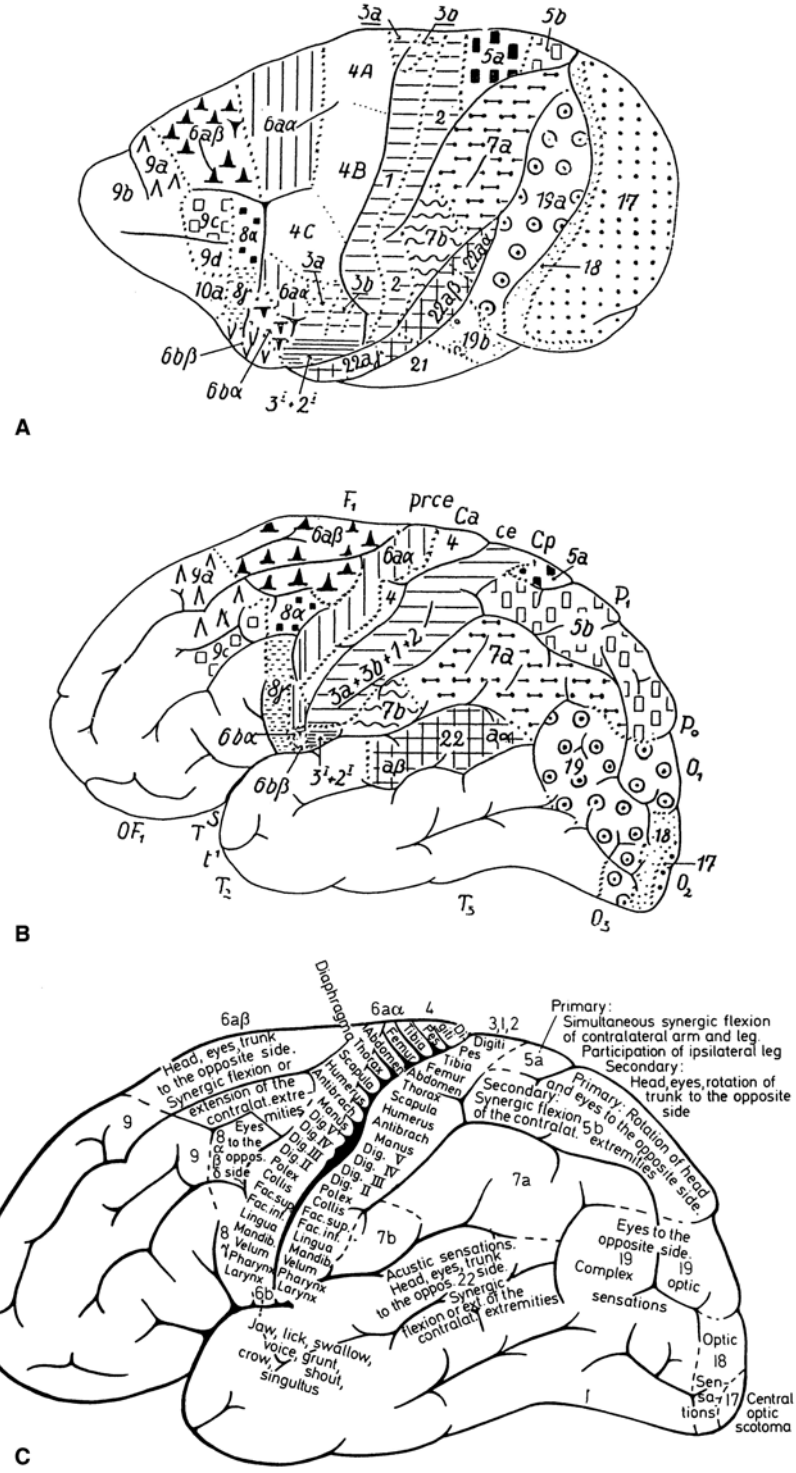


Fig. 15.18 A–C. Functional mapping by electrical stimulation. **A** The various effects of electrical stimulation of the cerebral cortex of the monkey *Cercopithecus*, plotted with *particular symbols* on a cytoarchitectonic map of the same species. **B** Comparable stimulation effects, elicited in humans, plotted with the *same symbols* on a cytoarchitectonic map of the human cortex. **C** Chart of motor effects elicited by electrical stimulation of the human cerebral cortex. **A** and **B** are reproduced from Vogt and Vogt [787]; **C** is taken from Foerster [197]

map of the same species, using different symbols for the various reaction patterns (Fig. 15.18 A). It appeared that almost all of the areas characterized by particular reactions exactly matched with a particular cytoarchitectonic area. (2) Next, they compared the cytoarchitecture of *Cercopithecus* monkeys with that of humans and were able to identify and to delineate in the latter equivalents of all the structurally and functionally characterized areas in the monkey brain. (3) Finally, they transferred the results of the stimulation experiments in humans (Fig. 15.18 C) to their map of the human brain, using the same symbols for the various reaction patterns as had been used in the monkey (Fig. 15.18 B). They concluded that many cortical areas in the monkey area are structurally and functionally equivalent (i.e. homologous and analogous) to particular areas in the human cortex. It is noteworthy that Vogt and Vogt [787] proposed to reserve the term *cortical field* ("*Rindenfeld*") for areas representing both structural and functional units.

Electrical stimulation experiments on the human cerebral cortex in awake patients undergoing brain surgery have also been performed by Penfield and his associates [544, 545, 548]. These experiments have extended our knowledge concerning the somatotopic organization of the primary somatosensory and primary motor areas considerably. They showed that, in both of these cortical areas, the different parts of the body are represented in territories of very different sizes. Thus, in the somatosensory cortex, the face and hand areas are very large, whereas the trunk and the proximal parts of limbs occupy relatively small territories (Fig. 15.19 A). In the motor cortex those parts of the body capable of performing the most differentiated and delicate movements have the largest representation (Fig. 15.19 B).

Woolsey and collaborators [830–833] have carefully mapped the somatosensory and motor cortical areas in a variety of mammals, using electrical stimulation and also recording evoked cortical potentials. These studies have given results concordant with those in humans.

Studies using single-cell recordings and electrical stimulation of cells have generated important findings with regard to the functional organization of the neocortex. Thus, it has been shown that most of the post-Rolandic cortex is devoted to processing specific aspects of a single sensory modality and that numerous separate areas for processing unimodal sensory information are present in this vast region. Monkeys have over 30 cortical areas for processing visual information, at least 15 for somatosensory information, and some 20 for auditory information [353]. Moreover, it has been shown that many of these areas are occupied by orderly representations or maps of receptor surfaces.

Recording the activity from single neurons under particular experimental or behavioural conditions has yielded important clues about the functional significance of the areas in which the elements studied are embedded. Thus, in the visual cortex, there are neurons that respond selectively to various directions of motion, specific colours, the orientation of line segments, the density of visual texture and many other visual features [313, 536]. In the extrastriate infratemporal visual area IT, many cells respond only or best to highly complex stimuli and some are selective for faces [258]. Cells in the anterior premotor cortex play a role in the preparation of movements [828], whereas the activity of neurons in certain parts of the prefrontal cortex is correlated with delayed-response performance and hence with working memory [215].

Returning to the systems level of functional localization in the neocortex, it should be mentioned that in 1965 Norman Geschwind (1926–1984) published a series of seminal papers on disconnection syndromes in animals and humans [227]. Referring to the studies of Wernicke, Liepmann and Déjerine (see above), he posited that many disorders of the higher functions of the nervous system, such as the aphasias, apraxias and agnosias, may be considered disturbances produced by anatomical disconnection of primary receptive and motor areas from one another. He emphasized the importance of long cortico-cortical connections emanating from the unimodal sensory association areas and pointed out that disconnection of cortical areas can be achieved by le-

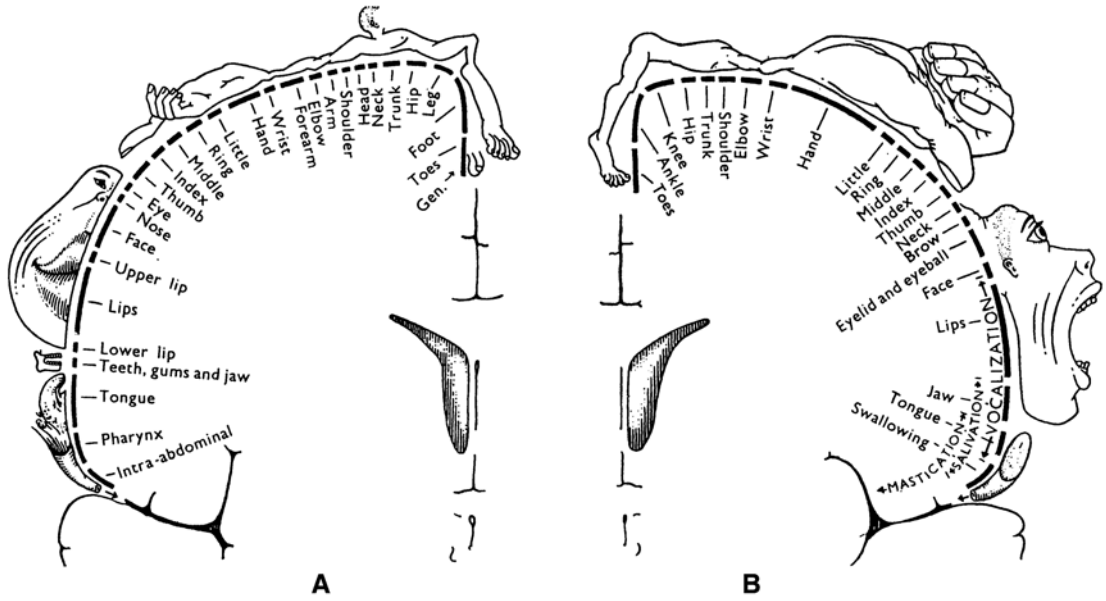


Fig. 15.19. Diagrams showing the relative proportion of the representation of the different parts of the body in (**A**) the postcentral primary somatosensory cortex, and (**B**) the precentral primary motor cortex. From Penfield and Rasmussen [548]

sions involving either white matter connections or by damage to association areas that constitute obligatory way stations between the primary sensory, motor, and limbic regions of the brain. Herewith Geschwind provided a general conceptual framework for higher brain disturbances, based on the neocortical wiring pattern (Fig. 15.20). Geschwind's papers became the manifesto of behavioural neurology and played an important role in the development of the current concept that networks of interconnected multiple specialized cortical territories form the morphological substrate of higher brain functions [3, 92, 464, 465].

It is noteworthy that, according to Catani and ffytche [92], not only disconnection, but also local hyperconnectivity or combinations of these two abnormalities may play a role in the pathogenesis of neurological and psychiatric disorders. Thus, it has been suggested that, in autism, a combination of fronto-frontal hyperconnectivity with frontal disconnection from other brain regions may be present [115].

Functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) play a prominent role in localizing functions and functional complexes in the neocortex. Maps constructed by these techniques depict neural activity as coloured spots or blobs, either on the surface of the brain or on brain sections in various directions. PET and fMRI monitor changes in blood flow or metabolism in specific regions of the brain while human subjects perform various sensory, motor or cognitive tasks. The blood flow signals and metabolic signals reflect changes in neuronal, particularly synaptic, activity [602].

Neuroimaging studies have not only confirmed and extended previous knowledge about localization of function in the primary sensory and motor cortical areas, but have also demonstrated a pervasive form of localization in a wide variety of cognitive tasks [83]. The activity of identifying and localizing cortical areas related to specific sensorimotor or behavioural events, using imaging techniques, is generally denoted as *brain mapping*. The resultant maps or charts (Fig. 15.21) show a striking resemblance to the early-nineteenth-century, phrenology-based maps (Fig. 15.16), as well as to the early-twentieth-century, clinical evidence-based map of Kleist (Fig. 15.17). All of these maps show detailed functions, allocated to distinct territories of the cortex. However, an important difference is that the phrenology maps and the Kleist map, contrary to neuroimaging maps, are typical "one-function–one-brain-area maps".

It stands to reason that, in order to become scientifically meaningful, the raw products of brain imaging, i.e. the activity-related blobs and patches, have to be placed in the context of the structural and functional architecture of the brain. As regards morphological architecture, many authors confine themselves to indicating the location of the spots of activity detected in terms of the gross anatomy of the cortex, for instance: activity in "the inferior parietal lobule" or in "the posterior part of the superior frontal sulcus". Many others use Brodmann's map (Fig. 15.8), as extrapolated by Talairach and Tournoux [727] onto a standardized brain atlas, as a frame of reference. Given the considerable interindividual variability of the human brain at both the gross anatomical and the structural levels, neither of these two approaches is entirely satisfactory [66]. We will come back to this issue in a later section.

Insight into the functional architecture of the neocortex may be gained by considering the following features of neuroimaging data.

1. In most cognitive tasks, two or more cortical areas are activated [83]. The activated areas may be considered as nodal points in the networks underlying the different cognitive processes being investigated.
2. Reviews of functional neuroimaging results across different cognitive domains clearly show that cortical regions, such as the prefrontal cortex and the parietal area 7, are engaged in a wide variety of cognitive demands. The most parsimonious explanation of this kind of activation is that they reflect cognitive processes that are tapped by tasks in different domains [83]. However, it is also conceivable that more refined analyses will lead to a further functional parcellation of the areas involved.

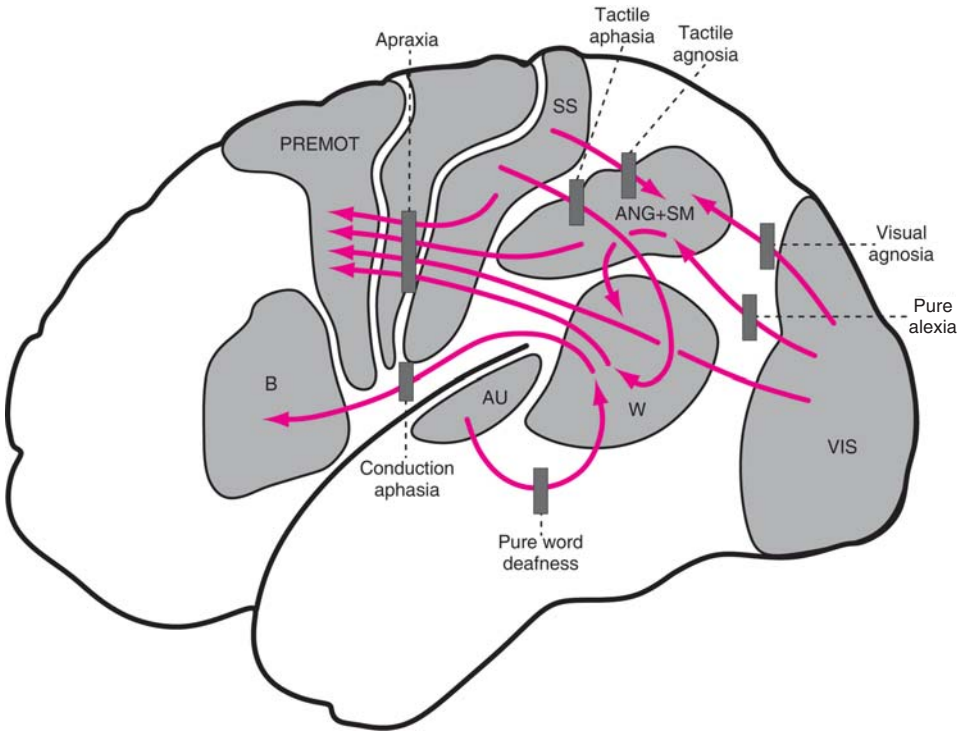


Fig. 15.20. Geschwinds' disconnection syndromes. Cortico-cortical pathways in the human brain and the disconnection syndromes to which their interruption may lead. Geschwind and his predecessors Liepmann and Déjerine also indicated that damage to sectors of the corpus callosum may also lead to typical disconnection syndromes. These have been omitted from this scheme (based on [92]). *ANG+ SM*, angular and supramarginal gyri; *AU*, auditory cortex; *B*, Broca's speech area; *PREMOT*, premotor cortex; *SS*, somatosensory cortex; *VIS*, visual cortex; *W*, Wernicke's speech area

a Attention [684]
b Calculation [684]
c Activation arising from a working memory task [66]
d Processing of incorrect arithmetic equations [461]
e Maternal love [39]
f Performance of a verbal working memory task [583]
g Reading aloud irregular words [289]
h Meditative state [418]
j Finger opposition task [713]
k Visual-spatial orienting [450]
l Coherence processes in language comprehension [184]
m Executive function in working memory [523]
n Embarrassment [724]
o Perception of visual motion: V5 [808]
p Written sentence comprehension [109]
q Processing of color patterns [38]
r Verb comprehension [259]
s Judgement of the grammaticality of sentences [807]
t Selective auditory attention [413]
u Evaluation of unpleasant, arousing words [435]
v Cross-modal sensory processing [396]
w Error processing [460]
x Categorization of written object descriptions [260]
y Pursuit eye movements [50]
z Painful visceral sensation [662]
a^1 Saccades [684]
b^1 Visual stimulation [506]

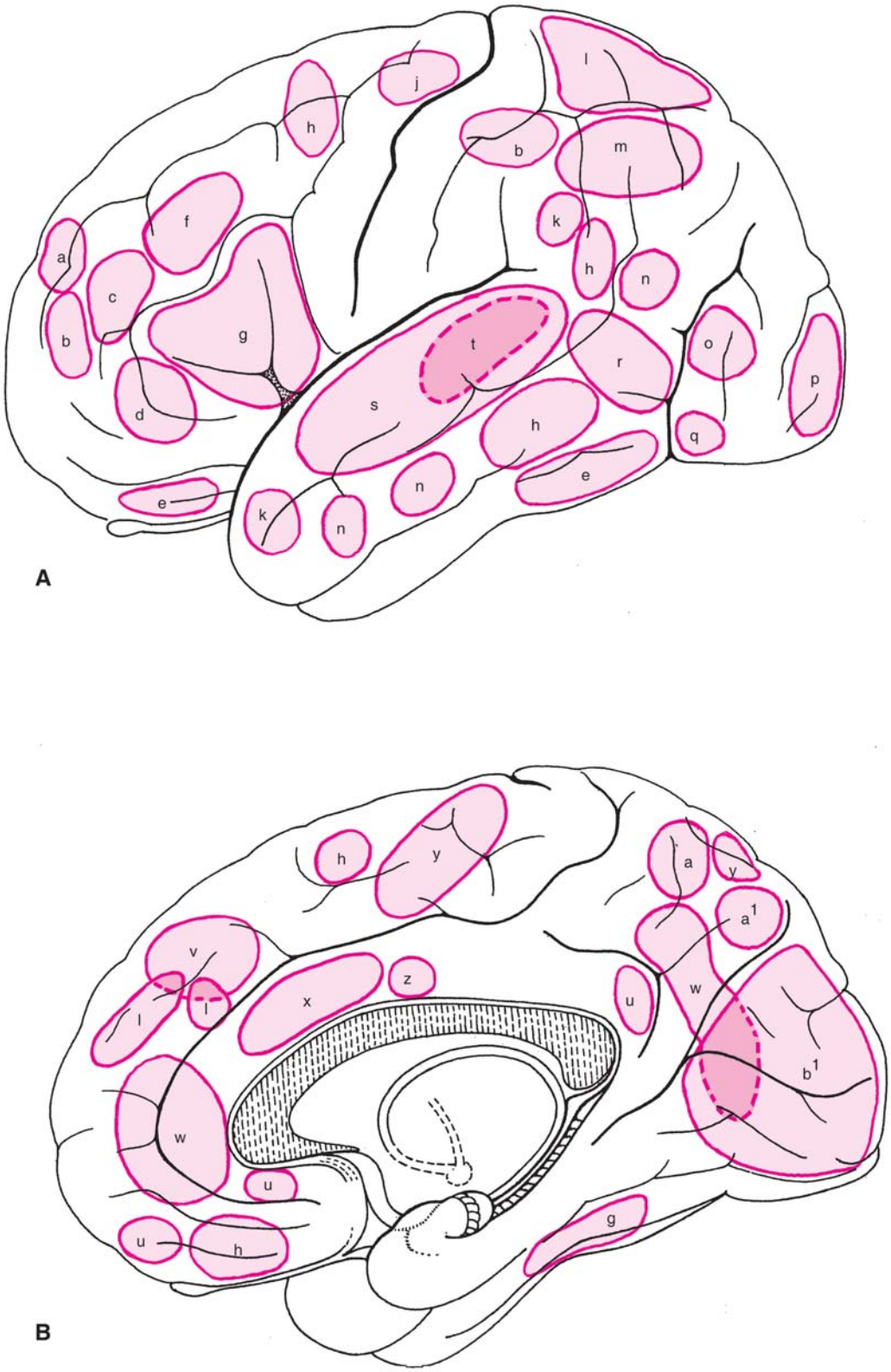


Fig. 15.21. Activation loci, found in a number of functional imaging experiments, projected upon the lateral (**A**) and medial (**B**) surface of the cerebral hemisphere. For significance of letters, see opposite pape

3. Combining neuroimaging data with the results of single-cell recordings in non-human primates may help determine the functional specialization of a given area in more detail.
4. The functional role played by any cortical area is defined largely by its connections. Thus, it is important to complement the results of neuroimaging experiments with studies aimed at determining the afferent and efferent connections by which the areas (spots of activity) detected are embedded in the cortical network.

Although techniques have recently become available to globally trace the tracts of the living human brain [40, 108, 335, 488, 588], information concerning the connectivity of particular areas in the human cortex still must be derived and extrapolated from experimental studies in monkeys. Nevertheless, we have at present a fairly accurate picture of the connectional frameworks involved in a large number of specific cognitive and behavioural operations, such as spatial orientation, object recognition, language [464, 465], attention [553] and decision forming [522]. The neural circuitry related to many of these operations is not confined to the neocortex, but also includes one or several subcortical centres. The cerebellum is consistently activated in a variety of cognitive processes, but the nature of its role in these processes is still obscure [83].

Structural and Functional Subdivision: Overview

1. The structure of the neocortex is not homogeneous throughout.
2. Many authors have attempted to subdivide the neocortex or parts thereof into structural entities, using cytoarchitectonic and/or myeloarchitectonic criteria. Most of these authors considered the resultant architectonic areas or fields not merely as structural entities, but also as functional units. We have seen that, on the basis of clinical evidence, Kleist provided nearly all of the areas delineated by Brodmann (Fig. 15.8) with a detailed functional label (Fig. 15.17), and that the Vogts sought to identify structural-functional units in the neocortex of monkey and humans, by combining the results of cytoarchitectonic analyses with those of electrical stimulation experiments (Fig. 15.18).
3. The primary sensory and motor areas are structurally and functionally distinct. They can be easily identified as heterotypical agranular and granular areas (types 1 and 5 of von Economo: Fig. 15.10), and as early maturing myelogenetic projection areas (Fig. 15.14). Hodologically, the primary sensory areas are defined by receiving the thalamocortical endsegments of the great sensory projections, whereas the primary motor cortex is characterized by its massive corticobulbar and corticospinal projections.
4. The remainder of the neocortex is formed by Flechsig's late-maturing association cortex. In the vast region occupied by this cortex, the structural differences between the different areas are rather subtle, which explains why the results of the various cytoarchitectonists are less concordant here than in the primary areas. All of the areas forming part of the association cortex occupy, as homotypical areas, an intermediate position in von Economo's classification system (Fig. 15.10).
5. Experimental studies on the cortico-cortical connections are and have been of paramount importance for both the morphological and functional interpretation of the association cortex. However, because such studies cannot be performed on humans, they have to be carried out on laboratory animals, preferably monkeys. Hence, in practice, the acquisition of data on the fibre connections of a given area in the human cortex involves the following four steps: (1) identifying and locating an area in the human cortex; (2) identifying and locating the homologue of that human area in the cortex of the monkey; (3) establishing the fibre connections of that area in the monkey cortex by using experimental tract-tracing techniques, and (4) extrapolating the results of these experiments to the human brain. A

serious limitation of this indirect method is that many areas in the human neocortex have no obvious homologue in the monkey (Figs. 15.8, 15.12) [120].

Experimental studies in the monkey have shown that (a) the primary somatosensory, visual and auditory cortical areas project via short connections to adjacent unimodal association areas; (b) these unimodal sensory association areas project in turn to two strips of heteromodal sensory association cortex, situated in the lateral and medial parts of the parietal and temporal lobes; (c) the unimodal and heteromodal sensory association areas project massively to the prefrontal cortex which, on this account, should be considered as a higher association cortex, and (e) sequences of short connections successively link the various prefrontal areas, the premotor area and the primary motor area (Fig. 15.15). It is important to note that the boundaries between the various association areas thus defined do not show a close correspondence to those of the cytoarchitectonic fields, as delineated by Brodmann and others.

6. A combination of connectional data with the results of microphysiological studies has shown that the wiring of the neocortex may be characterized as a distributed hierarchical network that contains numerous intertwined processing streams.
7. Unit activity recordings, the effect of lesions and particularly the results of neuroimaging studies have firmly established functional segregation as a principle of neocortical organization, not only in the primary cortices, but also in the association regions (Fig. 15.21). This having been said, it should immediately be added that the precise morphological identification of the functionally segregated domains is a difficult problem and much current research is devoted to this (see below).
8. As regards the functional organization of the neocortex, there are three different concepts or paradigms: localizationism, anti-localizationism or holism and (dis)connectionism.

Localizationism claims that each region of the neocortex represents an independent organ, dedicated to a complete and distinct function. This idea was first put forward by the phrenologists Gall and Spurzheim (Fig. 15.16), culminated in the work of Kleist (Fig. 15.17) and is still tangible in many current mapping studies aimed exclusively at localizing functions. Such functional cartography with the aid of neuroimaging techniques has been characterized by some [508, 601, 744, 745] as "neophrenology".

Anti-localizationism or holism holds that higher cognitive and mental functions are distributed homogeneously throughout the cortex and require the integrated activity of the entire cortex. The degree of cognitive or behavioural impairment following a cortical lesion is simply proportional to the amount of tissue destroyed, with localization being entirely irrelevant. The most prominent anti-localizationists were Flourens, in the early nineteenth century, Goltz, in the late nineteenth century, and Lashley, in the twentieth century.

The presently prevailing concept of *(dis)connectionism* has its roots in the clinical work of Wernicke, Liepmann, Déjerine and Geschwind and has been further developed by Mesulam [463–465], Van Essen [180, 770], Friston [201, 211] and many others. It states that, although functional localization and functional specialization are important principles, they do not offer a complete or sufficient explanation of cortical organization. The physiological changes elicited in the cortex by particular cognitive processes or behaviours should be explained in terms of distributed patterns of changing neural activity in networks of interconnected, functionally specialized areas. Cognitive and mental abilities are not the product of single and separate cortical regions, but rather result from the functional integration of the elementary processing operations occurring in a smaller or larger number of functional areas. The neural mechanism of many neurological disorders can be understood as dysfunction within specific neural circuits.

Structural and Functional Localization in the Neocortex: Current Research and Perspectives

Current research on the subdivision of the neocortex concentrates on the following two interrelated questions: (1) what are the true and fundamental neocortical units, and (2) how do we determine and visualize the location and extent of these units.

As regards the first question, we have seen that Campbell, Brodmann, the Vogts and von Economo held that the cytoarchitectonic and myeloarchitectonic fields they delineated represent fundamental structural as well as functional units. Although there is much respect and appreciation for the work of the classical architectonists, it is generally felt that their analyses show two serious methodological shortcomings and, hence, do not provide a reliable baseline for further studies on the organization of the cortex. These shortcomings are: (1) the classical parcellations are based on the study of microscopic sections stained according to a single technique, either the Nissl technique for neuronal perikarya or the Weigert technique for myelinated fibres, and (2) the areal boundaries were established using purely visual inspection of histological sections and were, hence, influenced by varying observer-dependent conditions, such as individual abilities in pattern recognition [660]. In current architectonic studies these methodological shortcomings are avoided by using several complementary histological techniques [747] and/or applying observer-independent procedures [659, 660]. Thus, Carmichael and Price [86] presented an architectonic division of the orbital and medial prefrontal cortex (OMPFC) of the macaque monkey based on nine different cytoarchitectonic, myeloarchitectonic and immunohistochemical stains. These stains included Nissl, myelin and acetylcholinesterase, and immunohistochemical stains for parvalbumin (PV), calbindin (CB) and a membrane-bound glycoprotein. A cortical area was defined as distinct if it was differentiated in at least three different stains. This analysis subdivided many of the areas originally described by Brodmann [70] and Walker [802] and resulted in the identification of 22 different areas in the OMPFC of the macaque monkey. A similar architectonic analysis of the human OMPFC, carried out by Öngür et al. [518], revealed that all of the areas recognized in the macaque monkey have counterparts in humans. On the basis of these results and of studies on the fibre connections of the various areas in the monkey [88, 89], Öngür et al. concluded that each of the cortical areas distinguished is a module with specific input-output relations and a unique role in information processing. They considered it likely that much of the cortex consists of such *discrete structural and functional modules*.

Observer-independent procedures in the structural parcellation of the cortex include computer-assisted quantification of cortical morphology in terms of (a) cell density, neuron size and laminar thickness [605, 659, 660]; (b) packing density and laminar distribution of myelinated fibres [12]; and (c) receptor architecture, i.e. the density and laminar distribution of different receptor types as visualized by autoradiography [230, 851]. Areal boundaries are fixed at locations where these features change significantly.

Roland and Zilles [626] expect that combining the results of quantitative morphological studies that apply observer-independent procedures with data derived from functional neuroimaging studies will lead to the detection of *functional cortical fields*. They advance the hypothesis that the organization of the cortex is based on such functional fields, each occupying a certain, relatively large territory of the cortex, and postulate that all neurons and synapses within these fields perform a co-operative computation.

A preliminary reconnaissance of the current literature on the neocortex, aimed at detecting entities comparable to, or at least foreshadowing the *modules* of Öngür et al. [518] or the *functional fields* of Roland and Zilles [626], yields the following results:

1. Just as the classical architectonists indicated, the human neocortex can be subdivided into a number of juxtaposed structural fields.
2. Recent investigations on the primary sensory and motor areas generally confirm the results of the classical architectonists [7,

231, 598–600], although two subfields [230] have been detected within the primary motor cortex and three subfields [489] within the primary auditory cortex.
3. Detailed quantitative analyses have confirmed the presence of Brodmann's frontal areas 9 and 46 [604, 605] and 44 and 45 [6, 8] as distinct architectonic entities.
4. In many regions of the neocortex, including the orbitofrontal cortex [518, 751], the parietal cortex [849], the cingulate region [783], the retrosplenial region [376] and the extrastriate visual region [352, 408, 850], the number of architectural areas detected is larger, and sometimes considerably larger than in the classical studies.
5. Taking these data together, we estimate that about 150 juxtaposed structural and potentially functional entities are present in the human neocortex.

Comparative architectonic studies [516, 518, 577, 580, 581, 605] have shown that many of the delineable structural entities in the human neocortex have distinct counterparts (homologues) in the neocortex of the macaque monkey. The results of experimental studies on the afferent and efferent connections of these comparable areas in the cortex of the monkey can be transferred to the human brain and may provide important clues as to the functional significance of the entities involved. Using data collected in the macaque connectivity database CoCoMac [710], Passingham et al. [541] demonstrated that each cortical area has a unique pattern of cortico-cortical connections, a defining *"connectional fingerprint"*. They suggested that the connectional fingerprints underlie the cell-firing differences observed between areas during different tasks or task events. Passingham et al. [541] designate this pattern as a *"functional fingerprint"*. They indicate that functional brain imaging will be a useful tool for detecting such functional fingerprints because it enables us to compare activations across many cortical areas and across a wide range of tasks.

The second central questions in current research on the neocortex – how do we determine and visualize the location and extent of structural and functional units – has to do with two further shortcomings, or rather limitations, of the work of the classical architectonists. Firstly, these studies were all based on a single or a few brains and, hence, interindividual variations in the position and extent of the various architectonic areas were completely neglected. Secondly, the classical architectonists only analysed the superficially exposed parts of the cortex, leaving the sulcal cortices largely unexplored. This is a serious limitation indeed because, as already mentioned, in humans almost two thirds of the cortex are hidden away in the depths of the sulci.

As regards the first limitation, the pioneering studies of Filimonov [186] on the visual areas 17, 18 and 19, and of Kononova [383] on the frontal areas 44 and 45 have brought to light that these areas show a considerable intersubject variability (Fig. 15.22). Their observations have been fully confirmed by later studies on the same areas [6–8]. Similar variability has also been reported for many other cortical areas, including the primary motor [230, 598, 599] and somatosensory cortices [231, 232], the primary auditory cortex [489, 600], the prefrontal areas 9 and 46 [604, 605] and the orbitofrontal cortex (Fig. 15.23) [751].

Interindividual variability appears to be a general feature of neocortical architectonic areas and it should be added that this microstructural variation is superimposed upon the also considerable macrostructural variation pertaining to the overall size and shape of the hemispheres as well as to the sulcal and gyral pattern. It will be clear that this variability seriously hampers the establishment of spatial relationships between structural and functional domains.

In human brain imaging studies, it is common practice to determine the location of the activation foci detected by transferring these loci to the three-dimensional version of Brodmann's chart, incorporated in the stereotaxic reference system of Talairach and Tournoux [727]. Because the considerable structural variability of the cortex is completely neglected in this procedure, it is apt to lead to erroneous conclusions [748].

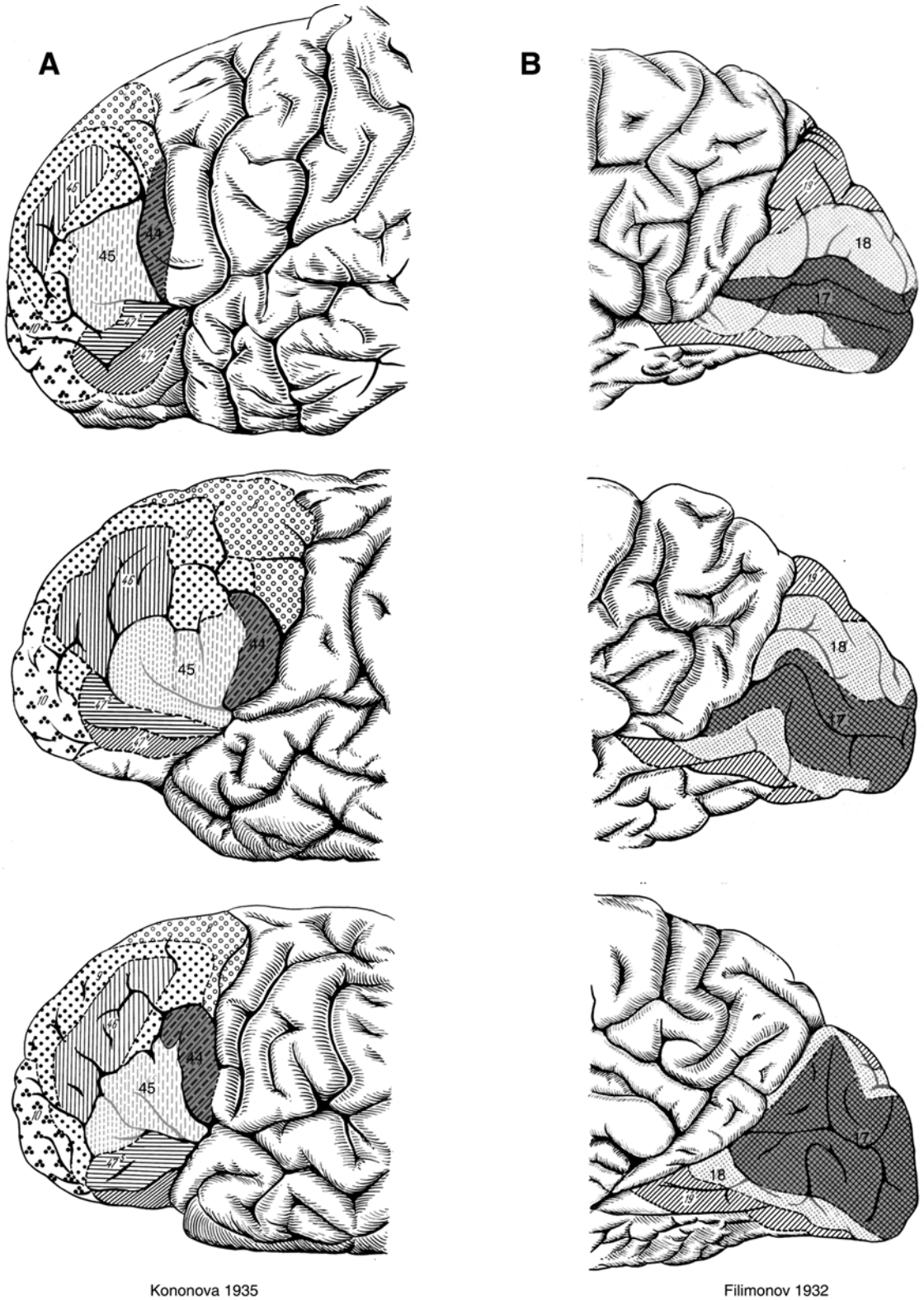


Fig. 15.22 A, B. Interindividual variability of cytoarchitectonic areas in normal human adults. **A** Prefrontal cortical areas, among them areas *44* and *45*, which together form Broca's motor speech region; **B** the visual cortical areas *17*, *18* and *19*. Reproduced from [748]. References cited: Kononova [383], Filimonov [186]

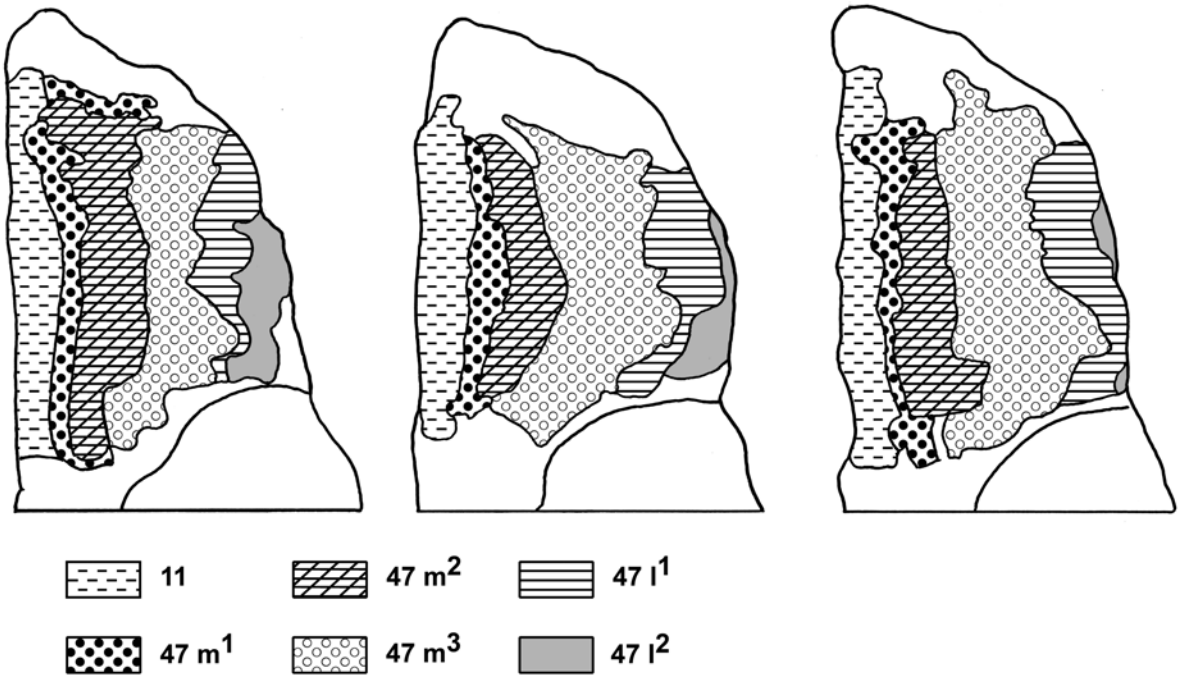
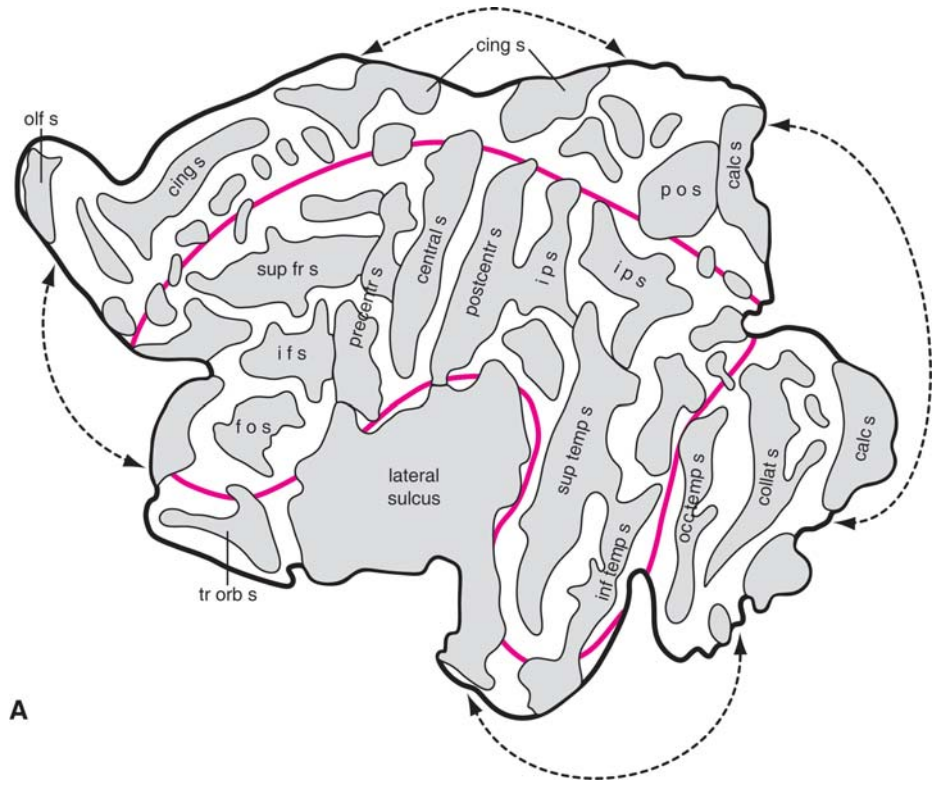


Fig. 15.23. Cytoarchitectonic (sub)areas covering the orbital surface of the frontal lobe in three different brains. Note the considerable interindividual variability (cf. Fig. 15.11) (based on Uylings et al. [751])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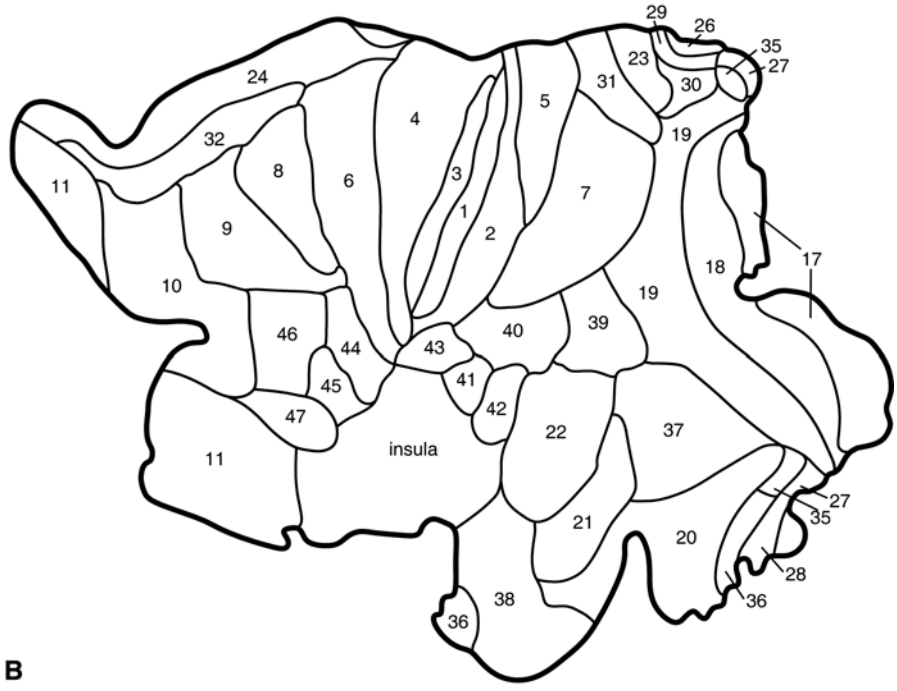
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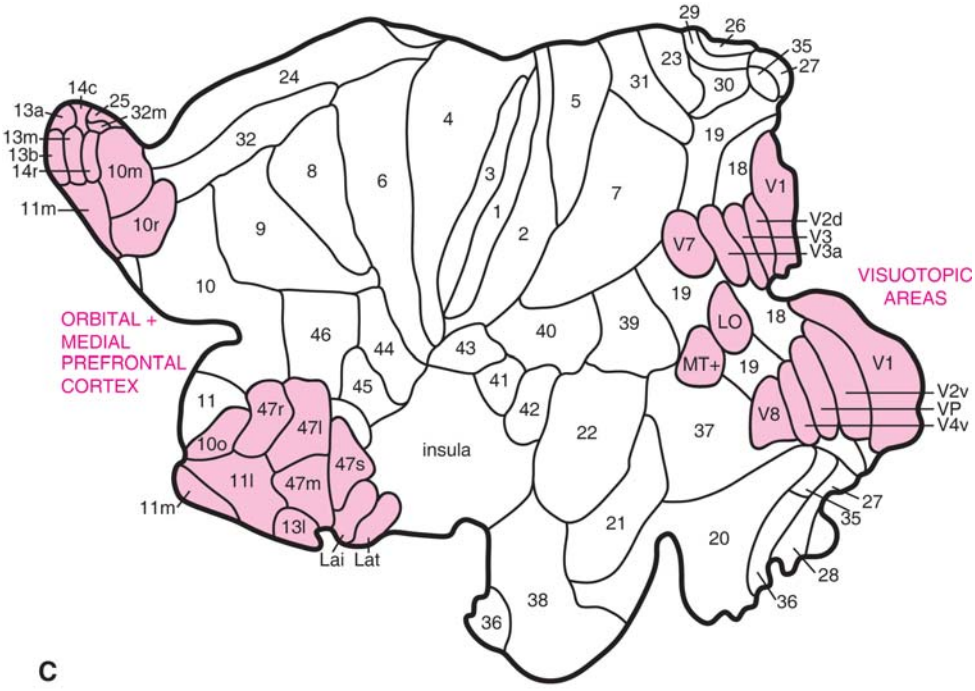


Fig. 15.24 A–C. Flat maps of the surface of the left human hemisphere, according to Van Essen [765]. In order to avoid gross distortions, several cuts have been made in the regions corresponding to the medial surface of the hemisphere. The *dashed*, *arrow-headed curves* in (**A**) connect corresponding points. In (**A**) the sulcal surfaces are *shaded* and the principal sulci are *labelled*. In order to facilitate orientation, outlines of the structures visible in a lateral view of the hemisphere are shown in *red*. In (**B**) The cytoarchitectonic fields of Brodmann (see Fig. 15.8) have been extended over the sulcal parts of the neocortex. In (**C**) the results of a detailed architectonic study of the orbital and medial prefrontal cortex [518] and of a number of functional imaging studies on the localizations of visuotopic areas [275, 590, 736, 764] have been superimposed on Brodmann's subdivision. It is noteworthy that the 30 (sub)areas delimited, together occupy 20% of the neocortical surface. Extrapolating from these data, it may be estimated that the neocortex is composed of some 150 (sub)areas or units. *calc s*, calcarine sulcus; *central s*, central sulcus; *cing s*, cingulate sulcus; *collat s*, collateral sulcus; *fos*, fronto-orbital sulcus; *ifs*, inferior frontal sulcus; *inf temp s*, inferior temporal sulcus; *ips*, intraparietal sulcus; *occ temp s*, occipitotemporal sulcus; *olf s*, olfactory sulcus; *pos*, parieto-occipital sulcus; *postcentr s*, postcentral sulcus; *precentr s*, precentral sulcus; *sup fr s*, superior frontal sulcus; *sup temp s*, superior temporal sulcus; *tr orb s*, transverse orbital sulcus

In order to cope with the problem of inter-subject variability of brain structures, computer-based, three-dimensional probability reference systems have been developed that incorporate data on the gross anatomy of a group of brains and provide an adequate probabilistic framework for both microstructural and functional studies [452–454, 624, 625, 627]. Spatial normalization procedures render it possible to fit structural data derived from individual brains (or groups of brains) into this reference system and the same holds true for the results of neuroimaging studies [66]. It is necessary to superimpose structural and functional data within the reference system so that structural-functional relationships can be rigorously tested. This procedure provides the basis for making sound statistical statements concerning the probability that a particular activity focus lies within a certain architectonic unit.

It will be appreciated that the generation of probability maps of all of the, say 150, structural units of the human neocortex is a formidable task. Two groups of neuroanatomists, that of Zilles and Amunts [6–8, 97, 169, 230–232, 489, 490, 599, 600], and that of Uylings [747, 748, 750, 751] are currently working on this mega-project, which will take at least 12 years to complete. Within the framework of this project, the neocortex of 10–15 normal human subjects will be analysed, using various staining techniques and observer-independent procedures. If the final results of this project matched with the results of large series of carefully carried out functional imaging studies would yield a (probabilistic) functional profile for all of the architectural units delineated, this neophrenological achievement would still represent no more than a first step in the analysis of the structural-functional relationships in the neocortex. The next step would be to *systematically* analyse how these various units or centres are integrated in the circuits and processing streams subserving higher cognitive and mental functions.

The final problem left by the classical architectonists, i.e. the representation and charting of the vast neocortical areas hidden in the sulci, has been successfully tackled by Van Essen and colleagues [160, 180, 762–764, 766, 767]. These authors have worked out computerized procedures by which the entire surface of a cerebral hemisphere can be unfolded and flattened into a two-dimensional reconstruction or flat map. Three such flat maps are shown in Fig. 15.24. In the first (Fig. 15.24 A), the sulcal surfaces are shaded and selected sulci are labelled. In the second (Fig. 15.24 B), the cytoarchitectonic fields, which in Brodmann's chart (Fig. 15.8) cover the superficially exposed parts of the hemisphere, have been extended over the sulcal domains. This map should be considered as provisional and tentative because: (1) the borders of the sulcal parts of the fields have not been determined, but rather estimated, and (2) data concerning the interindividual variability of the fields have not been included. In the third flat map (Fig. 15.24 C), the results of a detailed architectonic study of the orbital and medial prefrontal cortex [268, 518] and of a number of fMRI studies on the localization of visuotopic areas [275, 590, 736] have been superimposed on Brodmann's parcellation. Flat maps allow the entire neocortical surface to be seen in a single view; in the present authors' opinion, therefore, they are very well suited for visualizing the results of such studies. If the data concerning the localization and variability of the approximately 150 neocortical architectonic units, once established (see above), would be transferred to a surface-based atlas, this mega-operation would yield a very useful probabilistic framework for the topical specification of fMRI results and other functional data. A probabilistic map of the human visual cortex is already available [771].

Neocortical Afferents

In the neocortex, the fibres of all extrinsic afferent systems follow a radial course. Golgi studies and experimental investigations using anterograde degeneration and tracer techniques have shown that most of these afferent systems, after having entered the cortex from

the deep white matter, distribute their terminal branches preferably in one or more layers.

Lorente de Nó [414, 416] provided a detailed description of thalamic afferent fibres in the rodent neocortex. His Golgi material displayed two different laminar distributions of terminal arborizations: the "specific" distribution, which is densely aggregated in lamina IV, with or without extension to lamina III (a, b in figure 15.25 A), and the "unspecific" distribution, which is sparsely distributed throughout all cortical layers, but appears predominantly in lamina VI (c in Fig. 15.25 A). The "specific" afferents were considered to originate from "specific" thalamic sensory relay nuclei, such as the medial and lateral geniculate bodies and the ventral posterior nucleus, and to terminate in specific sensory cortical fields. The "unspecific" afferents, which were observed to extend over multiple cortical fields, were believed to originate from other, as yet undetermined thalamic sources. Frost and Caviness [213] studied the intracortical distributions of the projections of a number of different thalamic loci to the neocortex in the mouse using an axon degeneration technique. They found that in this animal virtually the entire tangential extent of the neocortex receives a projection from the thalamus. The areas of termination of thalamofugal axons appeared to be segregated into three tiers: an outer tier in layer I, a middle tier in layer IV and/or III and an inner tier in layer VI. In most fields, terminating axons belonging to the middle or the inner tier or both were found to extend over some distance into layer V. Herkenham [291–293] examined the cortical projections of individual thalamic nuclei in the rat using tritiated amino acids as anterograde tracers. He found that the thalamic nuclei can be grouped into three classes according to the laminar patterns of their cortical projections. The first class includes the thalamic relay nuclei for vision, audition and somatic sensibility. Their cortical projections terminate mainly in lamina IV, lamina III or both. The fibres of this class clearly correspond to the "specific" afferents of Lorente de Nó [416]. The second class includes the intralaminar thalamic nuclei, which issue sparse but widespread projections to deep cortical layers (laminae V, VI or both). The third class encompasses a number of nuclei that share a pattern of dense, widespread projections to lamina I, though terminations in other laminae may or may not be present. Because these nuclei projecting to lamina I generally occupy a position adjacent to the intralaminar nuclei, they were collectively designated by Herkenham [293] as the paralaminar nuclei. The finding that different (groups of) thalamic nuclei project in a particular laminar fashion to smaller or larger parts of the neocortex has been confirmed by a large number of studies on different animals, although with regard to the projections of certain nuclei different results have been obtained by different authors. Thus, Berendse and Groenewegen [49], who studied the cortical projections of the midline and intralaminar thalamic nuclei in the rat using PHA-L as an anterograde tracer, reported that the fibres originating from the intralaminar nuclei do not terminate exclusively in the deep cortical layers (as reported by Herkenham), but also project to lamina I. Corresponding findings have been reported for the cat and the monkey [209, 364, 640, 641].

The cortical projections of some thalamic centres have been analysed in detail by placing multiple small focal injections of anterograde tracers within their confines or by introducing horseradish peroxidase (HRP) into the cortex using a micropipette after recording from individual thalamocortical fibres. Such an analysis of the ventroanterior-ventrolateral complex of the thalamus of the cat revealed, for instance, that fibres originating from the ventrolateral or the caudal part of this complex are distributed in laminae I, III and IV of the parietal cortex, whereas fibres arising from rostral or dorsomedial portions of the complex are almost always confined to lamina I [356]. However, the most detailed information of this type presently available concerns the projection from the lateral geniculate body to the primary visual cortex in primates. In this group, the lateral geniculate nucleus is a laminar structure in which separate magnocellular, parvocellular and intercalated zones can be distinguished. In

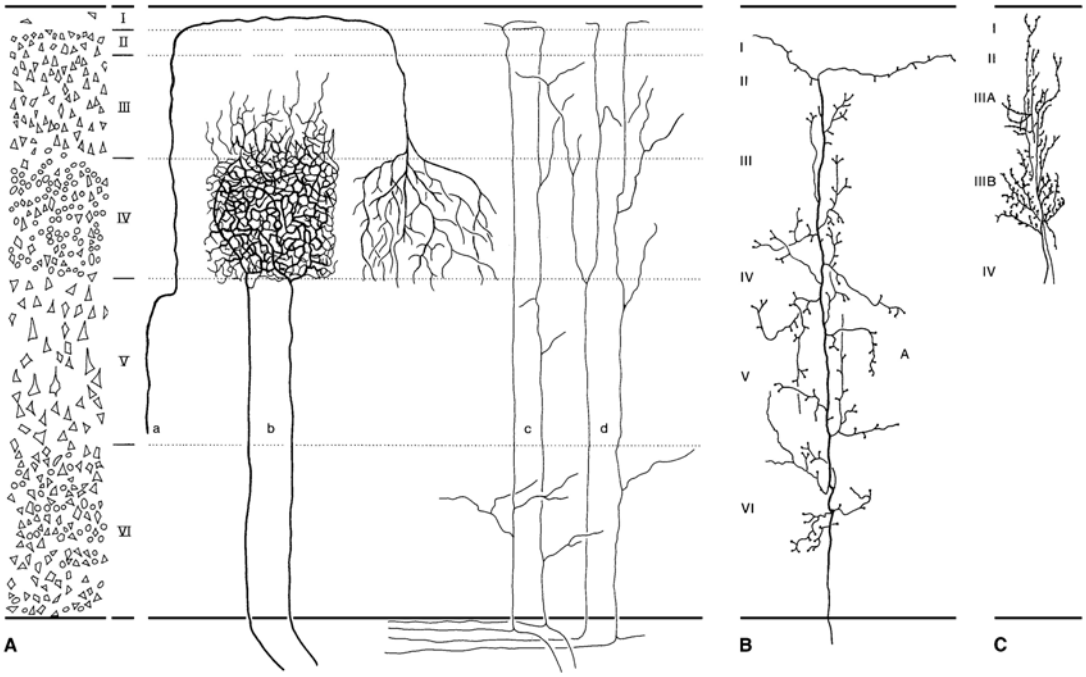


Fig. 15.25 A–C. Neocortical afferents. **A** "Specific" (*a,b*) and "unspecific" afferents (*c,d*) as observed in Golgi material of the somatosensory cortex of the mouse. *Left,* same cortical area as observed in Nissl preparations (based on Lorente de Nó [414]). **B** Cortico-cortical afferent fibre arborization in the auditory cortex of the macaque monkey (redrawn from Szentágothai [721]). **C** Callosal axons in the somatosensory cortex of the same species, anterogradely labelled by horseradish peroxidase injected in the corpus callosum. Redrawn from Jones [339]

the primate primary visual cortex, the laminar pattern is very distinct, and lamina IV can be divided into four subzones, designated as IVA, IVB, IVC*α* and IVC*β* (Fig. 15.26). Investigations of many different authors, summarized by Fitzpatrick et al. [189, 190] and Lund [425], revealed that there are at least six discrete populations of geniculocortical axons, differing markedly from one another in laminar distribution and tangential spread (Fig. 15.26):

1. Coarse fibres originating from the magnocellular layers of the lateral geniculate nucleus projecting to lamina IVC*α* with widespreading terminal fields that span the entire depth of the lamina.
2. Fibres resembling those mentioned above, the terminal fields of which are, however, confined to the upper half of lamina IVC*α*.
3. Axons originating presumably from both the parvocellular and the intercalated layers of the lateral geniculate nucleus forming small, dense clusters of terminal branches in lamina IVA and contributing some rising collaterals to the adjacent zone of lamina III.
4. Fibres originating from the intercalated layers of the lateral geniculate nucleus, the terminal arborizations of which participate in the formation of small, dome-shaped formations in lamina III.
5. Fibres from the parvocellular layers forming small, dense terminal fields in lamina IVC*β*.
6. Fine fibres likewise originating from the parvocellular layers of the lateral geniculate nucleus, extending over large distances horizontally, that contribute terminals to upper lamina VI and to lamina I (for a detailed discussion of the visual system the reader is referred to Chap. 19).

Although the thalamus is a major source of subcortical input, it is not the only one. In fact, more than ten different extrathalamic subcortical structures projecting to the neocortex have been identified [734]. In most of these, the nature of the neurotransmitter utilized by their constituent neurons has been established.

These structures include: (1) the claustrum (Fig. 13.8); (2) the basolateral amygdaloid nuclei (Fig. 13.7); (3) the basal forebrain, including the nucleus basalis of Meynert, which sends numerous cholinergic as well as GABAergic fibres to the cortex (Fig. 14.15); (4) the hypothalamus, comprising orexinergic, histaminergic and melanin-concentrating hormone (MCH)-containing neocortically projecting neuron groups (Figs. 10.5, 10.7 B, 14.15); (5) the mesencephalic dorsal raphe and central superior nuclei, which provide the entire neocortex with richly ramifying serotoninergic fibres; (6) the ventral tegmental area and the substantia nigra, sending dopaminergic axons mainly, but not exclusively, to the prefrontal cortex; and (7) the locus coeruleus in the rostral pontine tegmentum, which is the source of noradrenergic fibres spreading over the entire neocortex.

The claustral and amygdaloid efferents have been discussed in Chap. 13. The neocortical projections from the basal forebrain, the hypothalamus and the upper brain stem together constitute the ventral branch of the ascending arousal system (Figs. 10.5, 14.15). A detailed discussion of these various projections is beyond the scope of the present work. As far as the cholinergic, GABAergic and monoaminergic projections are concerned, it may be stated that, although all of these projections innervate the entire cortex, they are not to be considered as "diffuse and non-specific" [538]. Rather, they show a high degree of anatomical specificity, both for particular cortical areas and for particular laminae within a single cortical area (Fig. 15.27 A–C) [198, 264, 331, 467, 492, 651]. In some regions, for instance the primary visual cortex, different monoamines may show clearly complementary laminar patterns of innervation (Fig. 15.27 C, D). These data strongly suggest that the effects of the cholinergic, GABAergic and monoaminergic systems are not generalized excitation or inhibition but rather region-specific enhancement or diminution of activity in limited neuronal ensembles during certain stages of information processing [198].

Immuno-electron microscopic studies have shown that cholinergic [13, 43, 307], dopaminergic [677], noradrenergic [534] and serotoninergic axons [141, 535] in the neocortex form synaptic contacts with pyramidal as well as

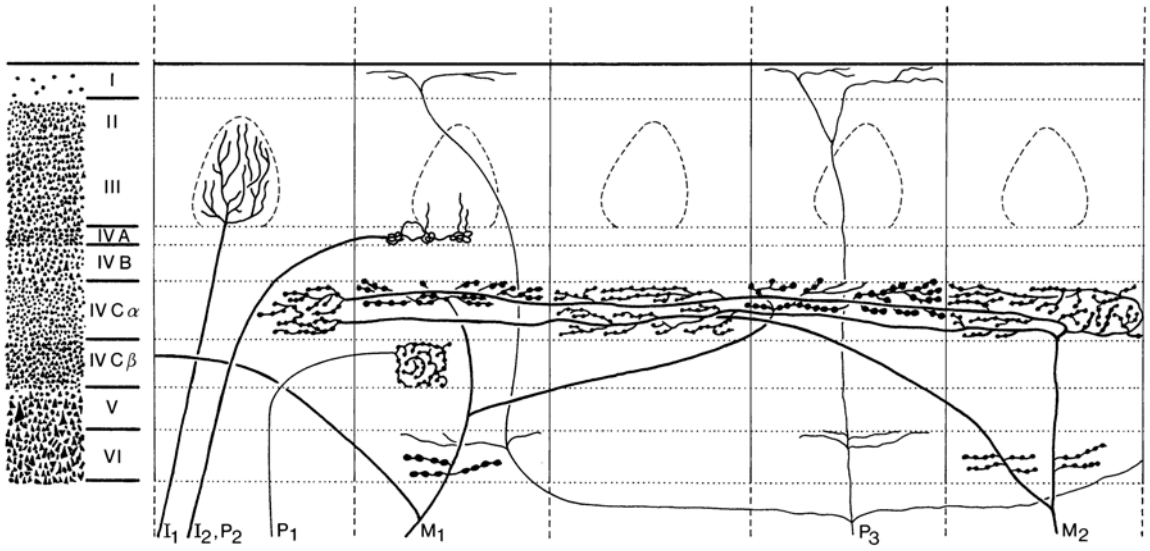


Fig. 15.26. Distribution of thalamic inputs from the lateral geniculate nucleus to the primate primary visual cortex of the macaque monkey. M_1, M_2, input from magnocellular layers; P_1–P_3, input from parvocellular layers; I_1, I_2, input from intercalated layers. The ocular dominance bands are indicated by *dashed lines*, 400–500 μm apart. *Left,* same cortical area as observed in Nissl preparations. Redrawn from Lund [425]

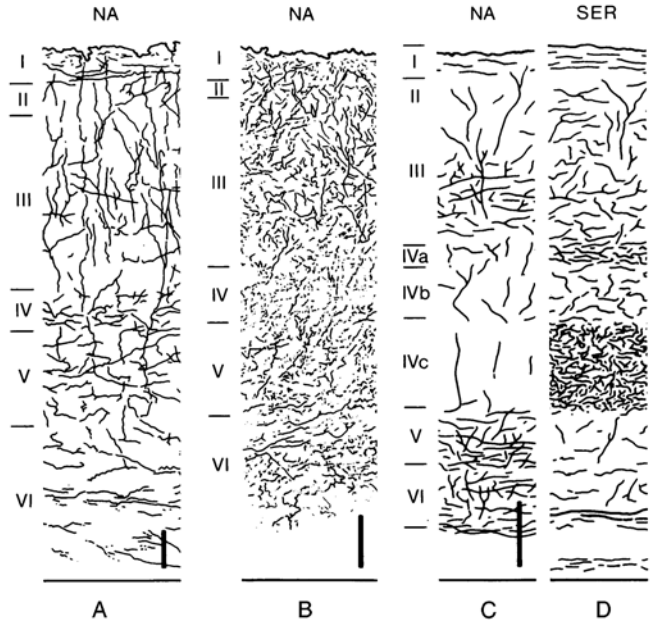


Fig. 15.27 A–D. Monoaminergic innervation of three different regions of the neocortex of the squirrel monkey. **A–C** Noradrenergic (*NA*) innervation of the dorsolateral prefrontal cortex (areas 9, 10), the primary somatosensory cortex (areas 3, 1, 2) and the primary visual cortex (area 17), respectively. **D** Serotoninergic (*SER*) innervation of the primary visual cortex. *Bars* represent 200 μm. Slightly modified from Morrison and Magistretti [491]

with (GABAergic) non-pyramidal cells. Descarries and colleagues have devoted a long series of publications, summarized in [148], to the synaptology of cholinergic and monoaminergic axons. They found that, in the neocortex, these axons are provided with varicosities and terminals which, although filled with typical "synaptic" vesicles, quite often lack the membrane functional complexes that are typical of synapses. They consider it likely that these non-junctional structures are involved in non-synaptic or volume transmission. Evidence in support of the occurrence of this mode of neurotransmission in the neocortex has been presented by Smiley and Goldman-Rakic for both the serotoninergic [692] and for the dopaminergic projections [691].

It is known that the various ascending extrathalamic pathways modulate the responsiveness of cortical neurons that process sensory input, co-ordinate motor output and perform higher brain functions, such as mood, attention, motivation, cognition, learning and memory [198, 264].

The dopaminergic projection is a key modulator of motivational cognitive and motor functions [244, 652] and the serotoninergic projection helps regulate wake-sleep cycles and modulates the sensory gating of behaviourally relevant cues in the environment [465].

The cholinergic projection to the neocortex is implicated in arousal, sleep-wake cycles, visual information processing learning, memory and selective attentional functions [239, 650, 835].

The noradrenergic projection to the neocortex arises, as mentioned, from the locus coeruleus in the rostrodorsal pons. Traditionally, this nucleus has been thought to play a role in vigilance and in responsiveness to novel stimuli [21, 199].

Recently, Aston-Jones and Cohen [19, 20] and Bouret and Sara [59] have developed new concepts on the function of the locus coeruleus. Aston-Jones and Cohen point out that during the waking state, the locus coeruleus neurons exhibit two modes of activity, phasic and tonic. Phasic activity is driven by the outcome of task-related decision processes and is proposed to optimize task performance (exploitation). When utility in the task declines, locus coeruleus neurons exhibit a tonic activity mode, associated with disengagement from the current task and a search for alternative behaviours (exploration). The locus coeruleus is supposed to produce these patterns of activity under the control of the cingulate and orbitofrontal cortices, both of which project strongly to it.

From studies of the cognitive context governing the activity of locus coeruleus neurons in rats and monkeys, Bouret and Sara concluded that these neurons are activated in situations requiring interruption of on-going behaviour and rapid adaptation. This locus coeruleus activation appeared to occur whenever there is a change in the environmental imperative, such as the appearance of a novel, unexpected sensory event. They suppose that the noradrenaline signals from the locus coeruleus facilitate changes in the forebrain networks that are mediating specific cognitive functions.

In addition to thalamic and extrathalamic subcortical afferents, each particular neocortical area also receives a strong input from other neocortical areas. These association fibres come from either the same or the opposite hemisphere; in the latter case they are called callosal fibres. According to Lorente de Nó [414, 416], the association fibres give off collaterals in the deep laminae, especially VI, but their main territory of distribution is in laminae I–IV, and especially II and III (d in Fig. 15.25 A). Goldman and Nauta [242] made small focal injections with tritiated amino acids into various areas of the association cortex of monkeys. They found that the anterogradely transported label accumulated in narrow, 200- to 300-μm-wide columns in relatively distant regions. On the basis of a study of Golgi material, Szentágothai [721, 723] concluded that the arborization space and pattern of individual cortico-cortical axons correspond in size with the columns revealed by isotopic labelling. He observed that these fibres pass radially through the cortex and issue relatively short branches at all levels (Fig. 15.25 B). Cortico-cortical fibres defining a narrow radial zone of termina-

tion have also been observed in the primate sensorimotor cortex [286, 339]. Such a fibre, labelled by HRP injected in the corpus callosum is depicted in Fig. 15.25 C. The major layers of termination of callosal fibres in the primate somatosensory areas are laminae I–IV. In the motor cortex, they terminate in a comparable pattern in laminae I–III. Studies on cortico-cortical projections based on the tracing of individual fibres, like the one cited above, are scant. However, an overall picture of the mode of termination of these fibres can be deduced from axon degeneration studies of cortico-cortical projections and from tracer studies in which such fibres are labelled en masse. A detailed survey of this literature, presented by Innocenti [322], revealed that most cortico-cortical fibres terminate in layers III and IV in primates.

Rockland and Pandya [623] reported that, in the visual cortex of the rhesus monkey, the pyramidal neurons of the superficial layers project to the middle layer (principally layer IV) of their cortical target areas, whereas the deep layer pyramids project outside the middle layers, mainly to layers I and VI. It has already been mentioned that Felleman and Van Essen [180] classified the projections to layer IV as feed-forward pathways and those projecting outside layer IV as feed-back projections.

From the foregoing, it appears that most of the extrinsic cortical afferent systems distribute themselves in layered arrays, and it may be added that, in the primary sensory cortices, an elaborate laminar segregation of thalamic inputs appears to be reflected in the stratification visible in the cellular architecture. Morphological evidence suggests that all extrinsic neocortical afferents are excitatory, raising the question of how the intrinsic machinery of this cortex is driven by these afferents.

Lamina I contains the apical dendritic bouquets of pyramidal cells of laminae II, III and V. Because in this layer only sparsely scattered intrinsic neurons are present, it is reasonable to assume that the extrinsic thalamic afferents spreading in it synapse principally with pyramidal neurons and thus have a direct access to the long-axonal outflow of the cortex. Superficial pyramids situated in lamina II extend not only their apical dendrites in lamina I; these elements often have basal dendrites which pass laterally from the soma and ascend to layer I [779]. These elements are most probably strongly excited by the lamina I extrinsic afferents. It is interesting to note that the afferents from different thalamic nuclei, which, after having traversed the cortex, spread in lamina I, terminate in different subzones of that layer [290] and the apical dendritic tufts of the pyramids thus receive stratified input from different sources.

Until recently, it was widely held that the specific sensory thalamic afferents mainly distributed to lamina IV (or its sublayers) of the primary sensory cortices contact only a single category of neurons, i.e. the spiny stellate cells, and that the input is then processed sequentially by hierarchically organized chains of neurons (see e.g. Hubel and Wiesel [308, 310] and Eccles [166]). Golgi-electron microscopy studies combined with degeneration and tracer experiments [814, 815] conclusively showed that the specific sensory thalamic afferents to the cortex synapse with pyramidal cells and with non-pyramidal intrinsic cortical elements. According to White [814, 815], this finding challenges the concept that thalamic input is processed by hierarchically organized chains of neurons and lends support to the notion that the function of the cerebral cortex depends heavily on parallel processing mechanisms. However, it should be noted that in highly differentiated sensory cortices different groups of local circuit neurons may well be involved in the parallel processing of sensory information. We have seen that, in the primary visual cortex of primates, the magnocellular zones of the lateral geniculate nucleus project to sublamina IVC*a*, whereas the parvocellular zones project to IVC*β* (Fig. 15.26). These two sublaminae are characterized by the presence of different classes of spiny stellate cells and by an almost complete lack of pyramidal neurons [422–424, 446]. Moreover, it has been established that the principal projection of the IVC*a* spiny stellate neurons is to sublamina IVB, whereas the majority of IVC*β* spiny stellate neurons project to

sublaminae IIIC and IVA [190, 422]. These findings suggest a continued separation of magnocellularly and parvocellularly derived information within the primate primary visual cortex [425].

We have seen that the deeper layers of the cortex (V and VI) also receive direct thalamic inputs. It is known that these layers contain many pyramidal and pyramid-like cells and only a relatively small number of intrinsic elements. The axons of many of these deep pyramidal cells possess recurrent, ascending collaterals and the axons of a certain proportion of the local circuit neurons in laminae V and VI are also directed to more superficial cortical layers. There is experimental evidence indicating that, in the deeper layers of the primary somatosensory cortex of the mouse, thalamocortical afferents contact both pyramidal and non-pyramidal cells [294, 295, 813]. The deep pyramidal cells may well receive an "aspecific" thalamic input via collaterals spreading in lamina VI (Fig. 15.25 A (c) and a "specific" thalamic input via their apical dendrites in lamina IV.

Finally, the callosal and ipsilateral association fibres form nearly all their synapses with the spiny dendrites of pyramidal cells [322, 815]. Because these fibres terminate principally in laminae III and IV, it seems likely that the superficial pyramidal neurons form their main target.

Neocortical Neurons and Their Synaptic Relationships

Introductory Note

The neurons of the neocortex can be classified as belonging to two basic types: pyramidal cells and non-pyramidal cells. The former can be subdivided into typical and atypical pyramidal cells (Figs. 15.28–15.30). The elements belonging in these categories will now be discussed.

Typical Pyramidal Cells

The typical pyramidal cells constitute the largest and most characteristic category of neocortical neurons. In the visual cortex of rat, cat and monkey, according to Winfield et al. [824], these elements account for about 65% of the total neuronal population, and in other cortical areas this percentage may be even higher. A typical pyramidal neuron is provided with a radially oriented apical dendrite that forms a terminal tuft in laminae I and II, with basal dendrites that radiate out from the base of the soma and with an axon descending downward to leave the cortex (Fig. 15.29). The apical dendrites may give rise to one or more horizontal or obliquely ascending side branches. All of the dendrites of typical pyramidal cells are more or less densely covered with spines (Fig. 15.30 A) [561]. Positionally, the apical dendritic tuft with its ramifications in laminae I and II is the only feature shared by all typical pyramidal cells. The somata and their basal dendritic systems may vary in position from lamina II to lamina VI, and the length of the apical dendrites varies accordingly (Fig. 15.29). In the following discussion of the typical pyramidal cells, the afferents impinging upon the various parts of their receptive surface will be considered first; the relation between the position of their somata and the destination of their axons will then be dealt with. Finally, attention will be paid to the patterns of distribution of their collaterals.

The somata of the pyramidal cells are not under the direct influence of any extrinsic afferent system. Rather, they are specifically addressed by one type of local circuit neuron, i.e. the basket cell (Fig. 15.31 A), although several other types of non-pyramidal cells may contribute to some extent to the somatic innervation of pyramidal cells [137]. The somata of the basket cells, which, like those of the pyramidal cells, vary in distance from the pia and are concentrated in laminae III and V [177, 436]. Their poorly ramifying dendrites, which bear few or no spines, radiate in all directions, with a tendency toward vertical and horizontal trajectories. The axons are either ascending or

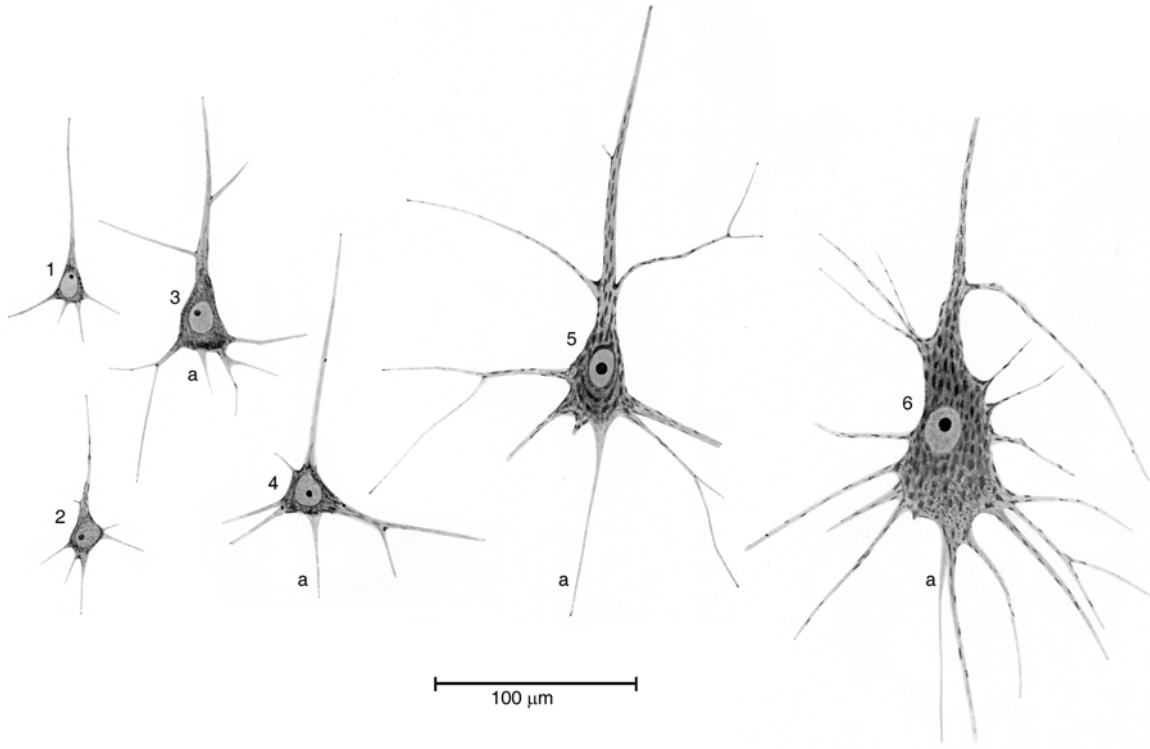


Fig. 15.28. Pyramidal neurons, as observed in Nissl preparations of the human neocortex (reproduced from [786]). *1*, Largest pyramidal cell from the IIIrd layer of area 17; *2*, stellate cell from the VIth layer of area 18; *3*, large pyramidal cell from the IIIrd layer of area 18; *4*, Meynert cell from the Vth layer of area 17; *5*, largest pyramidal cell from the IIIrd layer of area 4; *6*, Betz cell from the Vth layer of area 4. Note that the Meynert cell and the Betz cell, both of which represent by far the largest cell type in their respective cytoarchitectonic areas, and which, hence, are both designated as "giant cells" [84], differ considerably in absolute size. *a*, axon

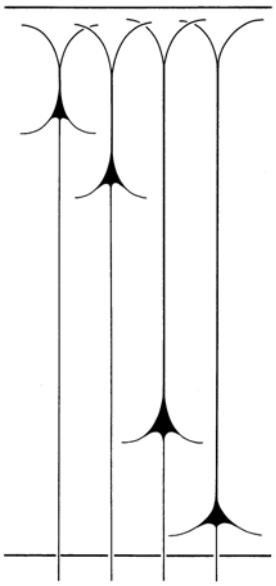


Fig. 15.29. Typical pyramidal neurons in the mammalian neocortex

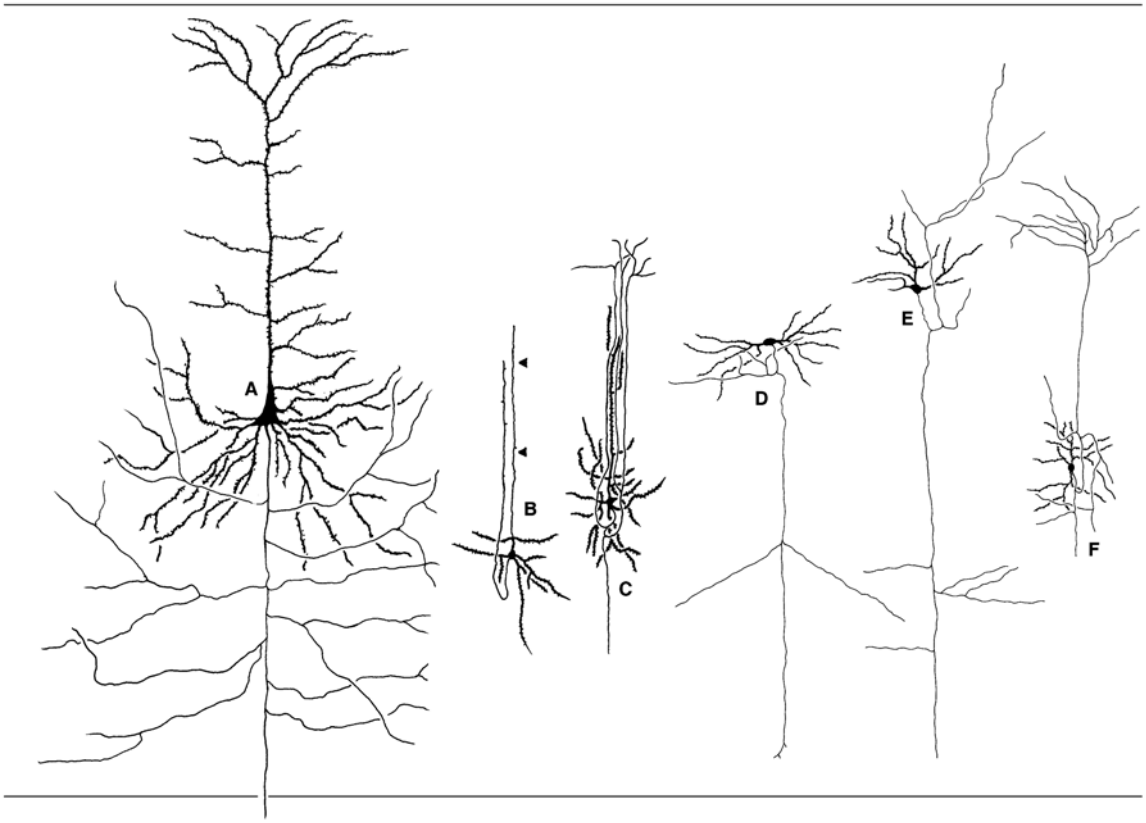


Fig. 15.30 A–F. Typical and atypical pyramidal neurons in the primate neocortex. **A** Typical pyramidal cell in the human neocortex [84]; **B** small pyramidal neuron with poorly developed apical dendrite (*arrowheads*) and a recurving axon from the striate cortex of the macaque monkey [422]; **C** a "star pyramid" in layer IV of the somatosensory cortex of the squirrel monkey [336]; **D–F**, spiny stellate cells in layers IVB, IVA and IVC*β*, respectively, of the primary visual cortex of the macaque monkey [422, 426]

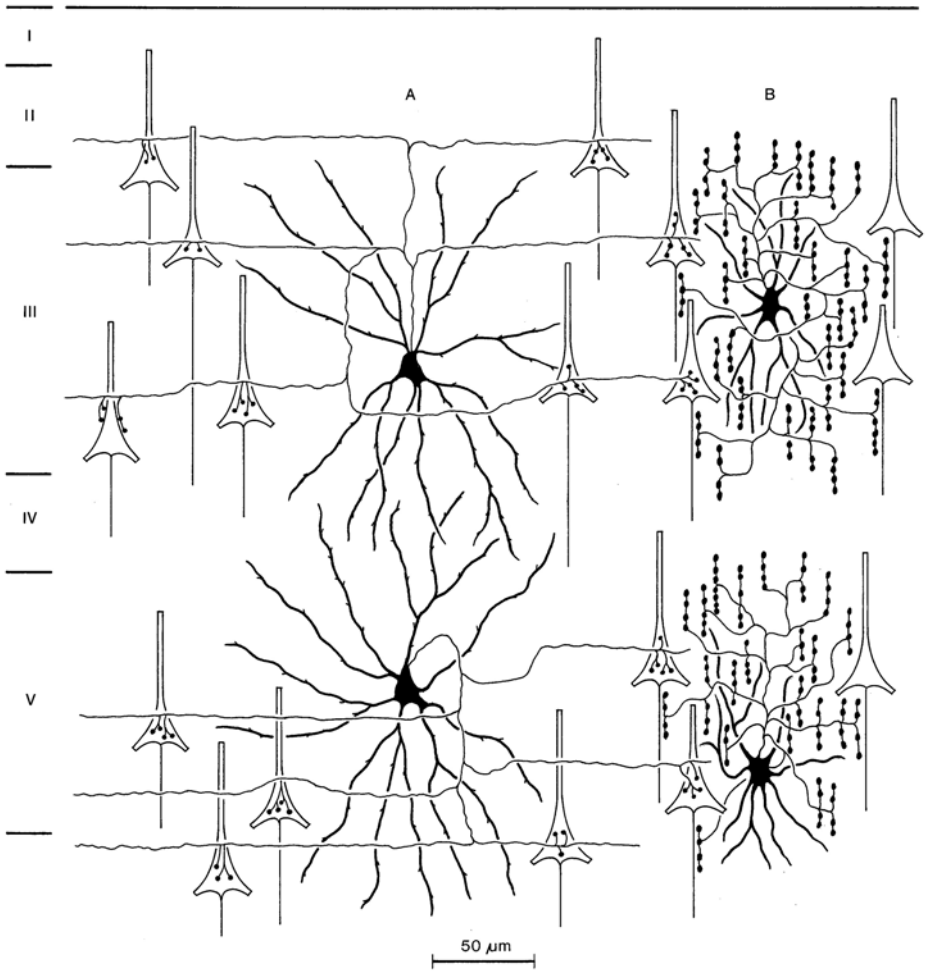


Fig. 15.31 A, B. Intrinsic cortical neurons contacting specific parts of the receptive surface of the pyramidal cells. **A** Basket cells, whose axonal terminals participate in the formation of pericellular nests surrounding the somata and proximal dendrites of pyramidal cells (partly based on Jones [339]). **B** Chandelier cells, whose numerous vertical axonal terminal portions specifically contact the axon initial segments of pyramidal cells. Based on Peters [555], Fairén et al. [177], Somogyi et al. [701] and Jones [339]

descending and provide four or more horizontal collaterals at various levels. The horizontal collaterals, which can extend for 1 mm or more in either direction, issue at intervals short side branches. These side branches terminate in pericellular baskets surrounding the somata and proximal dendrites of pyramidal cells. The basket cell terminals contain flattened vesicles, and the synapses made with the pyramidal cells are of the symmetrical variety. They use GABA as a neurotransmitter and exert a powerful inhibitory action on their target elements [343]. There is evidence suggesting that the basket cells are major recipients of thalamic and commissural inputs [555, 690, 700]. Moreover, the somata of the basket cells are contacted by numerous GABAergic terminals, which may well arise from the axons of other basket cells [287].

Like the somata, the axon hillocks and initial axonal segments of the pyramidal cells are also the target of a special category of local circuit neurons, i.e. the axo-axonic or chandelier cells (Fig. 15.31 B) [176, 555, 699]. These elements occur in laminae II–V, but are most prominent in lamina III. Their dendrites may be grouped in an upper and a lower tuft or spread in all directions. The axon ramifies many times and produces a dense plexus in the vicinity of the parent soma. From this axonal plexus, numerous (up to 300) vertically oriented arrays of terminals arise that contact the initial axonal segments of pyramidal cells. The axo-axonic synapses between the chandelier cells and the pyramidal neurons are symmetrical, and the vesicles in the presynaptic axon terminals are flattened [178, 345, 690].

It has been shown that the axon terminals of the chandelier cells contain the inhibitory neurotransmitter GABA; hence, it may be assumed that these elements inhibit the pyramidal cells [570]. Because the chandelier cells exert this action at a strategic site, i.e. the trigger zone for the initiation of action potentials, they may be considered to have a decisive influence on the output from the pyramidal neurons. It has been found that the number of axo-axonal synapses along the initial segments of pyramidal cells is much larger in the supragranular layers than in the infragranular layers [570, 690]. Because the pyramidal neurons projecting via the corpus callosum to the contralateral hemisphere are situated mainly in laminae II and III, it has been suggested that the chandelier cells principally influence cortico-cortical circuitry [570, 698].

In the hippocampal cortex, the perikarya of the pyramidal neurons are concentrated in a single layer, and all of these elements extend their basal dendrites in one and the same plexiform zone, the stratum oriens (Fig. 12.9). However, in the neocortex, the pyramidal somata are situated at different levels and, given the laminar organization of many extrinsic and intrinsic cortical fibre systems, it is to be expected that the basal dendritic systems of different pyramidal neurons are involved in different synaptic relationships, depending on the laminae or sublaminae within which these dendritic systems occur. Thus, it has been established that the basal dendrites of pyramidal cells situated in laminae II and III receive callosal afferents [100] and that lamina III border pyramids extend their basal dendrites into lamina IV, where they are contacted by terminals of thalamocortical fibres [303, 643]. Intrinsic cortical axons, i.e. axons of local circuit neurons and collateral branches of pyramidal cells, are concentrated in lamina IV and deep in lamina V, where they form the external and internal striae of Baillarger [340, 756]. The basal dendrites of certain groups of pyramidal neurons exhibit a specific affinity to the terminal ramifications of the axons within these striae. In the primate primary visual cortex, the external stria of Baillarger (also known there as the line of Gennari) is strongly developed and occupies a discrete sublayer IVB, in which no thalamic afferents are present (Fig. 15.26). According to Valverde [755], its axonal components include horizontal collaterals of descending axons of pyramidal and stellate cells of sublayer IVA, horizontal branches of axons of neurons located within sublayer IVB and ascending ramifications of spiny stellate cells residing in sublayer IVC. Lund [422] reported that the basal dendrites of pyramidal neurons situated in sublayer IVA turn sharply

downward from the soma to enter sublayer IVB, where they fan out horizontally, markedly avoiding any ramifications within lamina IVA (Fig. 15.32E). To the author's knowledge, the question of which neurons contribute axons or axonal branches to the internal stria of Baillarger has never been specifically addressed; however, the Golgi studies by Cajal [84] and Valverde [755, 756] suggest that the axons of both superficial and deep pyramids issue numerous horizontally oriented collaterals into this stria and that certain local circuit neurons with ascending axons, situated in lamina VI, also contribute collaterals to it. In the primate motor and visual cortices, basal dendrites of pyramidal cells form a conspicuous plexus within the domain of the internal stria. In both of these cortices, large pyramidal neurons occur, known in the motor cortex as Betz cells and in the visual cortex as Meynert cells (Fig. 15.28 (4, 6). Beyond their extraordinary size, these neurons have several other features in common. Both cells are characterized by the presence of long horizontally oriented basal dendrites that extend into the internal stria, and both further contribute to this stria with additional horizontal dendrites emanating from the lateral surface of the soma and even from the proximal stem of the apical dendrite [63, 64, 84, 654, 657]. The long, coarse collaterals of the Meynert cells may also contribute to the internal stria (Fig. 15.35) [622].

Whereas the horizontal axonal systems discussed so far contact the basal dendrites of pyramidal neurons situated at one particular level, the neocortex also contains vast numbers of vertically oriented axonal elements, which potentially contact the basal dendritic systems of pyramidal elements situated at different levels. These vertical axonal elements, which play a prominent role in the so-called radial coupling of neuronal elements and hence in the columnar functional organization of the cortex, may be categorized as follows:

1. *Thalamocortical and cortico-cortical association fibres* (Fig. 15.25).
2. *Axons and recurrent collaterals of pyramidal neurons* (Figs. 15.30 B, C, 15.32 D–F). Ultrastructural analyses of pyramidal neurons labelled by intracellular injections with HRP have conclusively shown that the axon collaterals of these elements make contact predominantly with the dendrites of other pyramidal cells [218, 370, 457].
3. *The vertically elongate axonal systems of some types of cortical local circuit neurons*. These elements, which will be discussed below, include spiny stellate cells (Fig. 15.30 D–F) and various types of smooth or sparsely spiny non-pyramidal neurons (Fig. 15.36 (M–Q).

The recurrent ascending axons or axonal branches of pyramidal neurons, as well as the ascending and descending axons of spiny stellate cells, have been observed to assemble in highly characteristic, radially oriented bundles [177, 423, 755, 756].

Turning now to the apical dendritic shafts of the typical pyramidal cells, it is important to note that these conspicuous processes are well placed to receive input from a variety of axonal pathways known to terminate within specific cortical layers. There is considerable variation in apical shaft length, ranging from essentially no shaft at all (pyramidal cells in the superficial zone of lamina II) to apical dendrites of 2 mm or more (pyramidal cells in lamina VI). Moreover, particularly in primates, the apical dendrites of many deep pyramidal cells do not extend into the subpial cortical zone, but rather terminate in a variably developed terminal tuft deeper within the cortex. Given these variations in length and in position of their apical dendrites, it is evident that different pyramidal cells may receive different samples of lamina-specific extracortical and intracortical afferents, and these differences are still further accentuated by the fact that the apical dendrites of different pyramidal neurons may exhibit different specific affinities to particular afferent systems. The evidence for such specific affinities includes (1) the presence of distinct, lamina-specific differences in the density of spines along the apical dendrites, (2) the presence of lamina-specific side branches on the apical dendrites and (3) direct proof that apical dendritic segments of different pyramidal cells passing through a particular layer

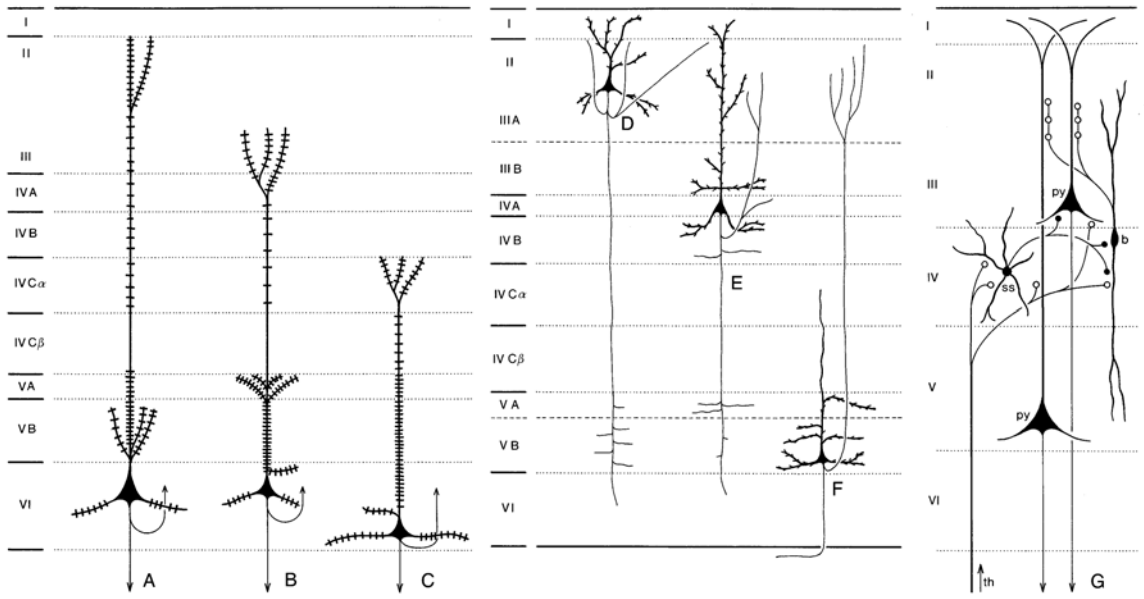


Fig. 15.32 A–G. Features of pyramidal neurons. **A-F** Semidiagrammatic representations of pyramidal neurons in the primary visual cortex of the rhesus monkey. The apical dendrites of the elements **A–C** issue their side branches and terminal tufts in particular (sub)layers; the density of spines along these processes show distinct lamina-specific differences. The elements **D–F**, which are situated at different levels, contribute axon collaterals to particular levels. **G** shows two pyramidal neurons, whose apical dendrites receive multiple asymmetrical synapses (*open circles*) from the axons of a bipolar cell. **G** also shows that smooth or sparsely spiny, non-pyramidal cells (*ss*) form symmetrical synapses (*filled circles*) with pyramidal (*py*) and bipolar cells (*b*) and that thalamic afferents (*th*) contact pyramidal, bipolar and smooth or sparsely spiny, non-pyramidal cells forming asymmetrical synapses (**A–C** are redrawn from Lund [423]; **D–F** are redrawn from Lund and Boothe [426]; **G** is based on Peters [554])

may receive highly different numbers of synapses from the afferents concentrated in that layer. These three aspects will now be briefly discussed.

1. *The presence of distinct, lamina-specific differences in the density of spines along the apical dendrites.* Spines are present in abundance on the dendrites of pyramidal neurons, where they function as the primary postsynaptic structures of the cell [178]. Quantitative analyses have shown that these spines are not evenly distributed along the dendrites. Characteristically, the most proximal portions of the dendrites emanating from the pyramidal somata are devoid of spines. From these initial segments onward, the concentration of spines increases gradually, attains a maximum some 80 μm away from the soma and then declines again distally [240, 561, 753]. Superimposed over this general pattern of spine distribution, the apical dendrites of pyramidal neurons may display distinct, lamina-specific changes in spine density. For example, Lund [422] found that in the primary visual cortex of the monkey, the apical dendrites of pyramidal cells lying in laminae V and VI show markedly fewer spines in lamina IVC*β* than in the densely spiny portion of the same shafts in laminae V and VI. The number of spines on these apical dendrites in general increases again in laminae above IVC*α*, but not to the level shown on the proximal portion of the shaft (Fig. 15.32A,B). According to Lund [422], this reduction in spines on the apical dendritic shaft as it passes through laminae IVC*β* is true of the great majority of the pyramidal cells of laminae V and VI, including the giant pyramidal cells of Meynert. It is known that lamina IVC*β* receives afferents specifically from the parvocellular layers of the lateral geniculate nucleus. Thus, the findings of Lund [422] might suggest that, in the monkey, the deep pyramids in the visual cortex are not the primary targets of these particular afferents.

2. *The presence of lamina-specific side branches on the apical dendrites.* The apical dendrites of many pyramidal neurons issue small numbers (some three to eight) of oblique or horizontally oriented side branches (Fig. 15.30 A). At first sight, these side branches seem to be randomly distributed along the apical shafts. However, systematic studies of large numbers of apical dendrites have shown that in several cortical areas these processes are given off at selective levels, i.e. as they pass through particular layers. Thus, Lorente de Nó [415] observed that, in the entorhinal cortex, the ascending shafts of the pyramids of the deeper laminae always issue some side branches in lamina III, but give off none at all during their passage through lamina II. Lund and Boothe [426] observed that the apical dendrites of a particular population of lamina VI pyramidal neurons in the primate visual cortex issue side branches selectively in lamina IVC*α*, whereas the apical dendrites of another lamina VI pyramidal population in this cortex give off side branches at the border of lamina V and IVC*β* and split up into their terminal dendritic tufts in lamina IVA (Fig. 15.32 B, C). According to Lund [425], these various dendritic patterns suggest that deeper pyramidal neurons may receive thalamic input within laminae IVC*α* and IVA.

3. *Direct proof that apical dendritic segments of different pyramidal cells passing through a particular layer may receive highly different numbers of synapses from the afferents concentrated in that layer.* The thalamocortical connectivity of pyramidal neurons has been the subject of a series of quantitative studies by White and collaborators [294–297, 817, 818, 820]. Hersch and White [294, 295] reported that, in layer IV of the primary somatosensory cortex of the mouse, the proportion of thalamocortical synapses received by apical dendrites belonging to various sizes of Golgi-impregnated lamina V and lamina VI pyramidal neurons ranged from 1.3% to 14.6% of all the asymmetrical synapses formed onto these dendrites. In subsequent work in the same cortex, the number of thalamocortical synapses in lamina IV on the apical dendrites belonging to deep pyramids that project from the primary somatosensory cortex to either the ventrobasal nucleus of the thalamus [296, 818], the primary motor cortex [820] or the ipsilateral striatum [297] was determined. It appeared that these three populations of pyramidal neurons have very different thalamocortical connectivity patterns. Thus only 0.3–0.9% of the total number

of apical dendritic synapses in lamina IV of corticostriatal projection neurons were made with thalamic afferents. For the cortico-cortical and corticothalamic elements examined, these values were 1–7% and 7–20%, respectively.

So far, I have dealt with tangentially oriented afferent systems establishing synaptic contacts with particular segments of the apical dendrites of pyramidal neurons. However, there is also evidence for the presence of radially oriented afferents that make repeated contacts with these processes. Thus, Scheibel and Scheibel [656] mentioned that "non-specific" cortical afferent fibres originating from the brain stem and the medial thalamus break up into a series of branches that ascend radially through the cortex, establishing sequences of axodendritic contacts with the spines of apical shafts and terminal branches of pyramidal neurons. It is also known that the axons of a certain category of cortical local circuit neurons, known as bipolar cells, typically give rise to vertically oriented branches which parallel the trajectories of clustered pyramidal apical dendrites (Fig. 15.32 G). These branches form multiple asymmetrical synapses with the spines of the apical dendrites [179, 554]. Apart from "non-specific" cortical afferents and the axons of bipolar cells, collateral branches of pyramidal cell axons may also make repeated, climbing fibre-like contacts with the apical dendrites of (other) pyramidal cells [218].

The final part of the dendritic system of typical pyramidal neurons to be considered is the set of dendritic branches emanating from the tip of the apical dendrite. These so-called apical dendritic tufts or terminal dendritic bouquets extend into lamina I, in which, together with numerous tangentially running axons, they constitute a typical plexiform zone. The axonal components observed within this zone include:

1. Fibres originating from the intralaminar and midline thalamic nuclei [49, 640].
2. Monoaminergic fibres arising from the brain stem [438].
3. Recurrent collaterals of the axons of pyramidal neurons, principally situated in laminae II and III [414, 656, 755].
4. Ascending axons from multipolar or bitufted neurons situated in deeper cortical layers. These elements, which have smooth or sparsely spinous dendrites, are known as Martinotti cells (Fig. 15.36 Q). Large elements of this type are found in laminae V and VI, but they are also present in the more superficial cortical layers [177]. Marin-Padilla [438] reported that the morphology of the axonal termination of Martinotti neurons resembles quite closely the arborization of the apical dendritic tufts of pyramidal cells and considered it likely that Martinotti cells form dual sets with pyramidal neurons of similar cortical depth. With regard to the function of the Martinotti cells, Marin-Padilla [438] suggested that these elements are inhibitory and that the inhibition takes place specifically between the axonal terminals of a given Martinotti cell and the dendritic tufts of the pyramidal neurons with which it forms a dual set.
5. Axons of so-called horizontal neurons, which are situated within lamina I itself [84]. The dendrites and axonal branches of these elements are entirely confined to lamina I and extend parallel to the surface of the cortex (Fig. 15.36 D). Some of their axonal branches may attain a considerable length. There is immunohistochemical evidence (summarized by Vogt [779]) indicating that the horizontal neurons are all GABAergic and also contain the neuropeptide cholecystokinin.

In summary, it may be stated that the apical dendritic branches of neocortical pyramidal neurons receive input from various sources. Thalamic afferents and recurrent collaterals of pyramidal cells presumably exert an excitatory influence on these dendrites, whereas the axonal endings of the Martinotti cells and the horizontal cells may well exert an inhibitory influence on them. The horizontal cells have been suggested to receive a specific input from monoaminergic fibres originating from neurons situated in the brain stem [438], but thalamic afferents may also impinge on these intrinsic lamina I elements and the monoaminergic fibres may also directly contact the pyramidal apical dendrites. However, it should be em-

phasized that so far none of the synaptic contacts suggested by light microscopy material has been verified with the aid of experimental ultrastructural techniques.

Having discussed the afferents making contact with the various parts of the receptive surface of the typical pyramidal neurons, I will now turn to the axons of these elements. It has already been mentioned that these processes all leave the cortex and pass either to other ipsilateral or contralateral cortical regions or to one or several subcortical centres. The latter may include the striatum, i.e. the nucleus caudatus and the putamen, the various "specific" and "non-specific" thalamic nuclei, the nucleus ruber, the superior colliculus or tectum mesencephali, the pontine nuclei, the medulla oblongata and the spinal cord.

Retrograde tracing studies have shown that the cell bodies of pyramidal neurons projecting to particular cortical or subcortical targets are preferentially located in particular cortical layers or sublayers (Fig. 15.33). The following summary of the laminar relationships of cortical efferent cells is based on reviews by Jones [337] and White [815], to which the reader is referred for the primary sources.

Cortico-cortical and callosally projecting fibres arise predominantly from pyramidal neurons in lamina II and III; however, in rodents and primates, significant numbers of these fibres have been found to originate from elements situated in the infragranular layers. As regards the superficial layers, it has been established that the smaller, more superficially situated pyramids tend to project to ipsilateral cortical areas situated nearby, whereas the larger, more deeply placed cells tend to project to contralateral and to more remote ipsilateral cortical areas.

Pyramidal neurons situated in lamina V have been shown to project subcortically to the intralaminar and other "aspecific" thalamic nuclei, the striatum, the red nucleus, the tectum, the medulla oblongata and the spinal cord. The smallest and most superficially situated elements in this layer project to the striatum, while the largest and most deeply situated cells project to the spinal cord. The elements projecting to the remaining subcortical sites tend to occupy an intermediate position.

The corticothalamic projections to the "specific" thalamic relay nuclei arise exclusively from large pyramids in lamina VI.

Although most cortical neuronal populations projecting to a particular cortical or subcortical target show a distinct laminar specificity, it is not uncommon to find some degree of overlap in the boundaries demarcating different populations of projection neurons. This raises the question of the extent to which projections to particular targets of cortical efferent neurons are made up by collaterals of axons projecting to other centres. In this context, it may be recalled that Cajal [84] noted in his Golgi studies of the brains of rodents that numerous subcortical centres are supplied by collaterals of corticofugal fibres. Thus, he observed that, during their descent through the internal capsule, such corticofugal fibres issued numerous collaterals to the striatum or thalamus and that pyramidal tract neurons in the brain stem gave off collateral branches to several centres, including the red nucleus, the pontine nuclei, and the dorsal column nuclei. Double-labelling experiments, i.e. experiments in which two different and distinctive retrogradely transported labels are injected into two different known terminal fields, have revealed that double-projecting neurons do occur in the neocortex. Catsman-Berrevoets and Kuypers [93] reported the presence of double-labelled cells in the motor cortex of the monkey after injecting markers into the magnocellular part of the red nucleus and spinal cord, and Rustioni and Hayes [644] found double-labelled cells in the sensory cortex of the cat after injecting markers into the dorsal column nuclei and spinal cord. However, in these and other comparable experiments, the number of double-labelled cells appeared to be very small, implying that the degree of subcortical collateralization of corticofugal fibres is limited, too [337]. The abundance of such collaterals observed by Cajal [84] might well have to do with the fact that the Golgi material studied by that author was exclusively derived from the brains of very young animals.

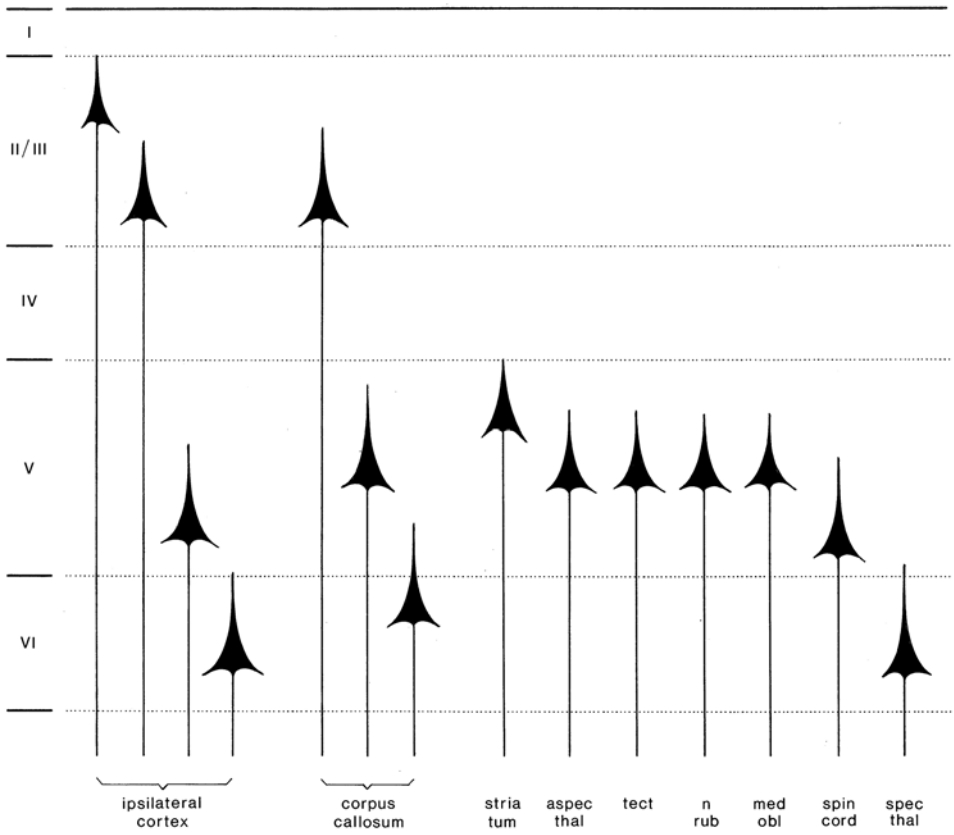


Fig. 15.33. Laminar location of the perikarya of pyramidal cells projecting to other parts of the cerebral cortex and to subcortical centres. *aspec thal*, aspecific thalamic nuclei; *tect*, tectum; *n rub*, nucleus ruber; *med obl*, medulla oblongata; *spec thal*, specific thalamic nuclei; *spin cord*, spinal cord. Based on White [815]

The axons of all typical pyramidal neurons release a number of collaterals before entering the subgriseal white matter (Fig. 15.30 A). These collaterals may ramify within close proximity in the parent cell body or may descend, ascend or travel for shorter or longer horizontal distances within the cortex. Early studies of the intracortical distribution of pyramidal cell axon collaterals were based exclusively on the study of Golgi material, but the real extent of these processes has only recently been revealed by experimental studies in which single pyramidal cells were intracellularly injected with HRP, or in which small extracellular injections of tracer substances, such as biocytin or biotinylated dextran amine (BDA), are placed in the trajectory of fibres or collaterals. Given the numerical preponderance of pyramidal neurons, there can be no doubt that the intracortical collateral branches of these neurons together constitute the largest single category of axons in the neocortex. The endings of these collateral branches, like those of the main axons, all make synapses of the asymmetrical/round vesicle variety and use the excitatory amino acids glutamate and aspartate as neurotransmitters.

The local axon collaterals of pyramidal neurons may show quite characteristic distribution patterns. Thus, Lund and Boothe [426] found that the axons of pyramidal cells situated in different layers of the primary visual cortex of the macaque monkey selectively issue short, horizontal, collateral branches in different layers (Fig. 15.32 D, E).

Apart from local collaterals, the axons of pyramidal neurons may also give rise to long, horizontally disposed branches (Figs. 15.34, 15.35). Pyramidal neurons emitting such long-range collaterals have been the subject of numerous studies, of which the following may be mentioned (for the sake of brevity, the animals studied, the cortical areas and laminae in which the parent somata were located and an indication of the length of the collaterals observed are included in the references): DeFelipe et al. ([138]: monkey sensory motor cortex, lamina III, up to 6 mm); Kisvárday et al. ([370]: cat visual cortex, lamina III, 1500 μm); Gabbott et al. ([218]: cat visual cortex, lamina V, up to 2.64 mm); Ojima et al. ([515]: cat auditory cortex, laminae II, III, 0.7–2.5 mm); McGuire et al. ([457]: macaque visual cortex, lamina III, 2 mm); Kisvárday and Eysel ([368]: visual cortex, lamina III, up to 2.8 mm); Melchitzky et al. ([459]: macaque prefrontal cortex, lamina III, 6 mm); and Rockland and Knutson ([622]: macaque primary visual cortex, lamina VI, 8 mm).

As regards the extent of the long-range collaterals, it has been observed that processes of this type do not remain within the cytoarchitectonic area in which their parent soma lies, but may project to adjacent cortical areas [138, 218].

The number of major collaterals with long horizontal trajectories issued by the main axons of pyramidal neurons varies; most of the cells examined by DeFelipe et al. [138] had one to three long collaterals, whereas the elements studied by Ojima et al. [515] issued two to five such processes.

The long-range primary collaterals are usually coarse and well myelinated.[1] They give off thin, unmyelinated, bouton-laden secondary branches that are predominantly oriented perpendicular to the cortical surface. Remarkably, these secondary branches are emitted in clusters at more or less regular intervals (Fig. 15.35). Because of the overall vertical orientation of the individual secondary branches, these clusters often have a column-like appearance. Secondary branches arising from different major collaterals of the same parent axon in different layers often converge upon the same cluster [138, 370, 515]; the same holds true for the focussed terminal branches of major collaterals of different pyramidal cells [138]. Rockland and Knutson [622] observed that the axons of Meynert cells, i.e. large pyramidal elements in the infragranular layers of the primary visual cortex, issue a number of coarse, remarkably long (up to 8.0 mm) collateral branches, which pass horizontally through the VIth layer of that cortical area. Each of

[1] Myelinated fibres fail to impregnate with the Golgi stain; this may explain why these long-range collaterals remained unnoticed in the classical Golgi studies by Cajal [84] and Lorente de Nó [414, 416].

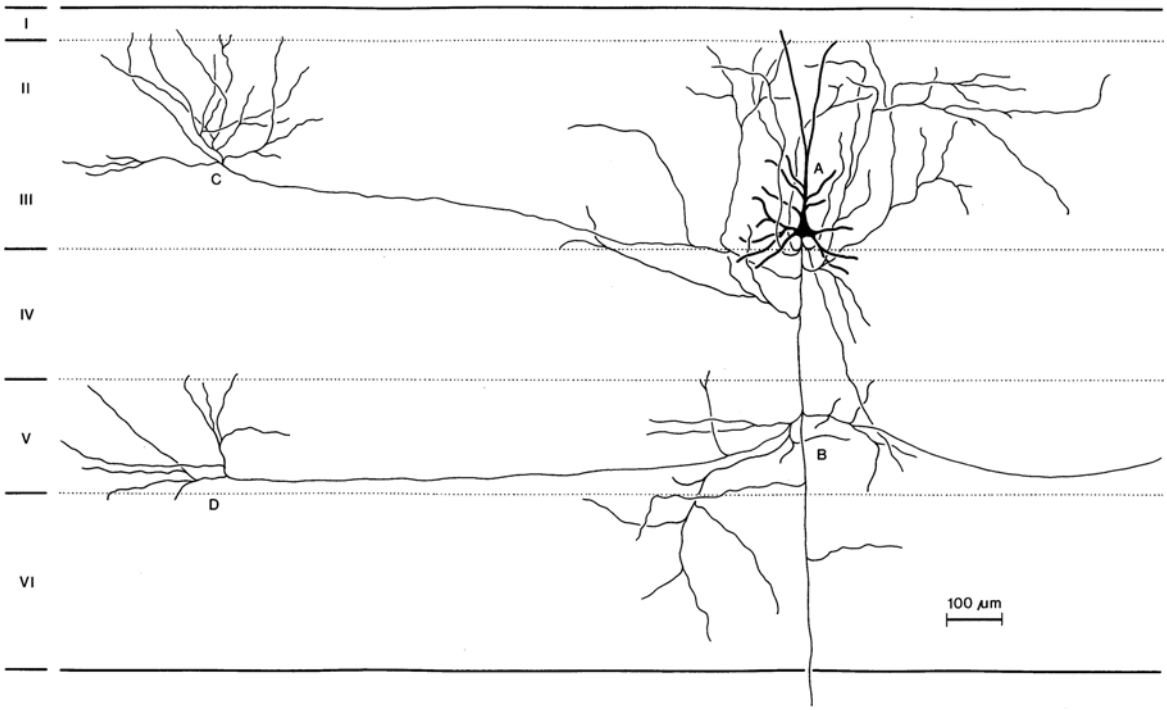


Fig. 15.34. A pyramidal neuron in layer III of the primary visual cortex of the cat. The element was intracellularly filled with horseradish peroxidase and reconstructed from 80-µm-thick serial sections. The intracortical system of collaterals forms distinct clusters, one near the cell's dendritic field in layer III (**A**), another just below the cell in layer V (**B**), and two at a distance of some 1000 µm from the soma in layers III and V (**C, D**). Modified from Kisvárday et al. [370]

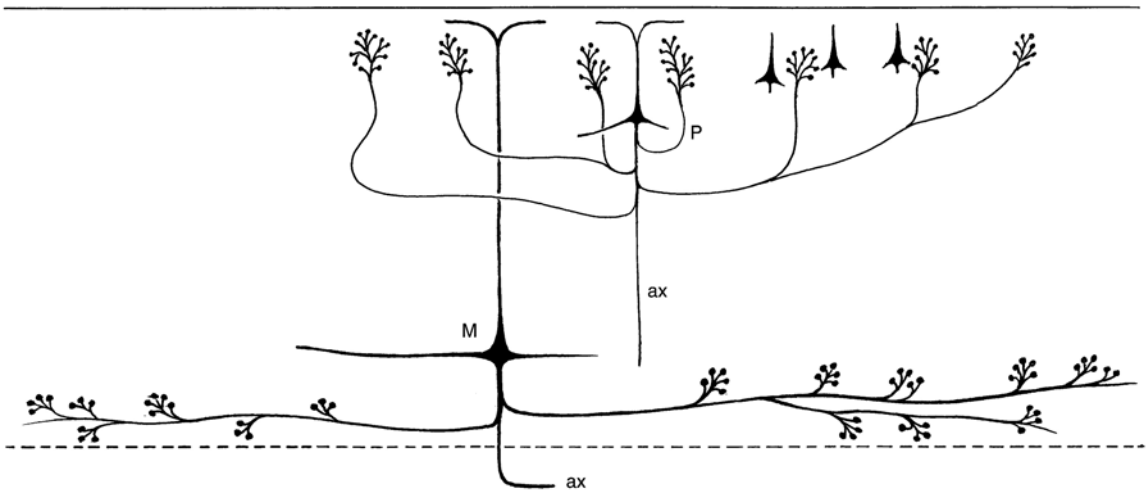


Fig. 15.35. Diagrammatic representation of a Meynert cell (*M*) and a lamina III pyramidal cell (*P*) in the primary visual cortex of the macaque monkey. The Meynert collaterals have (1) relatively small terminal clusters concentrated in lamina VI; (2) large terminal specializations; (3) a small number of terminations per cluster, and (4) a termination-free zone in the vicinity of the soma. On all of these points, these collaterals differ from those of the smaller supragranular pyramidal cells. Modified from Rockland and Knutson [622]. *ax*, axon

these collaterals forms a number of small terminal clusters, containing a small number of large terminal boutons (up to 3.0 μm), and each of these collaterals has an initial termination-free zone. All of these features appeared to be markedly different from those of horizontal intrinsic connections in the supragranular layers of the primary visual cortex (Fig. 15.35). It is noteworthy that the basal dendrites of Meynert cells show a remarkable asymmetrical spread (Fig. 15.35) [84]. It has been proposed [515] that their asymmetrical dendrites make Meynert cells sensitive to visual motion, and in particular to motion in one direction. Comparable asymmetry does not characterize the collateral axonal fields of supragranular pyramidal neurons [622]. Li et al. [409] recently investigated how Meynert cell collaterals are mapped in relation to the functional architecture of the primary visual area in macaque monkeys. They found that such collaterals may cross over several pairs of ocular dominance columns and contact both left- and right-eye ocular dominance columns. According to Li et al. [409], these findings suggest hat the system of Meynert intrinsic collaterals is involved with binocular interactions over wide sectors of the visual field. The main axons of the Meynert cells project to the middle temporal visual area (MT) and to subcortical targets including the superior colliculus [778].

In order to gain insight into the way in which pyramidal neurons participate in the intrinsic circuitry of the neocortex, the synaptic connections of axon collaterals belonging to neurons of this type have been examined with the electron microscope in several areas and in different species [128, 172, 218, 365, 370, 456, 457, 459, 816, 817, 819, 825]. The results of these studies may be summarized as follows:

1. Collaterals of pyramidal cells only form synapses of the asymmetrical/round vesicle variety and, hence, may be considered to excite their targets.
2. Practically all of the synaptic contacts made by these collaterals are on dendritic spines or dendritic shafts.
3. Different types of pyramidal neurons may show striking differences in their local output relationships. Most pyramidal cells examined appeared to synapse predominantly with other pyramidal elements. However, the collaterals of groups of corticothalamic projection neurons in the primary sensory cortex of the mouse were observed to form over 90% of their synapses with the smooth dendrites of non-pyramidal neurons [819]. Pyramidal neurons whose axon collaterals contact the dendrites of pyramidal and non-pyramidal cells in about equal numbers have also been found [456, 825].
4. The number of synapses made by the collaterals of a given pyramidal neuron with one other individual pyramidal neuron is presumably generally very limited [218, 370, 456, 457, 720, 721]. However, the collaterals of one pyramidal cell contact numerous other pyramidal cells and, conversely, one pyramidal cell receives the converging input of numerous other pyramidal cells.
5. Neurons contacted by the collaterals of pyramidal neurons have been identified as non-spiny bipolar cells [456], non-spiny multipolar cells [819] and basket cells [457], and it has also been established that some of the dendrites postsynaptic to pyramidal collaterals are immunoreactive to GABA [370]. It is known that most types of non-spiny or sparsely spiny non-pyramidal cells, including basket cells, chandelier cells and double bouquet cells, use GABA as a neurotransmitter and that these elements are the principal source of the GABAergic, symmetrical synapses that impinge upon the somata, proximal dendrites and axon initial segments of pyramidal neurons [306]. All in all, it seems reasonable to assume that the GABAergic interneurons in the neocortex receive input directly from the axon collaterals of pyramidal neurons and in turn synapse with pyramidal neurons. These circuits probably provide the morphological substrate for both feed-forward and feed-back inhibition of pyramidal neurons [306, 815].

If we survey the data concerning the typical pyramidal neurons discussed above, it appears that these elements show a quite remarkable

structural diversity. This diversity may concern their size, their laminar position, the branching pattern of their dendrites, the density of spines along their apical dendrites, their affinity to particular afferent systems, the cortical or subcortical target regions to which their main axons project, the distribution of their axonal collaterals and their patterns of intracortical synaptic output. Certain structural properties are clearly correlated. It has been demonstrated that the somata of pyramidal neurons projecting to a particular target are not only located in one and the same layer or sublayer, but also show striking similarities with regard to dendritic morphology, thalamocortical connectivity and distribution of their axon collaterals. It seems likely that all pyramidal neurons projecting to a particular target are in receipt of similar extracortical and intracortical inputs and that they participate in a similar way in the intrinsic circuitry of the cerebral cortex.

Atypical Pyramidal Cells

In the mammalian neocortex, neurons occur that lack one or several of the features characterizing typical pyramidal cells, but that are nevertheless considered to belong to the pyramidal cell group. These atypical pyramids include: (a) elements in which the apical dendrites are shortened (Fig. 15.32 B, C), reduced (Fig. 15.30 B) or absent [171, 756, 775]; (b) "star pyramids", in which the dendrites radiate out from the soma in all directions, rather than forming a basal skirt (Fig. 15.30 C); (c) sparsely spiny pyramidal cells [149, 277, 315, 836, 837]; (d) "pure" projection pyramidal neurons, whose axons do not emit any intracortical collaterals [234]; and (e) intrinsic pyramidal neurons, whose axons remain within the cortex and often ascend (Fig. 15.30 B) or form ascending and descending branches (Fig. 15.30 C) [363, 756]. However, the most remarkable modified pyramidal neurons are doubtless the so-called *spiny stellate cells* (Fig. 15.30 D–F). These elements occur exclusively in lamina IV of primary sensory areas of the neocortex, where they may be abundant [336, 422, 823]. Their small, spherical or ellipsoid somata in Nissl preparations often form one or several conspicuous granular zones, which is why laminae I–III and V–VI in the sensory cortices are often designated as the supragranular and infragranular layers. The dendrites of these spiny stellate cells are emitted at several points from their soma and are generally confined to the fourth layer or to the sublayer in which their soma is situated. They may be strongly stratified horizontally or may show a radiating or even vertically elongated distribution [423]. The spiny stellate cells are most probably the principal, but not the exclusive targets of the thalamocortical afferents terminating in lamina IV of the sensory cortical areas [208]. Ahmed et al. [4] studied the connectivity of spiny stellate cells in the visual cortex of the cat. They presented evidence suggesting that, of the asymmetrical synapses on these elements, 45% comes from lamina VI pyramidal cells, 28% from other spiny stellate cells and 6% from thalamic afferents. The source of the remaining 21% of asymmetrical synapses remained obscure. Spiny stellate cells presumably receive inhibitory afferents from neurogliaform cells, basket cells and chandelier cells [338, 424, 815].

The axon of the spiny stellate cells may ascend to more superficial layers or descend to deeper layers. Many of these elements are provided with both ascending and descending axonal branches. Short collateral branches establishing synaptic contacts within the sublayer of origin are invariably present (Fig. 15.30 D–F). The axon terminals of spiny stellate cells form asymmetrical synapses mainly with dendritic spines [446, 646, 779]. The investigations of Lund and collaborators [422–424, 426] have shown that the spiny stellate cells, present in the various sublayers of layer IV of the monkey primary visual cortex, differ markedly with respect to their projections to other layers. It seems likely that the short local collaterals of the spiny stellate cells mainly contact other spiny stellate cells [646] and that their ascending and descending axonal branches establish numerous synaptic contacts with superficial

and deep pyramidal neurons, but direct evidence for the existence of such outputs is lacking [137]. Nevertheless, it may be safely assumed that spiny stellate cells play a crucial role in the radial propagation of the activity fed by thalamocortical afferents into layer IV of primary sensory cortical areas.

Although spiny stellate cells represent typical local circuit neurons and lack an apical dendrite, they nevertheless have to be considered as modified pyramidal neurons [423, 756]. The reasons for this interpretation are as follows:

1. The dendrites of pyramidal neurons as well as those of spiny stellate cells are densely covered with spines and the axon terminals of both cell types form synapses of the asymmetrical type, mainly with dendritic spines [403, 646].
2. In lamina IV of the primary sensory areas containing spiny stellate cells, neurons provided with a more or less developed apical dendrite are frequently observed that in all other respects cannot be distinguished from typical spiny stellate neurons. The "star pyramids" in the somatosensory cortex of the squirrel monkey [336] are a good example of such an intermediate form (compare Fig. 15.30 C with F).
3. Peinado and Katz [543] have presented evidence that during ontogeny lamina IV stellate cells initially extend an apical dendrite to lamina I and only later lose this process and develop their mature stellate morphology.

Local Circuit Neurons

In the preceding sections, the neocortical pyramidal neurons have been discussed. It was pointed out that this category not only encompasses true pyramidal cells, but also atypical elements that have lost one or several of the typical pyramidal characteristics. Pyramidal neurons account for 60–85% of the total neuronal population of the neocortex [240, 556, 589, 824]. The remaining 15–40% of neocortical neurons include a variety of morphological types that have the following features in common:

1. They are evidently non-pyramidal, i.e. they have no conical soma and lack a dominant apical dendrite. On that account, the group is often referred to as non-pyramidal, but this designation is not entirely satisfactory because many neurons belonging to the pyramidal category do not show a pyramidal morphology (Fig. 15.30 C–F).
2. Their dendrites bear only few spines or are entirely spine-free. This is a very important distinguishing feature, even though the dendrites of some otherwise typical pyramidal neurons are also aspinous [315].
3. Their somata have both symmetrical and asymmetrical axosomatic synapses, whereas pyramidal cell bodies possess only symmetrical axosomatic synapses [557].
4. Their axons do not leave the cortex, which is why the cells under consideration are often referred to as local circuit neurons. However, it should be recalled that many pyramidal cells also possess exclusively intracortical axons (Fig. 15.30 B–F) and, hence, also belong to the category of cortical local circuit neurons.
5. With a single exception, their axon terminals contain flattened vesicles and form symmetrical synapses with their postsynaptic targets, both features suggesting an inhibitory function [177, 403, 539].
6. An inhibitory function is also suggested by the fact that most of the cells under consideration use GABA as their primary neurotransmitter [285, 306, 371, 558, 616].
7. A certain proportion (25–30%) of the GABAergic cortical neurons also express one or several neuropeptides. The neuropeptides detected in cortical neurons include substance P, vasoactive intestinal polypeptide (VIP), cholecystokinin (CCK), neuropeptide Y (NPY), somatotropin-release-inhibiting factor (SRIF), corticotropin-releasing factor (CRF) and tachykinin (TK) [304, 350, 440]. Several subpopulations of GABAergic cortical neurons appeared to be definable on the basis of their immunoreactivity for certain neuropeptides. To give a few examples: in the visual cortex of the rat a subpopulation of bipolar cells can be labelled with antibod-

ies to VIP [559], whereas in the neocortex of the monkey, subpopulations of chandelier cells and of double bouquet cells have been shown to be immunoreactive for CRF [406] and TK [140], respectively. Another subpopulation of double bouquet cells has been shown to be immunoreactive for SRIF [133].

8. It has been shown that differential immunoreactivity for the calcium-binding proteins parvalbumin (PV), calbindin (CB) and calretinin (CR) can be used as a selective marker for different subpopulations of neocortical local circuit neurons [105, 134, 174]. In the primate neocortex, among the most characteristic types of neurons immunoreactive for PV are chandelier cells and large basket cells, whereas for CB they are double bouquet cells, and for CR, double bouquet and bipolar cells [134].

In brief, the mammalian neocortex contains a large population of non-pyramidal, inhibitory interneurons with smooth or sparsely spinous dendrites. These elements use GABA as their primary neurotransmitter and some also produce one or several neuropeptides. The population of neocortical neurons thus outlined is morphologically heterogeneous, and numerous authors, including Lorente de Nó [416], Jones [336], Feldman and Peters [179], Peters and Jones [561], Fairén et al. [177], Lund [424], Lund and Yoshioka [428], Lund and Lewis [427], Lund et al. [430] and DeFelipe [136] have attempted to subdivide this population of neurons into different groups or types, using the size and shape of the somata, the shape of the dendritic field and the number, distribution, length and branching patterns of individual dendrites, the preferred direction of axons and axonal branches and configuration of axonal terminals as criteria. The following discussing of the non-pyramidal, smooth or sparsely spinous local circuit neurons in the mammalian neocortex is based on the publications cited above, on the excellent characterizations of particular cell types [338, 343, 554, 555, 563, 695], published in the first volume of the *Cerebral Cortex* [560], and on other sources to be quoted below. As has already been indicated, many of the morphological types of neocortical interneurons can be subdivided into two or more biochemically definable subgroups. The synaptic relationships of the various types of neocortical interneurons to be discussed are semidiagrammatically indicated in Fig. 15.37 B.

Stellate neurons are found in all cortical layers (Fig. 15.36 A, C, D) [416]. The dendrites of these elements radiate from the soma in all directions and branch infrequently. Their axonal arborization forms a local plexus occupying approximately the same territory as that covered by the dendrites. Distinctive axonal terminals are lacking [563] (Fig. 15.36 B). Because of the limited spread of their axonal system, the stellate cells are also referred to as local plexus neurons.

Neurogliaform or spiderweb cells form a special class of stellate cells (Fig. 14.36 B). These elements have a small, spherical soma and short sinuous dendrites. Their axons arborize profusely around the soma, forming a dense feltwork. Characteristically, small empty spaces appear in this feltwork, representing the positions occupied by the unstained somata of other neurons [338]. Neurogliaform or spiderweb cells have been observed in all layers of the cortex, but they are particularly concentrated in the primate somatosensory and primary visual cortex. The function of the spiderweb cells is unknown. Jones [338] considered it likely that the elements concentrated in lamina IV of sensory cortices receive thalamic afferents and synapse mainly with the spiny stellate cells of that layer. Kisvárday et al. [371] observed synaptic contacts between the axons of neurogliaform cells and the distal dendrites of pyramidal cells.

There are numerous neurons in the neocortex which, judging from the disposition of their dendritic tree, would fall in the category of stellate cells, but which are distinguished from the elements in that category by the course and/or mode of termination of their axons. The chandelier cells and basket cells, which have already been discussed in a previous section, represent two distinct types of such specialized stellate cells.

Chandelier cells have been thus named because their profuse axonal plexuses give rise to

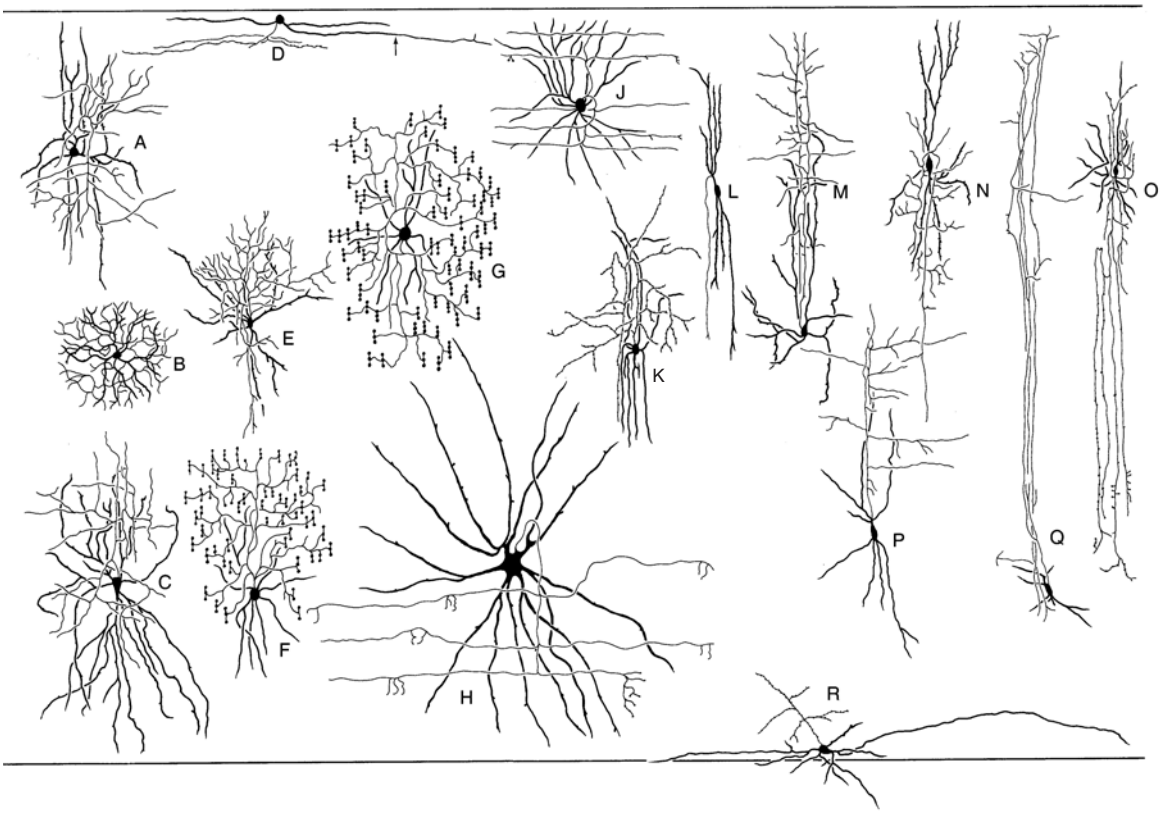


Fig. 15.36. Local circuit neurons with smooth or sparsely spiny dendrites in the neocortex. *A*, Multipolar neuron with axonal arcades in lamina III of the somatosensory cortex of the squirrel monkey (Jones [336]); *B*, neurogliaform or spiderweb cell from layer IV of the somatosensory cortex of the squirrel monkey (Jones [338]); *C*, stellate neuron with sparsely spiny dendrites extending from lamina IVC to lamina VI in the primary visual cortex of the macaque (Lund [422]); *D*, horizontal cell in lamina I of the neocortex of the hedgehog (Valverde and Facal-Valverde [757]); *E*, stellate cell from lamina IV in rat visual cortex (Peters and Saint Marie [563]); *F, G*, chandelier cells in laminae III and V of the neocortex of the macaque (Jones [340]); *H, J*, basket cells in laminae II and V of the neocortex of the macaque (Jones [340]); *K*, neuron with local, beaded axon in lamina IV of the prefrontal cortex of the macaque (Lund and Lewis [427]); *L*, bipolar or vertical cascade neuron in lamina III of the prefrontal cortex of the macaque (Lund and Lewis [427]); *M*, neuron with rising axon in lamina IV of the prefrontal cortex of the macaque (Lund and Lewis [427]); *N*, neuron with axon connecting laminae II and III in the prefrontal cortex of the macaque (Lund and Lewis [427]); *O*, double bouquet cell in lamina II of the primary visual cortex of the macaque (Werner et al. [810]; *P*, neuron with rising axon in upper zone of lamina V of the primary auditory cortex of the cat (Fairén et al. [177]); *Q*, Martinotti cell in lamina V of the visual cortex of the cat (Wahle [801]); *R*, horizontally oriented neuron in lamina VI of the prefrontal cortex of the macaque (Lund and Lewis [427])

a large number (up to 300) of highly characteristics, vertically oriented "candles", each consisting of a preterminal axonal branch that forms a short row of terminal boutons. These vertical arrays, which are designated as axon terminal cartridges, synapse with the axon initial segments of pyramidal cells (Figs. 15.31B, 15.36F, G) [177, 555]. The axon initial segments of spiny stellate cells may also receive synapses from chandelier cells [424].

Chandelier cells occur in layers II–V, but are most common in layer II. Because the pyramidal neurons projecting to the ipsilateral and contralateral neocortex are mainly situated in layers II and III and because the axon initial segments of these supragranular pyramids receive a much richer synaptic supply from the chandelier cells than the infragranular elements, it has been suggested that chandelier cells principally influence cortico-cortical circuitry [570, 698]. Chandelier cells typically express one or both of the calcium-binding proteins PV and CB [134].

It is noteworthy that the axon initial segments of pyramidal neurons are not exclusively contacted by chandelier cells. Gonchar et al. [250] detected in the visual cortex of rat and monkey a population of somatostatin-expressing, GABAergic neurons, whose axons innervate somata, dendritic spines and initial segments of pyramidal neurons. It is also noteworthy that, according to DeFelipe [135], loss of chandelier cells may represent a key component in the aetiology of epilepsy.

Basket cells are among the largest non-pyramidal cells in the neocortex (Figs. 15.31A, 15.36H, J). Their poorly ramifying dendrites radiate in all directions, but vertically oriented dendrites prevail in some and give these cells a bitufted appearance. The axons of the basket cells are either ascending or descending and give rise to four or more horizontal branches at various levels. These collateral branches are myelinated and may reach a length of 1 mm or more. At intervals, they issue short ascending or descending terminal branches that contribute to the formation of pericellular baskets around pyramidal cell bodies. Each terminal branch forms a series of synapses with its target soma. One basket cell contributes to numerous baskets, and terminal axonal branches of several basket cells contribute to a single, pericellular plexus. The somata of basket cells are concentrated in laminae II and V.

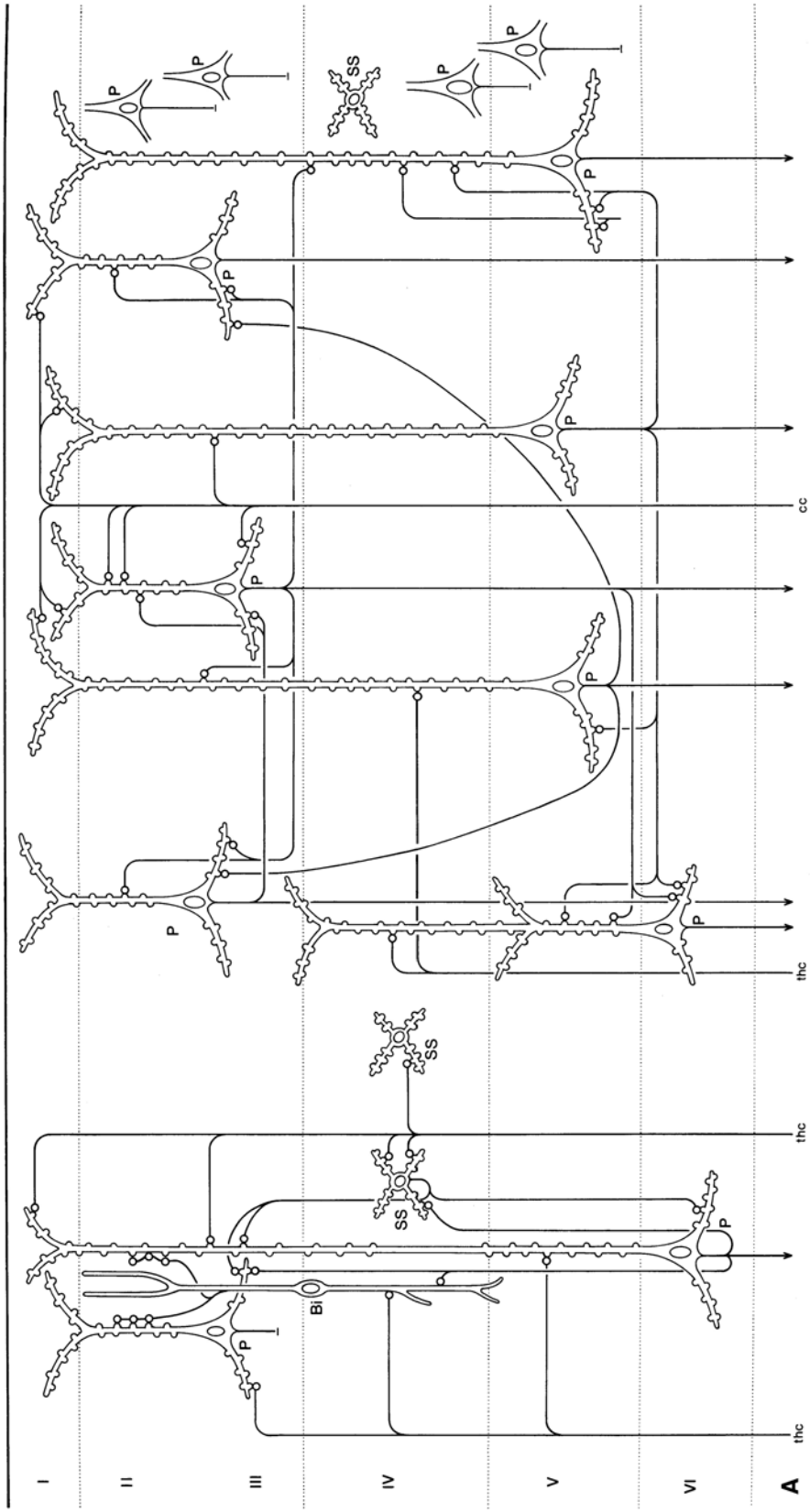
These cells – with their radiating short dendrites and their long horizontal axonal branches – form a distinct group of cortical local circuit neurons, which have been designated as *large basket cells* [177]. Cells of this type have so far only been observed in the cat and monkey [343]. They can express PV, CB, NPY, CCK and occasionally CR and SRIF. They never express VIP [440].

In the neocortex of different mammals, both "higher" and "lower" small, smooth or sparsely spinous intrinsic neurons have been observed, whose axons consistently produce multiple synaptic contacts on the somata of pyramidal cells. Fairén et al. [177] named these elements *small basket cells*. According to their observations, these small basket cells are multipolar elements with rather wide dendritic fields, sometimes showing a predominant dendritic tuft oriented towards the pial surface. The axon is primarily descending and typically produces frequently ramifying and "curvy" collateral branches. They differ from other basket cells in that they express VIP [440].

A third class of basket cells is formed by the so-called *nest basket cells*. These elements, which were only recently shown to represent a distinct class of soma-targeting cell, occupy an intermediate position between large and small basket cells [805]. Their primary axonal branches are long and ramify sparsely, much like those of the large basket cells, but their clusters of secondary axonal branches more closely resemble those of the small basket cells. The nest basket cells do not typically express CR and never express VIP [440].

Approximately 50% of all inhibitory neocortical interneurons are basket cells [440].

The classical descriptions of basket cells presented by Cajal [84] created the impression that these elements synapse exclusively with the somata and proximal dendrites of pyramidal neurons. However, in several later studies [207, 369, 697, 700], evidence was presented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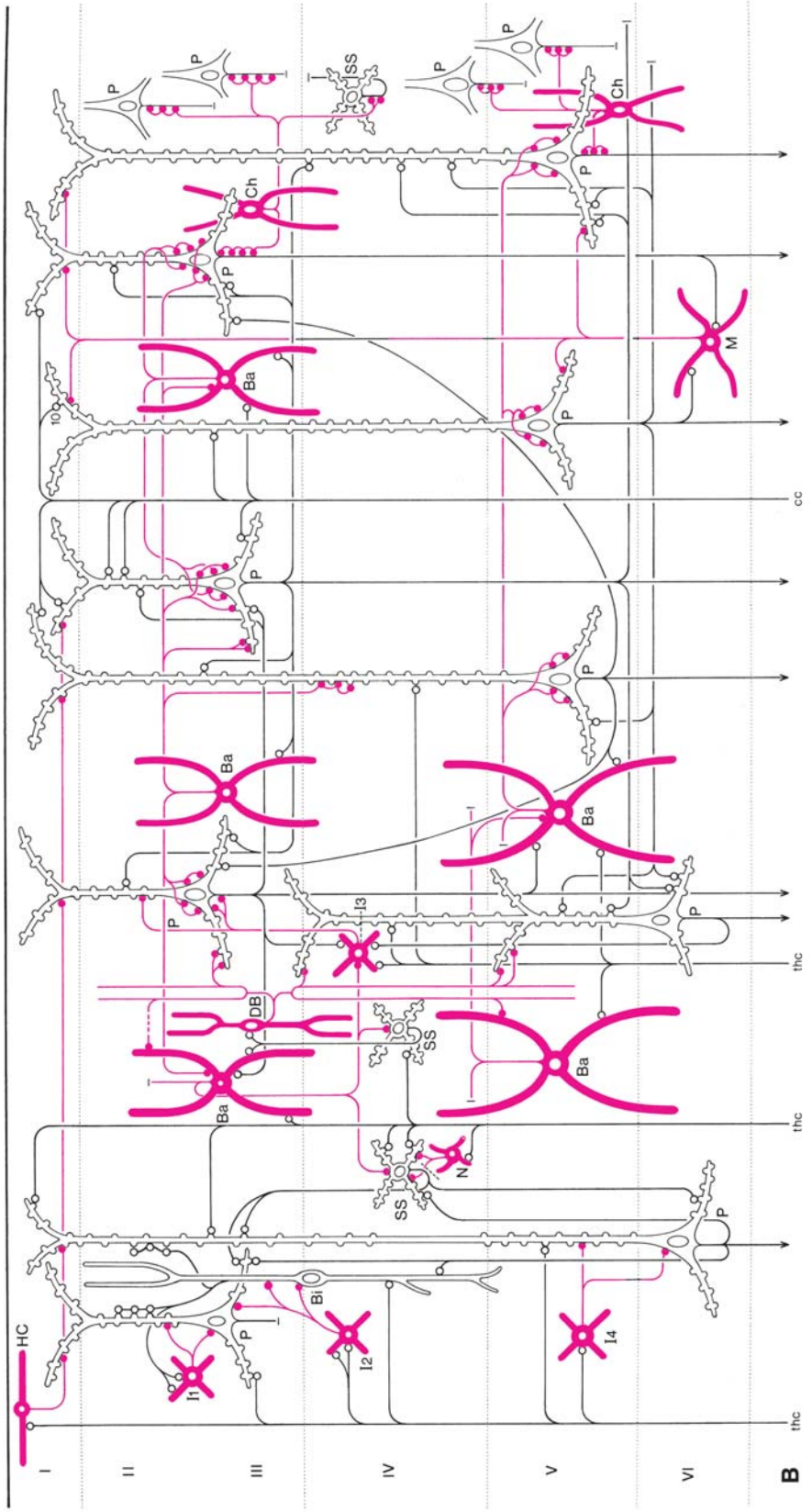


Fig. 15.37. Neocortical circuits showing excitatory elements in **A** and excitatory plus inhibitory elements in **B**. *Ba*, basket cells; *Bi*, bipolar cell; *Ch*, chandelier cell; *cc*, cortico-cortical fibre; *DB*, double bouquet cell; *HC*, horizontal cell of Cajal; *I1*, *I2*, etc., different types of interneurons mentioned in the text; *M*, Martinotti cell; *N*, neurogliaform or spiderweb cell; *P*, pyramidal neurons; *SS*, spiny stellate cells; *thc*, thalamocortical fibres; *I*, *II*, etc., cortical layers. Excitatory neurons and their synaptic terminals are shown by open profiles in *black*; inhibitory neurons and their terminals by filled profiles in *red*. Modified from Nieuwenhuys [509]

suggesting that axon terminals of basket cells also synapse with the somata of spiny stellate cells, the distal dendrites and axons of pyramidal cells and the somata and dendrites of non-pyramidal neurons. Kisvárday et al. [372], using biocytin as a label and taking advantage of the fact that large basket cells are GABAergic and contain PV, demonstrated that in the visual cortex (area 18) of the cat these cells not only synapse with pyramidal neurons, but also establish an average of four to six perisomatic contacts onto other large basket cells. A large basket cell in lamina II was found to synapse with the somata of 58 other large basket cells, whereas a large lamina V basket cell appeared to contact 33 of its fellow cells. From these observations, Kisvárday et al. [372] concluded that large basket cells form an interconnected network in area 18 of the visual cortex. Assuming that the GABAergic large basket cells are inhibitory, they proposed that: (a) a large basket cell provided direct perisomatic inhibition onto a number of pyramidal cells (at least 200–300) and in the range of about 50 other basket cells, (b) the target cells of the directly inhibited basket cells become facilitated via a disinhibitory effect and (c) the number of neurons disinhibited through this process may well greatly exceed the number of elements that are directly inhibited by the large basket cells.

Vertically Oriented Neurons. If we consult the extensive inventories of neocortical neurons provided by Cajal [84], Lorente de Nó [414], Jones [336], Feldman and Peters [179], Fairén et al. [177], Lund [422, 424], Lund and Yoshioka [428], Lund and Lewis [427], Lund et al. [429, 430], DeFelipe [136] and others, it appears that numerous smooth or sparsely spinous local circuit neurons in this structure show an overall vertical orientation. This orientation may concern their dendritic trees (Fig. 15.36 K), their axonal systems (Fig. 15.36 M–Q) or both (Fig. 15.36 L). Among the neurons with vertically oriented axons, elements with rising axons (Fig. 15.36 M, P, Q), descending axons (Fig. 15.36 L, N) and both descending and rising axons (Fig. 15.36 O) may be distinguished. A discussion of all of the types of vertically oriented cortical interneurons described in the literature is not possible here. However, some, i.e. the bipolar cells, the bitufted cells, the double bouquet cells and the elements with ascending axons known as Martinotti cells, may be briefly commented upon.

Bipolar cells have a small, spindle-shaped, vertically oriented cell body, from which one primary ascending and one primary descending dendrite arises (Fig. 15.32 G (b)) [554]. These two processes and their ramifications, which bear few or no spines, extend for long distances through the depth of the cortex, producing a narrow and very elongated dendritic tree. The axons of the bipolar cells usually arise from one of the primary dendrites and form a plexus that is also narrow in spread and vertical in orientation [554]. Bipolar cells occur in layers II–VI and typically express VIP and CR [440].

Ultrastructural investigations have shown that there are two different populations of bipolar neurons, one forming symmetrical synapses and the other forming asymmetrical synapses [106, 177, 559, 562]. The bipolar cells with axons forming symmetrical synapses release principally GABA, but also express VIP [440, 458, 571]. The axons of these inhibitory elements preferentially synapse with dendritic shafts.

A certain proportion of the neocortical bipolar neurons that form symmetrical synapses can be labelled with antibodies to ChAT, a specific marker for cholinergic neurons. The axon terminals of these cholinergic bipolar cells most commonly synapse with small- to medium-sized dendritic shafts and less frequently with apical dendrites and with the somata of neurons [307, 540].

The bipolar cells that form asymmetrical synapses are excitatory by releasing only VIP [440]. The axons of these elements give rise to vertically oriented branches which parallel the trajectories of clustered apical dendrites of pyramidal neurons, forming multiple synapses with spines on these processes (Fig. 15.32 G) [562]. However, axonal branches of the excitatory bipolar cells have also been observed to contact the shafts of apical dendrites and the somata and dendrites of non-pyramidal cells.

Bitufted cells have dendrites arising mainly from the upper and lower poles of the soma, forming, as the name implies, two dendritic tufts [557]. The dendrites diverge initially, but at some distance from the soma often assume a radial orientation. Many neurons of this type have local axonal plexuses which partly overlap with the field occupied by their dendritic trees [557]. From these local axonal plexuses, radially oriented branches may extend into the adjoining cortical layers. Bitufted cells are dendritic-targeting cells that occur in layers II–VI [702]. They can express NPY, SRIF, VIP, CCK, CB and CR, but not PV [440].

Among the bitufted cells, elements are found whose axons produce tight, radially oriented long plexuses of thin, parallel axonal branches. These plexuses are generally designated as "bundles" or "horse-tails". Smooth or sparsely spinous cortical neurons provided with these highly characteristic long, fascicular axonal systems have been commonly referred to as double bouquet cells [177, 554, 561, 695]. Cajal [84] used the name *cellules à double bouquet dendritiques* to refer to a number of cell types with highly different axonal ramification patterns, including elements with the long radially oriented arrays of axonal branches discussed above. However, it has become customary to designate only smooth or sparsely spinous cells showing this particular axonal pattern as double bouquet cells. In the current literature, even elements with these long vertical axonal branches whose dendritic trees are not of a bitufted appearance are still referred to by this name (Fig. 15.36 O) [336, 695].

Typical double bouquet cells have only been observed in laminae II and III of the neocortex of cats and primates [33, 695]. It has been shown that double bouquet cells form symmetrical synapses containing flat or pleiomorphic vesicles with their target structures and use GABA as their principal neurotransmitter [139, 695]. It was formerly believed that the vertically oriented axons of double bouquet cells mainly synapse with the apical dendrites of pyramidal neurons [84, 103, 721]. However, the studies by Somogyi and Cowey [694] and by DeFelipe et al. [139, 140, 146] showed that the axon terminals of these cells do not form synapses with apical dendrites, but rather with basal dendrites and with oblique branches of the apical dendrites of pyramidal neurons and with postsynaptic structures belonging to non-pyramidal neurons. Double bouquet cells express CB [139, 146] and can also express VIP or CCK [440].

Martinotti cells are multipolar or bitufted neurons with smooth or sparsely spinous dendrites. Their distinguishing feature is a long ascending axon which reaches layer I, where it forms a terminal arborization. The axon emerges either from the upper surface of the soma or from an ascending dendrite. The initial part of the axon gives rise to a number of descending collaterals, which form a local terminal plexus [84, 177, 442, 643, 754]. "Classical" Martinotti cells have a single ascending axon, but Jones et al. [351] and Wahle [801] described "double bouquet type" Martinotti cells whose axon branched into a bundle of two to eight long, ascending collaterals (Fig. 15.36 Q).

Martinotti cells occur in all cortical layers except layer I, but they have been most frequently found in layers V and VI. They use GABA as a neurotransmitter [696] and may additionally contain a neuropeptide, e.g. TK [351] or somatostatin [801]. Little is known with certainty about the afferent and efferent connections of the Martinotti cells. On the basis of a Golgi study of the visual cortex of the mouse, Ruiz-Marcos and Valverde [643] suggested that Martinotti cells situated in layer V of the cortex receive terminals from both superficial and deep pyramidal cells, that their local axonal plexuses contact deep pyramidal cells and that their terminal plexuses in layer I impinge upon the apical dendritic tufts of pyramidal cells. It has been observed that the axons of certain Martinotti cells, after having reached lamina I, give rise to long, horizontal collaterals [414]. According to Szentágothai [721], these branches may run for several millimetres through lamina I, making synapses with the apical dendrites of numerous pyramidal cells.

Horizontal Cells. Local circuit neurons showing an overall horizontal orientation are almost

exclusively found in layers I and VI. It is important to note that these layers, although far apart in the adult cortex, are both derivatives of a single embryonic pallial zone, i.e. the primordial plexiform layer. During the formation of the cortex, immature bipolar cells migrate peripherally and together form a compact cortical plate, which splits up the primordial plexiform layer into a superficial and deep zone. The former becomes layer I, and the latter gives rise to the deep zone of layer VI in the mature cortex. The intervening layers are all derivatives of the cortical plate (Fig. 2.10 H–K) [437].

Horizontal Cells of Cajal. Bipolar neurons occurring in layer I of the cortex are known as the *horizontal cells of Cajal.* These elements are provided with one or a few long, smooth dendrites that pursue a course parallel to the cortical surface. Their axons, which pass horizontally like the dendrites, may attain a considerable length (Fig. 15.36 D). Curiously enough, horizontal cells in layer I may have more than one axon [84, 757]. The elements under discussion are GABAergic and additionally contain the neuropeptide CCK [779]. The axons of the horizontal cells probably enter into synaptic contacts with the apical dendritic branches of pyramidal neurons [416, 757]. Several authors [84, 167, 438, 537, 757] have expressed the opinion that the conspicuous Cajal-Retzius cells found in layer I of the immature cortex undergo morphological changes and transform to horizontal cells.

Horizontal Cells in Layer VI. The *deep zone of layer VI* contains numerous medium-sized horizontal cells (Fig. 15.36 R) [427, 497, 498]. One or a few long dendrites arise from the ends of their fusiform cell bodies, but some shorter dendrites may also arise from the upper and lower surface of the soma. Their axons, which like the principal dendrites often pursue a horizontal course, give off varicose side branches. In Golgi material, the axons of the horizontal cells under discussion can rarely be traced to their final destination, and very little is known about the afferent and efferent connections of these elements. The fact that the horizontal cells in layer VI most probably synthesize GABA [760] and that their cell bodies have both symmetrical and asymmetrical axosomatic synapses [556] indicates that they represent inhibitory local circuit neurons.

Remaining Inhibitory Interneurons. There are many other smooth or sparsely spinous, inhibitory neurons in the neocortex that are difficult to classify or that have not yet been recognized as belonging to a particular morphological type [136]. In Fig. 15.37 B some of these elements, designated provisionally as I1–I4, are included.

Element I1, which is situated in layer II, receives excitatory afferents from bipolar cells, whereas its axon forms symmetrical, presumably inhibitory synapses with the apical dendrites and the somata of superficial pyramidal neurons [562].

Element I2, which is situated in layer IV, is contacted by thalamic afferents and its axonal endings impinge upon the somata of superficial pyramidal neurons, as well as on the somata and proximal dendrites of bipolar cells [562].

Element I3 is a local plexus neuron situated in the upper part of layer IV. It receives afferents from thalamocortical fibres, from axon collaterals of superficial and deep pyramidal neurons, and from basket cells. Its ascending axon forms synaptic contacts with the apical dendritic shafts, somata, and axon initial segments of superficial pyramidal neurons [815].

Element I4, finally, is a local plexus neuron situated in the upper part of layer V. It receives terminals from thalamocortical fibres, and its axonal endings establish synaptic contacts with the somata and apical dendritic shafts of deep pyramidal neurons [815].

It is noteworthy that defects in the neurotransmission of GABAergic neocortical interneurons may well play a role in the pathophysiology of schizophrenia. A detailed discussion of the voluminous literature on this subject is beyond the scope of the present work (see [46] for a review). However, the results of two recent studies, those of Lewis et al. [407] and of Konopaske [384], may be briefly mentioned.

Lewis et al. [407] found that a deficiency in signalling by brain-derived neurotropic factor

through its receptor, the tyrosine kinase Trk (tropomyosin-related kinase) B, leads to reduced GABA synthesis in the PV-containing subpopulation of inhibitory GABAergic neurons in the dorsolateral prefrontal cortex of individuals with schizophrenia. They indicate that the resulting alteration in perisomatic inhibition of pyramidal neurons contributes to a diminished capacity for the synchronized neuronal activity that is required for working memory function.

Konopaske et al. [384] presented evidence suggesting that in schizophrenia the neurotransmission in another type of neocortical interneuron, the chandelier cell, might also be compromised. As has been discussed, the axon terminals of these GABAergic elements form linear arrays, termed cartridges, that synapse on the axon initial segments of pyramidal neurons (Fig. 15.31 B). These cartridges are immunoreactive for the GABA membrane transporter-1, which regulates the duration and efficiency of GABAergic neurotransmission. Konopaske et al. [384] reported that the density of GABA membrane transporter-1-immunoreactive cartridges is reduced in schizophrenia, particularly, but not exclusively, in the prefrontal cortex.

Microcircuitry of the Neocortex

Introduction

The data concerning the synaptic connections of neocortical neurons and principal neocortical afferents, discussed in the previous section, were employed to compose two summary diagrams of the microcircuitry of the neocortex (Fig. 15.37 A, B). Moreover, the principal results of some recent studies on the connectivity of a certain type of interneuron have been summarized in an additional diagram (Fig. 15.38). (The symbols used in the text – Ba, Bi etc. – correspond to those in the figures and are explained in the legend of Fig. 15.37.) Before commenting on these diagrams, a few cautionary remarks should be made.

1. The assembled data are derived from many different species and from many different cortical areas; hence, it can not be expected a priori that the diagrams present a reliable picture of *the* microcircuitry of *the* mammalian cortex. However, it is worthy of note that the extensive ontogenetic and cytoarchitectonic studies of Brodmann [70] have shown that all neocortical areas in all of the many species he investigated represent variations on a common basic plan, which he designated as "der sechsschichtige tektogenetische Grundtypus". Rockel et al. [620] counted the number of neuronal cell bodies in a narrow strip (30 µm) through the depth of the neocortex in several functional areas (motor, somatosensory, primary visual, frontal, parietal and temporal) and in many species (mouse, rat, cat, monkey and human). With the exception of the primary visual cortex in primates the same absolute number (about 110) of neurons was found in all areas and in all species. In the primate primary visual cortex there appeared to be approximately 2.5 times more neurons. According to Rockel et al. [620] these findings suggest that the intrinsic structure of the neocortex is basically uniform and that differences in cytoarchitecture and function reflect differences in extrinsic connections. On the basis of a study of a vast array of Golgi material, Szentágothai [721] concluded that the various neocortical cell types show only little variation from mouse to human. Moreover, the ratio of different cell types has been shown to be essentially the same in the motor and visual cortices of rats and cats [824]. It may be concluded that the neocortex of different mammalian species is built according to a common basic plan, and that, hence, the structural features assembled in Fig. 15.37 A, B may well present an image of that plan. However, the reservation should be made that the spiny stellate cells depicted (SS) occur only in specialized primary sensory cortices and that excitatory bipolar cells (Bi) have been demonstrated so far only in the primary visual cortex of the rat [559, 562] and cat [177].

2. If our diagram presents an image of the microcircuitry of the neocortex, it does so

merely in a qualitative sense. The total number of neocortical synapses in the neocortex has been estimated to be 3×10^{14} [104]. Our diagram contains 157 synapses. Because excitatory (grossly: pyramidal) neurons are by far more numerous than inhibitory (grossly: non-pyramidal) neurons and because the intracortical axon terminal- and collateral systems of most of the former are vastly more extensive than those of the latter, the excitatory synapses may be expected to outnumber the inhibitory synapses. The validity of these estimates has been confirmed by the quantitative synaptological studies of DeFelipe et al. [142]. These authors found that in neocortical areas as different as the hindlimb area of the rat somatosensory cortex and the human anterolateral temporal cortex, symmetrical synapses formed 10.7% and 11.5% of the total synapse population, respectively. However, in our diagram there are 76 excitatory and 82 inhibitory synapses. More specifically, about 10% of the excitatory synapses (7 out of 76) is formed by terminals of cortico-cortical fibres. Because cortico-cortical projections constitute by far the largest neocortical input system, this percentage is most probably much higher.

3. Several functionally important structural features have been neglected. For example, it is known that different thalamic nuclei project to different sets of neocortical (sub)layers and that the same holds true for particular cell types within some thalamic nuclei, for instance the lateral geniculate nucleus. In our diagrams no distinction has been made between these various projections. Rather, they are taken together as if representing one single thalamocortical system.

Networks of Pyramidal Neurons

The pyramidal neurons (P) are doubtless the principal neurons in the neocortex (Fig. 15.37 A). They are not only by far the most numerous cellular elements in that structure, but also constitute its sole output system and its largest input system. Separate sets of deep pyramidal neurons project to different subcortical targets, whereas cortico-cortical fibres arise mainly from superficial pyramidal neurons.

The very extensive axon collateral systems of pyramidal neurons primarily contact other pyramidal neurons. There is evidence suggesting that superficial pyramidal neurons contact other superficial and deep pyramidal neurons and that deep pyramidal neurons impinge on other deep and superficial pyramidal neurons. It is known that, in the primary visual cortex, the axon collateral systems of pyramidal neurons constitute reciprocal patchy networks, which can be traced over distances of up to 7 mm [368]. It has been suggested that these networks link sites with similar physiological characteristics, such as orientation preference. This would imply that, within the primary visual cortex, different interwoven networks of pyramidal axon collaterals are present and that the extent of these networks would be confined to that cortical area.

Another remarkable local network of interconnected pyramidal neurons is found in the prefrontal cortex. The prefrontal cortex (PFC) has been identified as the key neocortical region supporting working memory [244]. Extracellular recordings during delayed response tasks have shown that a considerable fraction of prefrontal cortical neurons remain active after the cue (e.g. a particular sensory stimulus or event) and until the task is completed. Such activity, which can persist for several seconds, has been proposed as the neural correlate of working memory [804]. It has been recently established [806] that the PFC of the ferret contains a network of heavily interconnected cells with characteristic dual apical dendrites and a particularly wide and dense system of basal dendrites. These "hyper-reciprocally" connected cells appeared to have synaptic and functional properties essential for supporting persistent activity in the PFC.

A continuous network of excitatory elements potentially involving the entire neocortex and even extending into the hippocampal region is constituted by the ipsilaterally and contralaterally projecting cortico-cortical pyramidal neurons. The continuity of this network is emphasized by the fact that the cortico-cortical fibres terminate throughout the neocortex mainly in

the superficial layers, where the cortically projecting pyramidal neurons are concentrated. The presence of this strongly developed, ubiquitous network warrants the conclusion that the neocortex communicates first and foremost with itself. However, the fact that the cortico-cortical fibres most probably impinge not only on superficial pyramidal neurons, but also on the apical dendrites and terminal dendritic bouquets of deep pyramidal neurons indicates that the various subcortical centres to which these elements project are continuously kept informed about the successive transformation of data occurring along the cortico-cortical processing streams. This applies in particular to the caudate-putamen complex and to the pontine nuclei, centres which are known to receive projections from almost the entire neocortex.

Thalamocortical fibres (thc) synapse directly with pyramidal neurons, although the number of contacts made by such fibres with particular types of pyramidal neurons is subject to considerable variation [815].

Interneuronal Systems

All types of neocortical local circuit neurons have been reported to establish synaptic contacts with pyramidal neurons. Most of these elements, namely spiny stellate cells (SS), bipolar cells (Bi), neurogliaform cells (N), basket cells (Ba), horizontal cells of Cajal (HC) and cells of the provisional types I3 and I4, have been suggested to receive a direct input from the thalamus, and some of these (SS, Bi, Ba, I3) are also contacted by axon collaterals of pyramidal neurons. Martinotti cells (M) are primarily intercalated between different pyramidal neurons. The nature of the input to one type of local circuit neuron, the chandelier cell (Ch), is entirely unknown.

Several types of neocortical interneurons are in receipt of afferent contacts from other interneurons and/or establish efferent contacts with such elements. Prominent among them are the spiny stellate cells and the basket cells. Spiny stellate cells are contacted by basket cells and most probably by neurogliaform cells, chandelier cells and other spiny stellate cells and probably impinge on basket cells and double bouquet cells (DB). Basket cells receive afferents from other basket cells and probably from spiny stellate cells and double bouquet cells and make efferent contacts with spiny stellate cells and probably with smooth stellate elements (e.g. I3).

Excitatory local circuit neurons, i.e. spiny stellate cells and some bipolar cells, are, as far as it is known, confined to primary sensory areas. Inhibitory local circuit neurons are of many different types and occur throughout the neocortex. Some types of local circuit neurons are lamina-specific, i.e. their somata are situated mainly in one or in two adjacent layers (SS, DB, HC, M).

In the highly differentiated primary visual cortex of the rhesus monkey, thalamocortical fibres carrying particular kinds of visual information terminate in sharply defined sublayers of lamina IV (Fig. 15.26) [189, 190, 425]. The detailed Golgi studies carried out by Lund and her associates [424, 428, 430] showed that each of these thalamic recipient sublayers, and some other layers as well, contain several types of local circuit neurons. The dendritic trees of all of these elements are strictly confined to the layer or zone in which their soma is situated. Their axons project to more superficial layers, to deeper layers or to both. These interlaminar projections are highly specific, targeting from one to four laminar divisions, depending on the type of neuron. The strictly radial orientation of all of these projections is presumably connected with the preservation of the detailed topographical map existing within one of the thalamic recipient sublayers. Some of these types of local circuit neurons may well be involved in the selective processing and transfer of one particular type of visual information.

Important clues to the specific functional roles of the various types of inhibitory interneurons derive from their differential axonal arborizations (Fig. 15.36) and from the location of their synaptic connections with pyramidal neurons [25]. Most of these inhibitory cell types distribute their synaptic contacts preferentially to selected membrane domains of pyramidal elements [440, 702, 815]. Thus,

chandelier cells (Ch) terminate on the axon initial segments of pyramidal neurons, whereas basket cells (Ba) target the somata and proximal dendrites of these elements (Fig. 15.31). The contacts of the chandelier and basket cells are optimally localized for controlling the output and oscillatory synchronization of groups of pyramidal neurons [206]. Small stellate cells such as those belonging to the provisional types I1, I2 and I4 may also participate in these specific functions. Neurogliaform cells (N) preferentially innervate the proximal and mid-range dendritic domains. (This feature of the neurogliaform cells is not shown in Fig. 15.37 B.) The neurogliaform neurons are optimally positioned to influence dendritic processing and integration of synaptic inputs [440]. Finally, the preferential innervation of distal dendritic branches and apical tuft regions of pyramidal neurons by double bouquet cells (DB), horizontal cells of Cajal (HC) and Martinotti cells (M), allows these elements to affect local dendritic integration.

Double bouquet cells are abundant in the primate neocortex [146]. It has been frequently observed that the dendritic spines postsynaptic to the double bouquet cells receive, in addition, an asymmetrical synapse from a putative excitatory terminal [137]. In the human neocortex at least 47% of the spines postsynaptic to double bouquet cells were found to be in receipt of such a dual innervation [146].

Dendritic spines are the principal targets of the thalamocortical and cortico-cortical afferents and of the local axonal arborizations of pyramidal and spiny stellate cells, which are known to form asymmetrical, excitatory synapses [128, 137, 815]. However, because the majority of dendritic spines of pyramidal neurons are outside layer IV, i.e. the principal area of termination of thalamocortical afferents and spiny stellate cell axons, it may be assumed that the main source of asymmetrical (excitatory) synapses on spines with dual innervation is from intracortical axons (local and cortico-cortical). Hence, it is reasonable to assume that double bouquet cells control the level of excitation in circuits linking pyramidal neurons with other pyramidal neurons [146].

During the last decade, important new findings concerning the connectivity and the regulation of the activity of neocortical inhibitory interneurons have been reported. Thus, it has been shown that (1) groups of inhibitory interneurons are coupled through gap junctions, (2) the axons of certain types of interneurons form autapses at their own soma or dendrites, and (3) certain types of interneurons are specifically or preferentially contacted by particular extrathalamic neuromodulatory systems. These phenomena, and their (putative) functional significance, will now be briefly discussed (Fig. 15.38).

1. *Electrical coupling of neocortical inhibitory interneurons.* Gap junctions or electrical synapses are specialized loci where channels bridge the plasma membranes of two adjacent nerve cells. By providing a low-resistance reciprocal pathway for ions and small organic molecules, such electrical connections permit the direct transmission of electrical signals between neurons [107, 223, 693]. Gap junctions have been observed between smooth neurons in electronmicroscopic studies of the primate neocortex [688, 689]. Electrophysiological studies on slices of rat neocortex established the existence of a network of electrically coupled inhibitory interneurons [222]. These interneurons, which were functionally characterized as fast-spiking cells, could be identified as PV-expressing basket cells [729]. Fukuda et al. [214] found that large PV-containing cells in layer II/III of the cat visual cortex form about 60 gap junctions with other cells. Most, though not all of these junctions were between proximal dendrite sites. Further studies revealed that other types of neocortical inhibitory interneurons, designated as low-threshold-spiking [235], multipolar bursting [54] and late-spiking cells [99] also form type-specific, electrically coupled networks. The same holds true for neurogliaform cells [683]. However, the network formed by the latter cells appeared to be not strictly type-specific. In slices of rat somatosensory cortex, gap junctions connected approximately 50% of neurogliaform cells, but 20% of these elements also formed gap junctions with other interneurons, including fast-spiking basket cells, regular-spiking non-pyramidal cells

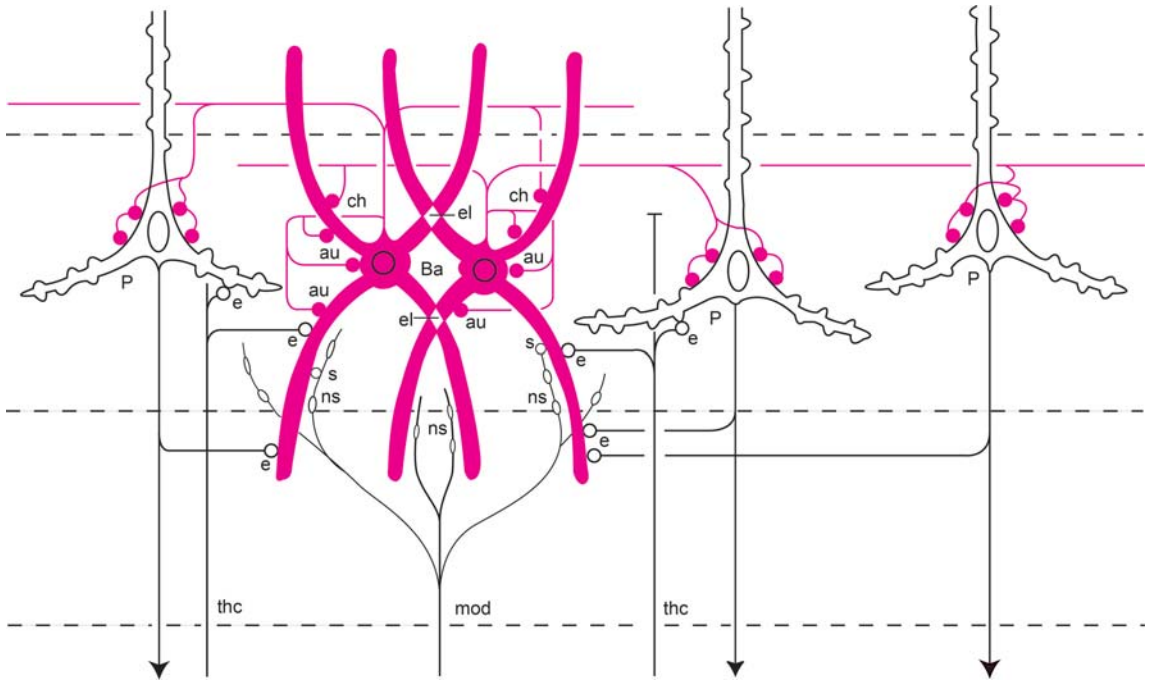


Fig. 15.38. Neocortical micronetwork. This micronetwork includes some specific afferent fibres from the thalamus (*thc*), a fibre representing a neuromodulatory system (*mod*), originating from an extrathalamic subcortical centre, a number of pyramidal neurons (*P*) and, finally, a set of GABAergic, inhibitory interneurons, represented by two basket cells (*Ba*). The thalamocortical fibres form excitatory synapses (*e*) with pyramidal and basket cells. The axons of the basket cells make inhibitory contacts with the somata of the pyramidal cells. When the basket cells are triggered by their thalamocortical afferents, they will exert a strong feed-forward inhibition on the pyramidal cells. The axons of the pyramidal neurons leave the cortex. These processes are provided with collateral branches, which establish excitatory synaptic contacts with other, related pyramidal neurons (not shown) and with the inhibitory interneurons (i.e. the basket cells) from which they receive input. The pyramidal axon collaterals and the basket cells form pathways for feed-back inhibition. The neuromodulatory system selectively addresses the set of inhibitory interneurons (Ba) with which they make some synaptic (*s*) and numerous non-synaptic (*ns*) contacts. This system may exert an excitatory or an inhibitory influence, depending on the neurotransmitter used by its afferent fibres and/or by the receptors expressed by their target neurons. The interneurons are interconnected by excitatory, reciprocal electrical synapses (*el*) as well as by inhibitory chemical synapses (*ch*). Moreover, the axons of the interneurons (Ba) emit collateral branches that form numerous autaptic contacts (*au*) with their own soma and proximal dendrites

and bitufted cells. It is not known whether the networks of inhibitory interneurons extend indefinitely across the neocortex or whether they have distinct boundaries [107].

The cerebral cortex displays synchronized, rhythmic activity, and a variety of oscillations accompany states of sensory perception, motor performance, arousal and sleep [45, 82]. The diverse networks of inhibitory interneurons most probably operate as precision clockworks for the entrainment of the various types of cortical oscillations.

2. *Autaptic innervation of neocortical inhibitory interneurons.* Autapses are transmitter release sites made by the axon of a neuron on its own soma or dendrites. Tamás et al. [728] studied the synaptic relations of various types of neurons in the visual cortex of the cat during intracellular biocytin labelling and correlated light and electron microscopy. They found that the axons of two types of inhibitory interneurons, namely basket cells and dendrite-targeting cells form significant numbers (10–20) of synaptic contacts with their own somatodendritic surfaces. These autapses appeared to be domain-specific, i.e. those formed by basket cells concentrated on the perisomatic region, whereas those formed by dendrite-targeting cells were located on more distal dendrites. Bacci et al. [23] recorded autaptic activity in neocortical fast-spiking GABAergic interneurons. It appeared that in these neurons the autaptic activity has significant inhibitory effects on repetitive firing and increased the current threshold for evoking action potentials.

As noted above, during cortical oscillations, fast-spiking elements (as well as other types of inhibitory neurons) probably synchronize the activity of groups of pyramidal neurons [45, 82]. It is believed that inhibitory autaptic transmission enables fast-spiking cells "to sense their own firing and regulate it in phase with that of other fast-spiking cells, resulting in synchronous inhibitory neurotransmission onto pyramidal neurons" [25].

3. *Several extrathalamic neurotransmitter systems ascend to the neocortex, where they specifically or preferentially target particular types of inhibitory interneurons.* In a previous section of the present chapter, it was shown that several neurotransmitter systems, including those containing acetylcholine, serotonin, dopamine and noradrenaline, ascend to the neocortex, and that interneurons are a major target of these systems. It was also demonstrated that, although a certain proportion of the terminals of these systems make classical synapses, many others are not associated with a specialized postsynaptic structure. The neurotransmitter molecules released by these non-synaptic terminals diffuse over some distance through the extracellular space to act on extrasynaptic receptors. This mode of intercellular communication – known as volume transmission – enables the various extrathalamic neurotransmitter systems to exert a simultaneous modulatory influence on large numbers of interneurons.

Xiang et al. [835] studied the influence of acetylcholine on the excitability of two types of inhibitory interneurons in layer V of the rat visual cortex, namely fast-spiking cells and low-threshold spike cells. They found that acetylcholine elicits hyperpolarization in fast-spiking cells through activation of muscarine receptors, resulting in disinhibition of their pyramidal cell targets. The low-threshold spike cells, on the other hand, appeared to be excited by acetylcholine through the activation of nicotine receptors. Bacci et al. [25] cited evidence suggesting that the dopaminergic, noradrenergic and serotoninergic systems exert similar selective and differential modulations on particular subgroups of inhibitory interneurons, thus providing a substrate for fine control of information flow through cortical networks.

Yoshimura and Callaway [841, 842] recently provided some further examples of "fine-scale specificity" in the organization of cortical networks. Studying the mutual functional relationships between pyramidal neurons and those between pyramidal neuron and fast-spiking interneurons in layer II/III of the rat visual cortex, they found that (1) layer II/III pyramidal neurons only share common input from layer IV and from within layer II/III in the minority of cases in which they are directly interconnected to each other; (2) fast-spiking inhibitory interneurons connect preferentially to

neighbouring pyramidal cells that provide them (via their axon collaterals) with recurrent excitation; and (3) these pairs of reciprocally connected fast-spiking interneurons and pyramidal cells share common specific excitatory input. Yoshimura and Callaway [841] considered it likely that these sets of reciprocally connected neurons contribute to the synchronization of activity within particular neuronal subpopulations.

Each neocortical area contains at least several types of pyramidal neurons. In a previous section of this chapter, it was shown that these types of pyramidal neurons may differ from each other with regard to (1) the laminar position of their perikarya; (2) the laminar spread of their dendritic branches (Fig. 15.32); (3) the laminar density of their dendritic spines, and, hence, their laminar afference (Fig. 15.32); (4) the destination of their axons (Fig. 15.33); and (5) the spread and extent of their cortical axon collaterals (Figs. 15.34, 15.35). These data indicate that the various types of pyramidal cells are differently embedded in the microcircuitry of the neocortex. Given the fact that pyramidal neurons of the same type are strongly and reciprocally connected by axon collaterals [806, 841], it may be concluded that each particular neocortical area contains a number of networks of interconnected, type-specific pyramidal neurons. The number of pyramidal networks present within a given neocortical area is unknown and the same holds true for the actual extent of these networks.

In light of the recent literature reviewed above, it seems likely that the various pyramidal elements belonging to a particular network are in receipt of afferents from cohorts of inhibitory interneurons, each cohort contacting a specific domain of the receptive surface of the pyramidal neurons involved. The inhibitory interneurons forming these cohorts are all of the same type and are generally reciprocally connected by inhibitory chemical synapses and by excitatory electrical synapses [729].

Thalamic inputs selectively contact and strongly excite the interneurons belonging to particular cohorts, while others receive weaker or no thalamic inputs [235].

Finally, each of the various cohorts of inhibitory interneurons impinging on a particular pyramidal network is specifically addressed by one or more of the extrathalamic modulatory systems. The influence exerted by these systems depends on the nature of the neurotransmitter used by their afferent fibres and on the receptor types expressed by their target neurons.

It is important to note that not only the inhibitory input, but also the excitatory input to pyramidal neurons belonging to the same network may be specific. Yoshimura et al. [842] studied the connections to pyramidal neurons in layer II/III of the visual cortex of the rat. They found that reciprocally connected pyramidal neurons share common excitatory input from layer IV and within layer II/III. However, adjacent layer II/III neurons that were not connected to each other appeared to share very little (if any) common excitatory input from layers IV and II/III.

The question arises as to how strict the separation is between the various pyramidal networks, including their satellite cohorts of inhibitory interneurons? The answer to this question is largely unknown. However, it seems likely that the abundant double bouquet cells with their vertically oriented axonal systems contact pyramidal neurons belonging to different networks, and we have seen that the neurogliaform cells form gap junctions with several other types of inhibitory interneurons.

Neocortical Columns and Modules

Introduction

During the last 50 years, physiological and morphological evidence has accumulated indicating that several parts of the neocortex of many different mammalian species are composed of radially oriented, column-like units or modules. The concept that column-like modules represent fundamental units of the mammalian neocortex has gained wide acceptance in the literature. In the following, a survey will

be presented of the findings and considerations that led to this concept. This survey will be followed by a brief critical and cautionary commentary.

The Investigations of Lorente de Nó: Elementary Units and Glomérulos

The first to propose a modular structure of the neocortex was Lorente de Nó [416]. He claimed that, in small radially oriented cylinders having a specific thalamocortical fibre as their axis, all elements of the cortex are represented and that in these *elementary units* the whole process of transmission of impulses from the afferent fibre to the efferent axon may theoretically be accomplished. Lorente de Nó's concept was based on the observations that (a) the terminal branches of thalamocortical fibres may form discrete cylindrical patches in lamina IV of the cortex, (b) the efferent system of the cortex is formed by radially oriented axons of pyramidal neurons and (c) the axons of many cortical local circuit neurons are likewise radially oriented.

The results of earlier investigations of Lorente de Nó have played an additional role in the development of the ideas concerning columnar organization of the neocortex. In 1922 Lorente de Nó [414] described discrete cylindroid aggregations of cells in lamina IV of what he believed to be the auditory cortex of the mouse, which he termed *"glomérulos"* (Fig. 15.39 A). Golgi material revealed that the specific thalamic afferents to this cortex constitute dense patches of terminal ramifications which coincide with the glomérulos (Fig. 15.39 B) and that the dendrites of the neurons in lamina IV are largely confined to the glomérulo in which their soma is located (Fig. 15.39 C). The glomérulos appeared to contain numerous spinous stellate cells. The axons of these local circuit neurons were found to descend to the deeper cortical layers, where they issue numerous collaterals. Some of these collaterals were observed to ascend to lamina III.

Some 50 years later, it became clear that Lorente de Nó [414] had actually analysed the portion of the somatosensory cortex to which the large mystacial vibrissae on the snout project via relays in the main trigeminal nucleus and in the thalamus. It appeared that each "glomérulo" or *"barrel"*, as they came to be called, is the primary cortical representation of one vibrissal follicle. The vibrissae are arranged in a stereotypical grid-like pattern in which each vibrissa has a unique position. Within the somatosensory cortex, each barrel also occupies a unique position and the topographical arrangement of these structures closely corresponds to that of the vibrissae. The largest barrels in mice are elliptical in cross-section, with a greatest diameter of 300 μm (Woolsey and van der Loos [834]; van der Loos and Woolsey [759]). According to van der Loos [758], barrels are the visible lamina IV counterparts of cortical columns.

Staiger et al. [704] recently studied the spiny neurons in layer IV of the somatosensory cortex of the rat. It appeared that this layer, in addition to numerous spiny stellate cells (58%), also contains star pyramidal cells (25%) as well as pyramidal elements (18%). As regards the spread of the axonal ramifications of these cell types, the authors reported that the axonal arbors of the spiny stellate cells are largely confined to their related columns, that the pyramids show extensive transcolumnar axonal branches and that the star pyramids occupy an intermediate position (Fig. 15.39 D). It is noteworthy that the columns denoted by the authors have no structural boundaries above and below layer IV.

The Columnar Organization of the Somatosensory Cortex

Mountcastle [494–496] analysed the functional organization of the somatosensory cortex in the cat, using microelectrodes to record the activity of single cells. During radial penetration, he encountered cells with similar receptive fields throughout the depth of the cortex that responded to stimulation of the same type of cutaneous receptors located at a particular site. Penetrations parallel to the pial surface and

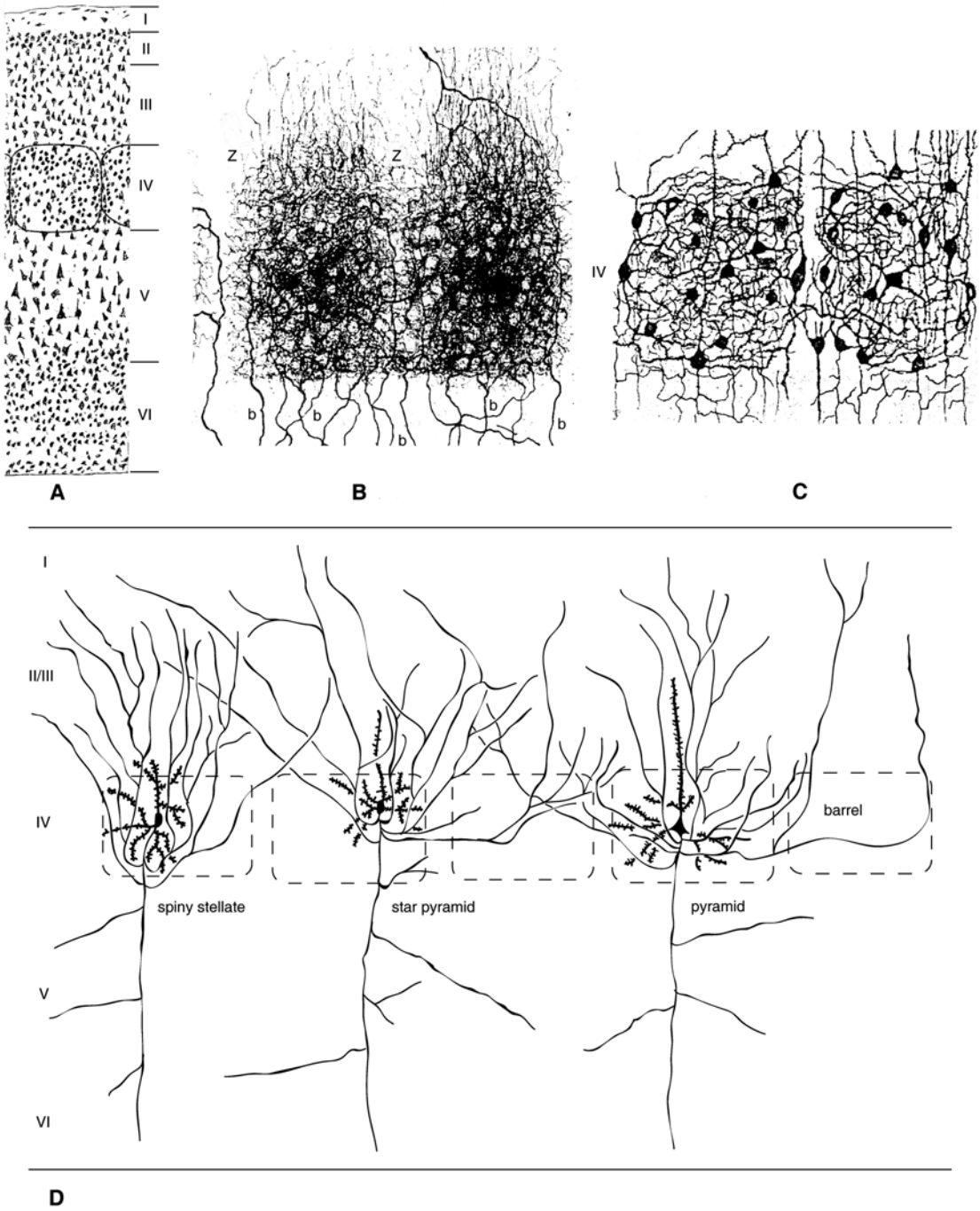


Fig. 15.39 A–D. The somatosensory cortex of rodents. **A** Cytoarchitecture; the fourth layer contains specialized structures consisting of a cylinder of densely packed cells surrounding a region of lower cell density. These structures were designated as glomérulos by Lorente de Nó [414] and as barrels by Woolsey and van der Loos [834]. **B** Specific somatosensory efferents (*b*) from the thalamus form patches of a dense terminal feltwork, which correspond to the glomérulos. These patches are separated by zones (*Z*), in which the axonal feltwork is clearly less dense. The fibres of the feltwork surround the neuronal somata in the fourth cortical layer. **C** Two glomérulos as observed in Golgi preparations. **D** The glomérulos or barrels contain three different types of spiny neurons: spiny stellates, star pyramids and pyramids. These cell types differ with regard to the spread of their axonal arbors. **A**, **B** and **C** are reproduced from Lorente de Nó [414]; **D** is based on Staiger et al. [704]

crossing the radial axis of the cortex appeared to pass through blocks of tissue 300–500 μm in size, and neurons with identical properties were encountered in each of them. Sharp transitions were observed from a block with one set of properties to the adjacent block with different properties. These findings led Mountcastle ([494], p. 430) to hypothesize that "there is an elementary unit of organization in the somatic cortex made up of a vertical group of cells extending through all the cellular layers." He termed this unit a *"column"*. On the basis of experiments in which multiple, closely spaced penetrations were made, Mountcastle concluded that the individual columns have a width of maximally 500 μm. He believed that functionally active columns are able to isolate themselves from their surroundings by exerting an inhibitory action on neurons in their inactive neighbours, a process which he designated as "pericolumnar inhibition".

The Columnar Organization of the Visual Cortex

The detailed physiological and morphological studies performed by Hubel and Wiesel and collaborators [308, 310–314, 404, 412] on the primary visual cortex of the monkey have led to the identification of three different kinds of column-like structure in that area: orientation columns, ocular dominance columns and blobs. Sets of these three column-like structures are conjectured to be united in larger entities, termed hypercolumns.

The *orientation columns* were detected by electrophysiological recordings. During radial penetrations with microelectrodes, cells having identical axes of orientation (i.e. cells that responded strongest to a bar of light in one particular orientation) were encountered throughout the thickness of the cortex. During tangential penetrations, the electrode encountered a shift in the axis of orientation of the light bar of about 10° every 300–100 μm. The morphological substrate of the functional columns thus detected could be visualized with the aid of the 2-deoxyglucose technique of mapping relative changes in metabolic activity following peripheral stimulation.

Microelectrode recordings also revealed the presence of parallel stripes, about 500 μm wide, alternately receiving their input from the ipsilateral and the contralateral eye. The morphological correlate of these *ocular dominance columns* could be strikingly visualized using silver impregnation techniques and autoradiographically by means of transneural transport of radiolabelled amino acids injected into one eye.

In the monkey striate cortex, staining for the mitochondrial enzyme cytochrome oxidase revealed an array of densely staining, peg-like structures in laminae II and III, which can be seen lying in register with less densely staining formations in the cortical layers below lamina IV. These *blobs,* as they were termed, are ellipsoid in tangential sections, measuring roughly 150×200 μm. Their most conspicuous superficial (i.e. supragranular) parts receive a separate projection from the intercalated layers of the lateral geniculate body (Fig. 15.26). Physiological studies have shown that the cells within the blobs respond selectively to the colour of a stimulus, without regard to its orientation.

A *hypercolumn* is considered to represent the circuitry necessary for the analysis of a given, discrete region in the visual field. It is conceived to contain a set of nine orientation columns, together encompassing a complete cycle of orientation through 180°, an adjoining pair of right and left ocular dominance columns and several blobs.

In a previous section, it has been mentioned that the axons of many neocortical pyramidal neurons give rise to long, horizontally running collaterals, which issue clusters of terminal branches at regular intervals (Fig. 15.35). Interestingly, experimental studies using different techniques, i.e. retrograde tracing, 2-deoxyglucose autoradiography and cross-correlation analysis, have produced evidence suggesting that, in the primary visual cortex, these horizontal collaterals mediate communication between functionally related columns, e.g. blobs of similar colour opponency and columns of similar orientation preference (for a review, see Gilbert [237]).

The Auditory Cortex

Evidence of a columnar organization of the primary auditory cortex has also been presented. During microelectrode penetrations normal to the cortical surface, cells with the same characteristic frequency were encountered throughout the entire depth of the cortex [1]. Binaural interaction bands have also been described, exhibiting either binaural summation or inhibition. Experiments in which single-unit mapping was combined with autoradiographic tract tracing revealed that, in the primary auditory cortex of the cat, clusters of summation responses coincide with bands receiving a heavy innervation from the contralateral primary auditory cortex, whereas suppression responses were recorded in regions of sparse contralateral innervation [75].

The Motor Cortex

Within the motor area of the neocortex, there are small loci where stimulation with weak currents produces movements executed by a single muscle. It has been demonstrated that the loci for producing contraction of a given muscle extend perpendicularly from the surface to the depth of the cortex. These radial arrays of stimulation points have been called *cortical motor columns*. The diameter of these columns is approximately 1 mm in cross-section [16]. Using two penetrating microelectrodes, one for stimulation and the other for recording, it was demonstrated that stimulation of a given column produces a pericolumnar zone of inhibition [18]. Whereas the afferent input arriving at the somatosensory columns is modality specific, the cortical motor columns receive polymodal input from sensors in the target muscle itself, from the joint to which the muscle inserts and from the skin overlaying the muscle, i.e. sensors that are stimulated when the target muscle contracts [17].

Columnar Patterns Shown by the Cells of Origin and the Terminal Ramifications of Cortico-cortical Connections

Anatomical evidence for the existence of vertical columns or bands in the cerebral cortex has been provided by studies on the origin and termination of cortico-cortical connections. Thus, Jones et al. [347], using an anterograde tracer, demonstrated that both commissural and ipsilateral cortico-cortical fibres arising and terminating in the somatic sensory cortex of monkeys terminate in distinct vertically oriented columns with a variable width of 500–800 μm. Each of these columns appeared to be separated from its neighbours by a gap of approximately 500 μm. Each column was considered to represent the terminals of a bundle of cortico-cortical axons emanating from cells at the centre of each of the loci in which the tracer was injected. Using a retrograde tracer, Jones et al. [347] also demonstrated that the cells of origin of the cortico-cortical projections investigated, found predominantly in lamina III, are also aggregated in vertically oriented clusters (Fig. 15.40). Goldman and Nauta [242] injected an anterograde tracer into three cytoarchitectonically distinct regions (areas 4, 9 and 12) of the frontal lobe of rhesus monkeys. Neurons in these various regions are known to project both contralaterally and ipsilaterally to cytoarchitectonically diverse areas within the frontal, temporal and parietal lobes. They found that all of these cortico-cortical projections terminate in vertically oriented columns, 300–700 μm wide, which alternate in regular sequence with zones of comparable width that are free of such terminals. Interestingly, the pattern and dimensions of cortical columns in the prefrontal cortex, defined by cortical afferent inputs, appeared to be strikingly similar in the rat, squirrel monkey and rhesus monkey, although the brains of these animals differ considerably in size [76, 325]. In order to determine the pattern of termination of two converging cortico-cortical systems in the same animal, Goldman-Rakic and Schwartz [246] followed a double anterograde labelling strategy. Using rhesus monkeys, they im-

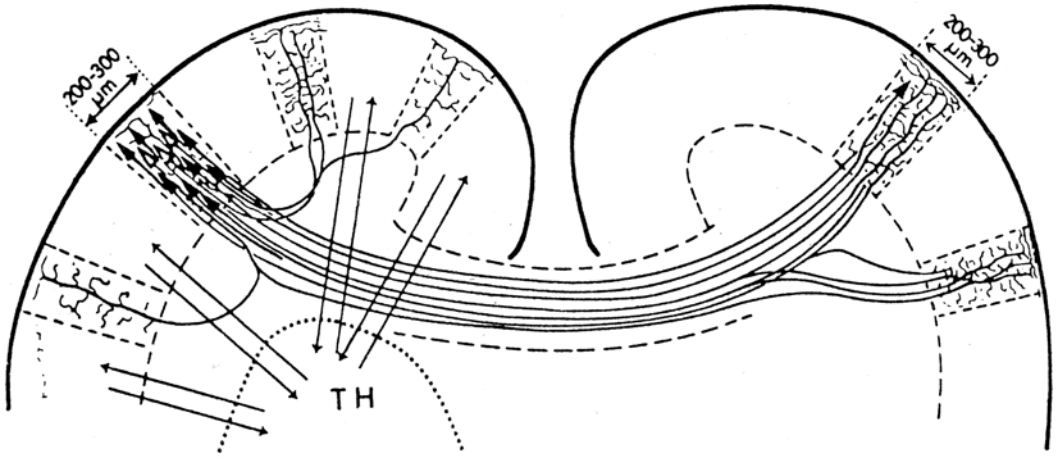


Fig. 15.40. The general arrangement of cortico-cortical fibres, shown diagrammatically in a lisencephalic brain. The fibres interconnect radial columns with a diameter of 200–300 μm. Ipsilateral connections originate mainly from pyramidal neurons in layer III (cells shown at *left* in *outlines*), while commissural connections (shown in *solid black*) derive from layers III, V and VI. Reproduced from Szentágothai [721]. *TH*, thalamus

planted HRP pellets in area 7 of the parietal lobe in one hemisphere and injected a mixture of tritiated amino acids in area 9 of the frontal lobe of the other hemisphere. It appeared that, in the prefrontal cortex, contralateral callosal fibre columns interdigitate with ipsilateral associational fibre columns. Goldman-Rakic and Schwartz [246] also investigated the spatial organization of the populations of cells in the prefrontal cortex projecting to the parietal associational cortex and to the contralateral prefrontal cortex using HRP or fluorescent dyes as retrograde tracers. They demonstrated that these two populations are inversely related in their relative densities over portions of the prefrontal cortex examined. Moreover, in the HRP material, the high-density patches of retrogradely labelled neurons appeared to coincide with the afferent fibre columns revealed by anterograde transport. In a later study (Selemon and Goldman-Rakic [669]), terminal labelling originating from prefrontal and parietal injections in the same hemisphere was investigated in a large number of areas of convergence in both the ipsilateral and the contralateral hemisphere. In most of the target areas, prefrontal and parietal terminal fields formed an array of interdigitating columns, but in some other areas prefrontal and parietal projections converged on the same column or cluster of adjacent columns but terminated within different laminae. For instance, in the depths of the superior temporal sulcus, prefrontal terminals occupied laminae I, III and V, with parietal terminals filling complementary laminae IV and VI.

From the experiments of Goldman-Rakic and Schwartz [246] and Selemon and Goldman-Rakic [669], it appears that projections from two different (heterotopic) cortical regions (in the same or opposite hemispheres) remain segregated within common cortical targets, either by terminating in separate alternating columns or by concentrating in complementary laminae within the same column. The relationship between the termination zones of projections from paired *homotopic* areas was studied by McGuire et al. [457] in the cerebral cortex of the rhesus monkey. Injections with HRP and tritiated amino acids were made in two topographically matched regions of the frontal lobe in each hemisphere. The cortical projections from both of these homotopic pairs of areas appeared to converge in common columnar territories.

Minicolumns and the Radial Unit Hypothesis of Cortical Development

In 1979, Mountcastle [495] introduced what he believed to be "the basic modular unit of the neocortex" under the name *minicolumn*. He characterized this unit as a narrow chain of neurons extending radially across the cellular layers II–VI. Referring to the ontogenetic studies of Rakic (see below), he indicated that the minicolumn is produced by the iterative division of a small cluster of progenitor cells, and that the resultant neuroblasts migrate to their destination in the cortex along radial glial cells. According to Mountcastle, a minicolumn occupies a radial cylinder of cortical space with a diameter of about 30 μm. On the basis of cell counts in the neocortex of various mammals, carried out by Rockel et al. [619], Mountcastle estimated that each minicolumn contains about 110 neurons, except for the striate cortex where the number is about 2.5 times larger. He posited that minicolumns contain all the major cortical neural cell phenotypes, interconnected in the vertical dimension [496]. According to Mountcastle, the cortical columns, which he sometimes also designated as *macrocolumns* [495], are to be considered as aggregations of several hundred minicolumns bound together by short-range horizontal connections [496].

The studies of Rakic [606–610], on the ontogeny of the neocortex in the rhesus monkey, which strongly influenced the development of Mountcastle's minicolumn concept, may be summarized as follows: The matrix zone of the embryonic pallium is divided by glial septa into columns of precursor or stem cells termed "proliferative units". The postmitotic cells produced by these proliferative units find their way to the primordial cortex by following the

shafts of elongated, radially oriented glial cells, which stretch across the embryonic pallial wall. Eventually, all postmitotic cells generated in a single proliferative unit form a morphologically identifiable stack of neurons in the cortex. These entities, which may be designated as "ontogenetic" or "embryonic" columns, form, according to Rakic, the fundamental building blocks in the developing neocortex [608]. Each proliferative unit is supposed to produce multiple neuronal phenotypes. Rakic [608] advanced the idea that the proliferative units in the matrix zone of the embryonic pallium constitute a proto-map of prospective cytoarchitectonic areas. Each of these areas is composed of a large number of ontogenetic columns, which become the basic processing units in the cerebral cortex. According to Rakic [608], the relatively constant size of these units in different mammalian species suggests that, during evolution, the cortex has expanded by the addition of such radial units rather than by their enlargement. This postulate was designated as the *"radial unit hypothesis"* [608, 610].

Mountcastle's estimate that a minicolumn contains about 110 cells was, as he indicates, based on the work of Rockel et al. [619]. In this publication and in a later, more extensive study [620], the results of a quantitative comparative analysis of the neocortex were reported. The number of neuronal cell bodies were counted in a narrow strip, 30 μm wide, through the depth of the neocortex in several different functional areas (somatic sensory, visual, motor, frontal, parietal and temporal) in a number of different species (mouse, rat, cat, monkey and human). These counts gave remarkably constant values of 110 ± 10 cells in all areas and in all species studied. The only exception to this similarity appeared to be the binocular part of the visual cortex in a number of primate brains, in which approximately 2.5 times as many neurons were found. Rockel et al. [620] remarked that they chose a width of 30 μm for counting the cortical perikarya because, according to Hubel and Wiesel [312] and others, this is approximately the width of the simplest functional column in the neocortex. However, they pointed out that this is not necessarily the size of the simplest anatomical unit. In fact, their findings imply that, regardless of their areal size, modules will contain constant cell numbers (Swindale [719]).

Dendritic Clusters, Axonal Bundles and Radial Cell Cords As (Possible) Constituents of Neocortical Minicolumns

A number of examples of repeating microarrays of cortical elements could be interpreted as conforming to a minicolumnar radial pattern. These include the clusters of apical dendrites of pyramidal neurons, the bundles of myelinated axons and the column-like cell soma arrays running orthogonal to the horizontal laminae.

The existence of *clusters or bundles of dendrites* in the neocortex was discovered independently and almost synchronously by Peters and Walsh [568] in rat somatosensory cortex and by Fleischhauer et al. [196] in the rabbit and cat sensorimotor cortex. Since then, similar bundles of dendrites have been revealed in a number of other neocortical areas in mice, rats, rabbits and cats [140, 194, 195, 569, 826]. In each of these areas there appeared to be a similar basic organization: the apical dendrites of groups of layer V pyramidal neurons form clusters, which during their ascent are joined by the apical dendrites of pyramidal cells situated in the more superficial layers.

Radially oriented *bundles of myelinated fibres* occur in all parts of the neocortex (Figs. 15.4 C, 15.13). These bundles are known as radii or as the radiations of Meynert [85]. As already mentioned in a previous section of this chapter, local differences in the size and peripheral extent of these bundles play a prominent role in the myeloarchitectonic parcellation of the cortex.

Column-like *arrays of cell bodies* can be observed in many parts of the neocortex. They are particularly conspicuous in the human foetal cortex and in the mature temporal cortex of humans and other primates [341]. Brodmann [70], who beautifully depicted these cell arrays (Fig. 15.41), indicated that there is a correla-

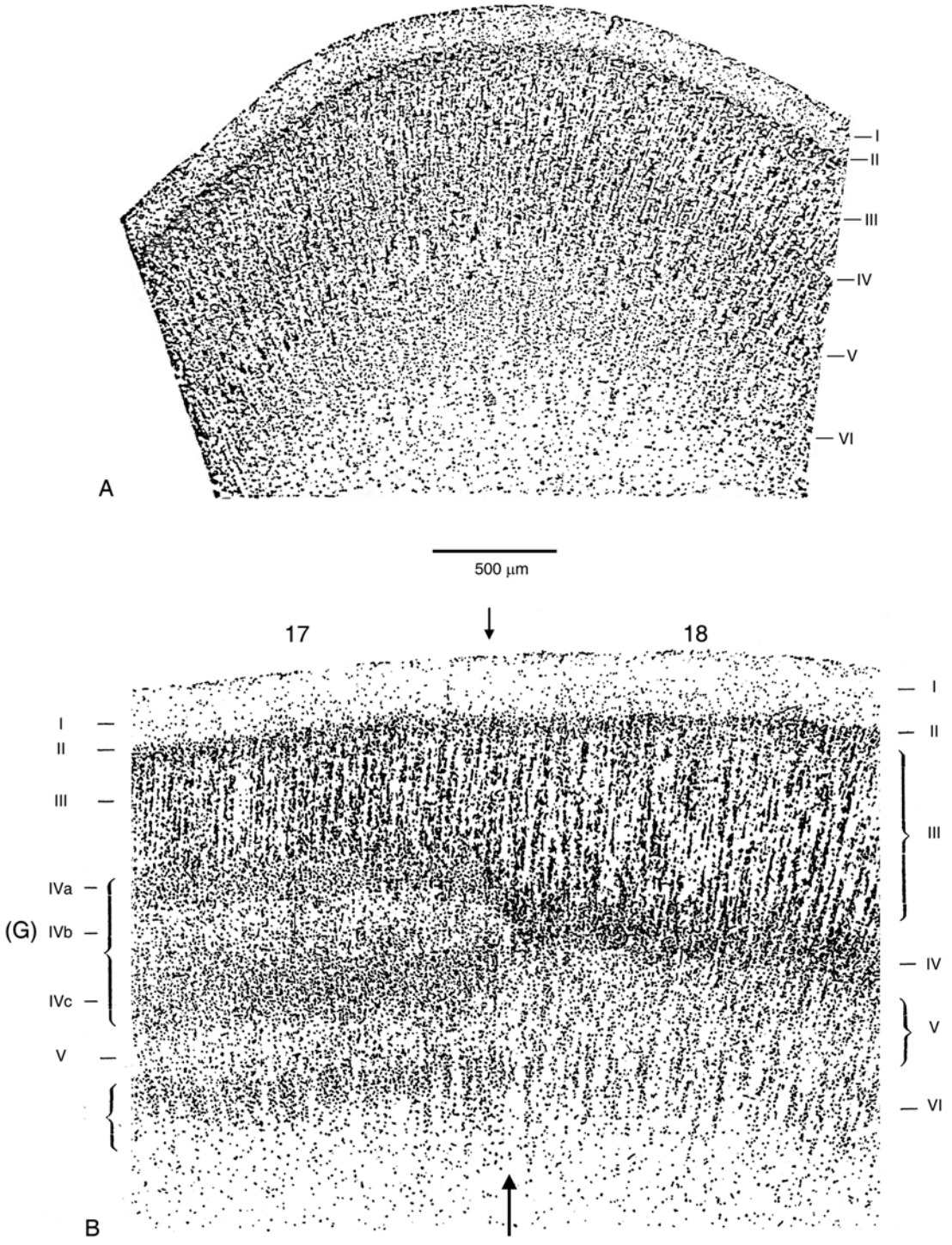


Fig. 15.41. Radial arrays of cell bodies in the primary motor area 4 (**A**) and the visual areas 17 and 18 (**B**) of 8-month-old human fetuses. Reproduced from Brodmann [70]. G, location of line of Gennari

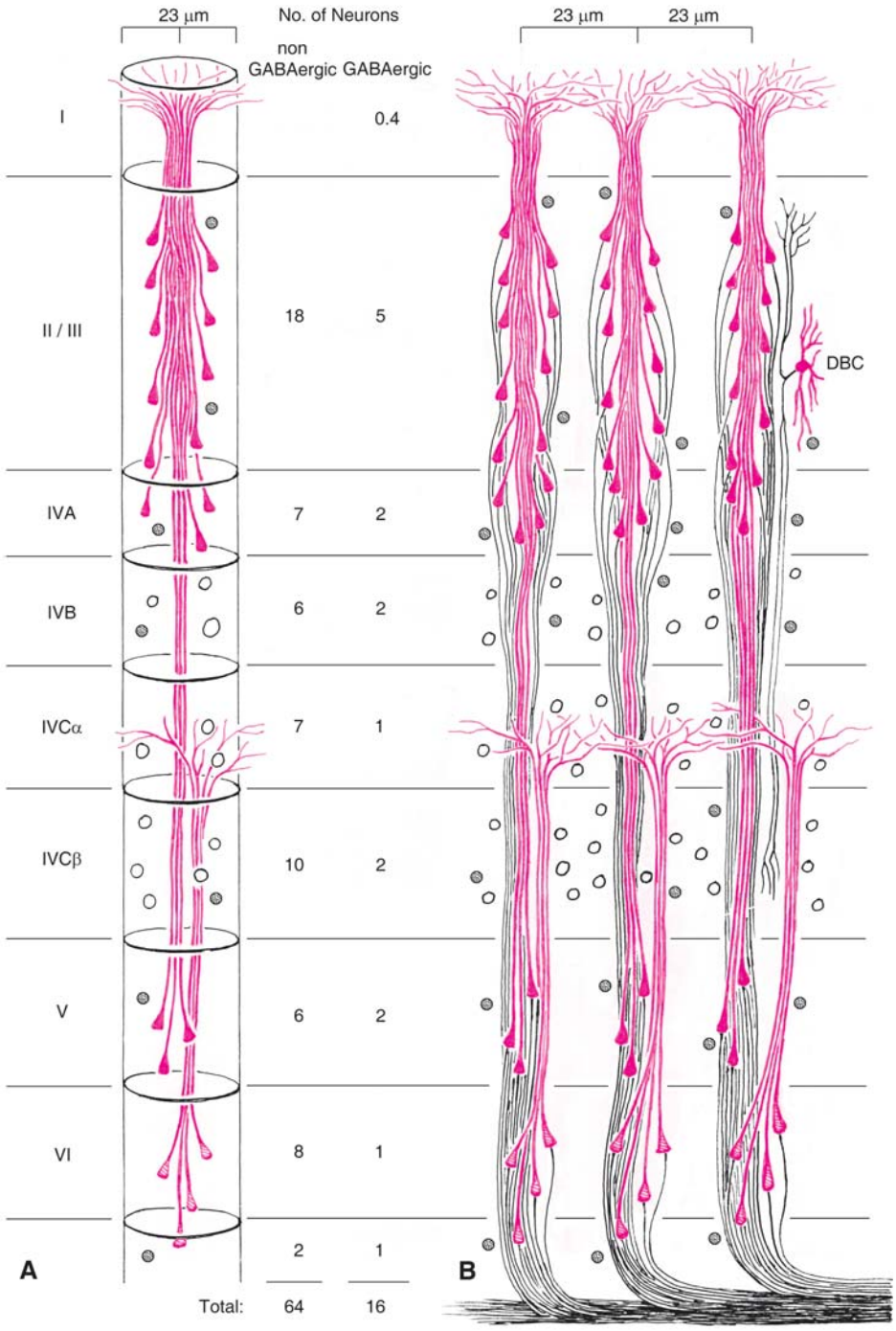


Fig. 15.42 A, B. Arrangement of pyramidal neurons and double bouquet cells in 23-µm-wide radial modules of the striate cortex of the macaque monkey. Neuronal somata and dendrites are shown in *red*, axons in *black*. **A** The arrangement of the apical dendrites of pyramidal cells in a module; for clarity, only one half of the neurons present are shown. The somata of spiny stellate cells are represented by *open circles*, while those of inhibitory, GABAergic neurons are represented by *circles filled with small dots*. The total *number* of spiny (excitatory) and GABAergic (inhibitory) neurons within each layer are given on the *right*. **B** A representation of three modules to show the arrangement of the dendrites and axons of the pyramidal cells. Each module contains one double bouquet cell (*DBC*). The axonal system of the double bouquet cell runs alongside the clustered apical dendrites of pyramidal neurons in layers IV and II/III and then alongside the bundle of myelinated axons. Modified from Peters and Sethares [566, 567]

tion between them and the bundles of myelinated fibres, and several later authors, among them Fleischhauer [195] and Buxhoeveden and Casanova [81], arrived at a similar conclusion. However, von Economo and Koskinas [796], who thoroughly investigated this relation, stated that in certain cortical regions, in which the neuronal perikarya were clearly arranged in vertical columns, a corresponding pattern of radial fibre bundles was absent. It is important to note that neither in the foetal nor in the adult stage do the arrays of cell bodies extend uninterruptedly through all cortical layers.

The phenomenon of apical dendrite bundling led Peters and Sethares [564–566] to the concept that the neocortex is composed of *pyramidal cell modules*. In accordance with earlier studies on rodents and cats, these authors found that the apical dendrites of the pyramidal cells in layer V of the primary visual cortex of the rhesus monkey cluster together in distinct and regularly spaced groups as they ascend through the various sublayers of lamina IV and pass into superficial layers II/III. The apical dendrites of the pyramidal neurons in those layers are then added to the clusters of layer V apical dendrites so that the clusters of apical dendrites gradually increase in size as they ascend. Upon reaching layer I, the apical dendrites split up into their terminal tufts (Fig. 15.42 A). When fully formed, the clusters comprise the dendrites of some 50 pyramidal cells. The apical dendrites of the pyramidal neurons in layer VI do not add to the clusters, but rather ascend independently to form their terminal rufts in layer IV (Fig. 15.42 A).

On the basis of these findings, Peters and Sethares [566] proposed that the primary visual cortex is composed of pyramidal cell modules. This concept is shown diagrammatically in Fig. 15.42 B, where three such modules are depicted. The average diameters of the modules are equal to the mean centre-to-centre spacing of the clusters of apical dendrites, namely about 23 μm.

The primary visual cortex of the rhesus monkey also contains prominent vertical bundles of myelinated fibres. These bundles, which are largely composed of pyramidal cell axons, are regularly arranged, and their average centre-to-centre spacing is similar to that of the dendritic clusters. In the deeper layers of the cortex, each myelinated axon bundle can be paired with a nearby cluster of apical dendrites (Fig. 15.42 B) [566]. Peters and Sethares envisioned that the pyramidal cell modules represent the basic functional units in the cortex, and that in essence they are equivalent to Mountcastle's minicolumns.

Column-like domains of spontaneously coactive pyramid-like neurons have been observed in slices of neonatal rat cortex [844]. The neurons within each domain appeared to be coupled by gap junctions. It has been suggested [341] that these domains are comparable to the pyramidal cell modules. However, their diameter (50–120 μm) is much larger than that of the modules, whereas their number of constituent cells (35 ± 17) is smaller.

The investigations of Vercelli et al. [776] have shown that pyramidal cells that share an apical dendritic bundle may project to specific targets. Studying the rat visual cortex, they found that neurons projecting to the ipsilateral or contralateral cortex form bundles together and with neurons projecting to the striatum, but not with those projecting to the lateral geniculate body or the superior colliculus or through the cerebral peduncle. Bundles composed of the apical dendrites of neurons projecting to the striatum and through the cerebral peduncle were also observed. The layer VI neurons projecting to the lateral geniculate body formed separate dendritic bundles. Vercelli et al. [776] concluded that the neocortex is organized in minicolumns of output neurons. They considered it likely that the neurons in an output minicolumn are closely related. Before leaving the pyramidal cell modules, it may be mentioned that Peters and Sethares [567] related one type of interneuron, namely the double bouquet cells, to these entities.

Double bouquet cells are abundant throughout the primate neocortex [140, 146]. The cell bodies of these elements are situated in layer II and upper layer III. Their axons form tightly packed bundles of collaterals that descend to layer V, where they disperse in horizontal

branches. These vertically oriented double bouquet axonal systems or horse tails are equally spaced [140, 146]. Peters and Sethares [567] found that the average centre-to-centre spacing of the horse tails in the primary visual cortex of the rhesus monkey is about 23 μm, a value similar to that of the centre-to-centre spacing of the clusters of apical dendrites forming the axes of the pyramidal cell modules and that of myelinated axon bundles that contain the efferent axons of these neurons. It appeared that each pyramidal cell module is associated with one horse tail axon bundle (Fig. 15.42 B). Within the superficial layers II/III, the double bouquet cell axons run alongside the apical dendritic clusters, while in layer IVC they are closely associated with the bundles of myelinated axons. It is important to note that the double bouquet axonal branches do not synapse with the apical dendrites but rather with basal dendrites and with side branches of the apical dendrites of pyramidal neurons and with postsynaptic structures belonging to local circuit neurons [1, 136]. The branches of apical and basal dendrites of pyramidal neurons extend horizontally for hundred of micra; hence, it is clear that the influence exerted by the double bouquet cells does not remain confined to narrow cylindroid modules, but rather is dispersed over pyramidal neurons with apical dendrites located in many different apical dendritic bundles [341].

The third major radial configurations in the neocortex, i.e. the arrays of neuronal perikarya as observed in Nissl preparations, deserve little comment. On the basis of a study of the development of the human auditory cortex, Krmpotic-Nemanic [387] suggested that there is a direct continuum between the ontogenetic radial columns as described by Rakic and adult cell columns. These cellular columns are the focus of two recent reviews by Buxhoeveden and Casanova [80, 81]. The authors indicate that the visibility of these structures in Nissl preparations depends on the linear arrangement of pyramidal cells and the existence of cell-poor, neuropil zones surrounding them. In layers II, IV and VI of the adult neocortex, the radial arrays are usually one cell wide. Buxhoeveden and Casanova equate these radial arrays with Mountcastle's minicolumns.

Microcircuitry of Neocortical Columns

Two noted neuroscientists, Szentágothai and Eccles, attempted to present the microcircuitry of the neocortical columns. Szentágothai's [721–723] opinion was that "the basic unit of cortical architecture – the true cortical columns – is anatomically based not on the mode of termination of the specific sensory afferents, as one might logically assume, but on that of cortico-cortical afferents". The size of these columnar units of cortico-cortical afferent terminations, according to Szentágothai, is remarkably constant, measuring around 200–300 μm in diameter (Fig. 15.40). On the basis of light and electron microscopy data, Szentágothai indicated how the various types of presumed excitatory and inhibitory interneurons are connected with the cortical afferent system and with the cortical output neurons, i.e. the pyramidal cells. He emphasized that the internal connectivity of each columnar unit is predominantly vertical, in a way that would favour a subdivision of each column into narrower microcolumns, and that the space of many of these microcolumns is occupied by the dendritic and/or axonal ramifications of individual interneurons (Fig. 15.43). Eccles' [166] sketch of the neuronal structure of the cortical module conforms to that of Szentágothai and is largely based on the work of the latter.

Neocortical Columns and Modules: A Critical Commentary

In the preceding pages, the evidence leading to the concept that the mammalian neocortex is composed of repetitive radially oriented columnar units has been reviewed. Although this concept has dominated the neurobiological literature on the cortex for the last 50 years, it is by no means generally accepted. Numerous authors, including Towe [738], Valverde [756], Swindale [719], Purves et al. [597], Jones [341]

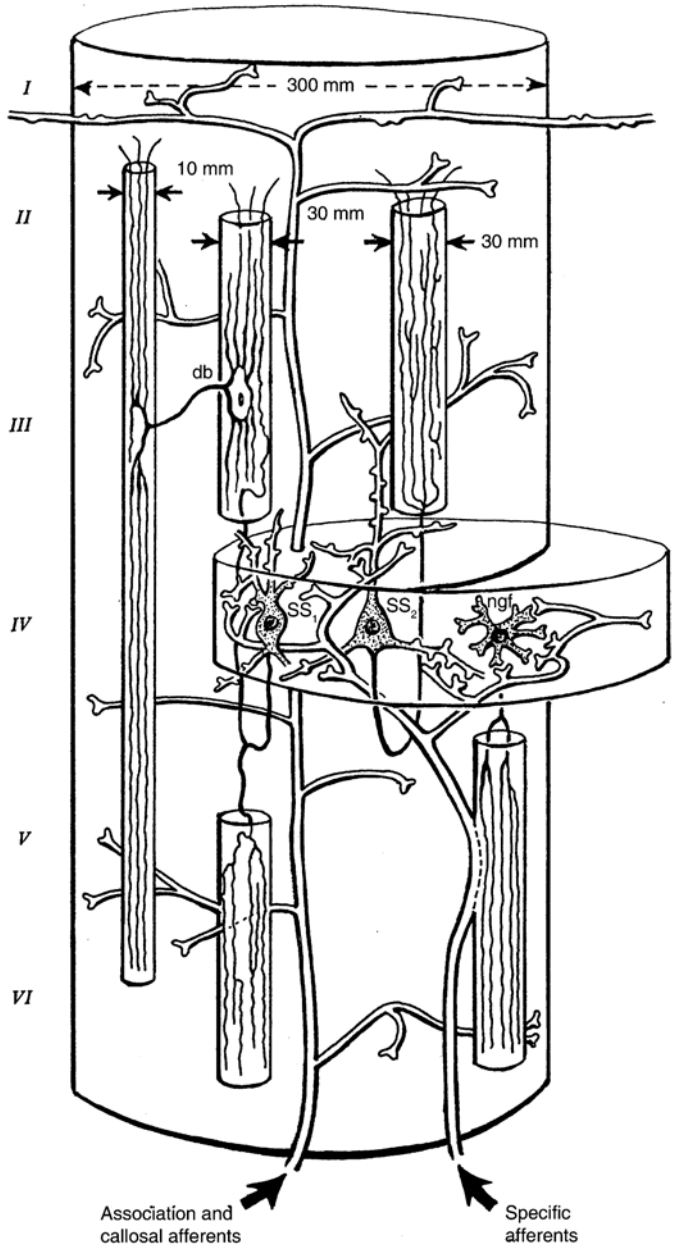


Fig. 15.43. Some features of the organization of a neocortical module or column, "defined" by a cortico-cortical (either association or callosal) afferent, ascending in its centre, as drawn by Szentágothai [721]. The module consists of a tall cylinder, 300 μm in diameter, extending through the full thickness of the cortex. The flat cylinder of the same diameter corresponds to the termination space of a specific thalamocortical afferent. This afferent fibre forms synaptic contacts with two different types of spiny stellate cells, *SS1* and *SS2*, as well as with a neurogliaform cell: ngf; SS1 has both an ascending and a descending arborization; SS2 has only an ascending arborization, whereas ngf has only a descending arborization. The ascending arborization of SS1 synapses with a typical double bouquet cell (*db*), whose bifurcating axon forms a long radial slender arborization. It should be mentioned that Szentágothai considered all of the neuronal elements depicted to be excitatory in nature. However, it is now known that neurogliaform cells and double bouquet cells are GABAergic, inhibitory interneurons. Reproduced from Szentágothai [721]

and Horton and Adams [305], have challenged the validity of this concept. Some of the main objections may be summarized as follows:

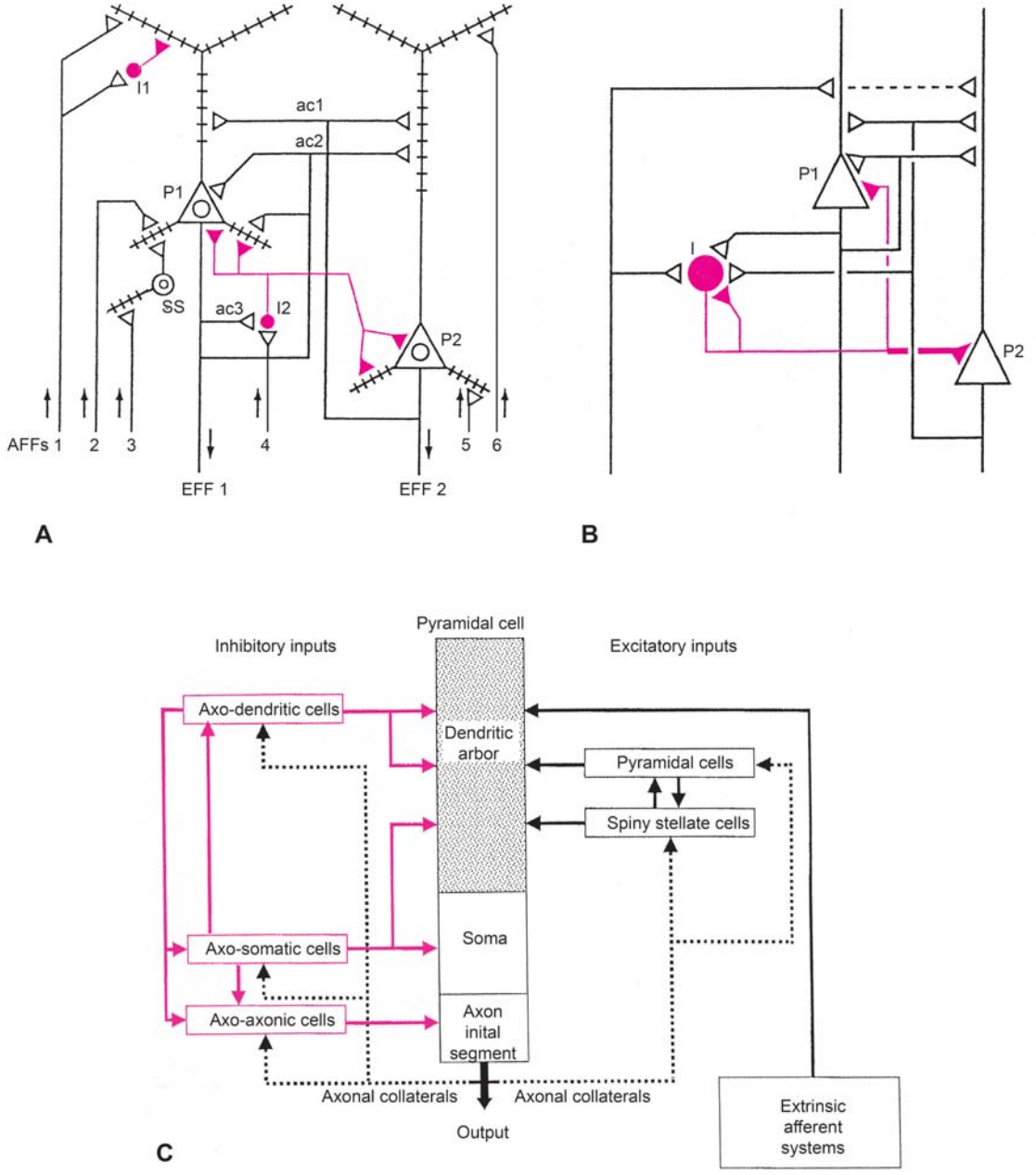
1. The original concept of Rakic, according to which all neurons forming a radial unit, both pyramidal and non-pyramidal, stem from a small cluster of progenitor cells in the pallial neuroepilium, is untenable. As has been discussed in Chap. 2, many, if not most, of the neocortical non-pyramidal cells are produced in the subpallial matrix and migrate tangentially into the developing pallium (Fig. 2.25).

2. The thesis that columnar structures form the basic structural and functional units of the neocortex has so far not been substantiated by direct evidence concerning the specific neuronal composition and the specific mode of operation of these units. The statement that the columns contain all cell phenotypes [76, 474] has not been proven and is even unprovable because an indeterminate number of cortical neurons have not been characterized in detail as yet. Moreover, recent histochemical and physiological studies have shown that the diversity of neocortical interneuron types is much larger than was previously thought [136, 507].

It is important to note that the models presented by Szentágothai [721, 723] and Eccles [166] are not based on analyses of the local connectivity within particular morphological units; rather, findings on cortical neurons and their connections derived from different cortical areas in different species were assembled and placed within the spatial framework of a cylinder with a diameter of 300 µm. Hence, these models should be considered as theoretical constructs, showing at best how the local circuitry within columns of cortical tissue, defined by streams of cortico-cortical afferents, could be organized. Mountcastle's [495] definition, stating that "a cortical column is a complex processing and distributing unit that links a number of inputs to several outputs", does not contain any information concerning the specific functional design of these columns.

3. According to the original concept of Lorente de Nó [416], the neocortex is built up of cylindrically shaped units, composed of vertical arrays of interconnected neurons that include all cortical layers. He designated these units as "elementary units of cortical operation", because he believed that within them "the whole process of the transmission of impulses from the afferent fibre to the efferent axon may be accomplished". Lorente de Nó did not specify the pattern of connectivity within these units, but during the last decades, several attempts have been made to characterize the basic neocortical microcircuit (see Fig. 15.44) [136, 157, 679]. However, in none of these attempts has the question been specifically addressed as to whether the elements involved in these microcircuits are confined to small, cylindrically shaped spaces. The pyramidal cell modules described by Peters and Sethares (Fig. 15.42) [565–567] could be the starting point for this type of research. Such a module would comply with Lorente de Nó's elementary unit concept if it could be shown that: (a) all axons of the constituent pyramidal neurons pass to the same target(s); (b) all constituent pyramid neurons are strongly and reciprocally connected by axon collaterals; (c) all sets of interneurons impinging on the various somatodendritic compartments of the pyramidal cells are situated within the confines of the module; and (d) all of its afferents terminate within the 23-µm-wide cylindrical space of the module. As regards (c), we have seen that the

Fig. 15.44 A–C. Neocortical microcircuits; excitatory elements in *black*, inhibitory elements in *red*. **A** *Basic neocortical circuit for sensory areas,* modified from Shepherd [679]. The diagram includes elements representing superficial and deep pyramidal cells (*P1*, *P2*), spiny stellate cells (*SS*) and inhibitory interneurons (*I1*, *I2*). Afferent inputs (*AFFs*) excite pyramidal cells (*1*, *2*, *5*, *6*) as well as inhibitory cells (*1*, *4*). In addition, there is feed-forward excitation (*AFF3*) through spiny stellate cells. The axons of the P cells have collaterals (*ac*) that recurrently and laterally excite the P cells (*ac1,2*) as well as inhibitory cells (*ac3*) that provide for feed-back and lateral inhibition. **B** *Canonical neocortical circuit,* based on the studies of Douglas et al. [157], as represented by Shepherd [679]. *P1* and *P2* represent the superficial and deep populations of (excitatory) pyramidal cells. Element *I* represents the population of inhibitory, GABAergic neurons. Neurons within each population form connections with other members of



that population. All three populations receive direct activation from the thalamus, but because the thalamic input provides only about 10% of the excitatory input, 90% of the excitation stems from intracortical connections between P cells. The excitation of nearby P cells is provided by axon collaterals of these elements. These axon collaterals also excite the interneuron-pool to provide feed-back and lateral inhibition. Modified from Shepherd [679]. **C** *Skeleton of the basic neocortical microcircuit,* according to DeFelipe [136]. The diagram shows the synaptic inputs and main patterns of local connections of the pyramidal cell. Excitatory inputs to this element arrive exclusively to its dendritic arbor and originate from extrinsic afferent systems and spiny cells (which include other pyramidal neurons and spiny stellate cells). Inhibitory inputs, which originate from GABAergic interneurons, terminate on the proximal dendrites, soma and axon initial segment. These interneurons are interconnected between one another, with the exception of the axo-axonic chandelier cells. Reproduced from DeFelipe [136]

double bouquet cells conform to the modules (Fig. 15.42 B) but that their axons most probably do not exclusively contact the dendrites belonging to the pyramidal cells situated within "their own" module. As regards (d), the cortical afferents are not of an appropriate size to match an individual pyramidal cell module. The terminal arbors of thalamocortical and cortico-cortical afferents are generally 200 µm or more in diameter (Figs. 15.40, 15.43). This does not exclude, of course, that these afferents participate in the formation of larger processing units (see below). An important general question to be addressed in the near future is: what is the relationship (if any) between the cylindrically shaped units proposed by Lorente de Nó, Mountcastle and others and the neocortical functional networks, discussed in the previous section of the present chapter.

The various column-like cortical entities have been distinguished on the basis of highly different morphological and/or physiological properties, e.g. similarity in physiological response properties, similarity in motor responses following stimulation, spatial segregation of sets of thalamocortical afferents, high concentrations of the enzyme cytochrome oxidase, concentrations of spiny stellate cells in lamina IV and the mode of termination of bundles of cortico-cortical fibres. It is unlikely that all of these entities are derivatives of one and the same basic cortical module, especially as they may differ considerably in size. It cannot be excluded that, as Szentágothai [722] surmised, the units defined by cortico-cortical afferents represent the "true cortical columns". With regard to these structures, however, it should be emphasized that (a) their presence has so far not been established in monotremes, marsupials or insectivores, (b) their intrinsic structure is unknown and (c) their functional significance remains to be elucidated [305].

It is also important to note that the vertically aligned rows of cell bodies observed in Nissl preparations of many cortical areas, which are often equated to cortical minicolumns, never extend uninterruptedly from layers II to VI and that most of the column-like formations described have no definite boundaries [621].

5. Although column-like entities of a given type are readily apparent in the neocortex of some species, they are often not detectable in other, sometimes closely related animals. The following examples of such inconsistencies are quoted from Purves et al. [597] and Horton and Adams [305], to whom the reader is referred for primary sources and details:

(a) Ocular dominance columns are present in Old World monkeys, but reportedly, absent in some New World monkeys.

(b) Remarkably, it was found in squirrel monkeys that some members of this species have ocular dominance columns in only part of the visual cortex, leaving other regions of binocular cortex bereft of columns.

(c) Blobs in the primary visual cortex of the rhesus monkey are reportedly concerned with processing information about colour. However, these structures are also present in nocturnal primates with cone-poor retinas (and, therefore, poor colour vision). Moreover, blobs are absent in some non-primate species with cone-rich retinas and excellent colour vision, such as the tree shrew and the ground squirrel.

(d) Barrels are well developed in the mouse, rat, squirrel, porcupine and walrus, but are absent in other species that have prominent facial whiskers such as the dog, cat, raccoon and tree shrew. Furthermore, barrels occur in the guinea pig, which hardly uses its whiskers, and in the chinchilla, another cavimorph that has no whisking behaviour at all.

6. The barrel cortex of rodents and the primate visual cortex are frequently cited as archetypical examples of columnar structures. However, Jones ([341], p. 5021) has pointed out that these two structures "represent endpoints in the evolution of the two orders, one of which noses and whisks its way around its environment and the other of which extracts an extraordinary richness of visual detail from its environment".

If we survey the data discussed above, the following conclusions seem to be warranted:

1. During the last 50 years, numerous different types of classes of column-like entities have been detected in different parts of the neo-

cortex of many different mammalian species with the aid of a variety of physiological and anatomical techniques. There is little evidence of a systematic relation between these classes of "columns".

2. There is very little evidence in favour of the concepts that (a) the entire mammalian neocortex is composed of column-like entities, (b) all of these entities represent variations on one and the same theme, (c) all of these entities essentially have the same structure and (d) they all essentially subserve the same function.

Comparative Aspects

If we compare the neocortex with the "older" parts of the mammalian cortex, i.e. the prepiriform or olfactory cortex (Figs. 11.5, 11.6) and the hippocampal cortex (Figs. 12.6–12.9), the following similarities and differences can be observed:

1. Pyramidal neurons occupy a central position in the circuitry of all of these cortices. These elements are provided with two, spatially separated, dendritic systems; an apical dendritic system, expanding in the most superficial cortical layer; and a basal dendritic system, the laminar position of which may vary considerably.
2. In all cortices, the pyramidal neurons are excitatory in nature and potentially constitute a continuous network extending throughout the cortex. Nearby connections in this network are provided by axon collaterals of pyramidal neurons, whereas longer intracortical connections consist of the main axons or axonal branches of more remote pyramidal neurons. In the neocortex, each pyramidal neuron receives by far its largest input from other pyramidal neurons.
3. Pyramidal neurons constitute the output system of all of these cortices.
4. In all cortices, the most superficial layer contains numerous tangentially running afferent fibres, making excitatory synaptic contacts with the apical dendritic extensions of pyramidal neurons. The sources of these fibres include the olfactory bulb, the thalamus and other cortical regions. The fibre composition of the superficial layer varies from region to region. Thus, in the prepiriform cortex, secondary olfactory fibres occupy a superficial position, whereas cortico-cortical fibres form a deeper zone. In the sensory part of the neocortex of primitive mammals, numerous thalamocortical fibres reach lamina I, but in the hippocampus and in neocortical association area, cortico-cortical fibres prevail in this layer. In lamina I of all cortices, fibres from different sources tend to be arranged in different sublaminae.
5. In neocortical sensory regions, thalamic afferents terminate massively in lamina IV. In the primary visual cortex of prosimians and primates, different laminae of the lateral geniculate nucleus project to different sublayers of lamina IV.
6. Inhibitory interneurons, using GABA as their neurotransmitter, occur in all cortices. All inhibitory interneurons in all cortices impinge directly with some or all of their terminals on pyramidal neurons. In all cortices, separate sets of inhibitory interneurons terminate mainly or exclusively on one of the three receptive domains of the pyramidal cells, i.e. the dendritic compartment, the soma and the axon initial segment.
7. Some inhibitory interneurons receive their principal input from extrinsic afferents and mediate feed-forward inhibition of pyramidal neurons, e.g. the horizontal cells in lamina I of the piriform cortex and in the neocortex. Other inhibitory interneurons receive their main input via axon collaterals of pyramidal neurons, thus forming part of feed-back loops (e.g. the large multipolar cells in lamina III of the piriform cortex) and still others, receiving excitatory inputs from extrinsic afferents and from axon collaterals of pyramidal cells, are involved in both feed-forward and feed-back inhibition of pyramidal neurons, e.g. basket cells in the hippocampus and the neocortex.
8. Inhibitory interneurons, exerting their influence on other inhibitory interneurons, and

thus a disinhibition of pyramidal neurons, are present in all cortices. The elements involved in such inter-interneuronal inhibitory circuits may be of the same type, e.g. the large multipolar cells in the piriform cortex and the basket cells in the neocortex, or of different types, e.g. the so-called L/M cells and the basket cells in the hippocampus and the basket cells and double bouquet cells in the neocortex.

9. In the neocortex as well as in the hippocampus groups of inhibitory interneurons have been observed that are interconnected via chemical synapses and gap junctions and also innervate themselves via autapses [24, 101, 362].
10. Excitatory interneurons have so far only been demonstrated in the neocortex. These elements, the spiny stellate cells, represent transformed pyramidal neurons. They are abundant in primary sensory cortices, where they play a prominent role in the radial propagation of the activity fed by thalamocortical afferents into lamina IV of these cortices.

Synopsis of Main Neocortical Regions

Introduction

In this section an overview of the structure and principal connections of the main neocortical regions will be presented. We will confine ourselves here mainly to cortico-cortical projections. Neocortical afferents have been discussed in a previous section of the present chapter and efferents of the motor cortex will be dealt with in Chap. 21. For discussion of the relations of the neocortex with the basal ganglia and cerebellum, we refer the reader to Chaps. 14 and 20, respectively. In this overview the classical subdivision of the hemisphere into the occipital, parietal, temporal, limbic, frontal and insular lobes will be followed (Fig. 1.4). It is important to note that this subdivision was based originally on the bones of the skull and, hence, has little to do with brain function. However, it appears to be possible to subdivide all of them into a number of functional domains. Throughout the description, the still widely used area parcellation of Brodmann (Fig. 15.8) will be used as a reference system. The discussion of the various lobes is prefaced with some remarks on the neocortical association and commissural connection and on the functional and structural asymmetry of the two cerebral hemispheres.

Association and Commissural Connections

Association and commissural fibres, which interconnect different neocortical areas, make up most of the white matter of the cerebral hemisphere. Commissural fibres cross in the corpus callosum and in the caudal part of the anterior commissure. Association systems can be rather arbitrarily subdivided into short and long association fibres. Short association fibres may remain within the grey matter of the cortex or pass through the superficial white matter between neighbouring cortical areas as U fibres. Long association systems are located in deeper parts of the white matter, lateral and medial to the corona radiata and the internal capsule. In the human brain, long association systems are mainly known from gross dissection [145, 421], although imaging techniques have recently become available, rendering it possible to visualize these bundles in the living human brain [40, 108, 335, 488, 588]. The most important long association systems are named and depicted in Figs. 15.45 and 15.46. It can be seen that these systems interconnect cortical regions in different lobes within the same hemisphere.

The *superior occipitofrontal (or subcallosal) fasciculus* is situated dorsolateral to the caudate nucleus, immediately underneath the most medial part of the radiation of the corpus callosum. Its fibres connect the occipital and temporal regions with the frontal lobe.

The *superior longitudinal fasciculus* is located along the laterosuperior border of the putamen. It is separated from the superior occipitofrontal fasciculus by the fibres of the most proximal

part of the corona radiata. It forms a large arcuate bundle that interconnects the frontal lobe with the three post-Rolandic lobes. Its posterior part splits up into a brachium posterius, which fans out into the parietal, occipital and posterior temporal lobes, and a strongly curved brachium anterius, which is connected with the anterior part of the temporal lobe.

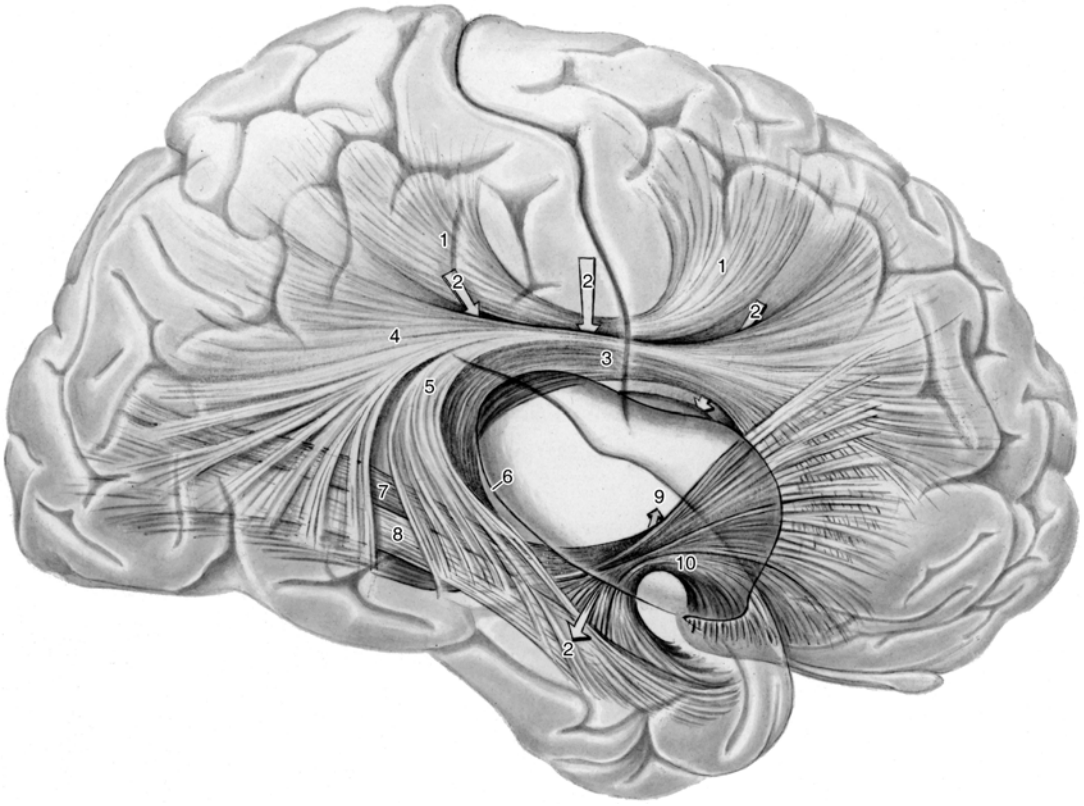
The *inferior occipitofrontal fasciculus* and the *uncinate fasciculus* form part of a single fibre complex. The compact, intermediate parts of these bundles are situated directly underneath the claustrum and pass via the limen insulae from the frontal to the temporal lobe. The inferior occipitofrontal fasciculus consists of fibres that connect the lateral parts of the frontal lobe with the inferior temporal and medial and lateral occipitotemporal gyri and with the occipital lobe. The uncinate fasciculus connects the inferior frontal gyrus and the orbital surface of the frontal lobe with anterior portions of the temporal lobe.

The *inferior longitudinal fasciculus* follows the lateral wall of the posterior and inferior horns of the lateral ventricle. It connects the occipital lobe with most parts of the temporal lobe. Tusa and Ungerleider [739] provided experimental evidence indicating that the inferior longitudinal fasciculus in the rhesus monkey consists of a series of U fibres that sequentially connect adjacent regions in the striate, prestriate and inferior temporal cortex. On that account they proposed replacing the term "inferior longitudinal fasciculus" by the term "occipitotemporal projection system".

The *cingulum,* finally, is a large system of shorter and longer association fibres, which is situated in the white matter of the cingulate gyrus, following this convolution throughout its entire length (Fig. 12.13). Anteriorly, it extends around the genu of the corpus callosum to the subcallosal area. Posteriorly, it arches around the splenium of the corpus callosum and continues downward and forward within the parahippocampal gyrus. From there, its constituent fibres fan out in the adjoining parts of the medial temporal lobe.

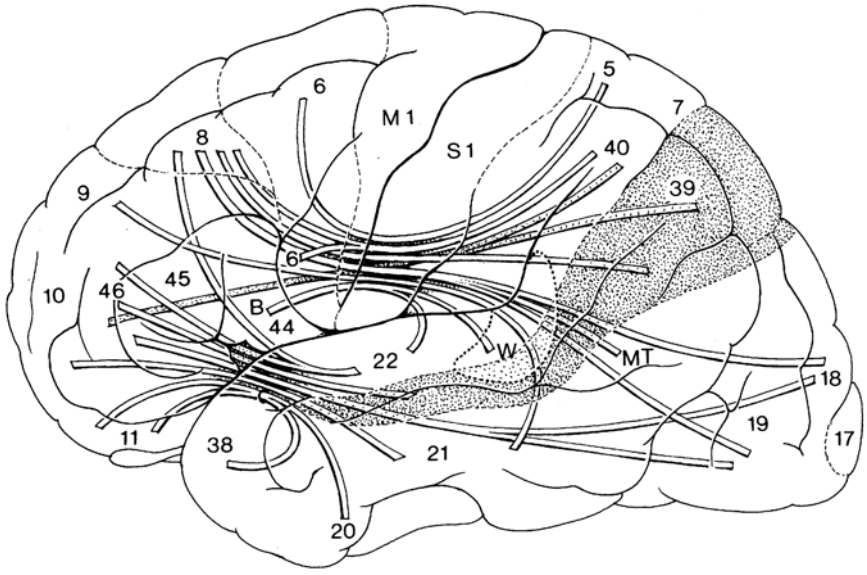
Although the neocortical association systems have already been dealt with in a previous section of the present chapter (Structural Subdivision 4: Connectivity), it may be good to repeat some general principles applying to the organization of the connections (Figs. 15.15, 15.46, 15.47). It should be emphasized that our knowledge of the cortico-cortical connections is almost entirely based on experimental studies in non-human primates [463–465, 526, 529, 532, 579, 773].

1. Cascades of short association fibres interconnect the primary, modality-specific areas of the cortex, which receive their sensory input from the thalamus, with the modality-specific parasensory association areas. The somatosensory association cortex is found in the parietal lobe, the visual association areas in the occipital lobe and the temporal lobe below the superior temporal sulcus, and the auditory association areas are in the superior temporal gyrus and the temporal operculum. These short connections will be reviewed according to their modality.
2. Modality-specific areas of parasensory association cortex are connected with multimodal sensory areas located at their borders. These areas constitute a belt extending from the junction of the occipital and parietal lobes, through the caudal part of the superior temporal gyrus, into the superior temporal sulcus. Long association systems connect the modality-specific parasensory association cortex and the multimodal areas in the occipital, temporal and parietal lobes with the premotor and prefrontal cortex of the frontal lobe. Short association fibres interconnect the prefrontal cortex, the premotor area and the motor cortex. Short association fibres interconnect the motor cortex and the primary somatosensory cortex.
3. Connections from the parasensory and multimodal association cortices and the prefrontal cortex to limbic structures pass by way of the cingulum to the medial part of the temporal lobe. Other fibres originating from parasensory association cortices reach limbic structures via the insula.
4. Most association connections are reciprocal.
5. Connections from the primary sensory areas to their neighbouring association areas usual-



1 Superior occipitofrontal fasciculus
2 Site of corona radiata
3 Superior longitudinal fasciculus
4 Superior longitudinal fasciculus, brachium posterius
5 Superior longitudinal fasciculus, brachium anterius
6 Outline of insula
7 Inferior occipitofrontal fasciculus
8 Inferior longitudinal fasciculus
9 Site of anterior commissure
10 Uncinate fasciculus

Fig. 15.45. Long association bundles of the right cerebral hemisphere in a lateral view (1/1×). Part of the superior longitudinal fascicle has been removed to show the superior occipitofrontal fascicle



B Broca's speech region
M1 primary motor area
MT Middle temporal visual association area
S1 primary sensory area
W Wernicke's speech region

Fig. 15.46. Long association connections of the neocortex of the left hemisphere. The multimodal association cortex in the superior temporal sulcus and the parieto-occipital sulcus is *dotted*

ly originate from the supragranular layers and terminate in and around layer IV. This type of connection is therefore considered to transfer information in a forward direction. The reverse (feed-back) connections originate in the infragranular layers and terminate in layers I and VI [623]. The laminar analysis of association connections may therefore reveal the direction of information transfer.

Fibres interconnecting neocortical regions in the two hemispheres pass through two commissural systems, the anterior commissure and the corpus callosum (Fig. 3.7). Both of these commissures develop in the commissural plate, i.e. the thickened, most rostral part of the lamina terminalis (Fig. 2.6).

The *anterior commissure* is throughout most of its extent a compact, transversely oriented bundle (Fig. 12.4). It comprises a small anterior limb and a much larger posterior limb (Fig. 15.48). The anterior limb interconnects olfactory structures, such as the anterior olfactory nuclei and the primary olfactory cortices, on the two sides (Fig. 11.7). The posterior limb, which passes laterally and somewhat backward through the most inferior parts of the lentiform nucleus (Figs. 5.5, 5.6, 5.21–5.24), interconnects the anterior portions of the middle and inferior temporal gyri.

A *corpus callosum* is lacking in monotremes and marsupials [511]. In eutherians, the size of the corpus callosum parallels that of the neocortex. Thus, it is small in primitive mammals such as the hedgehog (Fig. 12.1 D), larger in prosimians (Fig. 12.1 E), and attains its maximal size in humans (Fig. 12.1 C). During ontogeny, the human corpus callosum manifests itself initially as a small, compact bundle in the most dorsal part of the commissural plate (Fig. 2.6 A). During further development, it thickens, expands backwardly (Fig. 2.6 B–D) and ultimately covers the entire diencephalon (Fig. 7.1).

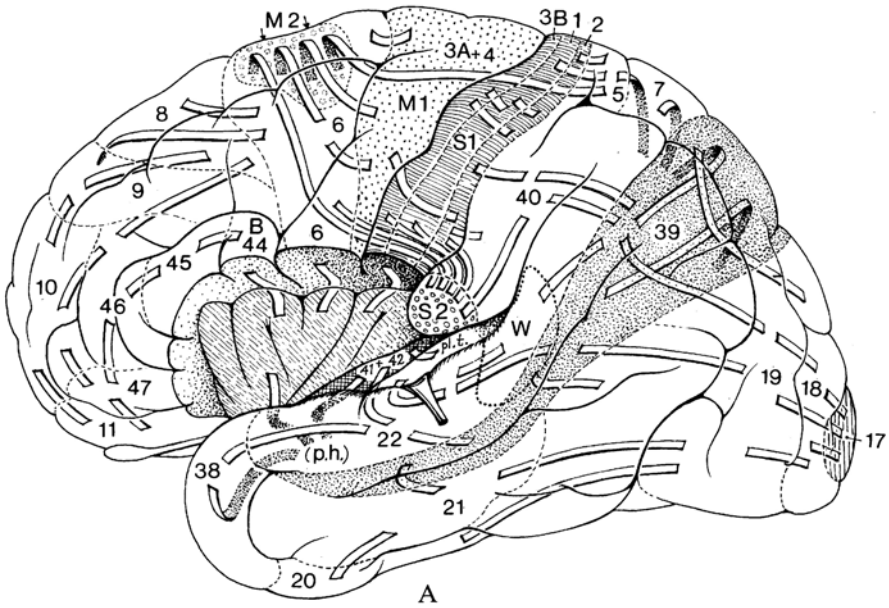
In the human adult, the corpus callosum is a broad plate of fibres that interconnects the neocortical portions of the two hemispheres. It forms the floor of the longitudinal fissure and the roof of the lateral ventricles (Figs. 5.4–5.11).

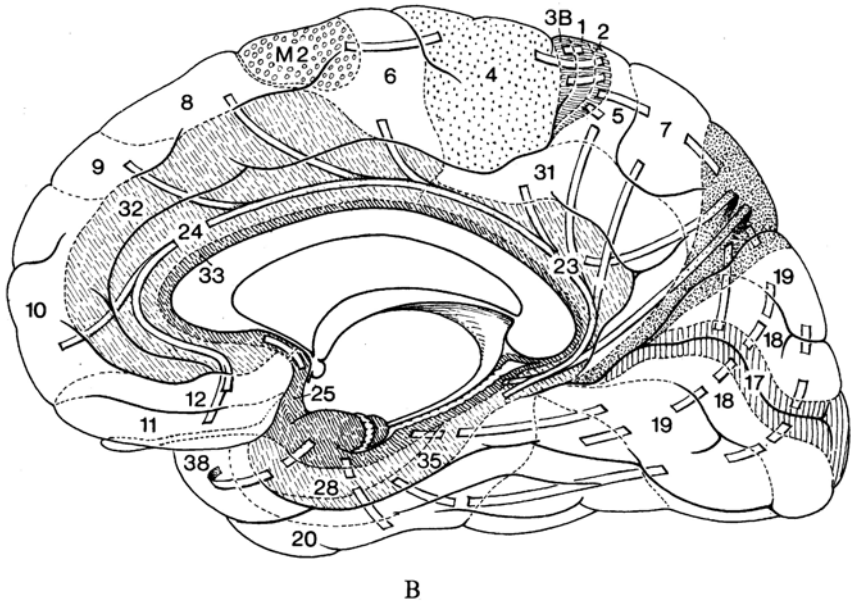
The corpus callosum is divided into a curved rostral part, the *genu*, a large middle part, the *body or truncus,* and a thickened caudal part, the *splenium*. A tapering *rostrum* connects the posteriorly recurved part of the genu with the lamina terminalis (Figs. 3.7, 15.48). The fibres of the corpus callosum, which fan out into the white matter of both hemispheres, form the *radiation of the corpus callosum* (Figs. 5.4–5.10). The extension of these fibres in the most frontal parts of the hemisphere is called *forceps minor*, whilst the similar but wider sweep of fibres toward the occipital poles is called *forceps major* (Figs. 5.29, 15.48). The fibres destined for the basal parts of the temporal and occipital lobes form a thin fibre plate, the *tapetum,* which accompanies the dorsolateral wall of the inferior horn of the lateral ventricle (Fig. 15.48).

Commissural connections are homotopic or heterotopic. *Homotopic fibres* interconnect corresponding cortical areas in both hemispheres. The fibres interconnecting the frontal lobes pass in the anterior half of the corpus callosum, the others pass in the posterior half, with the parietal fibres anterior to those from the temporal lobe, and the occipital lobe fibres most posteriorly, in the splenium [156, 533].

Experimental studies in rhesus monkeys [126, 361] have shown that there are considerable regional variations as regards the distribution of callosal afferents. Thus, commissural fibres are absent from most of the primary visual cortex (area 17) and the same holds true for the areas representing the distal parts of the limbs in both the primary somatosensory and the primary motor cortices. Most of the association areas, on the other hand, are strongly interconnected by callosal fibres.

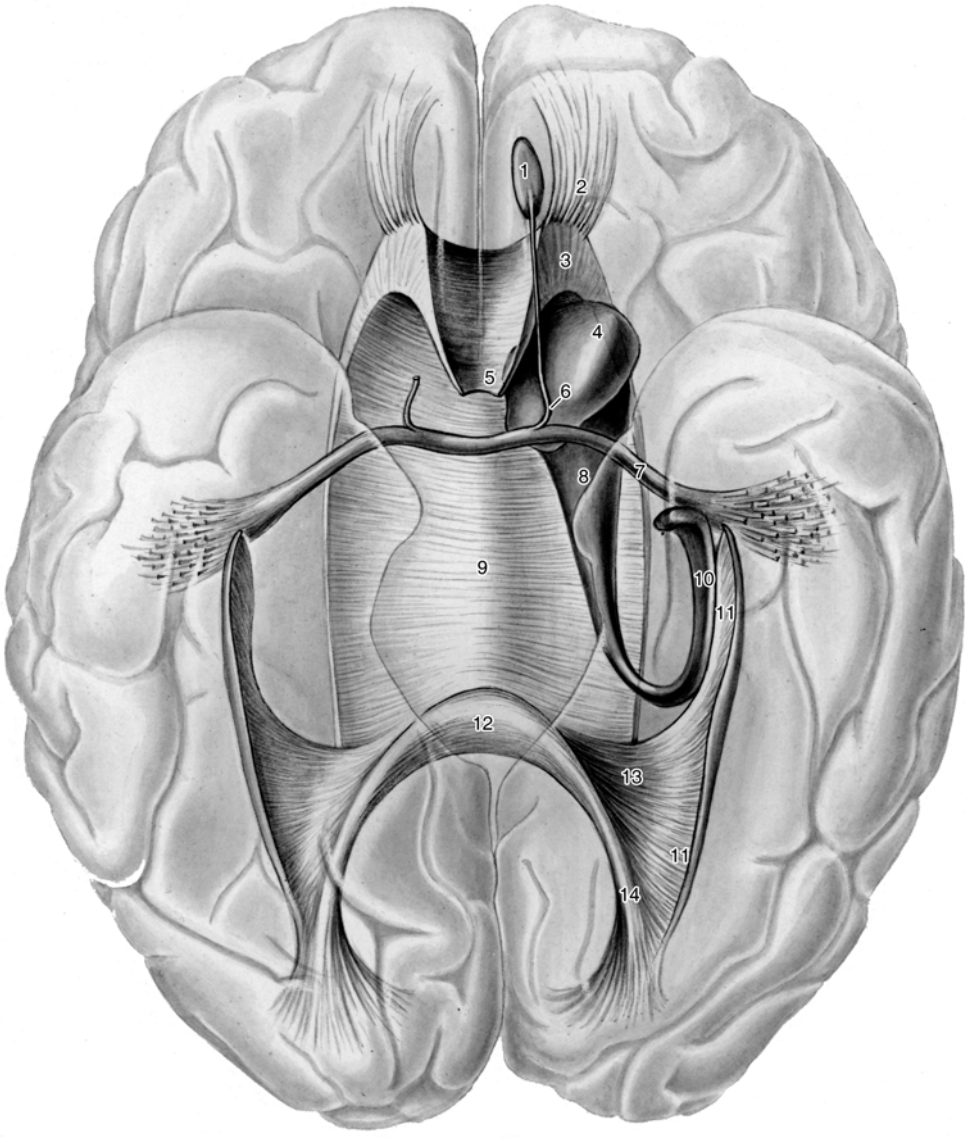
Heterotopic commissural connections connect a cortical area with non-corresponding areas in the contralateral hemisphere. The pattern of heterotopic connections of a particular cortical area often mimics its association connections with other areas in the ipsilateral hemisphere. It is sometimes possible to distinguish between forward and backward types of heterotopic connections on the basis of their laminar origin and termination [126].





B Broca's speech region
p.h. parahippocampal gyrus
pl.t. planum temporale
W Wernicke's speech region

Fig. 15.47 A, B. Short association connections of the cerebral cortex. **A** Lateral view. The frontal and part of the parietal operculum has been removed; the temporal operculum is retracted. **B** Medial view. The primary and secondary sensory areas (*S1* and *S2*), the primary and secondary motor areas (*M1* and *M2*), the primary visual and auditory cortices, the paralimbic association cortex and the insula, and the limbic cortex are indicated with *different shadings*. The multimodal cortex in the superior temporal sulcus and the parieto-occipital sulcus is *dotted*



1 Olfactory bulb
2 Forceps minor
3 Genu of corpus callosum
4 Head of caudate nucleus
5 Rostrum of corpus callosum
6 Anterior commissure, anterior limb
7 Anterior commissure, posterior limb
8 Body of caudate nucleus
9 Body of corpus callosum
10 Tail of caudate nucleus
11 Tapetum
12 Splenium of corpus callosum
13 Radiation of corpus callosum
14 Forceps major

Fig. 15.48. Commissural connections of the telencephalon as seen from the basal side of the brain (1/1×)

Association and commissural connections often originate from and terminate in strips, which in turn are separated from each other by strips lacking these particular connections. This pattern of alternating positive and negative strips has a periodicity of 200–1000 μm [243, 319, 332, 349]. In the somatosensory and auditory cortices, the strips extend perpendicular to the borders of the somatotopic or the isofrequency maps, but a periodicity in the origin and termination of cortico-cortical connections has also been observed for visual association areas and for the multimodal, frontal and paralimbic association cortices. Cells of origin and their homotopic terminations are located in the same strips. It is not certain whether the ipsilateral association and commissural pathways are complementary with respect to the strips [76, 246, 337, 344, 349, 667].

Association and commissural connections are involved in many higher functions of the nervous system. Damage to the primary sensory or parasensory association area may result in perceptual deficits. In contrast, the interruption of commissural connections or the association connections between the unimodal area and multimodal or paralimbic association areas may lead to disconnection syndromes. These syndromes have been extensively studied in experimental animals and in humans [227, 462, 703].

Functional and Structural Asymmetry of the Two Hemispheres

Functional asymmetry of the two hemispheres is a salient feature of human brain organization and cognition. This phenomenon is also termed "hemispheric specialization", "functional lateralization" and "cerebral dominance". These terms all refer to the fact that the right and left cerebral hemispheres have different roles in mediating behaviour and higher mental processes [226].

Evidence for functional asymmetry of the cerebral hemispheres is mainly derived from studies of the following types.

1. Clinicopathological studies. The modern era of neuroscientific investigation into cerebral asymmetry began in the 1860s and 1870s with the discovery of Broca [67] and Wernicke [811] that language functions are lateralized to the left hemisphere. The notion of a dominant hemisphere was first presented by Hughlings Jackson on the basis of the frequent occurrence of motor (and other kinds of) aphasia in right-handed persons when they suffer a hemiplegia of the right limbs, while a left-sided hemiplegia in such persons usually is not accompanied by aphasia [69].
2. Studies on the laterality of motor control. Such studies have shown that in all races more than 90% of the population is naturally more skilled with the right hand than with the left [112, 114]. As is well known, the right hand is controlled by the left hemisphere.
3. Studies in which one of the cerebral hemispheres is temporarily inactivated. In the so-called Wada test [799], a barbiturate is injected into the right or left internal carotid artery, by which the ipsilateral hemisphere is inactivated for a short while. The test forms part of the presurgical assessment of hemispheric language dominance in patients suffering from intractable epilepsy. In the dominant hemisphere, such an injection transiently blocks speech. Results with this test have shown that 92–99% of dextral individuals are left hemisphere-dominant for language, while the pattern in non-dextral individuals includes leftward but also bilateral or even rightward dominance for language [417].
4. Studies in patients in whom the two cerebral hemispheres are surgically separated by transection of the corpus callosum and the anterior and hippocampal commissures. Operations of this type are carried out to control intractable seizures [799]. Such "split-brain" individuals offer a unique opportunity to test the functions of each hemisphere independently of the other [224, 225].
5. Neuroimaging studies, which render it possible to identify and localize changes in metabolic activity in the brain, correlated with cognitive and mental tasks, have been

widely applied to the study of functional asymmetries. Moreover, MRI scans can be used for in vivo morphometry of brain structures [417, 708].

Overall, the studies listed above have shown that in right-handed persons the left hemisphere is mainly concerned with verbal and linguistic functions, mathematical skills and analytical thinking, whereas the right hemisphere is primarily involved in spatial relationships, musical and artistic functions and in the recognition and expression of emotions.

Left-handed persons form a heterogeneous group. Only 15% of left-handers show the expected right-hemisphere dominance; a full 70% of them is left-hemisphere dominant, while the remaining 15% has bilateral language abilities [226].

Crow and Mitchell [123, 473] concluded from lesion studies in stroke patients and functional imaging studies of healthy people that some language functions, including discourse planning/comprehension, understanding humour, sarcasm and metaphors, are mediated by the right hemisphere rather than the left. It may be added that, according to these authors, the language deficits in patients with schizophrenia can be interpreted as abnormalities of lateralization.

Possible morphological correlates of the functional asymmetries just discussed have been described by numerous authors. Geschwind and Levitsky [229] reported left–right asymmetries in the temporal speech region. They measured the size of the planum temporale, i.e. the posterior region of the superior surface of the temporal lobe, in 100 brains and found it to be larger on the left than on the right in 65, with no asymmetry in 24 and with a reversed pattern in 11 brains. Their observations have been confirmed by several other investigators, among them Witelson and Pallie [829], Wada et al. [800], Rubens [642] and Steinmetz [708]. Habib et al. [271] demonstrated that the leftward volume asymmetry of the planum temporale is related to the degree of right-handedness. Asymmetries in the planum temporale have also been demonstrated in the volume of cytoarchitectonically defined areas. Thus, Galaburda et al. [221] measured an auditory association area, designated as Tpt in four brains. Distinct leftward asymmetries were seen in this area, whereby in one case the left area Tpt was 620% larger than the right. Moreover, a perfect rank-order correlation was found between the magnitude of asymmetry of area Tpt and the degree of planum temporale asymmetry.

It is generally accepted that areas 44 and 45 of Brodmann in the inferior part of the frontal lobe constitute the cytoarchitectonic correlates of Broca's speech region. Amunts et al. [6] delineated these two areas in 10 human brains. They found a left-larger-than-right asymmetry of area 44 in all brains studied.

Histological asymmetries have also been found in areas related to language. Scheibel et al. [655] reported differences in the complexity of the dendritic trees of pyramidal cells between the speech areas in the left hemisphere and their counterparts on the right side, and Hayes and Lewis [281] found that the pyramidal neurons in layer III of Broca's area 45 are consistently larger on the left than on the right side. Finally, it may be mentioned that evidence, recently summarized by Hutsler and Galuske [318], indicates that the width of individual columns in the posterior language-oriented areas is greater in the left hemisphere than in the right.

Occipital Lobe

The occipital lobe occupies the most posterior portion of the hemisphere on its lateral, medial and basal surfaces (Figs. 1.4, 15.49). On the lateral or convex surface of the hemisphere, the anterior boundary is formed by a somewhat irregular parieto-occipital line which, starting from the superior end of the parieto-occipital sulcus, partly follows the anterior occipital sulcus (Fig. 3.2). On the medial surface, the anterior boundary of the occipital lobe is marked by the parieto-occipital sulcus (Fig. 3.6). An arbitrary, transversely oriented occipitotemporal line, cutting through the medial and lateral

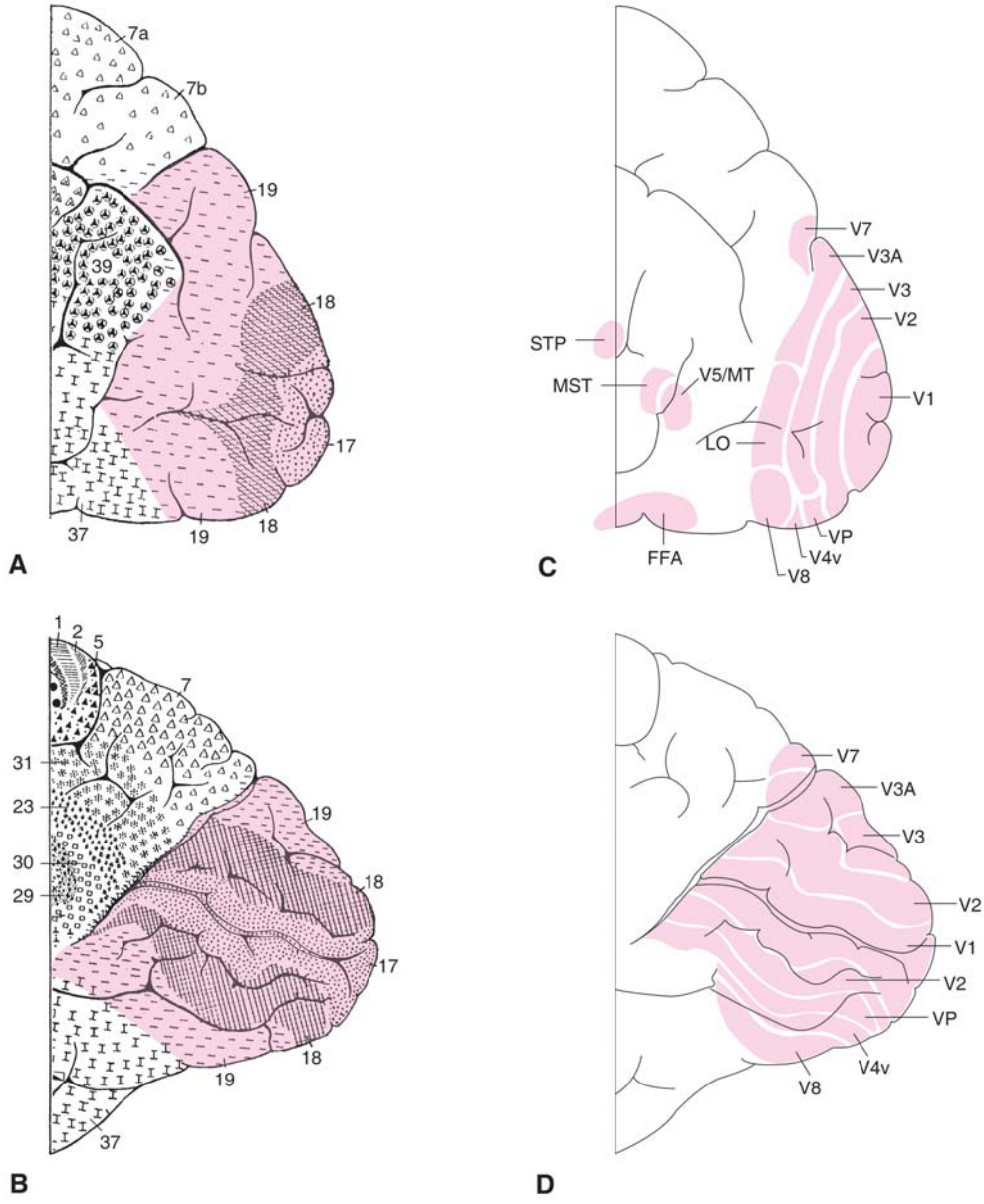


Fig. 15.49 A–D. The occipital lobe. Subdivision (*numbers*) according to Brodmann, lateral (**A**) and medial (**B**) views. The occipital lobe is shown in *red*. Functional areas adopted from Tootell et al. [737], lateral (**C**) and medial (**D**) views. *FFA*, fusiform face area; *LO*, lateral occipital area; *MST*, middle superior temporal visual area; *MT*, middle temporal visual area; *STP*, superior temporal polysensory area; *V1*, *V2*, *VP*, etc., visual areas

occipitotemporal gyri, forms the anterior boundary of the occipital lobe on the basal side (Fig. 3.5). On the medial aspect of the hemisphere, the deep calcarine sulcus separates the cuneus from the medial occipitotemporal gyrus. Anteriorly, the calcarine sulcus joins the parieto-occipital sulcus (Fig. 3.6).

The occipital lobe is occupied by three concentrically arranged cytoarchitectonic areas, the areas 17, 18 and 19 of Brodmann (Figs. 15.8, 15.49 A, B).

Area 17 surrounds the calcarine sulcus. It is also known as the area striata because it is characterized by the presence of a dense layer of myelinated fibres, known as the line of Gennari. This line is clearly visible in unstained, macroscopical sections (Figs. 5.13, 5.14, 5.30, 5.31). Histologically, the area striata is typified by its richness of small, granular cells ("koniocortex"). The internal granular layer is subdivided into three sublayers, IVa–c (Figs. 15.6, 15.41 B). The transition zone between layers V and VI contains the large cells of Meynert (Figs. 15.28 (4), 15.35).

Areas 18 and 19 show a homotypical lamination pattern. The borderline between areas 17 and 18 is very distinct. The line of Gennari stops abruptly and the various sublayers of layer IV merge into a single internal granular layer (Figs. 15.6, 15.41 B). The anterior borders of areas 18 and 19, on the other hand, are hard to establish. The borders of areas 17 and 18 show a considerable intersubject variability (Fig. 15.22 B) [7, 186].

Area 17, which receives its principal afferent projection from the lateral geniculate body, represents the *primary visual cortex (V1)*. The areas 18 and 19, which surround area 17, are collectively designated as the *parastriate belt*. The areas 18 and 19, which are strongly visually responsive, receive their principal afferents either directly or indirectly from the striate area and are, hence, also characterized as *extrastriate visual areas*. However, the total extrastriate visual cortex is not confined to the occipital lobe, but rather extends anteriorly into the parietal and temporal lobes. The overall extent of extrastriate visual cortex (or *visual association cortex*), as estimated from a combination of fMRI, PET and lesion studies, includes Brodmann's areas 7, 18–21, 37 and 39 (Fig. 15.50) [161]. By this estimate, roughly a third of human neocortex is associated with visual processing [771].

Our present-day knowledge of the central visual system is largely based on experimental studies in non-human primates, particularly the rhesus monkey. These studies have shown that there is a far-reaching "division of labour" in the analysis and processing of visual information. Many cortical areas outside the primary visual cortex appear to be specialized for the processing of specific aspects of vision, such as form, motion or colour.

The extrastriate cortex of the macaque monkey has been shown to contain a large number of visual areas defined by three or more of the following criteria: (i) presence of retinotopic representation of the contralateral visual hemifield or of part of it; (ii) functional specialization of neurons; (iii) specific effects of lesions; (iv) specific connectivity pattern and (v) specific cyto-, myelo- and/or chemoarchitecture [850]. More than 30 different areas have been identified in the extrastriate visual cortex of the rhesus monkey [180, 408, 761, 770, 771]. Some of these are labelled with a capital "V", standing for visual area, followed by a number: V2, V3 etc. Others are designated with combinations of letters, indicating their topographical position. Mainly on the basis of functional imaging studies, putative equivalents of 8–10 of the functional areas detected in the extrastriate cortex of the rhesus monkey have been identified in the human brain (Figs. 15.24 C, 15.49 C, D).

As regards V2, Zilles [849] indicates that this area corresponds to Brodmann's area 18, although Kaas [352] claims that V2 is much narrower than area 18. V2 is strongly activated during shape discrimination [267].

Area 19 of Brodmann has been shown to harbour a considerable number of functional areas within its confines, including V3, VP, V3A, V4v, V8 and V5/MT. V3, which adjoins the anterior border of the upper part of V2, contributes to dynamic form perception. Many of its neurons are both orientation- and mo-

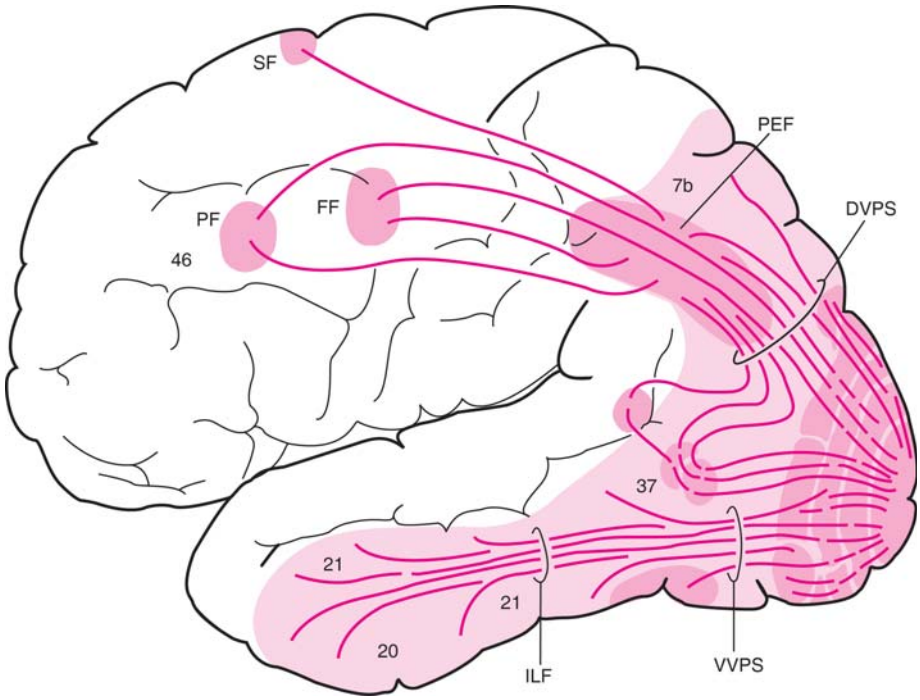


Fig. 15.50. Principal visual projections. The total brain area dominated by visual projections is shown in *light red*; visual centres in *darker red*. *DVPS*, dorsal visual processing stream; *FF*, frontal eye field; *ILF*, inferior longitudinal fasciculus; *PEF*, parietal eye field; *PF*, prefrontal eye field; *SF*, supplementary eye field; *VVPS*, ventral visual processing stream; *7b*, *20*, etc., areas according to Brodmann

tion selective [849]. VP, the ventroposterior visual area, is situated anteriorly to the basal part of V2. It has been argued that this area is not a separate functional entity, but rather represents the ventral part of V3 [847]. V3A occupies the most superior part of the occipital lobe, extending over both the lateral and the medial surface of the hemisphere. V3A, V7 and adjoining areas in the parietal lobe form a complex that is activated by saccades and attention [124]. LO, the lateral occipital area, is situated anteriorly to V3. Human imaging studies have shown that this area is involved in shape processing. It responds strongly to images of objects, but not to scrambled control stimuli [241]. V8, which is sometimes designated as V4 [737], borders laterally to LO and extends basally over the posterior parts of the lateral and medial occipitotemporal gyri. Functional imaging studies have shown that this area is involved in colour perception [60, 266, 275, 846]. Lesions in this region cause *central colour blindness (achromatopsia)*. As its name indicates, the fusiform face area (FFA) is located in the fusiform (or lateral occipitotemporal) gyrus, directly in front of V8. Functional imaging studies and single unit electrophysiology from nonhuman primates have shown that this area is selectively responsive to faces [241, 658, 737]. Lesions in FFA lead to *prosopagnosia, a selective difficulty identifying faces*. V5 or MT, the middle temporal visual area, is located in the area where the inferior temporal sulcus meets the anterior occipital sulcus. This area, which is common to all primates studied so far [352], is morphologically characterized by its dense myelination [761]. Functional imaging studies have shown that this area is strongly activated by moving visual stimuli [266, 317, 846]. Bilateral lesions that include this area cause a severe *impairment in detecting the movements of objects,* known as *cortical akinetopsia*. MT is surrounded by several other specialized areas which process higher order aspects of motion perception and motor planning [653]. One of these, the middle superior temporal visual area, MST, is situated anteriorly to MT [241].

For a detailed discussion of the visual system, the reader is referred to Chap. 19. Here we confine the discussion to a brief survey of the principal connections of the various components of the occipital lobe (Fig. 15.50).

Efferent fibres from the lateral geniculate body pass to the primary visual cortex (V1) and to the middle temporal visual area (MT) [687]. In V1, the fibres from the magnocellular, parvocellular and intercalated layers of the lateral geniculate body terminate in different layers, particularly in the various sublayers of layer IV (Fig. 15.26). The remaining visual centres in the occipital lobe receive their thalamic afferents principally from the pulvinar. Additional afferents to the occipital lobe arise from the amygdala (Fig. 13.7) [205] and the claustrum (Fig. 13.8). The afferents from the thalamus and the claustrum are reciprocated by efferent fibres. Several visual cortical centres, including V1–V3A, MT and MST, project to the pontine nuclei [210].

Short association fibres interconnect area 17(V1) with many extrastriate visual areas, including V2, V3, V3A, V4, V5/MT and MST [5, 161, 742, 768, 769].

Analysis of the connections of the various extrastriate visual areas has led to the concept that these areas are organized into two pathways: an occipitoparietal pathway or "dorsal stream" and an occipitotemporal pathway or "ventral stream" [32, 180, 181, 623, 686, 706, 735, 741, 743]. As discussed in a previous section of the present chapter (Structural Subdivision 4: Connectivity), the sequential processing of information in the areas along both pathways is progressively more complex and may, hence, be characterized as hierarchical.

The *dorsal, occipitoparietal processing stream* is engaged in the perception of relative spatial location of objects as well as visual guidance of movements towards objects *("where" system)*. It includes V1, V2, V3, V3A, V4, V5/MT, MST and STP (superior temporal polymodal) (i.e. a polysensory area situated in the dorsal bank of the superior temporal sulcus, and the so-called parietal eye field [32, 241, 686]. STP responds to visual, auditory and somatosensory stimuli. It interacts with the inferior temporal cortex. In the parietal lobe of the rhesus monkey, the territory surrounding the intra-

parietal sulcus contains a series of at least five different areas, all of which are concerned with highly specialized visual functions (see next section). These areas are collectively designated as the parietal eye field. Neuroimaging studies suggest that all of the areas included in this field have a functional equivalent (analogue) in the human brain [124]. The parietal eye field functions as a visual-motor interface. It is reciprocally connected with V1, V2 and V3 through direct and indirect pathways passing through MT, MST and V3A. The frontal lobe contains three fields which give rise to eye movements when stimulated, namely the frontal eyefield, situated in the most posterior part of the middle frontal gyrus, the prefrontal eye field, located more anteriorly in area 46, and the supplementary eye field, situated dorsally, in the most rostral part of area 6. These frontal eye fields are heavily and reciprocally connected with the parietal eye field. Moreover, most of the occipital extrastriate areas, intercalated in the dorsal processing stream, also project directly to the frontal and prefrontal eye fields [434, 579, 653].

The *ventral occipitotemporal processing stream* is concerned with pattern discrimination and the visual identification of objects (*"what" system*). Areas V1, V2, LO, V4/V8 and the entire inferotemporal cortex, composed of areas 37, 20 and 21, are included in the ventral stream. Most of the fibres, interconnecting the various areas participating in this stream, pass forwardly in the inferior longitudinal fasciculus (Fig. 15.45) [579]. The separation of the dorsal and ventral streams is not absolute. Thus, it is known that in the macaque monkey, the posterior part of the inferotemporal cortex is reciprocally connected with the parietal and frontal eye fields [155].

Interruption of the dorsal and ventral processing streams leads to distinct disconnection syndromes. Thus, judgements of spatial relations are impaired by lesions in the posterior parietal region, whereas object recognition is selectively impaired by lesions in inferior occipital and temporal areas [743].

Parietal Lobe

The parietal lobe is bounded on the lateral surface anteriorly by the central sulcus, posteriorly by the parieto-occipital line, and inferiorly by the posterior ramus of the lateral sulcus and an arbitrary parietotemporal line. The latter passes horizontally through the border area of the supramarginal and angular gyri, on the one hand, and the superior and middle temporal gyri on the other (Figs. 3.2, 15.51). On the medial surface, the boundaries are: the parieto-occipital sulcus, the subparietal sulcus and a vertical line connecting the superior limit of the central sulcus with the cingulate sulcus (Fig. 3.6).

The parietal lobe can be subdivided into four parts, the postcentral gyrus, the superior parietal lobule, the inferior parietal lobule and the parietal operculum. The postcentral gyrus runs parallel to the precentral gyrus and is situated between the central and postcentral sulci. The horizontally oriented intraparietal sulcus divides the region posterior to the postcentral sulcus into superior and inferior parietal lobules. The latter consists of two gyri, the supramarginal gyrus, arching around the upturned end of the lateral sulcus, and the angular gyrus, which surrounds the ascending, terminal part of the superior temporal sulcus (Fig. 3.2). The parietal operculum is not visible on the free surface of the hemisphere. It is situated deep to the posterior part of the lateral sulcus and connects the postcentral gyrus and the anterior part of the supramarginal gyrus with the insula. In Fig. 15.51 A, C, the parietal operculum is brought to the external surface of the hemisphere by rotation.

Brodmann [70, 71] divided the parietal lobe into nine cytoarchitectonic areas: 1, 2, 3, 5, 7, 31, 39, 40 and 43 (Figs. 15.8, 15.51 A, B). Areas 3, 1 and 2 occupy the postcentral gyrus as three narrow strips. They extend for some distance over the medial surface of the hemisphere into the anterior part of the superior parietal lobule. Area 3 was later subdivided into a small transitional zone 3 a, situated in or near the fundus of the central sulcus [388], and a larger zone 3 b. The areas 5 and 7 occu-

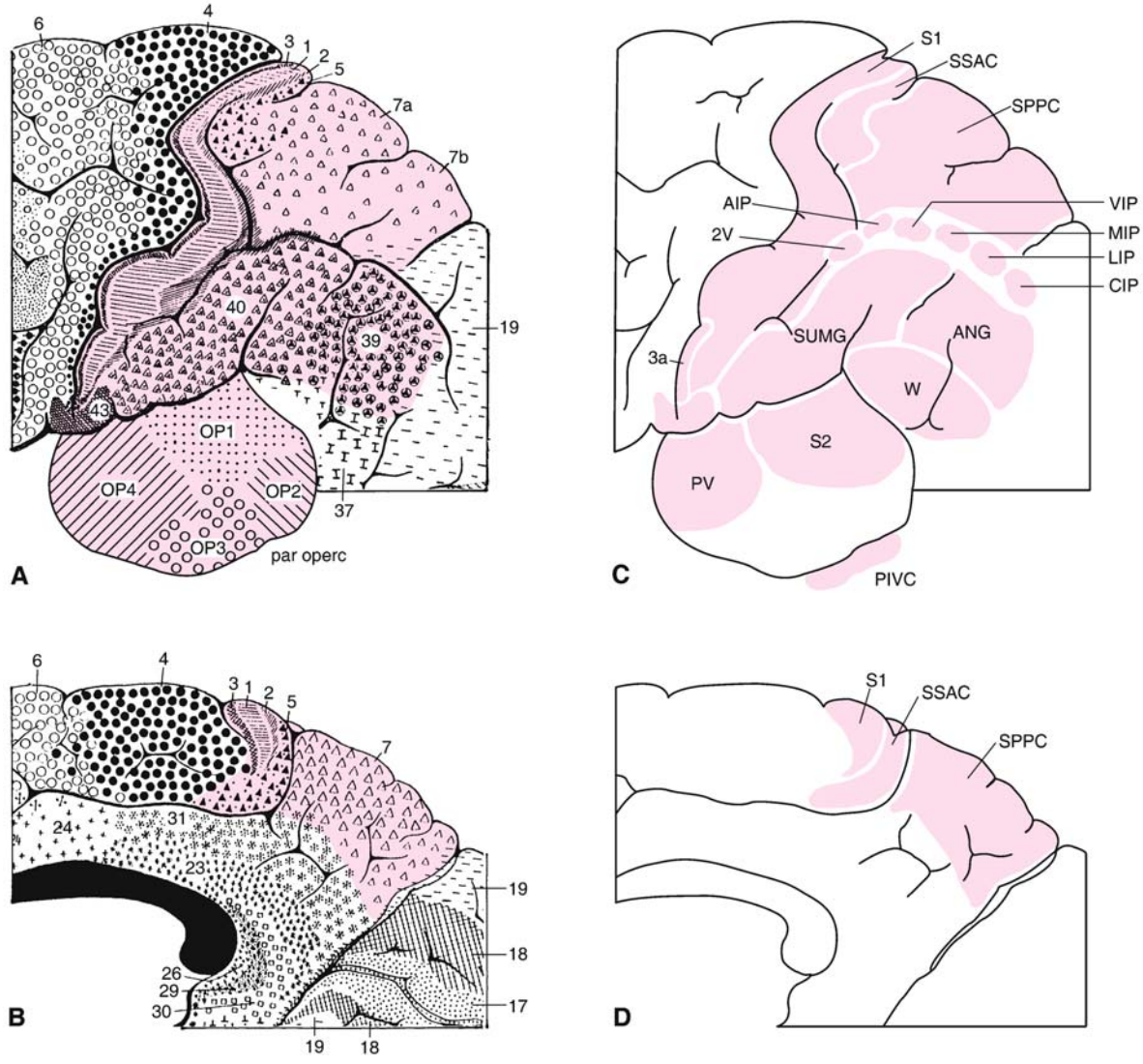


Fig. 15.51 A–D. The parietal lobe. Subdivision according to Brodmann, lateral (**A**) and medial views (**B**). The parietal lobe is shown in *red*. Functional areas, lateral (**C**) and medial views (**D**). In **A** and **C**, the parietal operculum is brought to view by rotation. *AIP*, anterior intraparietal area; *ANG*, angular gyrus; *CIP*, caudal intraparietal area; *LIP*, lateral intraparietal area; *MIP*, medial intraparietal area; *OP1–4*, parietal opercular areas, according to Eickhoff et al. [169, 170]; *par operc*, parietal operculum; *PIVC*, parieto-insular vestibular cortex; *PV*, parietal ventral area; *SPPC*, superior polymodal parietal cortex; *SSAC*, somatosensory association cortex; *SUMG*, supramarginal gyrus; *S1*, primary somatosensory cortex; *S2*, second somatosensory area; *VIP*, ventral intraparietal area; *W*, Wernicke's region; *1*, *2*, *3*, etc., areas according to Brodmann; *7 a, b*, subdivisions of area *7*; *2V*, *3 a*, vestibular cortical areas

py most of the superior temporal lobule. On the medial side of the hemisphere, area 7 extends over the precuneus. Areas 39 and 40 roughly coincide with the angular and supramarginal gyri, respectively. Area 31 is situated on the medial side of the hemisphere, where it adjoins the posterior part of the cingulate gyrus. It forms part of the limbic system and will not be further considered here. The cytoarchitecture of the parietal operculum was recently analysed by Eickhoff et al. [169, 170]. Four cytoarchitectonic areas, termed OP1–4, were identified, of which OP4 and possibly OP3 correspond approximately with Brodmann's area 43.

Cytoarchitectonically, four of the five fundamental cortex types, as distinguished by von Economo [795], are represented in the parietal lobe. Area 3 a, with its strongly developed pyramidal layers and inconspicuous granular layers, closely resembles the adjacent primary motor cortex (type 1). Area 3 b, which has a strongly developed internal granular layer IV and poorly developed pyramidal layers III and V, must be classified as a typical koniocortex (type 5). The remaining parietal areas are all homotypical, belonging either to types 2 or 3 (Fig. 15.10).

In the following discussion of the connectional and functional relations of the parietal lobe, this structure will be provisionally divided into four parts, the somatosensory and vestibular cortices, and the superior, intermediate and inferior polymodal parietal cortices (Fig. 15.51 C, D).

The *somatosensory cortex* occupies the postcentral gyrus and part of the parietal operculum. The cytoarchitectonic areas 3 b, 1 and 2, which cover the postcentral gyrus, are collectively known as the primary somatosensory cortex, S1. (Area 3 a is usually included in the motor cortex.) The contralateral half of the body surface is somatotopically mapped onto the S1 region of each hemisphere (Figs. 15.18 C, 15.19 A). The lower limb is represented in the upper part, the face in the lower part, and the trunk and upper limb in the intermediate part of S1. Each of the three primary sensory areas contain a complete body map [354] (Fig. 16.5 F).

The parietal operculum contains two somatosensory areas, the parietal ventral area and the second somatosensory area. The parietal ventral area (PV) is located immediately adjacent to the S1 cortex. It is posteriorly followed by the second somatosensory area (S2) (Fig. 15.51 C) [153]. PV and S2 roughly correspond to the cytoarchitectonic areas OP4 and OP1, respectively [169]. Areas PV and S2 both contain a somatotopic representation of the contralateral body surface. These two representations form mirror reversals of each other along their common border. The somatosensory system will be extensively discussed in Chap. 16. Here we confine the discussion to mentioning that the three parts of S1 are reciprocally connected with each other and with the various parts of the superior parietal lobule [346, 348, 389, 586, 781]. S2 is densely interconnected with the primary sensory area 3 b, PV and the inferior parietal lobule, whereas PV is interconnected with area 3 b, the superior and inferior parietal lobules, the premotor cortex, the frontal eye field and the medial auditory belt areas [154]. Some of these connections are diagrammatically indicated in Fig. 15.52 A.

The *vestibular cortex* includes an elongated area located in the inferior part of somatosensory area 3 a, an area 2 v situated around the anterior tip of the intraparietal sulcus and the parieto-insular vestibular cortex (Figs. 15.51 C, 15.72). The different vestibular cortical areas are interconnected and the PIVC occupies a central position in this network [265]. The vestibular system will be discussed in Chap. 17.

The *superior polymodal parietal cortex* occupies the superior parietal lobule, except for its most anterior part (area 5), which forms the (unimodal) somatosensory association cortex. There is evidence suggesting that this polymodal region is important for hand–eye coordination [333, 334, 733]. It is reciprocally connected with the prestriate cortex, via the dorsal processing stream, somatosensory area 5 and the dorsal part of area 8, which contains the smooth eye movement-related frontal eye field [400]. The superior parietal lobule also projects to the dorsal part of the premotor cortex (area 6) and to the supplementary motor area on the medial surface of the frontal lobe [444, 579].

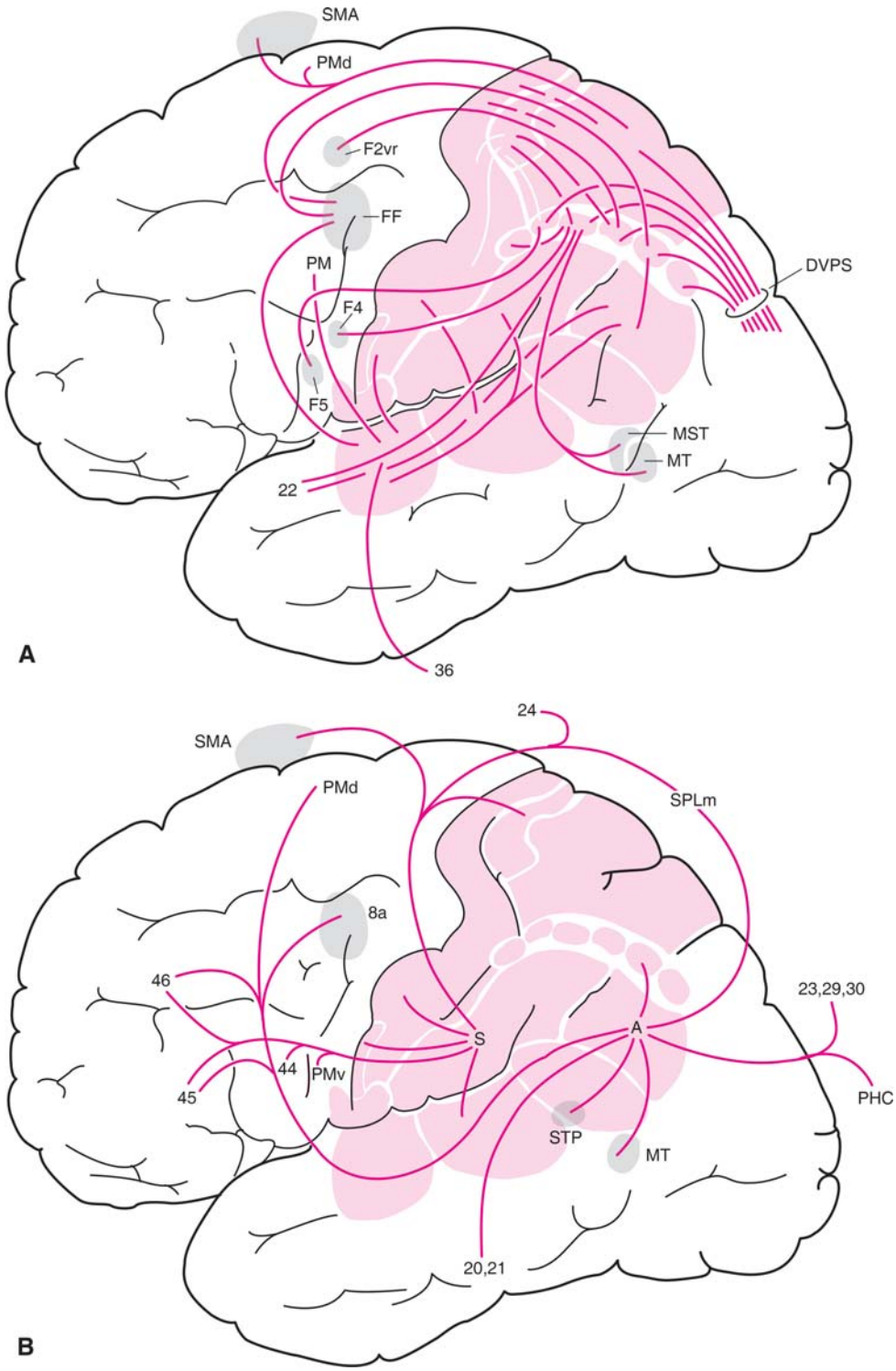


Fig. 15.52 A, B. Principal connections of the parietal lobe. Connections of the superior and opercular (**A**) and inferior parts (**B**) of the parietal lobe. *A*, angular gyrus; *DVPS*, dorsal visual processing stream; *FF*, frontal eye field; *F2vr*, *F4*, *F5*, specialized areas within the premotor cortex; *MST*, middle superior temporal visual area; *MT*, middle temporal visual area; *PHC*, parahippocampal cortex; *PM*, premotor cortex; *PMd,v*, dorsal and ventral subdivisions of premotor cortex; *S*, supramarginal gyrus; *SMA*, supplementary motor area; *SPL,m*, medial part of superior parietal lobule; *STP*, superior temporal polysensory area; *20*, *21*, etc., areas according to Brodmann

The *intermediate polymodal parietal cortex* is formed by a number of functional areas, which occupy the banks of the intraparietal sulcus. Recent morphological and physiological studies in monkeys and neuroimaging studies in humans have shown that the cortex bordering the intraparietal sulcus harbours multiple, highly specialized functional areas, some of which can also be morphologically characterized. In general, these areas serve as interfaces between perceptive and motor systems. They receive varying combinations of inputs from the surrounding visual, somatosensory, vestibular and auditory cortices and send strongly developed feed-forward projections to particular parts of the premotor cortex, which are reciprocated by feed-back projections [444]. The various intraparietal sulcal areas and their premotor targets form functional units, each of which is dedicated to a particular aspect of sensorimotor transformation [445]. The following survey of the various intraparietal sulcal areas is principally based on two review articles, by Culham and Kanwisher [124] and Grefkes and Fink [253], to which the reader is referred for references and details. The approximate positions of these areas are indicated in Fig. 15.51 C.

The *anterior intraparietal area (AIP),* which is located on the lateral bank of the anterior intraparietal sulcus (ips), is concerned with tactile and visual object processing. It plays a crucial role in the crossmodal transfer of object information between the sensorimotor and visual systems. The AIP is connected to the ventral premotor area, especially to a subunit known as F5. The neurons in this subunit discharge during specific object-related hand movements. It seems likely that AIP in combination with F5 transforms visual and somatosensory object data into finger movements for object grasping and manipulation.

The *ventral intraparietal area (VIP)* is located in the fundus of the ips. It receives projections from several visual areas, especially from MT and MST, from somatosensory, auditory and vestibular areas, and from other polymodal cortices. It is strongly connected with F4, another subunit of the ventral premotor cortex. There is evidence suggesting that VIP is involved in the perception of self-movements and object movements in near extrapersonal space. Premotor subunit F4 is known to be concerned with the transformation of object locations into appropriate movements towards them [445].

The *medial intraparietal area (MIP)* is located in the intermediate part of the medial bank of the ips. It receives somatosensory and visual afferents and is strongly connected with subunit F2vr, forming part of the dorsal premotor area. MIP and F2vr are known to be involved in the planning, execution and monitoring of reaching movements.

The *lateral intraparietal area (LIP)* forms part of a network of areas mediating saccades. It receives input from several visual areas and is interconnected with the frontal eye field (FF) and the superior colliculus. In the macaque monkey, LIP is found in the lateral wall of the ips, hence its name. However, comparative functional studies have shown convincingly that the human LIP equivalent is located in the medial ips rather than in the lateral ips.

The *caudal intraparietal area (CIP),* finally, is situated in the medial bank of the posterior ips. It receives afferents from several visual areas, including V3, V3A and V4. Experiments in macaque monkeys have shown that neurons in CIP are involved in the analysis of three-dimensional object features and are especially responsive to axis and surface orientations of objects in space. Neuroimaging studies have demonstrated that CIP is also activated during the analysis of surface and pattern orientation in humans.

Some of the connections of the intraparietal cortical areas just discussed are indicated in Fig. 15.52 A.

Choi et al. [97] recently studied the cytoarchitecture of the cortex within the anterior ventral bank of the human ips. They delineated two areas, which were termed the human intraparietal area 1 (hIP1) and the human intraparietal area 2 (hIP2). The areas hIP1 and hIP2 appeared to correspond with the functionally defined areas VIP and AIP, respectively.

The *inferior polymodal parietal cortex* occupies the inferior parietal lobule, composed of the angular and supramarginal gyri. As mentioned before, the extension of areas 39 and 40 of Brodmann correspond roughly to those of the angular and supramarginal gyri, respectively.

There are some differences of opinion concerning the interpretation of the structures under discussion. Geschwind [227] considered the human inferior parietal lobule as a "new anatomical structure". Crosby et al. [122] maintained that areas 39 and 40 have not been recognized in the macaque, and Zilles [849] designated these areas as "human specific", which means that they have no homologues in non-human primates. One of the reasons for the interpretation of these authors may be that Brodmann [70], in his map of the cortex of *Cercopithecus* (Fig. 15.12), labelled the entire region posteroinferior to the intraparietal sulcus as area 7 and did not delineate areas 39 and 40 in this species. However, it should be noted that Brodmann in his book repeatedly emphasizes that identical numbers do not indicate absolute homologies on the brain maps. In discussing the map of *Cercopithecus*, he indicates that area 7 of this species should be considered as an undifferentiated primordium of all human parietal areas, except for area 5, which is clearly distinguishable in both species. In line with this, Petrides and Pandya [579] interpreted the anterior and posterior parts of the inferior parietal lobule of the rhesus monkey (their areas PF and PG) as homologous to the human supramarginal and angular gyri, respectively. We fully agree with this interpretation because the areas mentioned occupy identical relative or topological positions in the monkey and the human. Hence, we feel justified in extrapolating the results of experimental studies on the fibre connections of the inferior parietal areas PF and PG in the macaque to the human situation.

Wernicke's speech region extends for an undetermined distance over the left inferior parietal lobule [463, 549]. The core of this region occupies the left temporal plane behind the transverse gyrus of Heschl and the posterior part of the left superior temporal gyrus. Damage to this area gives rise to receptive or Wernicke's aphasia, involving deficits in the comprehension of both spoken and written language. Long association fibres connect Wernicke's region, via the anterior limb of the superior longitudinal fasciculus, with the premotor region of the frontal lobe, including Broca's speech region in the inferior frontal gyrus [219, 346, 398, 532].

The following survey of the fibre connections of the angular (area 39, PG) and supramarginal gyri (area 40, PF) is principally based on the experimental studies of Cavada and Goldman-Rakic [94, 95], Neal et al. [503–505], Andersen et al. [11], Petrides and Pandya [579] and Gregoriou et al. [254], which were all carried out in the macaque monkey.

The *angular gyrus* is connected with visual areas of both the dorsal (MST) and the ventral (infratemporal cortex) processing streams, the medial part of the superior parietal lobule, the intraparietal oculomotor area LIP, the superior temporal polysensory area STP, and with limbic areas of the posterior cingulate, retrosplenial and parahippocampal regions. Frontal connections of the angular gyrus are principally directed to the anterior part of the dorsal premotor cortex, area 8a and prefrontal areas 45 and 46 (Fig. 15.52 B). There is evidence suggesting that the angular gyrus may play a role in the visual guidance of arm movements [254].

The most prominent connections of the *supramarginal gyrus* include those to the somatosensory areas S1, S2 and area 5, the medial part of the superior parietal lobule, the vestibular cortex, the anterior cingulate area 24, the supplementary motor area, the ventral premotor cortex, and the adjacent area 44, and prefrontal areas 45 and 46 (Fig. 15.52 B). Unit activity studies in monkeys indicate that the supramarginal gyrus is involved in the organization of co-ordinated hand and face movements [840]. Petrides and Pandya [579] suggested that the interactions between rostral inferior parietal cortex and the ventral frontal region in the monkey may be necessary for gestural communication, which may have preceded the

evolution of linguistic communication. An alternative view on the development of brain mechanisms that gave rise to language has been recently presented by Gil-da-Costa et al. [236]. These authors pointed out that monkeys possess a repertoire of species-specific vocalizations that – like human speech – seem to encode meaning in arbitrary sound patterns. Interestingly, they found that conspecific calls activate putative homologues of Wernicke's and Broca's speech regions in the rhesus monkey.

In the foregoing, we have divided the posterior parietal cortex provisionally into nine functional subregions (Fig. 15.51 C, D). If we survey the data collected on the connections and functions of these subregions, it appears that what has been said about the areas located in the banks of the intraparietal sulcus hold true for the remaining subregions as well. They are all specifically connected with one or some sections of premotor cortex, and all are dedicated to the selection and preparation of specific motor patterns, including eye movements, reaching movement, grasping movements and articulated speech [10, 445, 828].

It has already been mentioned that lesions of the inferior parietal lobule in the left hemisphere may lead to Wernicke's aphasia. When damage spares Wernicke's speech region, but involves the adjacent, more superior parts of the left inferior parietal lobule, complex combinations of anomia (naming disorders), alexia (reading impairment), construction deficits, alcalculia (difficulty in performing simple arithmetic calculations), agraphia (loss of writing skills), finger agnosia (inability to recognize, distinguish and name one's fingers or those of other persons) and right-left disorientation (inability to name or point to the right and left sides of objects or body parts) develop. The last four symptoms are collectively referred to as *Gerstmann's syndrome*.

Lesions in the inferior parietal lobule of the right hemisphere lead to characteristic deficits, including dressing difficulties, constructional difficulties and multimodal neglect of the left hemispace [463].

Bilateral lesions of the dorsal parts of posterior parietal lobules may give rise to the rare but dramatic *syndrome of Balint*, which is characterized by (1) simultanagnosia, (2) oculomotor apraxia and (3) optic ataxia. Simultanagnosia is the inability to see all the components of the visual scene in an integrated way. Oculomotor apraxia or psychic paralysis of gaze is the inability to voluntarily direct gaze toward a specific part of the visual field. Optic, or visuomotor, ataxia is the inability to direct movement of an extremity using visual guidance [151].

Temporal Lobe

The temporal lobe presents large lateral and basal surfaces and a more limited medial surface. The lateral surface is dorsally separated from the frontal and anterior parietal lobes by the lateral sulcus, and more caudally from the posterior parietal lobe by an arbitrary parietotemporal line (Fig. 3.2). The caudal border of the temporal lobe is formed on the lateral surface by the anterior occipital sulcus and on the basal side by the occipitotemporal sulcus and an arbitrary, transversely oriented occipitotemporal line (Figs. 1.4, 3.5, 15.53). Ventromedially, the temporal lobe is separated from the limbic lobe by the collateral and rhinal sulci (Fig. 3.6).

Two grooves, the superior and inferior temporal sulci, which roughly parallel the lateral sulcus, divide the lateral surface of the temporal lobe into superior, middle and inferior temporal gyri. The basal surface of the temporal lobe is formed by the basal part of the inferior temporal gyrus and most of the lateral and medial occipitotemporal gyri.

The superior temporal gyrus includes the temporal operculum because the gyrus extends medially to meet the inferior part of circular sulcus around the insula. On the opercular surface of the temporal lobe, which forms the floor of the lateral sulcus, there are one or two, more or less transversely running convolutions, the transverse temporal gyri of Heschl. The areas anterior and posterior to these gyri are known as the planum polare and planum temporale, respectively (Fig. 18.1 B).

Brodmann [70, 71] divided the cortex covering the temporal lobe into eight cytoarchitec-

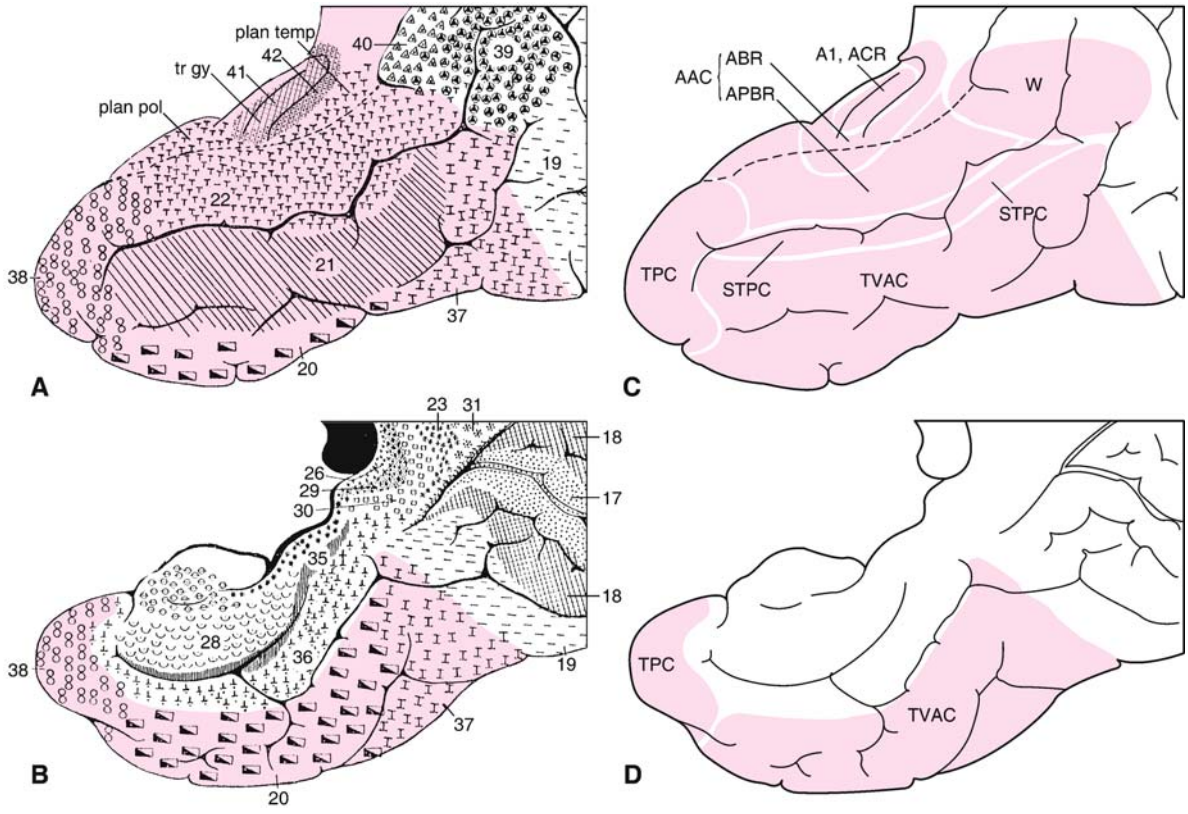


Fig. 15.53 A–D. The temporal lobe. Subdivision according to Brodmann, lateral (**A**) and medial (**B**) views. The temporal lobe is shown in *red*. Functional areas, lateral (*C*) and medial (*D*) views. In **A** and **C**, the upper surface of the superior temporal gyrus or temporal operculum is brought to view by rotation. The approximate boundary between the temporal operculum and the lateral surface of the superior temporal gyrus is indicated by a *dashed line*. *A1*, primary auditory cortex; *AAC*, auditory association cortex; *ABR*, auditory belt region; *ACR*, auditory core region; *APBR*, auditory parabelt region; *plan pol*, planum polare; *plan temp*, planum temporale, *STPC*, superior temporal polymodal cortex; *TPC*, temporopolar cortex; *TVAC*, temporal visual association cortex; *tr gy*, transverse gyrus of Heschl; *W*, Wernicke's region; *19*, *20*, etc., areas according to Brodmann

tonic areas: 41, 42, 22, 21, 20, 36, 37 and 38 (Figs. 15.8, 15.53 A, B). Area 41, the primary auditory cortex, is situated on the opercular surface of the temporal lobe. It forms a rather narrow strip which, extending from anterolateral to posteromedial, corresponds roughly with the (anterior) transverse temporal gyrus of Heschl. Area 42 is located directly posterior to area 41 and partly surrounds the latter (Fig. 15.8 insert). Most of this area is opercular, but its lateral part extends for some distance over the free lateral surface of the superior temporal gyrus. Areas 22, 21 and 20 were designated by Brodmann as area temporalis superior, -media and -inferior, respectively, indicating that they roughly correspond to the gyri of the same name. Area 20 extends basally over the anterior part of the lateral occipitotemporal gyrus. Area 36 is situated on the medial surface of the temporal lobe. It is bounded superiorly by the rhinal and collateral sulci and inferiorly by area 20. Area 37 occupies the posterior part of the temporal lobe, extending over its lateral and basomedial surface. Area 38, finally, covers the temporal pole.

In what follows, the temporal lobe will be divided into the following five functional regions: (1) the primary auditory cortex, (2) the auditory association cortex, including Wernicke's region, (3) the temporal visual association cortex, (4) the superior temporal polymodal cortex and (5) the temporopolar cortex (Fig. 15.53 C, D). The auditory system, including the auditory cortices, will be extensively discussed in Chap. 18; hence we confine the discussion here on these subjects to a brief overview.

The *primary auditory cortex,* or auditory core region, corresponds with area 41 of Brodmann. It has the typical koniocortical structure of primary sensory cortices, with a well-developed layer IV, consisting of densely packed granule cells. Morosan et al. [489] recently subdivided the primary auditory cortex into posteromedial, central and anterolateral subareas, which they designated Te1.1, Te1.0 and Te1.2, respectively. A similar tripartitioning of the primary auditory cortex was proposed for the monkey (Fig. 18.3 g). The functional significance of this parcellation remains to be elucidated.

The *auditory association cortex* can be divided into a belt and a parabelt region. The belt region borders on the primary auditory core, surrounding it anteriorly, laterally and posteriorly. Most of it is confined to the temporal operculum, but laterally it extends a short distance onto the superficial aspect of the superior temporal gyrus. The belt region consists of several cytoarchitectonic fields, among them Brodmann's area 42 [220]. The structure of the belt areas is intermediate between the typical koniocortex of area 41 and the homotypical structure of area 22 and the remainder of the temporal lobe.

The belt region is surrounded in turn by an extensive parabelt region that covers the remaining anterior and posterior parts of the temporal operculum and the lateral surface of the superior temporal gyrus with the exception of its anterior pole. It corresponds largely with Brodmann's area 22.

Short association projections connect the auditory core with the belt and the latter with the parabelt cortex [273, 485, 486, 528, 670]. Neuroimaging studies on the response to auditory stimuli show a spread of activity, beginning with activation by simple stimuli of a limited region of the temporal operculum, and expanding with more complex stimuli to the surface of the superior temporal gyrus [478].

Commissural connections of the auditory cortex are predominantly homotopical. Lesions in the core, belt or parabelt result in degenerating fibres in corresponding areas in the contralateral hemisphere [272, 486, 670]. The auditory commissural fibres are located in the posterior part of the truncus of the corpus callosum, together with the commissural fibres of the parietal lobe [531].

The auditory association cortex in the posterior parabelt region grades on the left side into the heteromodal cortex of Wernicke's speech region. The precise architectonic borders of this region are not known, but it is generally assumed that it includes the posterior portions of the planum temporale and superior temporal gyrus and the most basal parts of the an-

gular and supramarginal gyri [26, 398, 465]. Interruption of the auditory, visual or tactile projections to Wernicke's region lead to pure word deafness, pure alexia and tactile aphasia, respectively [227] (Fig. 15.20). As already mentioned, damage to Wernicke's region itself causes *receptive or Wernicke's aphasia*.

Experimental studies in rhesus macaques [274, 576, 579, 631, 632] have shown that the auditory association cortex is strongly and reciprocally connected with the prefrontal cortex. Romanski et al. [631, 632] found that these audito-prefrontal connections form two streams, anterior and posterior, connecting different sectors of the auditory association cortex with largely different prefrontal regions.

The anterior stream connects the anterior belt and parabelt cortex reciprocally with the frontal pole (area 10), the anterior part of area 46 and a ventral prefrontal region, including areas 12 and 45. In contrast, the posterior stream mainly interconnects the posterior belt and parabelt cortex with the frontal eye field (area 8) and the posterior part of area 46 (Fig. 15.54 A). Romanski et al. [632] pointed out that the regions receiving input from the posterior belt and parabelt are implicated in spatial processing, whereas those receiving input from the anterior belt and parabelt are implicated in non-spatial, higher functions. They drew a parallel with the central visual system, where separate processing streams, the dorsal "where" stream and the ventral "what" stream, follow different courses and terminate ultimately in roughly the same dorsolateral spatial and ventrolateral object-processing regions of the frontal lobe [822].

The *temporal visual association cortex* represents a rostral extension of the circumstriate belt, below the superior temporal sulcus. It includes areas 20, 21 and 37 of Brodmann, which may be collectively designated as the inferotemporal visual cortex. The posterior part of this region houses several functionally defined areas, including the middle temporal visual area, MT, the middle superior temporal area, MST, and the fusiform face area, FFA (Fig. 15.49 C). In rhesus macaques, neurons in the inferotemporal cortex respond almost exclusively to visual stimulation and not to stimulation in other sensory modalities [150]. Many of these neurons respond selectively to various complex visual features of objects [255, 730]. Recordings of field potentials from the surface of the brain in patients have shown that an area in the anterobasal temporal lobe is specifically involved in the processing of written words [512].

The inferotemporal cortex, including FFA but excluding MT and MIT, forms part of the ventral, occipitotemporal visual processing stream, which is concerned with pattern discrimination and visual identification of objects. The inferior longitudinal fascicle, which forms the axis of this processing stream, contains, apart from long occipitotemporal projections, numerous short fibres that sequentially connect adjacent regions in the striate, peristriate and inferotemporal cortices [155, 579, 715, 739, 809] (Fig. 15.45). Efferents from the basal amygdaloid nucleus pass caudally in or close to the inferior longitudinal fascicle, to terminate in the various cortical regions forming part of the ventral visual processing stream. These amygdalar efferents terminate mainly in the most superficial and deep layers of their cortical targets and hence resemble cortico-cortical feed-back fibres [204].

Efferents from the inferotemporal cortical region, particularly its rostral parts, relay extensively processed visual information to: (1) the adjacent superior temporal polymodal region [127]; (2) limbic cortical regions, including the temporopolar cortex, the perirhinal area 36 and the subiculum [647, 774]; (3) the lateral amygdaloid nucleus [204, 298]; and (4) the prefrontal cortex. The projection to the latter passes via the uncinate fasciculus and terminates mainly in areas 11 and 47/12 [579] (Fig. 15.54 B). Commissural fibres from the inferotemporal cortex cross in the posterior part of the body of the corpus callosum and in the anterior commissure [531].

Experimental neuroanatomical studies have shown that the cortex of the upper bank of the superior temporal sulcus in the rhesus monkey contains an elongated region that receives converging input from surrounding auditory, vis-

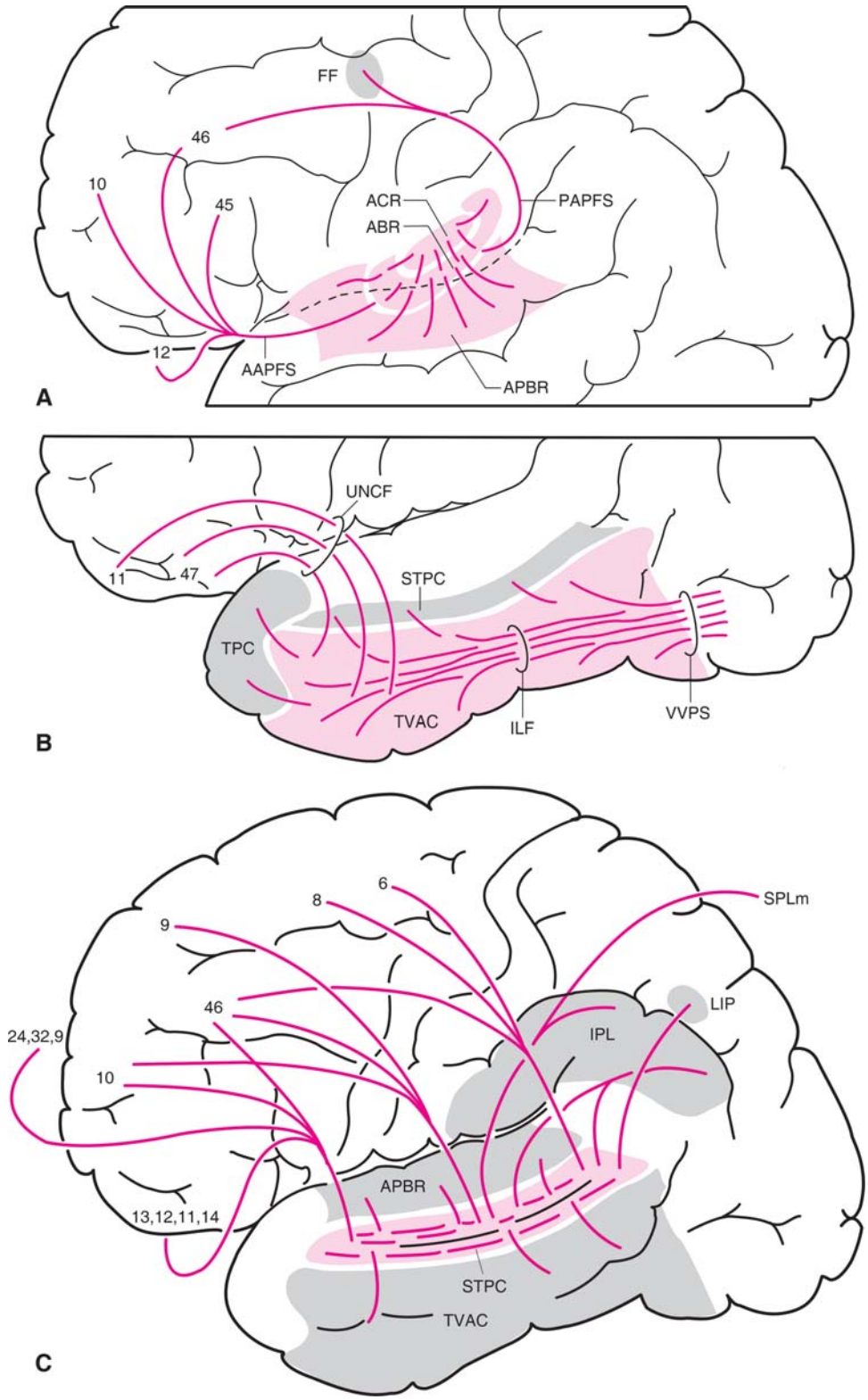


Fig. 15.54 A–C. Principal connections of the temporal lobe. Cortical auditory pathways (**A**); connections of the temporal visual association cortex (**B**) and connections of the superior temporal polymodal cortex (**C**). *AAPFS*, anterior audito-prefrontal processing stream; *ABR*, auditory belt region; *ACR*, auditory core region; *APBR*, auditory parabelt region; *FF*, frontal eye field; *ILF*, inferior longitudinal fasciculus; *IPL*, inferior parietal lobule; *LIP*, lateral intraparietal area; *PAPFS*, posterior audito-prefrontal processing stream; *SPLm*, medial part of superior parietal lobule; *STPC*, superior temporal polymodal cortex; *TPC*, temporopolar cortex; *TVAC*, temporal visual association cortex; *UNCF*, uncinate fasciculus; *VVPS*, ventral visual processing stream; *6, 8, 9*, etc., areas according to Brodmann

ual and somatosensory association areas [346, 670, 675]. Electrophysiological studies have revealed that neurons in this region respond to auditory, visual or somatosensory stimulation, including some whose response is bi- or trimodal [42, 47, 74, 150, 299, 472, 551, 707]. These findings have led to the conclusion that the sulcal cortex in question is polymodal in nature and should therefore be designated as the *superior temporal polymodal or STP cortex* [150, 346, 670].

The elongated strip of STP cortex has been divided on cytoarchitectonic and chemoarchitectonic grounds into four rostrocaudally arranged units, termed TPO1–TPO4 [125, 127, 670, 673, 676]. These units are tied together in a sequence of reciprocal connections, comprising shorter and longer, rostrally directed feed-forward and caudally directed feed-back projections [673].

The extrinsic connections of the STP cortex can be divided into a post-Rolandic and a pre-Rolandic group. The post-Rolandic connections relate the STP cortex to auditory, visual and somatosensory association cortices and to several limbic areas.

Auditory afferents to the STP cortex originate from the superior temporal cortex. They show a topical organization in that the caudal, middle and rostral zones of the superior temporal cortex project to areas TPO4, TPO2–3 and TPO1, respectively [675].

Visual projections to the STP cortex include afferents from (1) the LIP area in the intraparietal sulcus, which terminate in the TPO4, (2) the caudal inferior parietal lobule, terminating in areas TPO2–4, (3) the caudal inferotemporal cortex, targeting areas TPO3–4, and (4) the rostral inferotemporal cortex terminating in area TPO1. The inferotemporal cortex also projects indirectly to area TPO1 via some visual association areas, known as IPa, TEa and TEm, situated in the lateral bank of the superior temporal sulcus [155, 638, 647, 675, 772]. It is noteworthy that the visual projections converging on the STP cortex originate from areas forming part of both the dorsal and the ventral visual streams. Thus, the LIP area and the inferior parietal lobule belong to the dorsal stream, whereas the inferotemporal cortex belongs to the ventral stream.

Somatosensory afferents to the STP cortex emanate reportedly from mid-portions of the inferior parietal lobule and the medial parietal lobe [530, 671].

In addition to the sensory inputs just discussed, the STP cortex has extensive afferent connections with several limbic cortical structures. As with cortical sensory input, these projections have a rostral-to-caudal topographical organization. Projections from parahippocampal area 35, for example, target area TPO1; those from entorhinal area 28 target mid-area TPO, whereas area TPO4 receives input from the insular limbic cortex. Furthermore, areas TPO2–4 have afferent connections with anterior cingulate area 24, posterior cingulate area 23, and retrosplenial areas 29 and 30. Seltzer and Pandya [675], who described the limbic connections just mentioned, pointed out that certain sets of cortical areas projecting to the same rostrocaudal segment of the STP cortex are themselves interconnected. They mention as examples that the parahippocampal area 35 and rostral superior temporal cortex, which target area TPO1, have strong reciprocal connections and that the same holds true for the entorhinal area 28 and middle superior temporal cortex, which target areas TPO2–3.

Almost all of the sensory and limbic afferent systems to the various sectors of the STP cortex are reciprocated by efferent systems [37, 674].

The pre-Rolandic connections of the STP cortex are organized according to the rostral-to-caudal differentiation of this multimodal region. Area TPO1 projects to basal (areas 13, 12, 11 and 14), medial (areas 24, 32 and 9) and lateral (areas 10 and 46) sectors of the frontal lobe. Areas TPO2–3 project to rostral subdivisions of the lateral prefrontal cortex, namely areas 46, 9 and 10, whereas area TPO4 projects to caudal subdivisions (areas 46, 8 and 6) of the lateral frontal lobe (Fig. 15.54 C). All of these efferent projections, except for those to the basal (orbitofrontal) cortex, are reciprocated by afferent systems [672]. Luppino et al. [432] reported that not only the caudal, but

also the rostral part of the STP cortex projects to the premotor cortex (area 6).

The areal organization of the cortex surrounding the human superior temporal sulcus has not been explored so far. However, it seems reasonable to assume that this cortex, which forms the border region of areas 21 and 22 of Brodmann, contains a polymodal zone comparable to that in non-human primates [463]. Recent brain-imaging studies, summarized by Zilbovicius et al. [848], have shown that in humans, the superior temporal sulcal (STS) cortex is involved in the processing and integration of complex visual and auditory information, conducive to understanding of the mental states and intentions of other individuals. The information involved in this social perception includes eye gazes, gestures, facial displays of emotions and voice perception. Zilbovicius et al. [848] also cite brain-imaging results, suggesting that in autism, a mental disorder in which communication deficits are most prominent, anatomical and functional abnormalities in the STS cortex are implicated.

The *temporopolar cortex,* which corresponds to area 38 of Brodmann, is commonly designated as a paralimbic structure. Morphologically, it lies beyond the limbic lobe, but structurally it forms part of the so-called paralimbic belt. As discussed in Chap. 11 (and in the next section of the present chapter), the limbic lobe forms a large arcuate convolution on the medial aspect of the hemisphere, which extends from the frontal, via the parietal, into the temporal lobe. As shown by Fig. 12.3, its frontal and temporal ends are formed by infralimbic area 25 and perirhinal areas 35 and 36, respectively. According to Mesulam [463], the gap between the ends of the limbic lobe is bridged by three structures, the caudal orbitofrontal cortex (the posterior parts of areas 12, 13, 14), the anterior insula, and the temporopolar cortex (Fig. 15.55). Together with the cortices covering the various parts of the limbic lobe, these structures form the paralimbic belt. Architectonically, the belt areas provide a continuous transition zone between the simple, three-layered olfactory and hippocampal cortices, on the one hand, and the surrounding neocortical regions, on the other [463, 479].

The temporopolar cortex receives afferents from the adjacent auditory and visual association areas and has reciprocal connections with numerous paralimbic and limbic areas, including the caudal orbitofrontal cortex, anterior insula, entorhinal cortex, and the subicular complex [439, 479] (Fig. 15.56).

It has been demonstrated that single neurons in the temporopolar cortex of macaque monkeys exhibit oscillatory activities in response to the representation of complex visual stimuli such as photographs of familiar human faces, familiar foods, and familiar non-food objects [501, 502]. Bilateral lesions of the human temporopolar cortex cause marked retrograde amnesia, which includes the loss of all remote memories, but spares anterograde learning and recent memory [359, 360]. Typically, patients with these lesions not only lose episodic, autobiographical memories, but also the ability to recognize faces and names of famous persons learned in the remote past [359, 731]. Sewards and Sewards [678] inferred from these lesion data that the neuronal activities providing the awareness of remote (consolidated) object recognition occur in the temporopolar cortex. The fact that patients with retrograde recognition memory loss due to lesions of the temporopolar cortex do not lose the ability to recognize objects learned in the recent past, nor the ability to learn to recognize new objects, indicated, according to Sewards and Sewards, that there must be at least one other cortical area in which neuronal activities produce recognition awareness. They adduce clinical and experimental evidence indicating that such a centre, providing recognition awareness of objects learned in the recent past, does exist and is located in another paralimbic region, the medial orbitofrontal cortex.

Limbic Lobe and Paralimbic Belt

The limbic lobe, as defined by Broca [68], consists of a large, arciform convolution on the medial aspect of the cerebral hemisphere, which surrounds the interhemispheric commissures and the upper brain stem (Fig. 1.4B).

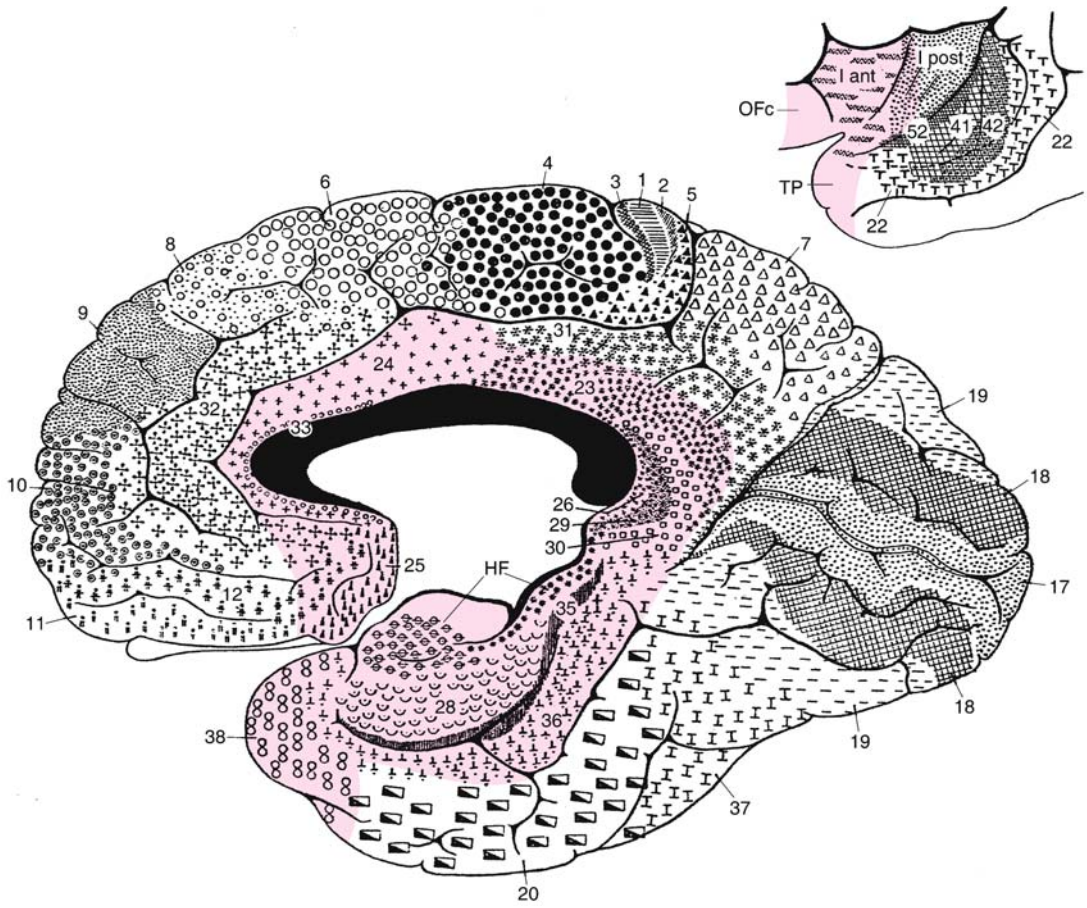


Fig. 15.55. Brodmann's cytoarchitectonic map of the medial hemisphere wall. Paralimbic areas are shown in *red*. The *insert* represents a small part of the lateral surface of the hemisphere. The lateral sulcus is opened to expose the insula. In combination with the main figure, it illustrates that the caudal orbitofrontal cortex, anterior insula and temporopolar cortex bridge the gap between the prelimbic area 25 and perirhinal areas 35 and 36, thus closing the paralimbic belt. Based on Mesulam [463]. *HF*, hippocampal formation; *I ant*, *post*, anterior and posterior insula; *OFc*, caudal orbitofrontal cortex; *TP*, temporopolar cortex

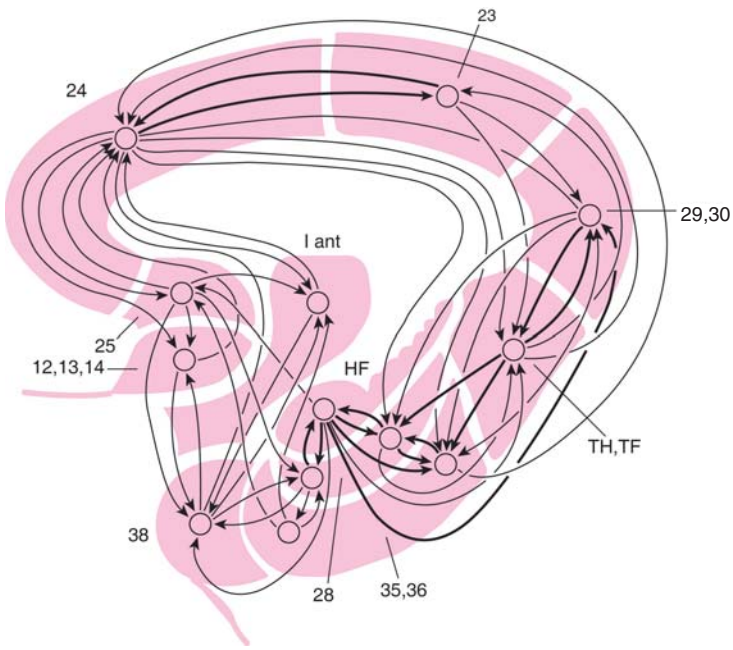


Fig. 15.56. Intrinsic cortical connections of structures forming the paralimbic belt. Particularly strongly developed projections are indicated by *heavy lines*. *HF*, hippocampal formation; *I ant*, anterior insula; *TH*, *TF*, medial temporal cortical areas according to von Economo and Koskinas [796]. *12, 13* etc., areas according to Brodmann

The limbic lobe includes the cingulate and parahippocampal gyri and also the hippocampal formation. Cytoarchitectonically, the limbic lobe encompasses the infralimbic cortex (area 25), the anterior and posterior cingulate cortices (areas 24 and 23), the retrosplenial cortex (areas 26, 29 and 30), the perirhinal cortex (areas 35 and 36), the entorhinal cortex (area 28) and the various parts of the hippocampal formation (dentate gyrus, Ammon's horn and subicular complex). Von Economo and Koskinas [796] demonstrated that a region roughly corresponding to the posterior parts of Brodmann's areas 35 and 36 contains two distinct separate entities, a superior area TH and an inferior area TF. As discussed in the previous section, the cytoarchitectonic areas just enumerated constitute, together with the caudal orbitofrontal cortex (areas 12, 13, 14 and caudal part of area 11), the anterior insula and the temporopolar cortex (area 38), the paralimbic belt (Fig. 15.55).

The intrinsic [55, 96, 152, 324, 377, 397, 439, 479, 482, 717, 772, 782, 843] and extrinsic connections of the various (para)limbic cortical structures [96, 152, 323, 324, 346, 377, 380, 397, 441, 480, 527, 579, 639, 716, 772, 782, 843] have been extensively studied in the rhesus monkey. The principal results of these studies are summarized and extrapolated to the human brain in Figs. 15.56 and 15.57. It will be seen that the various belt structures (a) are strongly and reciprocally interconnected (Fig. 15.56); (b) receive extrinsic cortical afferents from numerous unimodal (7, 19, 20, 21, 22) and polymodal (STSC, 9, 10, 11, 46) sensory areas (Fig. 15.57 A); and (c) send their extrinsic cortical efferents mainly to the same association areas (Fig. 15.57 B). For a further discussion of the limbic lobe, the reader is referred to Chap. 12. The limbic lobe and the more extensive paralimbic belt form part of a large functional entity, designated as the greater limbic system [510]. This functional system will be treated in the final chapter (Chap. 23) of the present work.

Frontal Lobe

The frontal lobe is strongly developed and comprises approximately one third of the entire hemisphere surface. On the lateral, convex surface it extends from the central sulcus to the frontal pole. Basolaterally, it is separated from the temporal lobe by the lateral sulcus. On the medial surface, the frontal lobe is separated from the limbic lobe by the cingulate sulcus, and from the parietal lobe by an arbitrary vertical line connecting the superior limit of the central sulcus with the cingulate sulcus.

The superolateral surface of the frontal lobe is traversed by three sulci, the precentral sulcus and the superior and inferior frontal sulci. The precentral sulcus runs parallel to the central sulcus. These two sulci border the precentral gyrus. The arciform superior and inferior frontal sulci divide the convex surface in front of the precentral gyrus into three convolutions, the superior, middle and inferior frontal gyri (Fig. 3.2). Short anterior and ascending branches of the lateral sulcus divide the inferior frontal gyrus into three parts: pars opercularis, pars triangularis and pars orbitalis (Fig. 3.2). These areas in the dominant hemisphere (usually the left in right-handed individuals) correspond to the region of Broca [67] associated with the motor aspects of speech.

The basal surface of the frontal lobe overlies the bony orbit; hence, the cortex in this region is designated as the orbitofrontal cortex. The olfactory bulb and tract lie in a longitudinal sulcus near the medial margin of the frontal lobe, known as the olfactory sulcus (Figs. 3.4, 3.5). The concave area lateral to the olfactory bulb and tract bears a number of sulci, which together form an H-shaped configuration. These sulci divide this area into four orbital gyri, anterior, lateral, posterior and medial. The latter is separated from a fifth orbital gyrus, the gyrus rectus, by the olfactory sulcus (Figs. 3.4, 3.5, 15.5 C, G).

The cytoarchitectonic subdivision of the frontal lobe, according to Brodmann [70, 71], is shown in Fig. 15.58 A, B. Among the 14 frontal areas distinguished by that author, there are agranular (4, 6, 24, 25, 32), dysgranular (8,

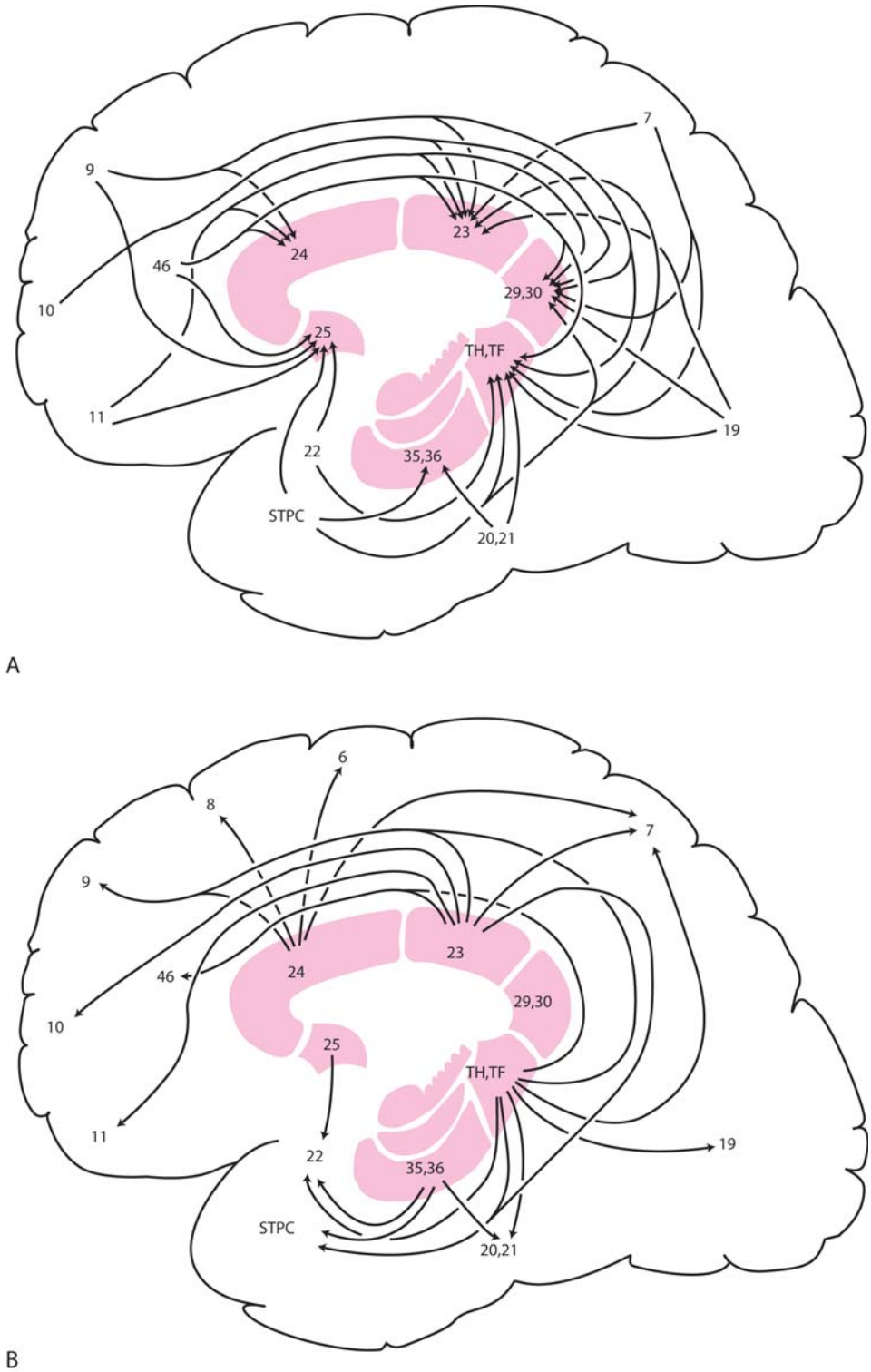


Fig. 15.57 A, B. Extrinsic cortical connections of paralimbic structures. **A** Afferents; **B** efferents. *STPC*, superior temporal polymodal cortex. Numbers and other abbreviations as in Fig. 15.56

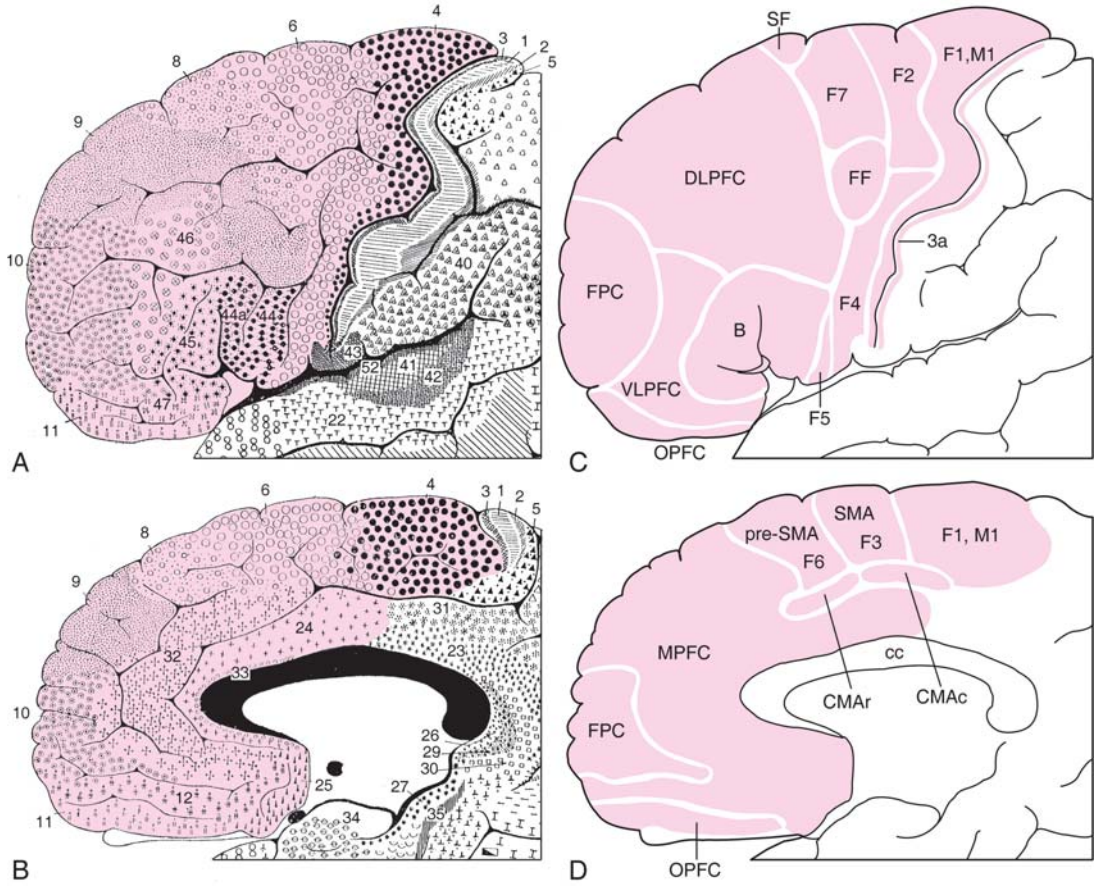


Fig. 15.58 A–D. The frontal lobe. Subdivision according to Brodmann, lateral (**A**) and medial (**B**) views. The frontal lobe is shown in *red*. Functional areas, lateral (**C**) and medial (**D**) views. *B*, Broca's speech region; *cc*, corpus callosum; *CAMc,r*, caudal and rostral cingulate motor area; *DLPFC*, dorsolateral prefrontal cortex; *F1–F7*, subdivisions of motor cortex; *FF*, frontal eye field; *FPC*, frontopolar cortex; *M1*, primary motor cortex; *MPFC*, medial prefrontal cortex; *OPFC*, orbital prefrontal cortex; *pre-SMA*, pre-supplementary motor cortex; *SF*, supplementary eye field; *SMA*, supplementary motor area; *VLPFC*, ventrolateral prefrontal cortex

44, 45), as well as granular areas (9, 10, 11, 12, 46, 47) (Fig. 15.7 A, F). According to the cytoarchitectonic typology of von Economo [795], areas 4, 6, 24 and 25 are heterotypical and belong to type 1, whereas all of the remaining frontal areas are homotypical. Of these, area 46 and part of area 10 belong to type 3, the orbitofrontal areas 11, 12 and 47 to type 4 and the remaining homotypical frontal areas to type 2 (Fig. 15.10).

The frontal cortex can be divided into two large functional domains, the motor cortex and the (associative) prefrontal cortex. The *motor cortex* is situated in front of the central sulcus and extends over the medial surface of the hemisphere. The *prefrontal cortex* occupies the large region that lies rostral to the precentral motor cortex [581] (Fig. 15.58 C, D).

The motor cortex comprises the primary motor cortex (M1) and the non-primary motor cortex. Matelli et al. [443, 445] have subdivided the somatic motor cortex of the rhesus monkey into seven areas designated F1–F7. This parcellation was based on cytoarchitectonic, histochemical, neurochemical, hodological and functional data. Modern architectonic analyses and functional evidence, mostly from neuroimaging studies, indicate that the organization of the human motor cortex closely resembles that of the rhesus monkey. Indeed, almost all of the structural/functional entities distinguished in the former can also be identified in the latter [188, 445, 585]. Hence, the following parcellation of the motor cortex applies to both species (Fig. 21.6).

Area F1 (or M1) represents the *primary motor cortex*. It corresponds to area 4 of Brodmann, which is characterized by the presence of the giant pyramidal cells of Betz (Figs. 15.7 F, 15.28 (6). Lassek [395] counted approximately 34,000 Betz cells in area 4 of the human brain.

Electrical stimulation studies of the primary motor cortex in both man [197, 544, 545, 548] and experimental animals [261, 784, 785, 830, 831] have revealed the presence of a topographical map within that cortex of the contralateral body half, comparable to that found in the adjacent primary sensory area (Figs. 15.18 C, 15.19).

Area 3 a is represented by a narrow strip of cortex, located in the fundus of the central sulcus. Its cytoarchitecture is similar to that of area 4, but it receives information from muscle receptors through the thalamus. Its cortical connections closely resemble those of the primary motor cortex.

The primary motor cortex receives afferents from both subcortical and cortical sources. The subcortical afferents arise principally from the contralateral dentate nucleus, via the posterior part of the ventral lateral thalamic nucleus and from the ipsilateral globus pallidus, via the anterior part of the same thalamic nucleus (Fig. 14.8). The cortical afferents to the primary motor cortex originate from several non-primary motor areas [164, 475], including the dorsal and ventral premotor areas [481, 711], the supplementary motor area [481] and the cingulate motor area [480], and from the primary somatosensory cortex (S1) and the somatosensory association cortex (area 5) [316, 542, 587]. The projection from S1, which arises from areas 1, 2 and 3 b, is topographically organized. The somatosensory association area is primarily concerned with the analysis of proprioceptive information. It seems likely that the efferents from this association area to the primary motor cortex provide the latter with information on the localization of body parts, necessary for the control of limb movements.

The primary motor cortex contributes substantially to the pyramidal tract. For a detailed discussion of this fibre system, the reader is referred to Chap. 21 and Fig. 21.9. Here, we confine the discussion to mentioning that this tract arises principally from the motor and somatosensory cortical areas surrounding the central sulcus. Its fibres originate from pyramidal neurons situated in cortical layer V and via the internal capsule descend to the brain stem and spinal cord. The pyramidal fibres originating from the precentral gyrus (areas 3 a and 4) pass to premotor interneurons and also directly to motoneurons. The direct corticomotoneuronal connections are established by coarse fibres, derived from the giant cells of Betz. These direct pyramidal tract connections to motoneurons, especially to those innervating

distal extremity muscles, appear to provide the capacity to execute highly fractionated movements, as typified by independent movements of the digits [390].

It has long been thought that the relation between the primary motor cortex and the skeletal muscular system is fixed and that this cortex is exclusively concerned with the execution of movements and is not responsible for the design of movement patterns. Both concepts have appeared to be incorrect. Recent evidence, summarized by Graziano [252], has shown that the connectivity between primary motor cortex and muscles is not fixed but plastic, changing constantly on the basis of feedback from the periphery. Moreover, it has been shown that with electrical stimulation trains of longer duration than used in the classical mapping studies cited above (500 ms instead of 50 ms), complex movements resembling meaningful actions, such as putting the hand to the mouth, defensive gestures, reaching motions and shaping the hand as if to grasp an object, can be elicited from the precentral cortex (Fig. 21.11 C).

Area 6 of Brodmann lies immediately anterior to the primary motor cortex. Just like the latter, it extends on the medial wall of the hemisphere (Fig. 15.58 A, B). The portion of area 6 situated on the lateral surface of the hemisphere corresponds to the *premotor cortex (PM), which can be subdivided into a dorsal (PMD) and a ventral zone (PMV).* Both of these zones can be further subdivided into caudal and rostral parts. The *caudal part of the ventral premotor zone, PMVc or area F4*, is located directly in front of the representation of orofacial movements in the primary motor cortex. The *rostral part of the ventral premotor zone, PMVr or area F5*, in the rhesus monkey contains two different functional areas, a caudal area F5ab and a more rostrally situated area F5c. It seems likely that the most rostroventral part of area 6 of non-human primates is homologous to Broca's speech region [445] in humans. The *dorsal premotor zone (PMD)* can be structurally and functionally subdivided into a *caudal PMDc* or *area F2* and a *rostral PMDr* or *area F7* (Fig. 15.58 C).

The medial portion of Brodmann's area 6 is occupied by two functional areas, the caudal *supplementary motor area (SMA) or area F7*, which is also known as M2, and the rostral *presupplementary motor area (pre-SMA) or area F6* [447] (Fig. 15.58 D). The medial wall of the hemisphere contains two further areas related to motor control. These areas, which may be designated as the *caudal and rostral cingulate motor areas, CMAc and CMAr*, are buried in the cingulate sulcus [188, 585]. The CMAc, which borders on the SMA and the rostral part of the primary motor cortex, forms a subfield of Brodmann's area 24. It contains a population of gigantopyramidal neurons, similar to those in the adjacent primary motor cortex [62]. The CMAr is located roughly at the same rostrocaudal level as the pre-SMA (Fig. 15.58 D). It also forms part of Brodmann's area 24 but probably encroaches upon area 32. CMAr and CMAc are also denoted as M3 and M4, respectively [482, 483].

Classically, the central skeletomotor system was looked upon as strictly hierarchical. The efferent pyramidal neurons in the primary motor cortex were collectively designated as the "upper motoneuron" or "final common pathway" for the central control of movements, impinging either directly or indirectly (i.e. via interneurons) on the "lower motoneurons" in the brain stem and spinal cord. Projections from other motor-related areas, converging upon the primary motor cortex, were thought to represent a hierarchical level superimposed on that of the "upper motoneuronal system". Recent experimental neuroanatomical studies, mainly in rhesus monkeys, have shown that the organization of the central motor system is much more complex than indicated by the hierarchical model just sketched. It has been shown that the motor part of the pyramidal tract, i.e. the "upper motoneuronal system", does not originate exclusively from the primary motor cortex. Rather, this fibre system has appeared to originate from many of the non-primary motor areas discussed above, including the PMVc and PMDc [162, 282], the SMA [163, 283] and the CMAr and CMAc [162, 163, 283]. Consequently, all of these areas have the potential to

influence the generation and control of movements independently of the primary motor cortex. All of the areas giving rise to pyramidal tract fibres also project to the primary motor cortex [131, 431, 475, 480, 682, 711]. Thus, they influence motor activity through at least two pathways, corticospinal projections and corticocortical projections to the primary motor cortex. The various non-primary motor areas mentioned, which are all somatotopically organized [282, 283, 480], do not project only to M1, but they are also strongly and reciprocally interconnected [131, 431, 480, 711]. Dum and Strick [164] recently studied the digit representations in M1, PMD, PMV and SMA of cebus monkeys. They concluded that the subareas of the various clusters concerned with the generation and control of hand movements form a densely interconnected network, within which a clear hierarchical organization is lacking.

Matelli et al. [445] have pointed out that the various motor areas can be grouped into two major classes. The caudal motor areas F1, F2, F3, F4 and F5 form the first class. They are typified by their projections to the spinal cord, to F1 and to each other. The rostral areas F6 and F7 form the second class. These areas do not project to the spinal cord, but their descending output terminates in various part of the brain stem. Furthermore, these areas are not directly connected with F1. According to Matelli et al. [445], the two classes also differ with respect to the sources of their principal "extrinsic" cortical inputs. The areas forming the caudal group receive a primary cortical input from the parietal lobe; therefore, they may be characterized as parieto-dependent motor areas. The rostral areas, on the other hand, receive their primary cortical input from the prefrontal cortex and may, hence, be characterized as prefronto-dependent motor areas. The areas forming the caudal group collectively correspond to Mesulam's [463] motor association area (Fig. 15.15). As regards the relationship with the parietal lobe, we have seen that this lobe contains a number of centres in which sensory information from various sources is processed, and that each of these centres is specifically and reciprocally connected with a particular frontal motor area. The various parietal centres and their frontal targets form functional circuits, each of which is dedicated to a particular aspect of sensory-motor transformation [445, 828, 847]. These parietofrontal circuits have been briefly dealt with in the section on the parietal lobe of the present chapter and will be further discussed in Chap. 21.

The areas forming the rostral group of Matelli et al. [445], i.e. the pre-SMA or F6 and the PMDr or F7, are tightly connected to the prefrontal cortex, particularly area 46, and to the caudal motor areas [419, 431, 433, 475]. They are believed to play a role in cognitive aspects of motor control such as temporal planning of actions and motivation [445].

The cingulate motor areas do not fit into the categorization of Matelli et al. [445]. Just like the premotor areas of the caudal group, CMAr and CMAc are reciprocally connected with the primary motor cortex [480, 481] and project directly to the spinal cord [163, 283]. However, unlike the caudal group and conforming with the rostral group, CMAr and CMAc receive a substantial projection from the prefrontal cortex [481]. The two cingulate motor areas are strongly interconnected [482], and neither projects only to the primary motor cortex (M1), but also to the supplementary motor area (M2) [480]. All of these connections are somatotopically organized.

The prefrontal afferents to the cingulate motor areas comprise a strong projection from the dorsolateral prefrontal cortex and less substantial projections from the ventrolateral prefrontal and caudal orbitofrontal cortices [481]. It is important to note that the cingulate motor areas, in addition to the prefrontal and motor-related cortical afferents discussed above, also receive inputs from diverse and widespread limbic cortical areas, including cingulate areas 24, 23 and 32, retrosplenial areas 29 and 30 and temporal areas 35, TF and TH [482].

The functional roles of CMAr and CMAc are not well understood. Neuroimaging studies during motor tasks, involving the execution of various arm movements, have shown that CMAr is activated in relation to complex tasks,

whereas CMAc is activated during simpler tasks [585]. Morecraft and Van Hoesen [482] suggested that the cingulate motor areas may play an important role in advancing emotional, motivational and memory-related information generated in the domain of the limbic lobe directly to the neocortical motor areas and, hence, to the voluntary motor system.

The non-primary motor cortex also comprises the frontal eye field and the supplementary eye field which, as their names indicate, are both involved in the control of eye movements, and Broca's speech region (Fig. 15.58 C).

The *frontal eye field (FF)* is situated at the caudal end of the middle frontal gyrus, in the vicinity of the precentral sulcus [653]. In Brodmann's map, this region is situated within the confines of area 6. However, Foerster [197] identified FF with a subfield of area 8, designated by Vogt and Vogt [784] as area 8$\alpha\beta\delta$ (Fig. 15.18 C). According to Rosano et al. [633], FF is predominantly situated just anterior to area 6, in a transition region between area 6 and area 8 and extending into area 8 proper. FF is functionally divisible into a rostral subregion concerned with the generation of saccades (FF sac) and a caudal subregion concerned with the generation of smooth eye movements (FF sem) [434] (Fig. 19.14 A).

The *supplementary eye field (SF)* is located in the rostrodorsal part of a subfield of Brodmann's area 6, designated by Vogt and Vogt [784] as area 6$\alpha\beta$ (Fig. 15.58 C) and by Matelli et al. [445] as a part of PMDr or F7 (Fig. 15.58 C).

The neocortex contains a number of highly interconnected regions that make direct contributions to the initiation and control of voluntary eye movements. In addition to FF and SF, these regions include the medial part of area 7, the lateral intraparietal area (LIP), the middle superior temporal visual area (MST) and the prefrontal eye field (PF), forming part of area 46 of Brodmann (Figs. 15.50, 15.51, 15.52 A). In a recent review, Lynch and Tian [434] summarized our current knowledge of the connections and functions of the cortical eye fields mentioned above. They point out that: (1) each of these eye fields is reciprocally connected to most or all of the other eye fields; (2) most of the eye fields receive direct input from several regions of visual association cortex; (3) in each of these fields electrical stimulation evokes eye movements; (4) surgical lesions or chemical inactivation of each field produces transient impairments of eye movements; and (5) each field demonstrates increased activity during eye movement tasks in functional imaging experiments in humans. Lynch and Tian also report that the saccade subregion of the frontal eye field (FFsac) and the pursuit region of the same field (FFsem) are selectively connected with distinct subregions in each of the other eye fields. On that account they propose that there are two parallel cortical oculomotor networks, one devoted to the control of saccadic eye movements and a second devoted to the control of pursuit eye movements.

The network mediating gaze control encompasses, apart from the cortical eye fields just discussed, numerous subcortical structures, including the thalamus, the basal ganglia, the cerebellum, the superior colliculus, the paramedian pontine reticular formation and, as a matter of course, the various oculomotor nuclei. The structural and functional organization of this network will be discussed in Chap. 19.

Broca's speech region is located in the opercular and triangular parts of the inferior frontal gyrus of the dominant (generally the left) hemisphere (Fig. 3.2). It is widely accepted that areas 44 and 45 of Brodmann constitute the cytoarchitectonic correlates of Broca's region [2, 6, 8, 70, 71, 746, 849] (Fig. 15.58 A, C). Both areas contain a thin, inconspicuous inner granular layer and can, hence, be classified as dysgranular [6]. The location and extent of areas 44 and 45 vary among subjects [383] (Fig. 15.22 A). A quantitative study of ten different brains [6] revealed that, although the volume of area 44 varied considerably among subjects, the volume of this area was larger on the left than on the right side in all ten brains. Area 45 did not show such interhemispheric differences. It seems likely that during evolution, areas 44 and 45 have developed from a primordium situated in the ventral premotor region in non-human primates [2, 591].

Damage to Broca's region generally leads to a *motor aphasia*. This aphasia, which is also known as *expressive or Broca's aphasia,* consists of a cluster of linguistic features including nonfluent, effortful speech, impaired repetition, and relatively preserved comprehension [26]. Nonfluency itself, apart from aspontaneous, sparse and slow speech, includes reduced or absence of grammaticality and reduced number of words per utterance (generally one or a few, expressed in a "telegraphic" style) [26, 151].

Broca's anterior speech region is strongly connected with Wernicke's posterior speech region and projects to the primary motor cortex. The fibres interconnecting Broca's and Wernicke's regions follow two different routes, dorsal and ventral. The fibres following the dorsal route pass dorsally on leaving Wernicke's region, arch around the posterior part of the lateral sulcus, and then travel rostrally beneath the supramarginal and somatosensory areas in the parietal operculum, to reach Broca's region. These fibres form part of the so-called arcuate fasciculus, i.e. the anterior limb of the superior longitudinal fascicle [145, 398, 532] (Figs. 15.45, 15.46, 15.59). The fibres following the ventral route pass directly forward from Wernicke's region and reach Broca's region by way of the extreme capsule, passing directly beneath the insular cortex [130], in which some of them may be synaptically interrupted. The efferent fibres from Broca's region pass to the lower part of area 4, in which the muscles of larynx, tongue and lips are represented.

It has already been mentioned that damage to Wernicke's region leads to a *sensory or receptive aphasia,* in which the comprehension of written and spoken language is severely affected. Interrupting the connections between Wernicke's and Broca's regions and between the fibres passing from Broca's region to the inferior primary motor cortex results in two other types of aphasia, known as conduction aphasia and subcortical motor aphasia. *Conduction aphasia* is characterized by a marked impairment in repeating spoken language, accompanied by preserved comprehension [26, 48, 151]. *Subcortical motor aphasia* clinically closely resembles *cortical motor aphasia* due to damage of Broca's region [165].

The anatomical structures and connections just discussed (and the clinical syndromes attached to their damage or interruption) together form the classical or Wernicke-Geschwind model of the neural architecture of language [48, 227, 228, 811, 812] (Fig. 15.59). During the past decades an enormous body of literature dealing with cerebral language organization and its disorders has accumulated. A detailed discussion of this literature is beyond the scope of the present work. Here, we only present a brief survey of some of the main results.

1. The classical model of the neural organization of language was exclusively based on postmortem studies on the brains of patients who had suffered from disturbances in comprehending and/or producing articulated speech. Numerous later studies, based on diverse approaches, such as intra-operative electrical stimulation of the brain [514, 547, 549], application of radioisotopes for the localization of brain infarcts [366], structural neuroimaging in patients with aphasic disorders (e.g. [385]) and functional neuroimaging in normal subjects during the execution of linguistic tasks (e.g. [200, 451, 593]), have all confirmed that the posterior part of the left inferior frontal gyrus and the left parietotemporal junction are critically important for the processing of language. However, several other authors [73, 821] failed to demonstrate any consistent association between aphasic syndromes and lesion locations.

2. Pure forms of the various aphasias do occur, but are very rare because the lesions involved (mostly infarctions in the left middle cerebral artery territory) seldom conform to a single functional site [65].

3. It has become clear that, apart from Broca's and Wernicke's regions, numerous other brain areas participate in speech and language (Fig. 15.60).

(a) Functional neuroimaging studies [668, 740] have shown that *the intermediate and posterior parts of the left superior temporal gyrus* play a crucial role in storage and retrieval of linguistic information and that the *left middle and inferior temporal gyri* are critically involved in lexical and semantic processing [320, 321, 645].

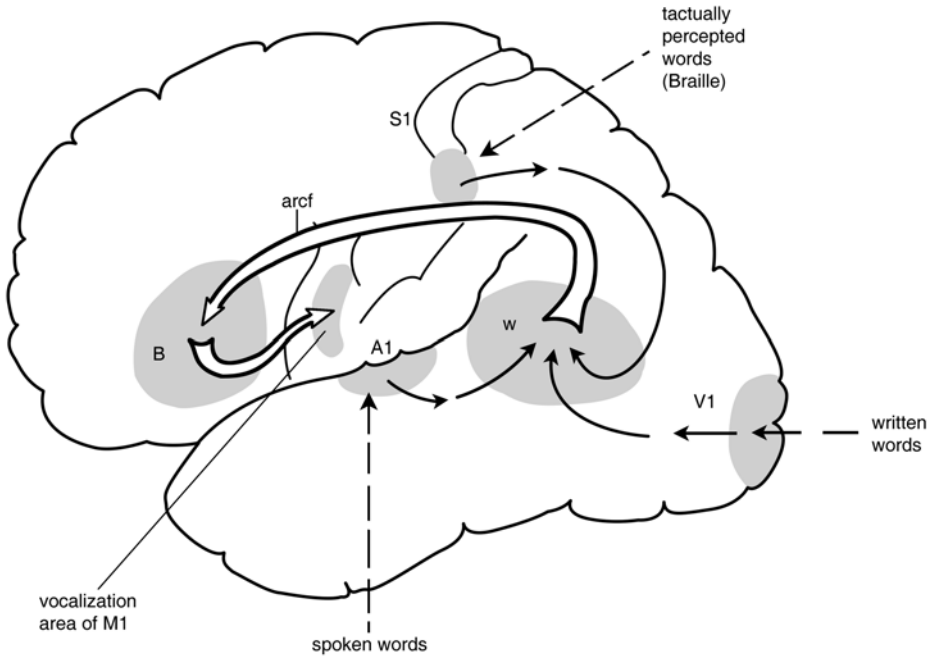


Fig. 15.59. The classical or Wernicke-Geschwind model of the circuitry related to the comprehension and production of language. *A1*, primary auditory area; *arcf*, arcuate fasciculus; *B*, Broca's speech region; *M1*, primary motor cortex; *S1*, primary somatosensory cortex; *V1*, primary visual cortex; *W*, Wernicke's speech region

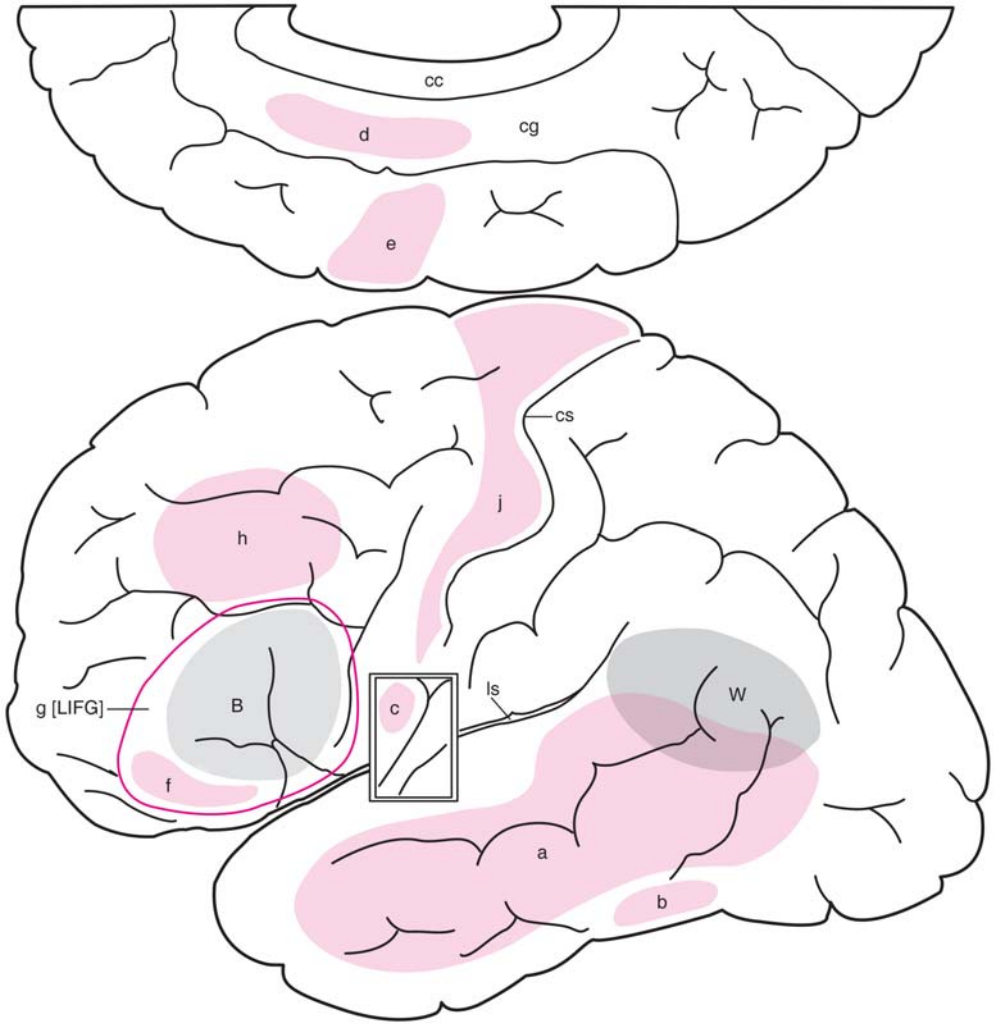


Fig. 15.60. Cortical areas involved in the comprehension and production of language. The classic regions of Wernicke (*W*) and Broca (*B*) are shown in *grey*; more recently discovered language-related areas are shown in *red*. The *small window* shows part of the insula. *a–g*, language-related areas discussed in the text; *cc*, corpus callosum; *cg*, cingulate gyrus; *cs*, central sulcus; *LIFG*, left inferior frontal cortex; *ls*, lateral sulcus

(b) Electrical stimulation in epileptic patients [77, 420] and fMRI studies [289, 593] have shown that an area situated in *the intermediate part of the left lateral occipitotemporal gyrus* (designated as the *"basal temporal language area"*) is involved in word retrieval.

(c) A study involving computerized lesion reconstruction in a series of aphasia patients [158] revealed that in patients with a disorder in co-ordinating the movements for speech articulation, an area situated in the *anterosuperior insula* was specifically damaged. The authors concluded that this insular area is specialized for the motor planning of speech. It has been suggested [466] that fibres passing from Wernicke's to Broca's region through the insula are synaptically interrupted in the posterior insular cortex.

(d) Functional neuroimaging studies have shown that the *anterior cingulate cortex* is involved in linguistic activities such as selecting verbs to lists of nouns [603] and translation [594].

(e) The *supplementary motor area* is consistently activated in functional imaging studies involving speech [159, 593].

(f) Neuroimaging studies [58, 185, 572, 573] have identified a small region in the left inferior frontal gyrus that becomes active during specific linguistic activities, such as processing semantic relationships between words or phrases and retrieving semantic information. This region corresponds roughly to Brodmann's area 47.

(g) Hagoort [276] has recently pointed out that the language-relevant part of the frontal cortex, apart from the classical Broca region, also includes the inferior prefrontal region corresponding to area 47 and presumably also the antero-inferior part of area 6. He denoted this new entity as *left inferior frontal cortex (LIFG)*. Hagoort adduces evidence indicating that LIFG is crucial in unification operations required for binding single word information received from memory into larger semantic, syntactic and phonological structures.

(h) Based on clinical evidence, Damasio [129] reported that certain higher-level aspects of language formation require an intact prefrontal cortex surrounding Broca's region. Hagoort [276] concluded from fMRI studies on subjects performing verbal control tasks that a network of areas consisting of the anterior cingulate cortex and *a dorsolateral prefrontal region encompassing parts of Brodmann's areas 9 and 46* is involved in verbal action planning and attentional control.

(i) Remarkably, the *primary motor cortex* is also involved in semantic processing. Hauk et al. [280] showed action words referring to face, arm and leg actions (e.g. to lick, pick or kick) in a passive reading test to normal volunteers under fMRI monitoring. The mere reading of these words appeared to activate loci of the motor cortex involved in the actual movement of the tongue, fingers or feet. These findings suggest that the brain areas that are used to perform a particular action are also involved in the comprehension of the words related to that action [132].

(k) Functional neuroimaging studies have shown that the right (non-dominant) hemisphere contributes substantially to many aspects of language comprehension and production, including the detection of syntactic errors, comprehending contextual and figurative meaning and prosody (melody, timing and intonation) [58, 391, 473].

4. There is evidence that the cortical domains dedicated to language are compartmentalized into separate systems for processing different aspects of language. Ojemann [514] cites lesion studies indicating the presence of separate areas for handling different languages, for handling different grammatical classes of words or for the naming of specific semantic categories, such as "animals" or "tools". Functional neuroimaging research, summarized by Bookheimer [58], has shown that within the left inferior frontal lobe separate subsystems are responsible for different aspects of language. It appeared that a rostroventral area, corresponding to Brodmann's areas (BAs) 47 and 45, contributes to semantic processing; an intermediate area, corresponding to BAs 45 and 44, has a role in syntactic processing; whereas a dorsocaudal area including parts of BAs 44 and 6 are involved in phonological processing. Similar subsystems, subserving partic-

ular specialized language-related functions have also been reported for Wernicke's region [827] and for both Broca's and Wernicke's regions [300].

5. The data reviewed indicate that the neural network involved in the comprehension and production of language is much more extensive than was originally envisioned. However, the precise wiring of this network remains to be established. The marked functional specialization detected within language-processing areas suggests that several parallel, though interrelated subnetworks are present. The language-related (sub)networks do not function in isolation. Neuroimaging studies, cited by Bookheimer [58] and Hagoort [276], have reported increased activity in Broca's region during various nonlinguistic tasks. Mesulam [464] indicates that many cortical nodes participate in the function of more than one cognitive network. Finally, it should be mentioned that the circuitry related to language functions is presumably not confined to the neocortex. Clinical studies, reviewed in [26, 48, 391], have shown that local lesions in the basal ganglia, thalamus and even cerebellum may lead to language deficits.

The *prefrontal cortex* is distinguished from the motor and premotor areas by (1) the presence of a pronounced internal granular layer, and (2) its strong reciprocal connections with the mediodorsal thalamic nucleus (MD) [402, 635]. On account of these features, the prefrontal cortex is sometimes denoted as the *granular frontal cortex* or as the *MD-projection cortex*. However, neither of these two criteria is absolute. Thus, the caudobasal part of the prefrontal cortex is dysgranular rather than granular, and studies with modern tracing techniques in the rhesus monkey have shown that most prefrontal areas that receive MD input are also connected to other thalamic nuclei, and that, conversely, the MD projections do not pass exclusively to the prefrontal cortex [592, 749]. Another important feature of the prefrontal cortex is that it receives inputs from all unimodal and heteromodal sensory association areas. On the basis of these afferents, the prefrontal cortex may be qualified as a *high-order heteromodal association area* [463] (Fig. 15.15).

Two groups of authors, Petrides and Pandya [580, 581] and Price and collaborators [86, 516, 518], modified Brodmann's original parcellation of the human prefrontal cortex on the basis of comparative studies on the brain of the rhesus monkey and the human. Both groups took Walker's [802] cytoarchitectonic analysis of the frontal lobe of the rhesus monkey as their starting point. In this analysis (Figs. 15.61 A, 15.62 A, 15.63 A), Walker used Brodmann's numbering scheme. With regard to their position, his areas 6, 8, 9, 10, 24, 45 and 46 are directly comparable to the similarly numbered areas of Brodmann's map (Fig. 15.58 A, B). However, Walker's area 46 is very extensive and occupies a considerable part of the lateral surface of the frontal lobe (Fig. 15.61 A). Contrary to its human counterpart, Walker's area 24 extends to the basal surface of the brain, and his area 25 largely corresponds to Brodmann's area 32 in the human brain (Figs. 15.58 B, 15.62 A). Walker designated an area occupying the ventrolateral part of the frontal lobe, corresponding positionally with parts of Brodmann's areas 11 and 47, as area 12 (Figs. 15.59 A, 15.63 A). However, Brodmann used number 12 in his latest map of the human cortex [71] to specify quite another area, occupying a ventromedial position in the frontal lobe (Fig. 15.58 B). Finally, Walker delineated two "new" areas on the basal surface of the frontal lobe, which he labelled as areas 13 and 14 (Fig. 15.63), neglecting the fact that Brodmann [70] used these numbers to specify other (insular) areas in the cortex of non-primate species.

The modifications of Brodmann's parcellation of the frontal cortex introduced by Walker [802] are clearly reflected in the comparative architectonic studies of Petrides and Pandya [578, 580, 581] and Price and collaborators [86, 516, 518]. As shown by Figs. 15.61 B, C, 15.62 B–E and 15.63 B, C, both groups use a mixed Brodmann-Walker nomenclature in their parcellations of the monkey and human cortex [748]. The most important deviations from Brodmann's subdivision of the frontal cortex, introduced by the two groups of investigators mentioned, are the following:

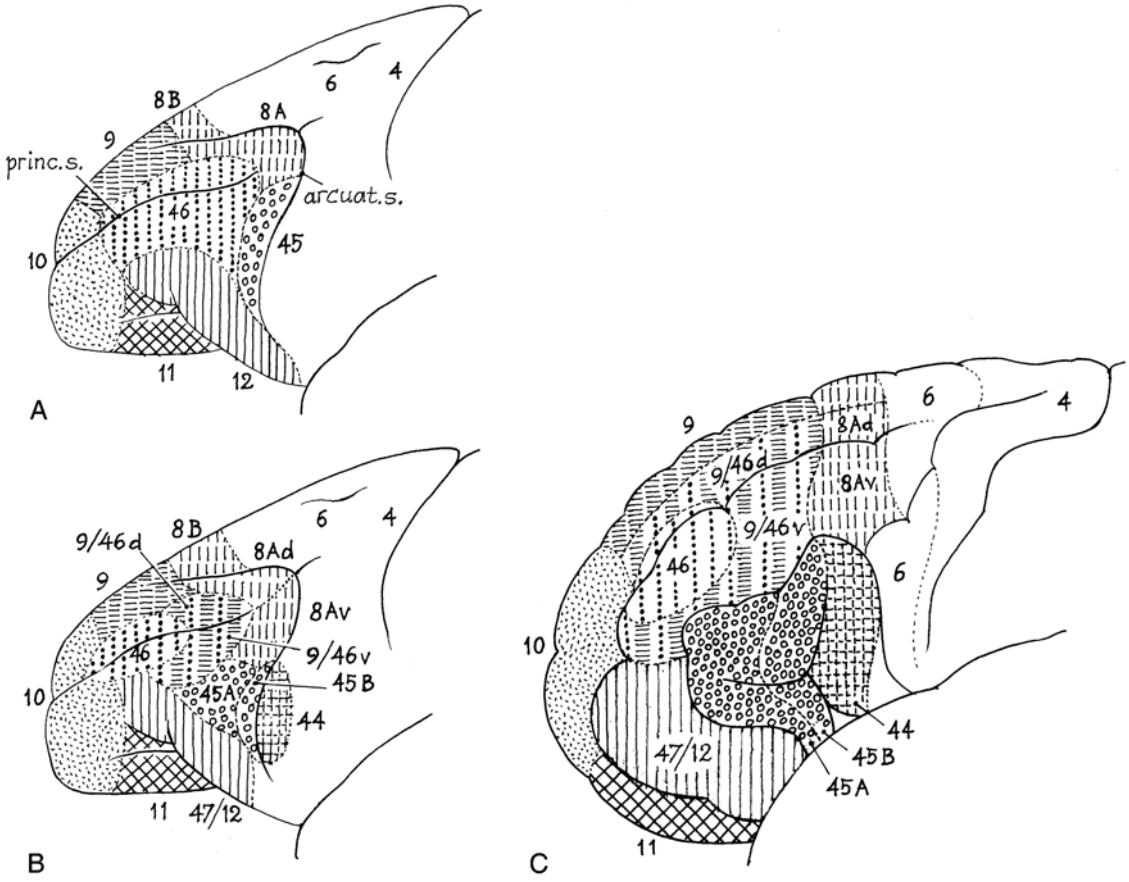


Fig. 15.61 A–C. Cytoarchitectonic maps of the lateral frontal cortex. **A** Rhesus monkey, according to Walker [802]. **B** Rhesus monkey, according to Petrides and Pandya [578]. **C** Human, according to Petrides and Pandya [578]. *arcuat s*, arcuate sulcus; *princ s*, principal sulcus

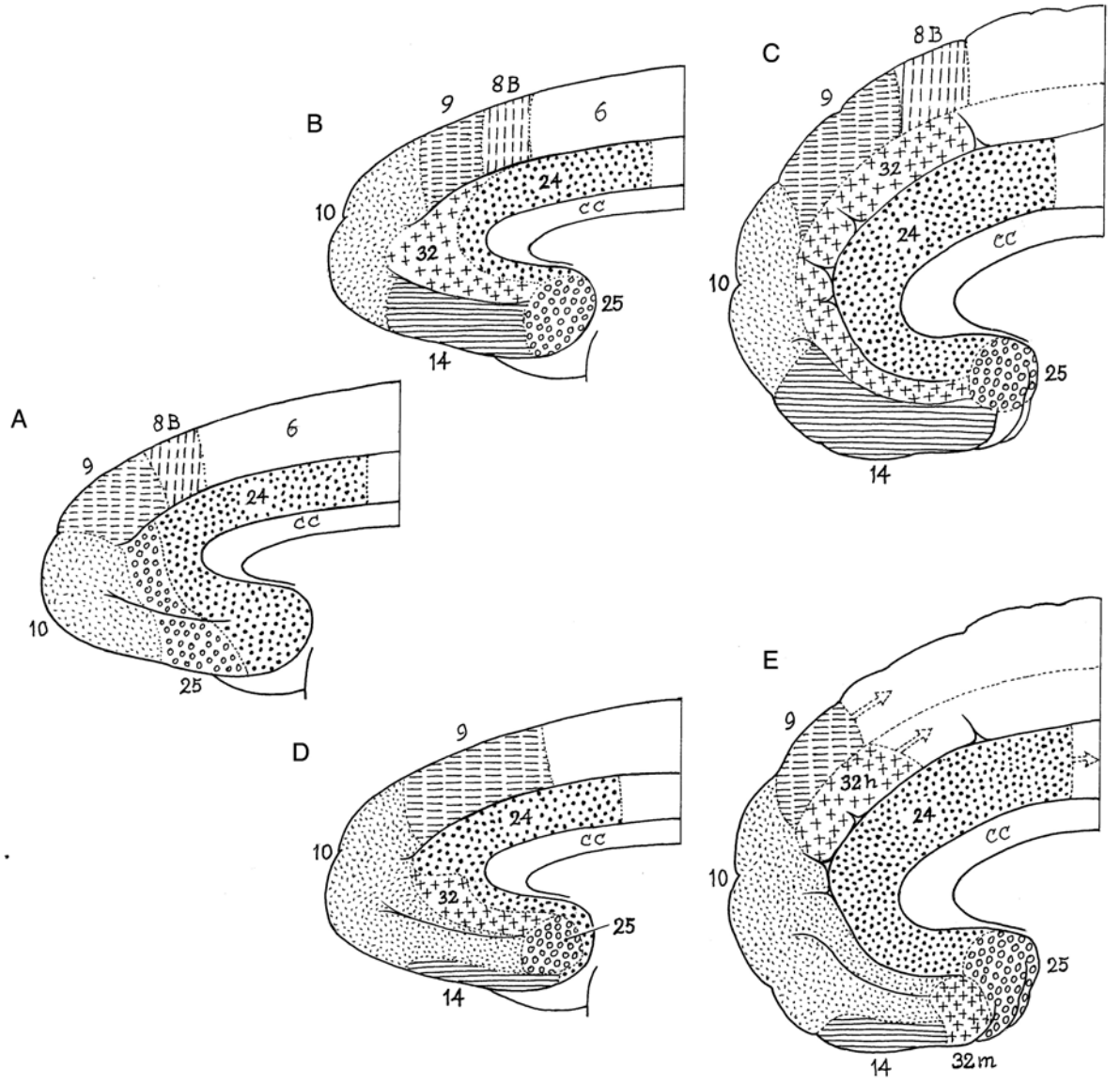


Fig. 15.62 A–E. Cytoarchitectonic maps of the medial frontal cortex. **A** Rhesus monkey, according to Walker [802]. **B, C** Rhesus monkey and human, respectively, according to Petrides and Pandya [578]. **D, E** Rhesus monkey and human, respectively, according to Öngür and Price [516]. *cc*, corpus callosum

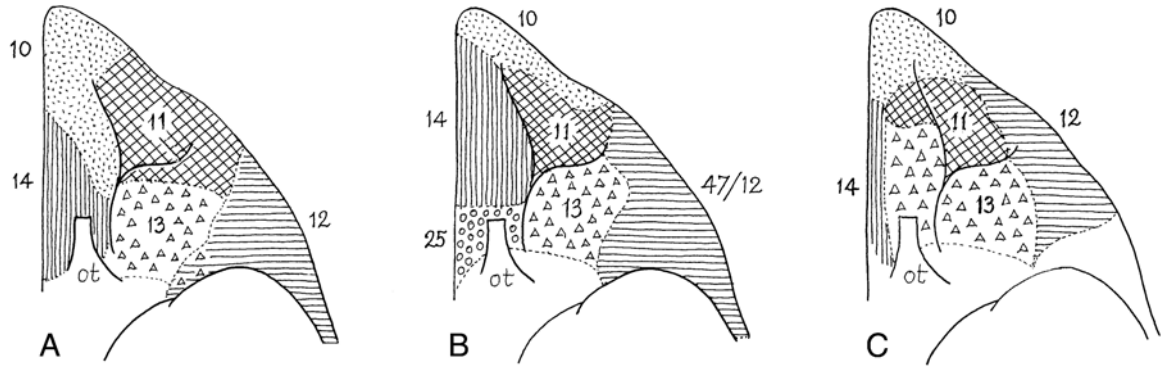


Fig. 15.63. Cytoarchitectonic maps of the orbitofrontal cortex of the rhesus monkey, according to Walker [802] (**A**), Petrides and Pandya [578] (**B**) and Öngür and Price [516] (**C**). *ot*, caudal part of the olfactory tract

1. In Brodmann's map, area 46, which occupies a central position on the lateral surface of the frontal lobe, is separated from area 8 by the ventrocaudal part of area 9 (Fig. 15.58 A). However, Petrides and Pandya [578] observed that the architecture of the portion of the middle frontal gyrus, labelled area 9 in the map of Brodmann, is more akin to area 46. They also observed that this cortex corresponds in architecture to the cortex found in the caudal part of the sulcus principalis in the rhesus monkey, and that has been included in area 46 by Walker (Fig. 15.61 A). Petrides and Pandya therefore labelled the portion of area 9 that lies on the middle frontal gyrus as area 9/46 (Fig. 15.61 C), to acknowledge its architectonic similarity to area 46 and its inclusion with area 9 in Brodmann's map.

2. In Brodmann's map, the region rostroventral to area 45 has been labelled area 47 (Fig. 15.58 A). Petrides and Pandya [580] observed that this region has architectonic features comparable to those of Walker's area 12 in the rhesus monkey (Fig. 15.61 A). They therefore labelled this region area 47/12 (Fig. 15.61 C).

3. On the medial surface of the human frontal lobe, Petrides and Pandya [581] (Fig. 15.62 C) as well as Price and collaborators [516, 518] have replaced area 12 and part of area 11 of Brodmann (Fig. 15.58 B) by area 14 of Walker (Fig. 15.63 A).

4. It is remarkable that in the map of Price and collaborators, the medial part of Brodmann's area 10 is extraordinarily large and abuts directly on area 24, splitting area 32 into a dorsal, human (h) and a ventral monkey (m) part (Fig. 15.62 E).

5. We have seen that Walker, in his architectonic analysis of the frontal lobe of the rhesus monkey, has delineated two "new" areas on the orbital surface of that lobe, which he labelled areas 13 and 14 (Fig. 15.63 A). Petrides and Pandya [581] and Price and collaborators [516, 518] confirmed the presence of these areas in the rhesus monkey (Fig. 15.63 B, C) and also identified them in the human (Fig. 15.11 E, G).

It is important to note that Price and collaborators divided most of the areas they delineated into two to four subareas (Figs. 11.8, 15.11 G).

We discussed the results of the architectonic analysis of Petrides and Pandya and Price and collaborators in some detail because they form the basis of extensive hodological studies on the frontal lobe of the rhesus monkey and that of a sound extrapolation of the results of these studies to the human brain. In what follows, wherever necessary, Brodmann's areas will be denoted with the letters "BA" and areas derived from the mixed Brodmann-Walker parcellation as "BWA".

The various cytoarchitectonic areas forming the prefrontal cortex are strongly and reciprocally interconnected [89, 581]. An important output channel from the prefrontal cortex is formed by sequences of short association fibres which, via the premotor cortex, converge upon the primary motor cortex [419, 711].

The fibre connections of the prefrontal cortex are multifarious. The afferents from the various association areas are reciprocated by efferent projections. It receives cholinergic and GABAergic afferents from the basal nucleus of Meynert, histaminergic, orexinergic and melanin-concentrating hormone-containing fibres from the hypothalamus, serotoninergic fibres from the mesencephalic raphe nuclei, dopaminergic fibres from the ventral tegmental area and noradrenergic fibres from the locus coeruleus. It has reciprocal connections with various parts of the limbic lobe (Fig. 15.57), the amygdala (Figs. 13.6, 13.7), septum and hypothalamus, and it projects to the caudate nucleus (Fig. 14.1), the periaqueductal grey (PAG) and the pons. Several of these connections will be further considered below.

The prefrontal cortex is critically involved in complex brain functions such as orientation and attention, decision making on the basis of current exteroceptive and interoceptive information and past experience, planning and sequencing of actions, emotionality and personality. Large bilateral lesions of the prefrontal cortex lead to a disorder known as *frontal lobe syndrome*. The essential features of this syndrome are [151]: (1) diminished capacity to sustain attention and concentration; (2) lack of spontaneity and initiative; (3) inhibition and impulsivity of affect, thought and action; (4)

inability to plan, organize and execute complex behaviour; and (5) loss of social decorum.

Comparable changes have been observed in psychiatric patients who underwent *prefrontal leucotomy*. The principle of this operation is to cut the fibre connections to and from the prefrontal region. This was done by inserting a "leucotome" through a burr hole and moving the instrument in a coronal plane (Fig. 15.64). As a rule these operations were performed bilaterally. Prefrontal leucotomy was introduced by the Portuguese neurologist Egas Moniz in 1936 [476] and was thenceforward strongly advocated by the Americans Walter J. Freeman and James W. Watts [202, 203]. In the two decades following its introduction, tens of thousands of severely disturbed psychiatric patients underwent leucotomies all over the world [330, 752]. For his discovery, Moniz was awarded the Nobel Price in 1949. The principal target group of the intervention consisted of chronic, hospitalized patients, suffering from depression, anxiety states and obsessive-compulsive disorders. Although Moniz [477] qualified prefrontal leucotomy euphorically as "highly effective and always safe", it soon became clear that the intervention produced serious changes in personality, including apathy, slowness, lack of initiative, carelessness, poor judgement and inhibited behaviour in social situations [803]. From a neuroanatomical point of view, the operations were very crude, with poor control of the actual place of the section, due to the considerable interindividual variations of brain size and shape, and skull-brain relationships. Furthermore, there were unintended side effects, such as haemorrhages, sometimes found far from the site of the section [468, 469] (Fig. 15.65). Fortunately, the advent of effective psychopharmaceuticals put an end to the era of prefrontal leucotomy.

The prefrontal cortex can be divided into three major regions: lateral, medial and orbital.

The *lateral prefrontal cortex* encompasses BAs 8, 9, 46, 10 and 47 (Fig. 15.58 A). BAs 9 and 46 together correspond to BWAs 9, 9/46d, 9/46v and 46. BA 47 roughly corresponds to BWAs 47/12 (Fig. 61 C). This cortical region is known to participate in numerous higher-order brain functions, such as integrating sensory analysis with motor activity, selective attention, working memory, planning and reasoning. In what follows, a brief survey of the principal connections of the lateral prefrontal cortex (LPFC) will be presented, to which some functional notes will be attached.

Experimental studies in rhesus monkeys [578, 580, 581] have shown that the various prefrontal areas are tightly and reciprocally interconnected and that this connectional network extends uninterruptedly over the medial prefrontal and orbitofrontal regions [89, 516].

The LPFC represents the highest level of sensorimotor integration. It receives highly processed information from multiple sensory modalities and plays a prominent role in the planning and organization of voluntary goal-directed behaviour. The sensory information is conveyed to the LPFC by massive projections emanating from post-Rolandic unimodal and polymodal sensory association area (Figs. 15.15, 15.46).

A combination of electrophysiological recordings and anatomical tract-tracing in rhesus monkeys [245, 513, 631, 632, 822], as well as neuroimaging studies in humans [113, 116, 147, 455], have shown that the LPFC is organized in separate dorsal spatial cognition- and ventral object cognition- and pattern cognition domains. For a discussion of the relevant electrophysiological and neuroimaging data, the reader is referred to the publications cited; here we confine ourselves to mentioning that the visual and auditory projection streams involved in the processing of spatial information converge upon the dorsal part of the LPFC, whereas visual and auditory streams, concerned with pattern discrimination, mainly target the ventral part of the LPFC (Fig. 15.66). However, this functional segregation is not absolute. In both domains units processing both object identity and location have been found [613].

All the pathways that convey sensory information from posterior cortical areas to the LPFC contain reciprocal fibres, projecting back to areas from which input was received [581, 582]. These feed-back fibres form part of the

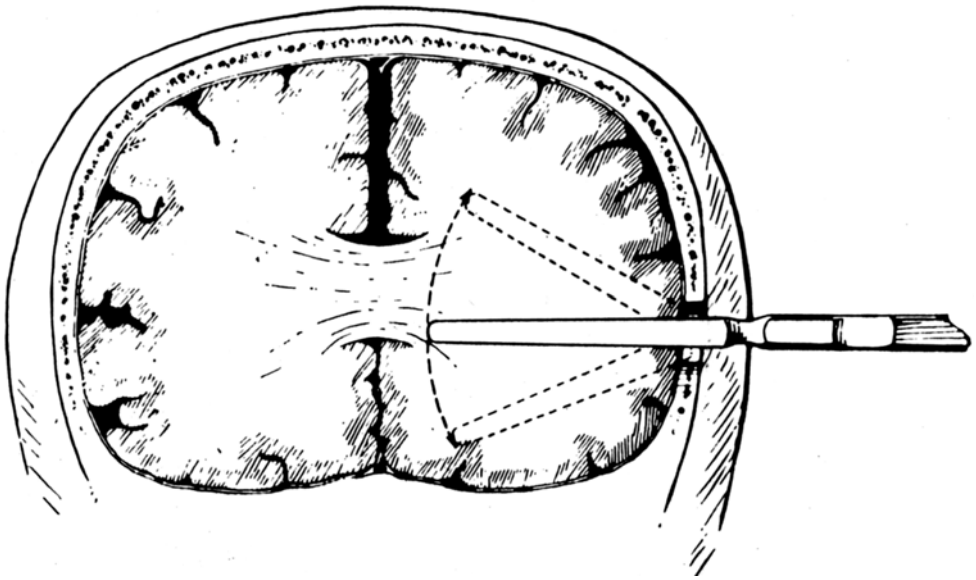


Fig. 15.64. Drawing showing how the brain is incised during a prefrontal leucotomy. An identical incision is made on the opposite side. Reproduced from Freeman and Watts [202]

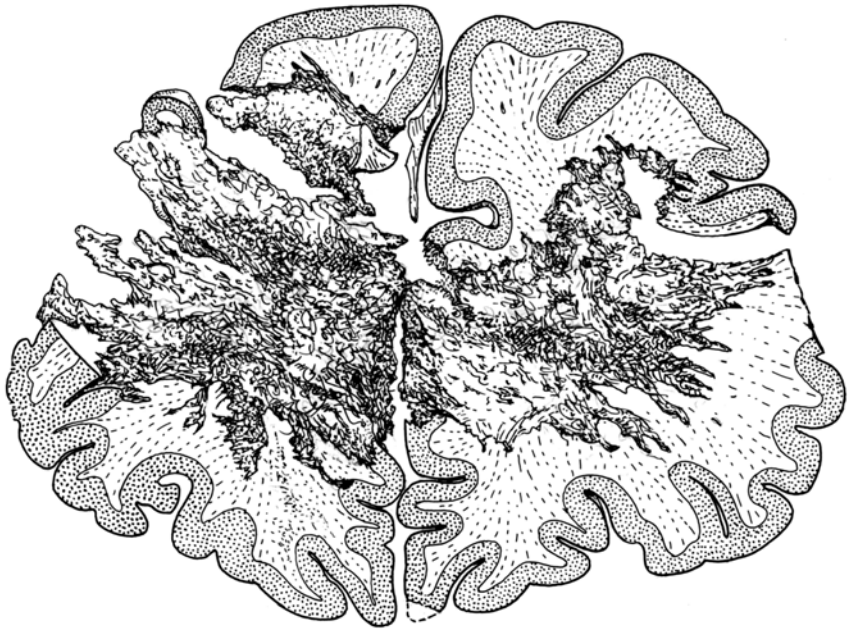


Fig. 15.65. Section of frontal lobes in plane of leucotomy incision, 4 months after operation in which the left anterior cerebral artery was injured. Based on a photograph in Freeman and Watts [202]

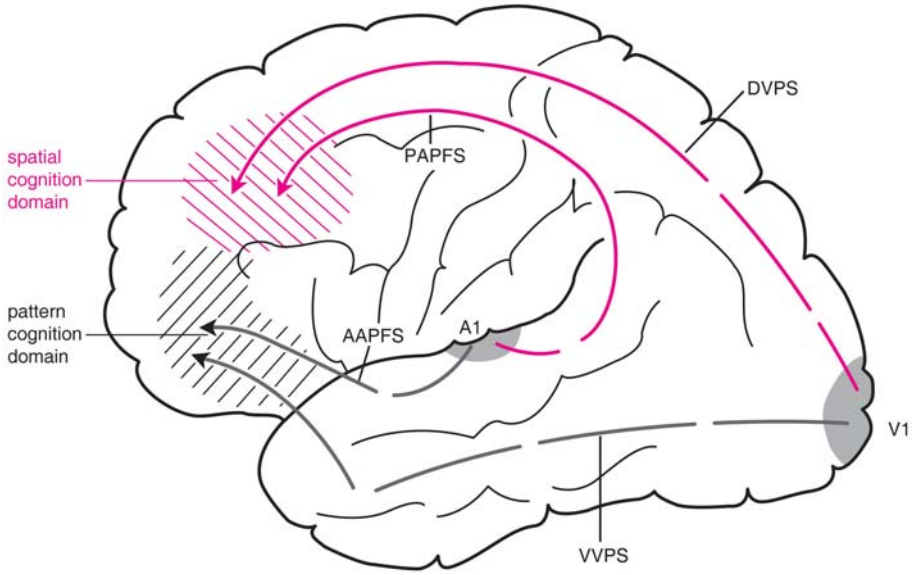


Fig. 15.66. Schematic diagram showing that visual and auditory projection streams involved in the processing of spatial information, target the dorsal part of the lateral prefrontal cortex (shown in *red*), whereas projection streams subserving pattern discrimination target the ventral part of the lateral prefrontal cortex (in *black*). *A1*, primary auditory cortex; *AAPFS*, anterior audito-frontal stream; *DVPS*, dorsal visual processing stream; *PAPFS*, posterior audito-prefrontal stream; *V1*, primary visual cortex; *VVPS*, ventral visual processing stream

morphological substrate of *attention,* i.e. the mechanism that enables us to direct our processing resources to a subset of the available information [124]. This mechanism allows us to selectively process the information relevant to current goals. A combination of the results of neuroimaging studies in humans with data derived from tract-tracing studies in monkeys suggests that, apart from the LPFC, the visual attentional control system involves several way stations in the dorsal and ventral visual processing streams (Fig. 15.67) [552, 553]. Egner and Hirsch [168] recently presented neuroimaging evidence suggesting that the LPFC exerts attentional control on post-Rolandic cortical areas by amplifying task-relevant information rather than by inhibiting distracting stimuli.

The organization of mental processes, such as the sequencing of complex goal-directed behaviours, not only depends on the selective attentional control of incoming sensory information, but also on the ability to keep the information selected available for some time. This ability to transiently maintain and manipulate a limited amount of information to guide thought or behaviour is known as *working memory* [405]. The LPFC plays a key role in working memory. Classic experiments on monkeys and chimpanzees in the 1930s [327, 328] have shown that, following bilateral lesions of the LPFC, the animals were still fully able to perform auditory or visual discrimination tasks or recall spatial orientation of objects, providing tests were made in immediate memory. However, the animals appeared to be unable to perform such tasks if a delay of more than a few seconds was introduced between the stimulus and the response. The relation between this temporal integrative function and the LPFC has been substantiated electrophysiologically [215, 217]. Cells in the LPFC of the monkey were found to fire persistently at high rates while the animals retained an item of visual information in short-term memory. Lesion studies in patients [575] and neuroimaging studies in normal human subjects [574] have also shown that the LPFC is critically involved in working memory.

Apart from the projections from the various sensory association areas, the LPFC receives afferents from the limbic lobe as well as from the mediodorsal, ventral anterior, and the anterior and posterior parts of the ventral lateral thalamic nucleus, and from a large number of subcortical, extrathalamic structures.

The afferents from the limbic lobe reach the LPFC via two fibre systems: the dorsal and ventral limbic pathways [579]. The *dorsal limbic pathway* originates from the rostral and caudal cingulate cortex (areas 24 and 23) and the retrosplenial cortex (area 30) and passes forward in the cingulate bundles to the LPFC. The *ventral limbic pathway* originates from the posterior parahippocampal cortex, particularly area TF, and reaches the LPFC via the extreme capsule [247, 397]. Both limbic pathways are bidirectional, i.e. they also contain fibres originating from the LPC and terminating in the cingulate, retrosplenial and parahippocampal cortices [247, 377, 397]. Neuroimaging studies have shown that various subregions of the cingulate cortex can be activated by stimuli related to simple emotions, such as happiness, sadness, anger and fear [780]. It seems likely that the cingulo-prefrontal projections may subserve the assigning of emotional valence to the sensory information processed in the LPFC. It is well known that the hippocampal formation and adjacent medial temporal structures represent essential components of the memory system (Chap. 12). Because these structures are tightly connected to all other parts of the limbic lobe (Figs. 12.13, 15.56), it has been suggested that the limbico-prefrontal pathways may also form part of the network involved in the encoding and retrieval of long-term memory [579, 685].

The LPFC is reciprocally connected with the lateral, parvocellular division of the mediodorsal thalamic nucleus [712]. As discussed in Chap. 8, this nucleus belongs to the so-called higher-order thalamic relays, which means that it receives its principal or "driver" afferents mainly from the cortex and plays a potentially significant role in cortico-cortical communication [681].

Fibres passing from the ventral anterior (VA) and anterior ventral lateral (VLa) thalamic nuclei to the LPFC represent the final stage

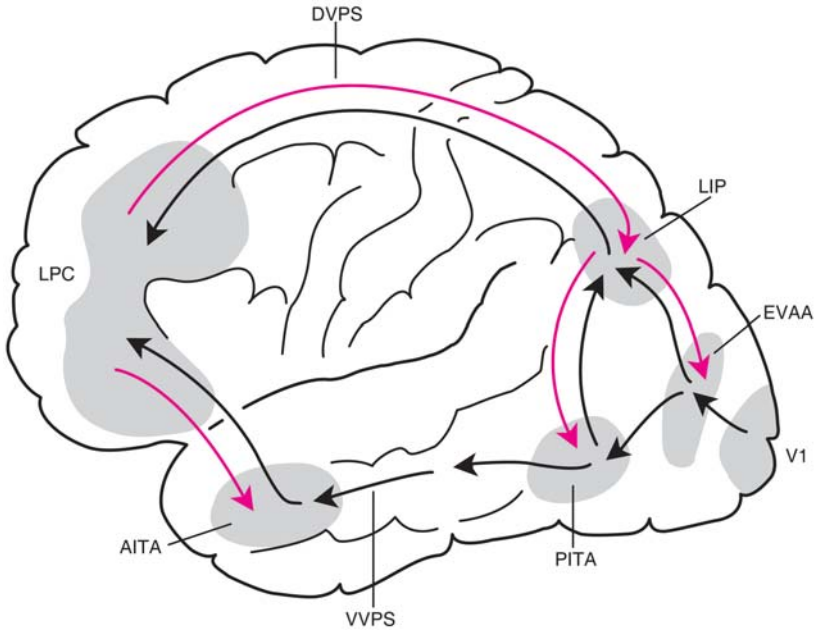


Fig. 15.67. Some centres involved in the processing of visual information. Their feed-forward connections (shown in *black*) originate from the primary visual cortex and proceed to the lateral prefrontal cortex, via the dorsal and ventral visual processing streams. *Red arrows* indicate potential feedback connections, forming part of the visual attentional control system. Based on Pessoa et al. [552, 553]. *AITA*, anterior inferior temporal area; *DVPS*, dorsal visual processing stream; *EVAA*, extrastriate visual association area; *LIP*, lateral intraparietal area; *LPC*, lateral prefrontal cortex; *PITA*, posterior inferior temporal area; *V1*, primary visual cortex; *VVPS*, ventral visual processing stream

of the *associative or cognitive loop*, forming part of the *direct striatal circuit* (for details, see Chap. 14). This loop is composed of: (1) corticostriate fibres which project to the caudate nucleus, (2) striopallidal fibres passing to the internal segment of the globus pallidus, (3) pallidothalamic fibres terminating in VA and VLa, and (4) the thalamocortical fibres already mentioned, which pass back to the same cortical region from which the loop originated (Figs. 14.1, 14.8, 14.17).

Classically, the striatum has been regarded as a part of the motor system, particularly because disturbances in its functions can lead to severe movement disorders. However, it has gradually become clear that the striatum also participates in cognitive functions. Lesions or electrical stimulation of the caudate nucleus result in cognitive deficits, as revealed by delayed response and delayed alternation tasks [839]. Neuroimaging studies indicate that the striatum is involved in procedural learning and memory processes [524], and patients with basal ganglia disorders exhibit impairments in the planning and execution of constructional tasks [399] and in the switching from one behavioural strategy to another [110, 111].

Just like the striatum, the cerebellum is not only concerned with motor control, but also participates in cognitive functions. The prefrontal cortex and the contralateral cerebellar cortex are interconnected by a complex corticocerebellar circuit, comprising a feed-forward or afferent limb and a feed-back or efferent limb. Topographically organized corticopontine and pontocerebellar projections form the feed-forward limb, whereas the feed-back limb is composed of cerebellar corticonuclear projections, efferents from the dentate nucleus to the posterior part of the ventral lateral thalamic nucleus (VLp), and efferents from the latter to the prefrontal cortex (Fig. 14.8). These connections are considered to represent the morphological substrate for the cerebellar control of cognitive processing. For a survey of the evidence indicating the participation of the cerebellum in cognitive functions, the reader is referred to the section "A brief excursion to the cerebellum" in Chap. 14. It has recently been suggested [611] that the prefronto-cerebellar system may facilitate the skilled execution of routine cognitive operations.

The afferents to the LPFC from extrathalamic subcortical centres do not differ from those to other neocortical regions. The structure and overall functions of these afferent systems have been discussed in the section "Neocortical afferents" of the present chapter. Let it suffice to recall that the neurons in several of these subcortical centres are particularly responsive to novel and motivationally relevant sensory stimuli and that their efferents modulate the excitability of the cortical neurons on which they impinge.

The LPFC exerts its control on motor behaviour by cascades of short projections, which reach the caudal premotor areas (F2–F5) and the primary motor cortex (M1, F1), after synaptic interruption in the rostral premotor areas (F6, F7) [419, 433, 445, 475, 578, 580]. The caudal premotor and primary motor areas, which send direct projections to the spinal cord, are closely involved in movement execution, whereas the rostral premotor areas process more "cognitive" aspects of motor control, such as sequence generation and motor learning [269]. It has already been mentioned that the LPFC has a substantial direct projection to the cingulate motor areas.

Based on fMRI evidence, several recent studies [238, 378, 379, 612] suggest that the human *frontal polar cortex* is specifically concerned with complex cognitive functions. Koechlin et al. [378] found that this cortical region is selectively activated when subjects held in mind a main goal while performing concurrent (sub)goals. Ramnani and Owen [612] concluded that the frontal polar cortex has a specific role in integrating the outcomes of two or more separate cognitive operations in the pursuit of a higher behavioural goal.

The complex of symptoms shown by patients with damage to the LPFC has been termed the *dysexecutive syndrome* [27]. Patients with this syndrome are characterized by diminished insight and judgement, poor planning and decision making and impairments of attention, working memory and the temporal organization of recent events [216, 483].

The *orbital prefrontal cortex (OPFC)* has been subdivided in different ways. Brodmann [70, 71], who did not study this region in detail, subdivided it into two areas: 11 and 47 (Fig. 15.11 A). Uylings et al. [751], who recently subjected the OPFC to a thorough cytoarchitectonic analysis, took Brodmann's parcellation as their point of departure. They confirmed the presence of Brodmann's areas 11 and 47, but subdivided the latter into three medial and two lateral subareas (Fig. 15.23). At present, the subdivisions of the LPFC, presented by Petrides and Pandya [580, 581] and Price and collaborators [86, 516, 518], which, as discussed before, are both derived from Walker's parcellation of the frontal cortex of the rhesus monkey [802], are most widely used. According to these subdivisions, the OPFC encompasses four areas, BWAs 11, 13, 14 and 47/12 (Fig. 15.11 E, G). It has already been mentioned that Price and colleagues [516, 518] subdivided each of these four areas into several subareas. There is an anterior-posterior trend in the cytoarchitecture of the OPFC [751], which manifests itself as a gradual reduction in the granularity of layer IV. Hence, the posterior portions of BWAs 13, 14 and 47/12 are either dysgranular or agranular. Mesulam [463] included this dysgranular/agranular region of the OPFC in what he called the paralimbic belt (Figs. 15.55, 15.56).

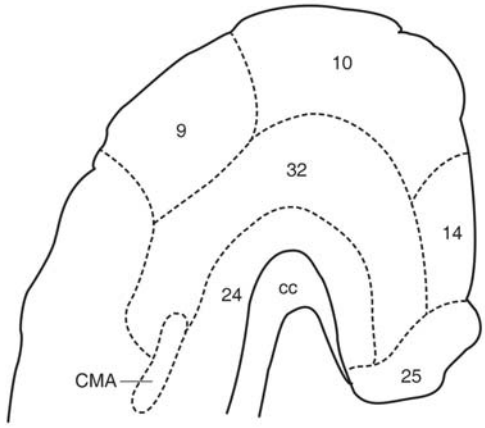
Apart from medially extending portions of BAs 9 and 10 and BWA 14, the *medial prefrontal cortex (MPFC)* includes Brodmann's anterior limbic area 24, prelimbic area 32 and infralimbic area 25 (Figs. 15.58 B, 15.62 C). BAs 24 and 25 are situated within the confines of the limbic lobe and form part of the paralimbic belt (Figs. 15.55–15.57).

Because the OPFC and MPFC share many connectional and functional features, they are commonly considered to form a single complex, the *orbital and medial prefrontal cortex (OMPFC)*.

The detailed experimental hodological studies of Price and collaborators [89, 516, 595] in the rhesus monkey have shown that the cytoarchitectonic areas of the OMPFC can be allocated to two groups or networks, one restricted to the OPFC and the other confined to the MPFC. In Fig. 15.68 A–D, these findings are extrapolated to the human brain.

As already discussed in Chap. 11, the OPFC receives extrinsic sensory afferents from five different sources. Olfactory, gustatory, autonomic, visual and somatosensory projections have been traced to restricted and different areas in the caudal and lateral parts of this region [89, 90] (Fig. 15.68 D). The olfactory projections originate from the primary olfactory cortex (Fig. 11.7). The gustatory and autonomic afferents stem from different parts of the parvocellular section of the ventral posteromedial thalamic nucleus and reach the caudal OPFC via synaptic relays in the insular cortex (see the next section of the present chapter). The visual afferents originate from the inferior temporal cortex and the somatosensory projections arise from the first and second somatosensory cortex and from the parietal association cortex. Anatomical, physiological and neuroimaging data [88, 89, 121, 355, 386, 628–630] indicate that the orbital areas in receipt of these sensory inputs and the network in which they are embedded are involved in the analysis and integration of food-related sensations and play an important role in the control of feeding. The caudal sectors of the orbital network provide a basis for convergence from the various unimodal sensory areas onto multimodal areas in the centromedial region of the OPFC (Fig. 15.68 D).

Fig. 15.68 A–E. The orbital and medial prefrontal cortex (OMPFC). Cytoarchitectonic parcellation of the medial (**A**) and orbital prefrontal cortex (**B**), according to Öngür et al. [518]. **C** Intrinsic connections comprising the medial cortico-cortical network (in *black*), and four prominent output channels of the medial prefrontal cortex (in *red*), originating from: (*1*) the infralimbic cortex; (*2*) the prelimbic cortex, (*3*) the anterior cingulate cortex, and (*4*) the cingulate motor areas. Based on Carmichael and Price [89], Price et al. [595], An et al. [9], Öngür et al. [517] and Morecraft and Van Hoesen [482]. **D** Intrinsic connections comprising the orbital cortico-cortical network (in *black*) and unimodal sensory inputs to the orbital prefrontal cortex (in *red*). Based on Carmichael and Price [89] and Price et al. [595]. **E** Connections between the orbital and medial cortico-cortical networks. Based on Carmichael and Price [89]. *cc*, corpus callosum; *CMA*, cingulate motor area; *facial n*, facial nucleus; *hypoth*, hypothalamus; *PAG*, periaqueductal grey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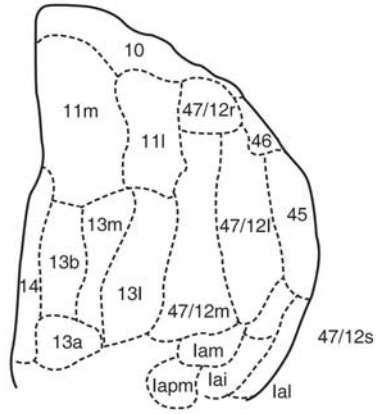
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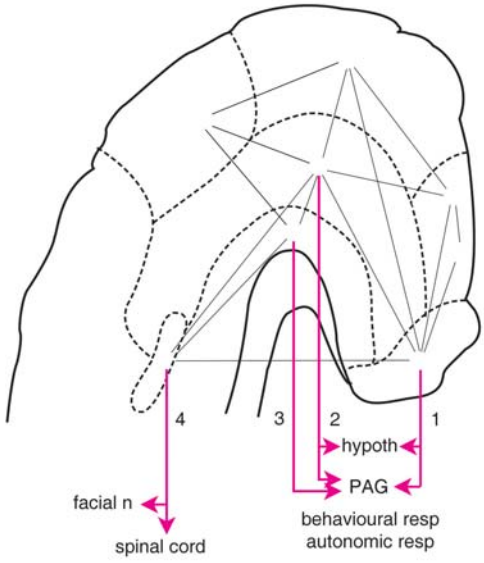
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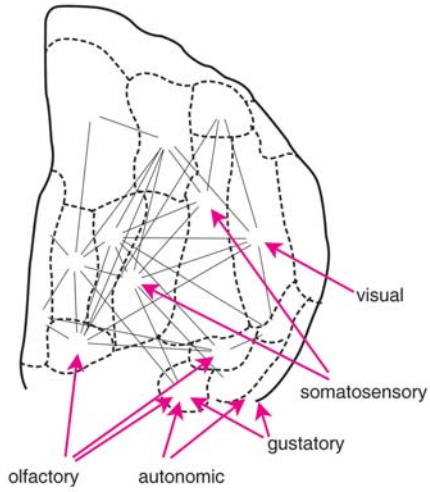
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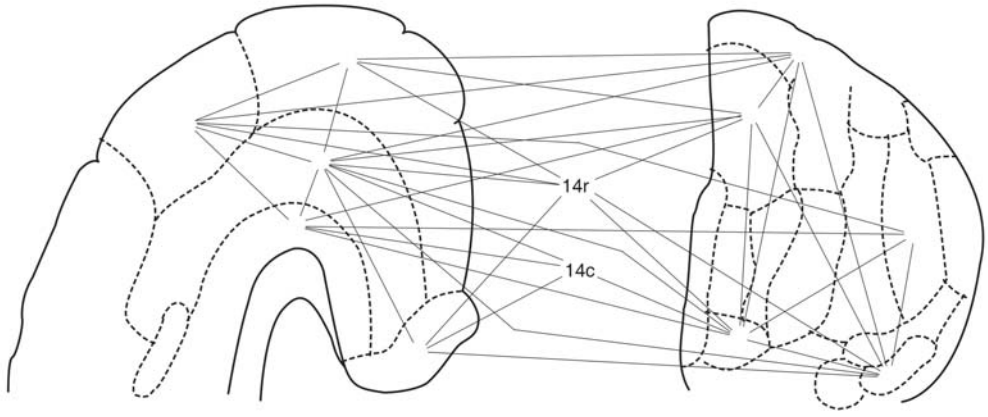
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E

Mention should be made here of a remarkable problem with regard to the exact localization of the olfactory zone in the OPFC. The orbitofrontal focus of olfactory activity in humans, as assessed by neuroimaging studies [251, 845], appeared to be situated considerably more anteriorly (Fig. 15.69 A) than that derived from an extrapolation of the experimental results of Carmichael et al. [90] in the rhesus monkey (Fig. 15.68 D).

It is important to note that the processing of sensory information in the OPFC is not confined to the physical and chemical properties of the stimuli but also involves their affective or emotional significance. Emotions can be classed as positive or negative. Positive emotions are elicited by rewards or positive reinforcers; negative emotions are evoked by punishments or negative reinforcers. A large meta-analysis of neuroimaging studies in humans [386] has shown that different subregions of the OPFC play different roles in the processing of emotional information. It appeared that activity in the medial OPFC is related to the monitoring, learning and memory of the reward value of positive reinforcers, whereas lateral OPFC activity is related to the evaluation of negative reinforcers ("punishers") that can lead to a change in behaviour (Fig. 15.69 B). This meta-analysis [386] also yielded evidence indicating that in the OPFC more complex or abstract reinforcers (such as monetary gain and loss) are represented more anteriorly than less complex reinforcers (such as taste).

The OMPFC projects densely to the hypothalamus and the mesencephalic periaqueductal grey (PAG) and moderately to lightly to many brainstem centres, including the ventral tegmental area, the mesencephalic raphe nuclei, the pedunculopontine nucleus, the locus coeruleus and the parabrachial nuclei. Almost all of these centres form part of the greater limbic system, discussed in Chap. 23. The fibres projecting to the hypothalamus arise from prelimbic area 32 and infralimbic area 25 on the medial surface of the frontal lobe, and from the orbital areas 13 a, 12/47 l and Iai [86, 517]. These three orbital areas are strongly connected to the medial network (Fig. 15.68 E). The medial wall areas 25 and 32 project to the anterior and ventromedial hypothalamic nuclei (AHN, VMH) in the medial hypothalamus. The orbital areas 13 a, 12/47 l and Iai selectively innervate the lateral hypothalamic area (LHA), particularly its posterior part [517]. The AHN and VMH are nodal points in networks subserving motivated or goal-oriented behaviours, i.e. behaviours essential in maintaining the individual and species, such as thermoregulation, agonistic behaviour and reproduction (see Chap. 10). The posterior LHA is involved in autonomic control.

The PAG can be subdivided into four longitudinal zones or columns: dorsal dorsolateral, lateral and ventrolateral [34, 91]. This structure is known to play a prominent role in co-ordinating behavioural and autonomic responses to escapable and unescapable stressful situations. Electrical or chemical stimulation of its lateral column evokes co-ordinated response strategies, such as threat display, fight or flight, accompanied by hypertension, tachycardia and a shift in blood from the viscera to the limb muscles. In contrast, stimulation of the ventrolateral PAG column elicits quiescence ("freezing") and decreasing of blood pressure and heart rate. Retrograde and anterograde tracing experiments in rhesus monkeys [9] have shown that the medial prefrontal areas 24, 25 and 32 and the orbital areas 13 a, 27/12 l and Iai project to the PAG and that projections from distinct cortical areas terminate primarily in individual PAG columns. The projections from areas 25 and 32 terminate primarily in the dorsolateral columns, bilaterally. Fibres from area 24 predominantly end in the lateral column, whereas fibres from orbital areas 13 a, 47/12 l and Iai terminate mainly in the ventrolateral columns. It seems likely that the OMPFC, by way of these projections, influences the integrated behavioural and autonomic responses mediated by the lateral and ventrolateral PAG columns. The functional significance of the cortical input to the dorsolateral column is not known. It is, however, important to note that this column receives a strong projection from the ventromedial hypothalamic nucleus [517], and that this nucleus is involved in both sexual and defensive behaviour (see Chap. 10).

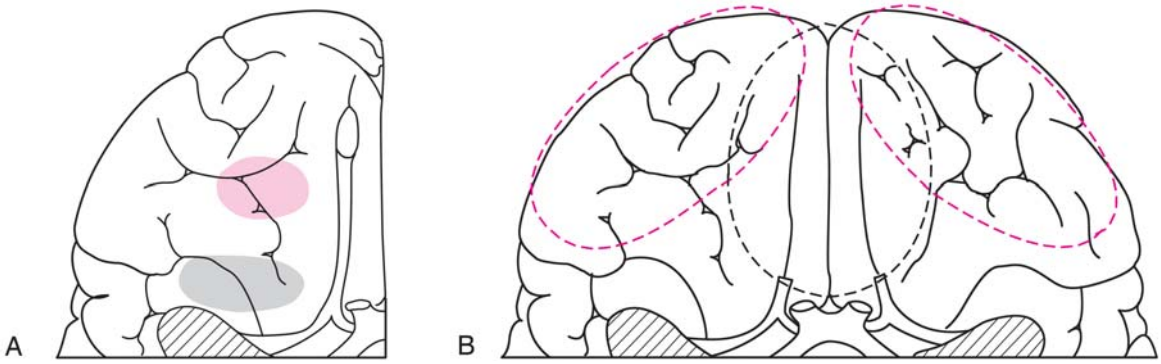

Fig. 15.69 A, B. The functions of the human orbitofrontal cortex. **A** The putative olfactory projection area (in *red*), as based on a meta-analysis of neuroimaging data, appears to be situated substantially rostrally to that extrapolated from experimental hodological studies in the rhesus monkey (in *grey*). Based on Gottfried and Zald [251]. **B** A large meta-analysis of neuroimaging data showed that there is a medial-lateral functional distinction in the orbitofrontal cortex, such that activity in the medial orbitofrontal cortex (*black dashed ellipse*) is related to the learning, monitoring and memory of the reward value of positive reinforcers, whereas lateral orbitofrontal cortex activity (*red dashed ellipses*) is related to the evaluation of negative reinforcers (punishers). Based on Kringelbach [386]. In the figures, temporopolar regions have been removed to allow visualization of the insula and caudal orbitofrontal cortex. The cut surfaces of the "temporal peduncles" are *hatched*

The projections from the OMPFC to the hypothalamus and PAG form part of the *limbic motor system,* which is also designated as the *emotional motor system* [302]. Fibres descending from the central nucleus of the amygdala and the bed nucleus of the stria terminalis also contribute to this system.

The complex formed by the strongly interconnected rostral and caudal cingulate motor areas M3 and M4, which is also embedded in the medial prefrontal network, projects via the corticobulbospinal tract to the facial nucleus and spinal cord. The complex is interconnected with other cortical motor areas, such as the primary motor cortex, the supplementary and presupplementary motor areas and the lateral premotor cortex [279, 481] and receives afferents from the lateral prefrontal areas 9 and 46 and from many limbic cortical areas, including posterior cingulate area 23, retrosplenial areas 29 and 30, temporal areas 35, TH and TF, temporopolar area 38 [482], as well as from the amygdala [483]. In light of these connectional data, Morecraft and Van Hoesen [482] suggested that the cingulate motor areas form a strategic cortical entry point for limbic influence on the voluntary motor system. They pointed out that patients with damage to the anterior cingulate cortex are often characterized as akinetic or docile, attention impaired, mute and lack emotional tone.

As indicated in Fig. 15.68 E, all medial prefrontal areas are connected to several orbital areas [89].

The data concerning the wiring of the OMPFC discussed above may be summarized as follows:

1. The cytoarchitectonic (sub)areas forming the medial and orbital prefrontal cortices are both embedded into a network of cortico-cortical connections.
2. The orbital network contains a "sensory pole" involved in the analysis and integration of food-related sensations.
3. The medial network contains a "motor pole", which potentially exerts influence on (a) subcortical networks subserving the execution of integrated motivated behaviours, (b) centres involved in autonomic control and (c) the voluntary motor system, via the cingulate motor areas.
4. The two networks are strongly interconnected. By way of these connections, sensory information screened for emotionally and motivationally relevant features is transferred to the medial network.

There is a certain resemblance between the limbic or emotional-motivational sensory-motor transfer system just outlined and the cognito-motor transfer system through the lateral prefrontal cortex (LPFC). In the latter system, highly processed information from sensory association areas in the parietal and temporal cortex converges onto the LPFC. The LPFC then produces voluntary motor actions based on this sensory input via sequences of short connections to premotor and motor areas (Fig. 15.15).

The OMPFC is connected to a large number of other brain structures, including the anterior temporal lobe, the amygdala and other limbic structure, and the basal ganglia. These connections will now be briefly discussed.

Experimental hodological studies in rhesus monkeys [36, 274, 381, 484, 576, 579, 581, 631, 672] have shown that the OMPFC is strongly interconnected with various parts of the anterior temporal lobe. Without going into details, it may be mentioned that many orbital areas receive afferents from the auditory association cortex in the superior temporal gyrus, the inferotemporal visual association cortex, and the multimodal sensory association cortex in the superior temporal sulcus (Fig. 15.54).

The amygdaloid complex projects to various parts of the OMPFC [90, 233, 484] (Figs. 15.70 A, 15.71). These amygdalocortical projections originate from the basal nucleus, and to a lesser extent from the accessory basal and lateral nuclei, and terminate principally in (a) the caudolateral entry zone for food-related information, (b) a medial orbital zone, which forms an interface between the orbital and medial networks, and (c) the medial prefrontal output areas 24 and 32 (Fig. 15.70 A). Most of these projections are reciprocated by projections from the cortex back to the amygdala.

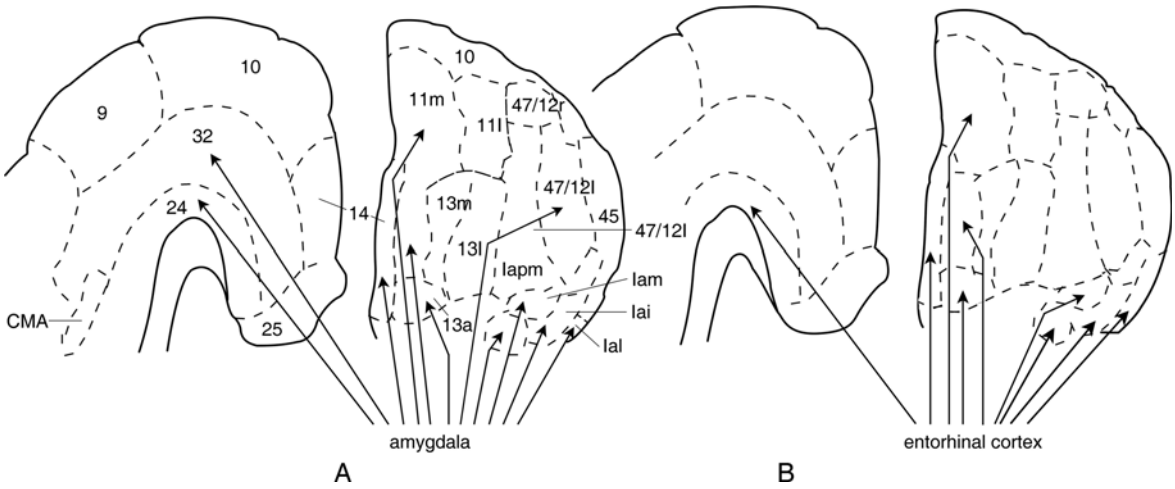

Fig. 15.70 A, B. Limbic inputs to the orbital and medial prefrontal cortex. **A** Afferents from the amygdaloid complex. **B** Afferents from the entorhinal cortex. Based on Carmichael and Price [87]

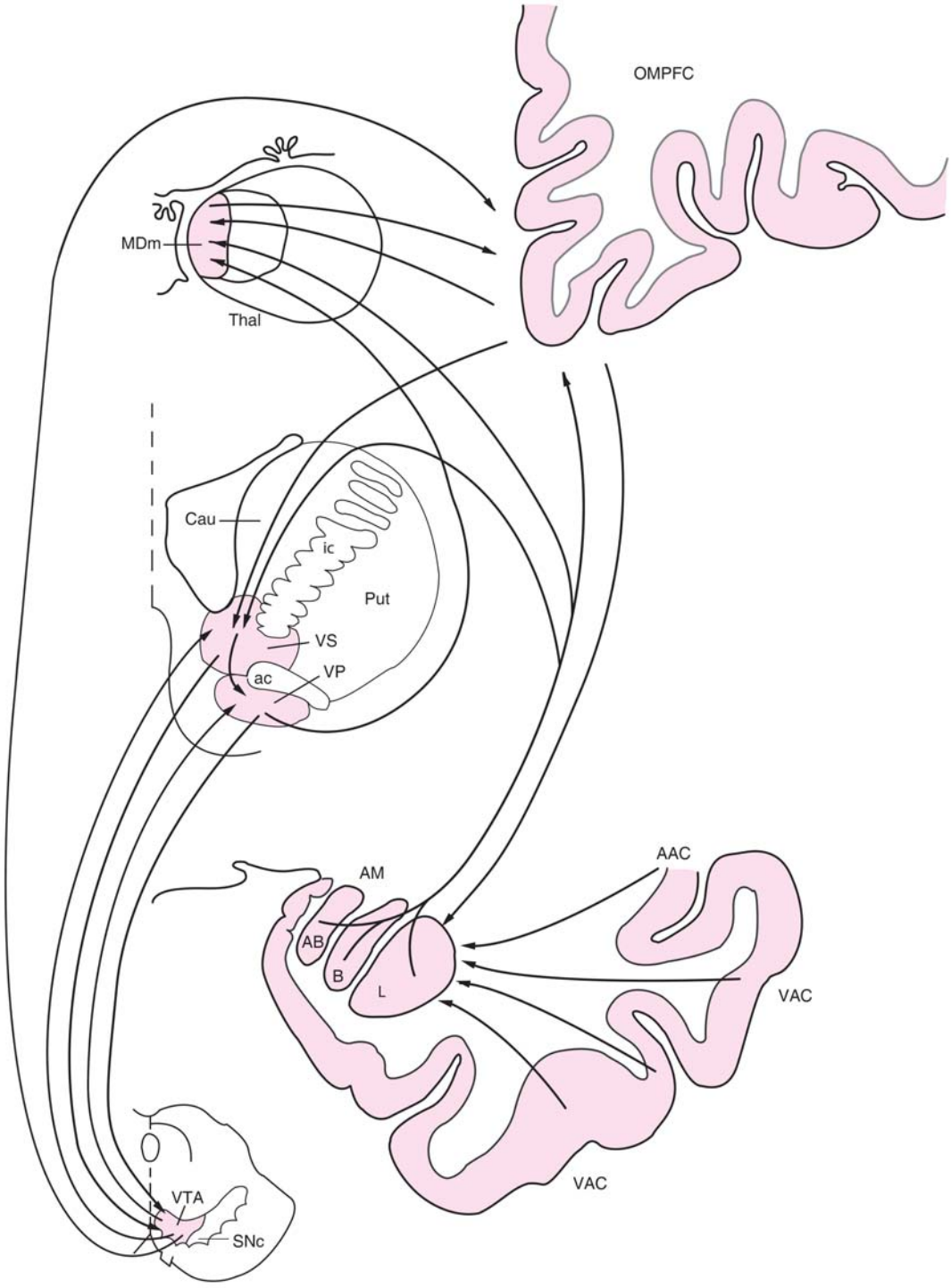

Fig. 15.71. Diagrammatic summary of connections of the accessory basal (*AB*), basal (*B*) and lateral (*L*) nuclei of the amygdaloid complex (*AM*), orbital and medial prefrontal cortex (*OMPFC*), magnocellular part of mediodorsal thalamic nucleus (*MDm*), ventral striatum (*VS*), ventral pallidum (*VP*) and mesencephalic ventral tegmental area (*VTA*) and adjacent pars compacta of substantia nigra (*SNc*). Partly based on Price et al. [595]. *AAC*, auditory association cortex; *ac*, anterior commissure; *Cau*, caudate nucleus; *ic*, internal capsule; *Put*, putamen; *Thal*, thalamus; *VAC*, visual association cortex

The basolateral nuclei of the amygdala are known to receive highly processed visual, auditory and somatosensory information and to be involved in evaluating the emotional and social significance of this information [41, 584] (see Chap. 13).

In addition to receiving inputs and sending outputs to the amygdala, the OMPFC is also connected with many other limbic structures, including the subiculum, entorhinal area 28, perirhinal areas 35 and 36, and parahippocampal areas TF and TH [87, 382, 484]. The subiculum, entorhinal and perirhinal areas are almost exclusively connected with the medial and caudal parts of the orbitofrontal cortex (Fig. 15.70 B). In contrast, the parahippocampal cortex is primarily connected with the medial prefrontal cortex, especially BAs 24, 25 and 32.

Apart from the direct projections from limbic structures to the OMPFC, there are also indirect projections, which are synaptically interrupted in the thalamus. The amygdala, entorhinal cortex and subiculum all project to the medial, magnocellular part of the mediodorsal thalamic nucleus (MDm), which in turn is reciprocally connected with all parts of the OMPFC [614].

As discussed in Chap. 14, the neocortex, basal ganglia and thalamus are interconnected by a number of parallel circuits or loops. One of these, designated as the *limbic loop,* involves the OMPFC and MDm. It originates from the medial BAs 24, 25 and 32 and the orbital BWAs 11, 13, 14 and 47/12. All of these areas project to the ventral striatum, composed of the accumbens nucleus and adjacent sectors of the caudate nucleus and putamen [270, 839]. The ventral striatum, in turn, projects to the ventral pallidum formed by rostral and ventral extensions of the globus pallidus. The ventral pallidum, then, projects to MDm, and connections between this thalamic nucleus and the OMPFC form the final link of the limbic loop (Figs. 14.17, 15.71).

Dopaminergic neurons in the mesencephalic ventral tegmental area (VTA) and adjacent parts of the substantia nigra, pars compacta (SNc) project to the OMPFC and ventral striatum. The ventral striatum projects back to the VTA and the latter is also reciprocally connected with the ventral pallidum [269] (Fig. 15.71).

There is physiological [14, 15, 61, 628, 666] and neuroimaging evidence [375, 664, 665] indicating that the limbic circuit, including its mesencephalic extension, is involved in the expectation and evaluation of reward and in the reward-guided selection of goal-oriented behaviours. Dopaminergic neurons in the VTA and adjacent SNc are known to play a key role in recognizing and predicting rewards [664, 665]. Dysregulation in the circuits interconnecting the orbitofrontal cortex, ventral striatum and dopaminergic midbrain are associated with several mental health disorders, including depression [448, 449], drug addiction [175, 357, 663, 792] and schizophrenia [284].

Lesions of the orbitofrontal cortex often induce dramatic changes in personality, as exemplified by the famous case of Phineas Gage [278], discussed in a previous section of the present chapter. Patients with such lesions are irritable, impulsive and disinhibited, with a characteristic tendency to tactlessness, vulgarity and disregard for social and moral principles. In addition, orbitofrontal patients exhibit a severe disorder of attention, and there are marked abnormalities in the realms of reasoning and decision-making [216, 483].

Medial prefrontal lesions commonly lead to apathy, manifesting as a severe reduction in spontaneity, motivation and general motility. Patients with such lesions also show a flattened affect and reduced interest in their environment. Large bilateral lesions may lead to akinetic mutism [216, 483].

Insula

The insula or island of Reil is buried in the depths of the lateral sulcus. It is covered by adjacent parts of the frontal, parietal and temporal lobe, known as the frontal, frontoparietal and temporal opercula (Figs. 2.23, 3.3). The insula is shaped like a triangle, the apex of which is directed anterobasally. The insular cortex is separated from surrounding opercular

cortices by a limiting or circular sulcus. A central sulcus divides the insular surface into a larger anterosuperior and a smaller posteroinferior portion. The anterior part is covered by some short gyri (gyri breves); the posterior part is incompletely separated into two long gyri (gyri longi) (Fig. 3.3).

As regards the structure of the insula, Brodmann [70] indicated that its cortex can be divided into an agranular anterior part and a granular posterior part, and that the boundary between these areas is formed by a vertical line which partly coincides with the central insular sulcus (Fig. 15.8). In the insular cortex of the rhesus macaque and human, Mesulam and Mufson [466] recognized three concentrically arranged zones, a rostroventral agranular zone, an intermediate dysgranular zone and a caudodorsal granular zone (Fig. 15.72 A). The intermediate zone is termed dysgranular because the granule cells in layers II and IV are rather scarce and do not display complete laminar differentiation.

The fibre connections and functions of the insula have been extensively reviewed by Mesulam and Mufson [466] and Augustine [22]. Much of what follows has been derived from these studies.

The insula receives afferents from the dorsal thalamus and is connected with the amygdala and with a large number of cortical areas (Table 15.3). The thalamic nuclei which project to the insula include the ventromedial posterior nucleus (VMPo), the ventral posterior superior and ventral posterior inferior nuclei, as well as the parvocellular part of the ventral posteromedial nucleus.

The ventromedial posterior nucleus (VMPo), which is situated in the posterobasal part of the thalamus (Fig. 8.2) [57, 118], is in receipt of nociceptive and thermoreceptive spinothalamic and trigeminothalamic lamina I neurons [98, 117]. This nucleus sends a somatotopically organized projection to the posterosuperior part of the insular cortex [72, 118]. This projection area may be designated as the *insular nociceptive and thermoreceptive cortex INTC.*

The ventral posterior superior (VPS) and ventral posterior inferior (VPI) nuclei form part of a shell surrounding the ventral posterior thalamic complex. These nuclei receive afferents from the vestibular nuclear complex and project to several cortical areas, including an area in the posterosuperior insula and adjacent operculum known as the *parietoinsular vestibular cortex, PIVC* [79]. This vestibular cortical area overlaps with the INTC.

The most medial sector of the parvocellular part of the ventral posteromedial thalamic nucleus (VMpc,m) is in receipt of gustatory projections from the most rostral part of the nu-

Table 15.3. Connections of the insula

	Ia	Idg	Ig	aff	eff
Somatosensory					
SI (areas 3, 1, 2)			++	+	
Area 5			++	+	
Area 7b			++	+	+
VMPo (thal.)			++	+	
Vestibular					
VPS, VPI (thal.)			++	+	
Auditory					
Audit. assoc. ctx (STP, PA)		+	++	+	
Motor					
Medial premotor (area 6)		++	++		+
High-order association					
Ant. orbfr. ctx (area 11)		++	++	+	+
Prefr. ctx (areas 45, 46)			++	+	+
Banks sup. temp. sulcus		+	++	+	+
Olfactory					
Olfactory cortex	++	+		+	+
Gustatory					
VPMpc, med (thal.)			++	+	
General viscerosensory					
VPMpc, lat (thal.)		++	+	+	
Limbic					
Entorhinal ctx (area 28)	++	+		+	+
Perirhinal ctx (areas 35, 36)		+			+
Temporopolar ctx (area 38)	++	++		+	+
Post orbfr. ctx (areas 12, 13)	++	+		+	+
Cingulate gyrus (areas 23, 24)		++	++	+	+
Amygdala, corticomedial	++	++		+	+
Amygdala, basolateral	++	++		+	+

Based on [22, 79, 466, 596, 648]

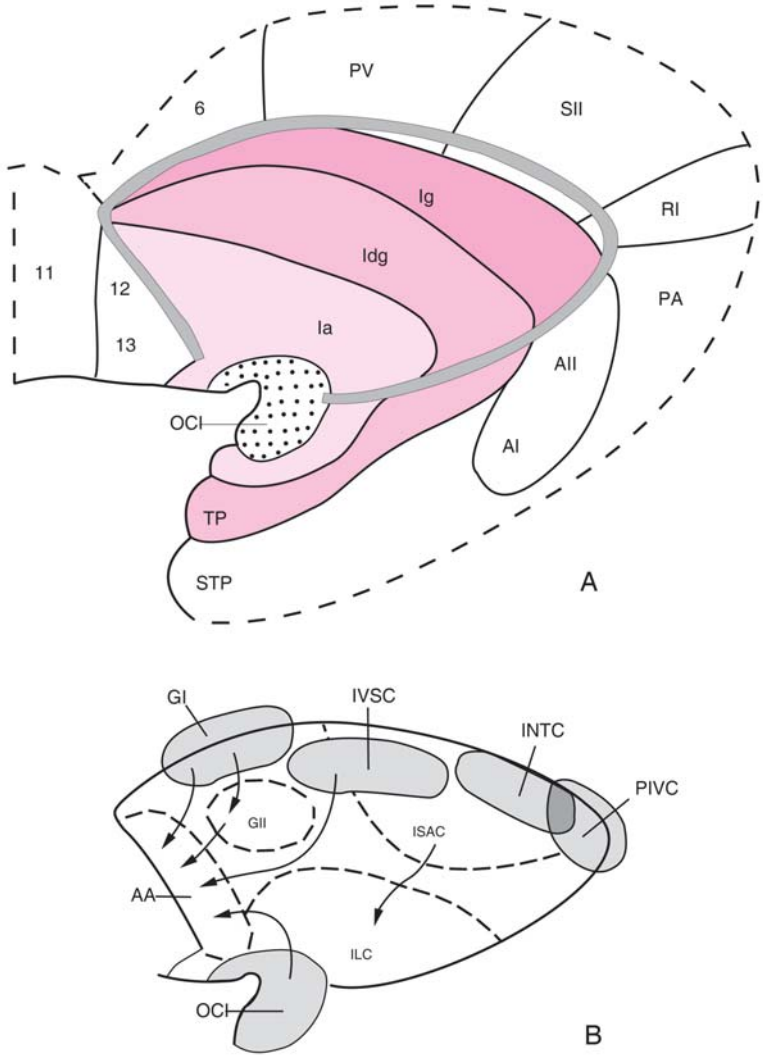

Fig. 15.72 A, B. The insula of the rhesus monkey. **A** Reconstruction of the insula and surrounding regions. The three types of insular cortex, agranular (*Ia*), dysgranular (*Idg*) and granular (*Ig*) are indicated with different hues of *red*. The *heavy grey line* represents the circular insular sulcus. Modified from Mesulam and Mufson [466]. **B** The approximate positions of functional areas in the insula and the course of some fibre connections. Primary sensory areas are *shaded*. *AA*, agranular anterior zone; *AI*, *AII*, primary and secondary auditory areas; *GI, II*, primary and secondary gustatory areas; *ILC*, insular limbic cortex; *INTC*, insular nociceptive and thermoreceptive cortex; *ISAC*, insular somatic association cortex; *IVSC*, insular viscerosensory cortex; *OCI*, primary olfactory cortex; *PA*, postauditory cortex; *PV*, parietal ventral area; *PIVC*, parietoinsular vestibular cortex; *RI*, retroinsular cortex; *SII*, secondary somatosensory area; *STP*, superior temporal plane; *TP*, temporopolar cortex

cleus of the solitary tract. This medial sector of the VPMpc projects to the granular anterosuperior part of the insula and the adjacent portion of the frontal operculum. This area, which represents the *primary gustatory cortex, GI,* projects to a more basally situated dysgranular and agranular insular area which, hence, may be designated as the *secondary gustatory cortex, GII* [596].

Via a synaptic relay in the external medial parabrachial nucleus, the intermediate and lateral sectors of VPMpc receive viscerosensory information from the intermediate and caudal parts of the nucleus of the solitary tract and project to an insular area located directly posterior to the gustatory areas. This area, which is known as the *insular viscerosensory cortex, IVSC,* shows an organotopic ordering. Physiological mapping experiments revealed that neurons responding to gastrointestinal sensations are located in its anterior part, whereas neurons responding to cardiovascular and respiratory afferents are located more posteriorly [648]. A similar topographical organization is observed in the postgustatory part of the nucleus of the solitary tract, where axons from the gastrointestinal tract end more rostrally than those from cardiovascular and respiratory structures. Hence, it seems likely that this topographical and viscerotopical ordering is maintained throughout the central viscerosensory pathway [648].

If we survey that data concerning the thalamic projections just discussed, it appears that the superior tier of the insula contains four anteroposteriorly arranged primary sensory areas: gustatory, viscerosensory, somatosensory (pain and temperature) and vestibular (Fig. 15.72 B).

The insula is also in receipt of primary and higher-order sensory projections from other cortical areas. Fibres from the primary olfactory (prepiriform and periamygdaloid) cortex project to an *agranular anterior zone (A A)* of the insula. This zone also receives afferents from the primary and secondary gustatory cortices and from the primary viscerosensory cortex (Fig. 15.72 B). As discussed in Chap. 11, it participates with the adjacent caudal orbitofrontal cortex in the formation of an "orbital network", functioning in the analysis and integration of food-related sensory information (Figs. 11.7, 11.8) [89].

The insula receives afferents from the primary somatosensory cortex SI, the somatosensory association areas 5 and 7 b, the primary vestibular areas 3 a and 2 v (located in the basal part of the central sulcus and the anterior tip of the intraparietal sulcus, respectively) and auditory association areas situated in the anterior and posterior parts of the temporal plane. All of these sensory cortical areas project to the posterosuperior part of the insula, which may hence be characterized as the *insular somatic association cortex (ISAC)*. Some high-order association areas, including the anterior orbitofrontal cortex (area 11), the prefrontal cortex (areas 45, 46) and the polymodal sensory association cortex occupying the banks of the superior temporal sulcus, are also known to be connected with the insula.

Finally, it may be mentioned that a considerable number of limbic cortical areas, including the entorhinal, perirhinal, temporopolar, posterior orbitofrontal and cingulate cortices, as well as the amygdaloid complex, are reciprocally connected with agranular and dysgranular sectors in the anterior and anterobasal parts of the insula. We designate these areas collectively as the *insular limbic cortex, ILC*. It has been suggested [466] that the insular somatic association cortex and the insular limbic cortex represent way stations in a somatolimbic projection (Fig. 15.72 B) and that this projection may provide a means for interrelating events in the extrapersonal world with relevant motivational states.

The insular cortex has been implicated in olfactory, gustatory, viscerosensory, visceromotor, somatosensory and vestibular functions. All of these functions, except for the visceromotor ones, can be readily associated with structures and connections discussed above, which are diagrammatically summarized in Fig. 15.72 B.

Olfaction. Electrical stimulation of the anterior insula in humans may lead to olfactory sensations [546].

Taste. The results of both stimulation and ablation experiments in monkeys point to the

presence of a gustatory centre in the anterior insula [28, 714]. The detection of taste-sensitive neurons in the same area further documents the presence of this centre [838]. Verhagen et al. [777] recently reported that, apart from numerous taste-sensitive neurons, the primary gustatory cortex in the rhesus monkey also contains elements responding to non-taste properties of oral stimuli, related to the texture (viscosity, grittiness) or temperature of food. Neurons responding to combinations of these inputs also appeared to be present. These observations further substantiate the concept that the anterior insula and the adjacent caudal orbitofrontal cortex are involved in the analysis and integration of food-related information.

Viscerosensory Functions. Electrical stimulation of the insula in humans produces nausea and a variety of gastric and abdominal sensations [546, 547]. Neuroimaging studies in humans demonstrated activation of an insular area, just caudal to the gustatory cortex, with visceral stimuli such as air hunger, maximal inspiration and Valsalva manoeuvre [35, 367].

Visceromotor Control. Electrical stimulation of the insular region in humans may elicit a variety of visceromotor phenomena, including vomiting and other alterations of gastrointestinal motility, respiratory arrest, as well as changes in heart rate and blood pressure [521, 546]. Ischaemic strokes involving the insula are frequently accompanied by atrial fibrillation and electrocardiographic abnormalities [102, 470, 520, 732]. These findings indicate that the insula plays a role in autonomic regulation. It is known that the subgenual part of the cingulate gyrus (BA25), which is involved in similar functions, projects to several subcortical autonomic control centres, including the perifornical part of the hypothalamus, the periaqueductal grey and the parabrachial nuclei [9, 96, 517]. However, such connections have so far not been described for the insular cortex. It is remarkable that the cardiac dysfunctions mentioned occur much more frequently after right-sided strokes than after left-sided ones [102, 470]. This finding suggests that the autonomic control of cardiac activity is lateralized and is mediated by the right-sided insular cortex.

Somatosensory Functions. Physiological studies in rhesus monkeys [617, 618, 661] have shown that neurons in the granular part of the insula respond to innocuous cutaneous stimuli. A PET study [78] revealed that the human insula can be activated by vibrotactile stimulation. The involvement of the insula in protopathic sensibility is documented by clinical evidence. Thus, Biemond [52] described a patient in whom a lesion involving the insula and SII was associated with a dramatic loss of pain perception, and Birklein et al. [53] recently reported that isolated insular infarction may lead to contralateral elimination of cold, cold pain and pinprick perception.

Vestibular Functions. Neurons in the parietoinsular vestibular cortex (PIVC) of the rhesus monkey respond to vestibular stimuli [262]. However, most of these elements also responded to somatosensory and visual stimulation and were, hence, classified as polymodal vestibular units [263].

Finally, it may be mentioned that some recent imaging studies [725, 726] have shown that the volume of the insula is significantly reduced in schizophrenia.

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