

Architecture of the Cerebral Cortex

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PRINCIPAL SUBDIVISIONS OF THE CEREBRAL CORTEX

The cerebral cortex of the human brain can be subdivided by *microscopic anatomical (histological) criteria* into two major parts, i.e. *isocortex* and *allocortex* (Vogt, 1910). Despite regional variations, the largest part of the adult

human isocortex is characterized by its six-layered structure visible in cell body-stained (e.g., Nissl-stained) sections. In contrast to the six-layered architecture of the isocortex, the allocortex shows a regionally variable laminar pattern reaching from a hardly subdivisible single cell band to an architectural organization with more than ten layers (e.g., entorhinal area; Braak, 1972).

Two isocortical regions of the adult brain show a reduction or an increase in the number of cortical layers. Such notable exceptions are (i) the frontal agranular cortex, which does not contain a clearly visible inner granular layer (layer IV) in the adult human brain; it represents the anatomical correlate of the motor cortex (primary motor cortex, premotor cortex, supplementary and pre-supplementary motor cortices), and (ii) the primary visual cortex, which displays a clearly visible subdivision of its layer IV into three sublayers, i.e. layers IVa, IVb, and IVc.

This principal cytoarchitectonical subdivision into iso- and allocortex is paralleled by Brodmann's (1909) developmental classification of a homogenetic and heterogenetic cortex. The homogenetic cortex develops a six-layered structure during fetal stages, which is preserved in the adult isocortex with the above-mentioned exceptions of the primary visual cortex and agranular motor cortex (see above). Therefore, the homogenetic cortex resembles the architectonically defined isocortex. In cases of disturbed development of the cortex, the normally occurring reduction of the motor cortex from the six-layered fetal pattern to the normal agranular five-layered cortical lamination around birth can fail, as shown in children suffering from cerebral palsy (Amunts et al., 1997b).

The isocortex contains primary sensory areas (primary somatosensory, auditory, or visual areas), which are the main targets of unimodal sensory afferents originating in the ventroposterior nucleus of the thalamus, medial, and lateral geniculate bodies, respectively. Primary sensory areas project to a set of higher-order unimodal sensory areas (secondary and tertiary sensory areas) in a hierarchical and parallel organization. The higher-order unimodal sensory cortices border to multimodal association areas. Multimodal areas send projections to the motor cortex, which is again subdivided into a primary motor area and non-primary motor areas (for a comprehensive description of the motor cortex, see Chapter 27).

The heterogenetic cortex never passes through a developmental stage with six layers nor does it show the six-layered architecture of the isocortex during adult stages. Thus, the heterogenetic cortex resembles the architectonically defined allocortex.

Finally, the allocortex precedes the isocortex during mammalian brain evolution. Using evolutionary criteria, the isocortex is called neocortex. According to Filimonoff (1947) and Stephan (1975), the allocortex can be further subdivided into paleocortex and archicortex. The paleocortex comprises the olfactory bulb, retrobulbar (anterior olfactory nucleus), olfactory tubercle, septal (including diagonal band), and (pre)piriform regions, as well as a minor part of the amygdala (the major part of the amygdala is classified as non-cortical, i.e. an assembly of subcortical nuclei). The archicortex includes the hippocampus (Ammon's horn, dentate gyrus, and subiculum), presubiculum, parasubiculum, entorhinal

cortex, retrosplenial cortex, and a cortical band in the cingulate gyrus (Stephan, 1975).

A functional imaging study of the human cerebral cortex (Qureshy et al., 2000) shows that the rostral parts of the allocortex mainly participate in olfactory functions (*rhinencephalon*), whereas the cingulate and the more caudal and medial temporal parts are cortical portions of the *limbic system*.

Isocortex and allocortex show a stepwise transition of the cyto- and myeloarchitecture at their common border. The isocortical part, which forms a transition zone to the allocortex, is called *proisocortex* (Vogt and Vogt, 1956; Sanides, 1962), whereas the adjoining part of the allocortex is called *periallocortex* (Filimonoff, 1947). Both transition zones together are also termed *mesocortex* (Rose, 1927). According to Filimonoff (1947), the periallocortex is subdivided into *peripaleocortex* (claustral region) and *periarchicortex* (entorhinal, presubiculum, retrosplenial, and parts of the cingulate gyrus).

Rose (1926) has proposed another system of subdividing the allocortex. According to him, the allocortex can be subdivided into *semicortex* (piriform and septal regions, amygdala, olfactory tubercle), *schizocortex* (entorhinal and presubiculum regions) and *holocortex bistratificatus* (retrobulbar and hippocampal regions).

Stephan (1975) has proposed a classification, which relies on comparative neuroanatomical studies in insectivores and primates. This system is adopted here (Figure 23.1), because it considers both evolutionary aspects and specificities of the human brain. The

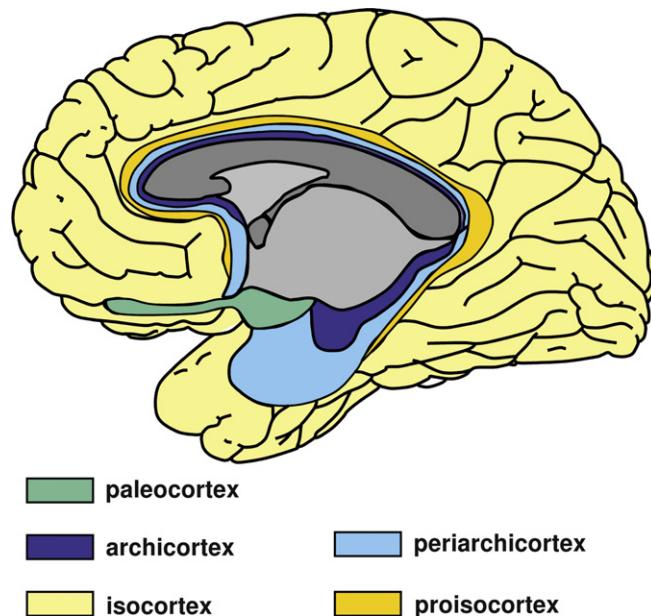


FIGURE 23.1 Medial aspect of the right hemisphere with the delineation of the principal subdivisions of the human cerebral cortex into paleocortex, archicortex, periarchicortex, isocortex and proisocortex. Modified after Stephan (1975).

olfactory bulb, anterior perforate substance, paraterminal body, uncus, parts of the cingulate gyrus, lateral olfactory, semilunar, parahippocampal, and ambiens gyri contain allocortical regions. All other gyri of the human brain belong to the isocortex.

QUANTITATIVE ASPECTS OF THE CEREBRAL CORTEX AND GENDER DIFFERENCES

The volume of the adult human cerebral cortex varies between 197 and 331 cm³ in the female brain (right hemisphere: 264 ± 24 cm³ (mean ± SD), left hemisphere 262 ± 24 cm³; n = 43; age between 16 and 90 years; mean age 65 ± 2.7 years), and between 242 and 358 cm³ in the male brain (right hemisphere: 292 ± 28 cm³, left hemisphere: 291 ± 29 cm³; n = 35; age between 32 and 91 years; mean age 64 ± 2.6 years) (Zilles, 1972). 11 and 16% smaller volumes are reported by Pakkenberg and Gundersen (1997) in male and female brains, respectively. Males have a significantly larger (11–18%) cortical volume than females (Paul, 1971; Zilles, 1972; Pakkenberg and Gundersen, 1997). A similar gender difference of 11% is reported for the weight of male and female cerebral hemispheres in 196 male and 190 female brains (age between 70 and 79 years) (Skullerud, 1985). The larger cortical volumes in males may be explained by their larger overall brain size (Haug, 1984). Skullerud (1985) reported a 110–115 g smaller brain weight in women compared to men even after correction of body size using a body mass index. Both sexes show the same volumetric proportion (46%) of the cortex to the whole brain, and the same ratio (1.158 males and 1.152 females) between cortical to subcortical volumes (including amygdala, basal ganglia, and thalamus) of the prosencephalon (Zilles, 1972). Forty-two percent of the isocortical volume belongs to the frontal, 23% to the temporal, 23% to the parietal and only 12% to the occipital lobes (Pakkenberg and Gundersen, 1997).

The total cortical surface of both hemispheres varies between 1469 cm² (Blinkov and Glezer, 1968) and 2275 cm² (Elias and Schwartz, 1969). Pakkenberg and Gundersen (1997) reported 1900 ± 209 cm² for male and 1680 ± 235 cm² for female brains. Less than 1% of the surface is covered by the paleocortex, 3.5% by the archicortex and nearly 96% by the isocortex (Blinkov and Glezer, 1968; Stephan, 1975). Thirty-two percent of the isocortical surface belongs to the frontal, 30% to the temporal, 23% to the parietal and only 15% to the occipital lobes. As in the volumetric data (see above), the cortical surface data indicate a predominance of the frontal and temporal lobes, which contain, beside motor and auditory cortices, multimodal association areas and language-related regions.

The thickness of the human isocortex varies according to von Economo and Koskinas (1925) between 3.3 and 4.5 mm (after correction for shrinkage 4.16–5.67 mm) in Brodmann area 4 (primary motor cortex) and 1.9–2.1 mm (after correction for shrinkage 2.39–2.65 mm) in area 3 (primary somatosensory cortex). It is influenced by the bending of the cortical ribbon (lowest values on the sulcal floor, highest values on the gyral height). A comparison between different isocortical areas of the human brain (Table 23.1) illustrates the regional variation in both total and laminar thicknesses. Pakkenberg and Gundersen (1997) reported a mean neocortical thickness of 2.72 ± 0.24 mm in male and 2.61 ± 0.21 mm in female brains (significant gender difference).

Cortical thickness is also frequently reported in MR imaging studies, but the accuracy with which it can be measured depends completely on the regionally variable tissue properties of cortical areas with higher or lower myelin density and the methods for the segmentation of the cortical ribbon from the underlying white matter in MR images. Cortical thickness is regularly underestimated in the primary motor cortex, where the transition between cortex and white matter is not correctly detectable in the MR-contrast, and over- or underestimated in other cortical areas (for a more detailed overview see Zilles and Amunts, 2011).

According to Pakkenberg and Gundersen (1997) the mean total number of cortical neurons in both hemispheres is 22.8 × 10⁹ ± 3.9 (mean ± SD) in male and 19.3 × 10⁹ ± 3.3 in female brains (49 left and 45 right hemispheres; age range 19–93 years). The gender difference of 15.5% is significant.

The packing density of neurons varies depending on the specific cortical area (Blinkov and Glezer, 1968; Haug, 1984). Pakkenberg and Gundersen (1997) reported a mean neuronal density of 44 × 10⁶ per cm³ with no significant difference between male and female brains.

TABLE 23.1 Thickness of different isocortical areas and layers in the human brain*

Layers	Area 4	Area 3	Area 41/42	Area 17	Area 18
I	200	220	260	246	272
II	100	280	280	89	92
III	1400	420	740	471	851
IV	—	280	450	653	148
V	900	220	530	218	279
VI	1250	400	640	278	395
I–VI	3850	1820	2900	1955	2037

* Thickness in µm. Data from von Economo and Koskinas (1925) and Zilles et al. (1986a).

The number of glial cells in the cortex equals approximately that of the neurons as stated in a review (Hilgetag and Barbas, 2009) of the literature, where glial cells have been counted using unbiased stereological methods. This report corrects the widespread opinion of a ten-fold higher glial cell than neuronal number (Blinkov and Glezer, 1968).

On midsagittal sections, the *corpus callosum* measures $6.2 \pm 0.2 \text{ cm}^2$ in male and $6.3 \pm 0.2 \text{ cm}^2$ in female brains (Zilles, 1972). While in agreement with the data of de Lacoste-Utamsing and Holloway (1982) and Witelson (1985), this difference is not significant, yet it seems remarkable that the commissural system in females reaches at least the same absolute size as in males, given that the female total cortical volume is significantly smaller. A significant correlation between the corpus callosum area and brain size has been shown (Zilles, 1972). This means a 10% larger commissural system in females, when scaled to cortical size. On the basis of a relatively larger commissural system, it was proposed that the female cortex shows a lesser degree of hemispheric lateralization (cf. also de Lacoste-Utamsing and Holloway, 1982). However, a recent MRI study using diffusion tensor imaging (DTI) seems to suggest a stronger interhemispheric connectivity between the frontal lobes in males than females (Westerhausen et al., 2011).

Several factors affect total brain size (Haug, 1984). Secular acceleration (0.6 g/year), age, gender, and body size are among the most important. The volume of the cortex of a 75-year-old individual is about 4% smaller than that of a 25-year-old individual. The frontal cortex shows the largest age-dependent decrease (12%). However, these findings and the frequently reported loss of cortical neurons with age must be critically reconsidered not only because of possible effects by potential cases of neurodegenerative diseases not detected in the postmortem samples, but also because of the effect of secular acceleration. It may lead to lower cell counts in the older brains compared with the younger brains in cross-sectional studies. The age-dependent differential shrinkage during histological embedding (Haug, 1984) may also alter cell counts when based on the measurement of cell numbers per volume cortical tissue.

One of the most prominent features of the human cortex is its distribution over a folded surface (*gyrification*). Only one-third of the human cortex is superficially exposed, two-thirds are buried in the sulci (von Economo and Koskinas, 1925; Elias and Schwartz, 1969; Zilles et al., 1988). The reasons for the gyrification of the brain are not completely understood, although van Essen (1997) has proposed a mechanical folding hypothesis to explain the mechanism behind gyrification.

Since vertically oriented and side-by-side positioned cell columns represent the basic modular organization

of the cerebral cortex, the cortical growth leads inevitably to a considerable enlargement of the cortical surface. A large unfolded cortical surface would require such an increase in volume of the skull, that a normal delivery would be impossible. Furthermore, the distance between cortical regions interconnected by projection fibers would increase to such a degree, that information transmission between distant cortical regions would be delayed. Thus, gyrification is a solution for large brains to pack a maximal cortical surface into a minimal volume, and to optimize the speed of neural transmission between neighboring cortical areas. All gyri and sulci are visible at birth, but the cortical surface amounts to only one-third of the adult surface. Particularly, the multimodal association areas double their surface during postnatal development compared to visual areas of the medial occipital cortex and the insular cortex (Hill et al., 2010). The depths of the sulci increase until two-thirds of the cortical surface are hidden in the sulci after the 20th postnatal year (Armstrong et al., 1995).

It has been demonstrated (Richman et al., 1975; Rakic, 1991) that the amount of gyrification depends on genetic and environmental constraints. Since Vogt (1910), Sanides (1962, 1972) and Hinds et al. (2009) have demonstrated that some of the sulci can indicate cortical regions of different function and somatotopy, the sulcal and gyral pattern of the human cortex is a sign of the functional, as well as evolutionary and individual development.

The human cortex shows the highest degree of folding, when compared with other primates (Zilles et al., 1988). Moreover, the degree of folding varies over the rostrocaudal extension of the hemisphere. The highest values are found in the prefrontal and parieto-occipito-temporal association cortex. The cortical regions where motor, premotor, and primary visual areas are located show the lowest degree of gyrification. The most significant increase in folding between human brains and those of non-human primates including gorilla, orang-utan, and chimpanzee is visible in the prefrontal cortex (Zilles et al., 1989).

ASYMMETRIES IN THE CEREBRAL CORTEX

First attempts to analyze brain asymmetries were initiated by the observation of language lateralization (Broca, 1861) and continued throughout the 19th century (Lichtheim, 1885; Eberstaller, 1890; Cunningham, 1892). An update of numerous structural brain asymmetries has been recently published (Amunts, 2010).

Numerous MR and CT studies have reported gross brain asymmetries. The left occipital pole is frequently wider and protrudes further posteriorly than the right,

whereas the right frontal lobe is often wider than the left, typically in male right-handers (LeMay and Kido, 1978; Kertesz et al., 1990). This *anticlockwise torque of the brain* includes also the frequent extension of the left occipital lobe across the midline. Similar asymmetries can also be found in non-human primates (Zilles et al., 1996a). This argues for an evolutionary trend of brain asymmetry. This view is further supported by a recent study analyzing relative cross species size changes in frontal lobe. The scaling coefficients in the left versus the right prefrontal hemispheres differ between each other. The coefficients suggest that the primary factor underlying the evolution of primate brain architecture is a left hemispheric prefrontal hyperscaling, whereby humans seem to be the extreme of a left prefrontal ape specialization in the ratio between white to gray matter volume (Smaers et al., 2011).

Slight right-over-left *asymmetries of the volumes of hemispheres and white matter* are found in 109 adult brains of both sexes, if the data of Paul (1971) and Zilles (1972) are pooled. The *cortical volume* of the right hemisphere is significantly larger than that of the left (Table 23.2). A slight right-over-left *asymmetry in weight* (mean 2.2 g) of hemispheres has also been described in 260 male and 207 female brains aged between 45 and 79 years (Skullerud, 1985). In contrast to cortical volumes, significant differences between the *cortical surfaces* of the right and left hemispheres have not been reported.

Left-over-right asymmetries of the planum temporale, Sylvian fissure, inferior frontal gyrus, lateral ventricles, and temporo-occipital region have been repeatedly reported (e.g., Geschwind and Levitsky, 1968; Galaburda et al., 1978a, 1978b; Galaburda and Geschwind, 1981) and correlated with functions (Zangwill, 1960; Geschwind, 1970). A paradigm for studies of functional, structural, and developmental plasticity of interhemispheric asymmetries is the human motor cortex, where correlations between macro- and microscopical as well as functional features (motor skill, handedness) were demonstrated (Amunts et al., 1996, 1997a, 1997c, 1999, 2000a). The only reported advantage of the right over

the left side is the width of the frontal lobe (for review see Galaburda and Geschwind, 1981).

Interhemispheric differences in length and slope of the *Sylvian fissure*, with the left being longer and running more horizontally than the right fissure have been described (Eberstaller, 1890; Cunningham, 1892). Although the morphology of the Sylvian fissure is highly variable (Ono et al., 1990), two subtypes can be distinguished according to the length of the posterior horizontal portion and the size of the two posterior rami. A long horizontal portion is more frequently found in the left hemisphere, and a shorter posterior horizontal portion is more frequently found in the right hemisphere (Steinmetz et al., 1990a, 1990b, 1991, 1995; Ide et al., 1996; Steinmetz, 1996; Jäncke and Steinmetz, 2004). The end of the Sylvian fissure is more dorsally extended in the right than in the left hemisphere already in fetal brains (LeMay and Culebras, 1972). A higher end in the left than right hemisphere was also found in great apes (Zilles et al., 1996a). Only a few studies correlated the asymmetry of the Sylvian fissure with functional lateralization. Witelson and Kigar (1992) found that 67 men with consistent right-hand preference had longer horizontal portions in both hemispheres than men without this preference.

Asymmetries of the transverse gyrus of Heschl with the primary auditory cortex and of the Planum temporale are described in Chapter 36.

Areas 44 and 45 represent *Broca's region*, and occupy the Pars opercularis and Pars triangularis, respectively. The cortical volumes of left area 44 are larger than those of the right hemisphere (Galaburda, 1980; Amunts et al., 1999), whereas the volumes of area 45 did not differ significantly between the hemispheres (Amunts et al., 1999). The cytoarchitecture of areas 44 and 45 differs between both hemispheres (Amunts and Zilles, 2001). The size of pyramidal cells in layer III of area 45 was found to be larger in the left than in the right hemisphere (Hayes and Lewis, 1996). A significant leftward asymmetry in the total number of neurons in area 44 of males has also been reported (Uylings et al., 2006). Significant interhemispheric cytoarchitectonic differences were already found in 1-year-old infants (Amunts et al., 2003). Asymmetry tended to increase with age. The adult left-larger-than-right asymmetry in the volume fraction of cell bodies was reached at an age of 5 years in area 45, and 11 years in area 44. The results supplement earlier data on interhemispheric asymmetry (Jacobs et al., 1993; Hayes and Lewis, 1995). These data are also in accordance with behavioral findings showing that adult-like syntactic processes (which rely mainly on area 44) are observed only around the age of 10 years, whereas adult-like semantic processes (which mainly involve area 45) are established much earlier (Friederici and Kotz, 2003).

TABLE 23.2 Cortical volumes in human male and female adult brains (data compiled from Paul (1971) and Zilles (1972))*

	Cortical volume (cm ³)	
	Male (N = 53)	Female (N = 56)
Right side	298.7 ± 4.2	267.2 ± 3.3
Left side	294.9 ± 4.1	263.8 ± 3.2
Right/left	3.8 ± 1.5	3.4 ± 1.7
	(p < 0.05)	(p < 0.05)

* Significance of hemispheric asymmetries is given in parentheses (the Wilcoxon matched-pair test).

Intersubject variability of this region combined with the loose association between cytoarchitectonic borders and sulcal landmarks may contribute to the conflicting results reported in this region. Wada and colleagues measured the surface of the Pars opercularis and the posterior portion of the Pars triangularis in 100 adult and 100 infant post-mortem brains (Wada et al., 1975a). They reported a rightward asymmetry of this region, particularly in the adults, but were aware that consideration of the intrasulcal portion may yield different results (Wada et al., 1975b). Falzi et al. analyzed the asymmetry of the Pars opercularis and Pars triangularis by measuring the area on the lateral convexity and the full intrasulcal area (Falzi et al., 1982). They found a significant leftward asymmetry of only the intrasulcal portion of the gyrus. A similar asymmetry was found in the Pars triangularis (Albanese et al., 1989; Foundas et al., 1995). Significant leftward asymmetry of the volume of the Pars opercularis has been reported in an MR study (Foundas et al., 1998; Keller et al., 2007). Other studies, however, did not reveal a significant leftward asymmetry in volume, surface area, or cortical thickness of the Pars opercularis (Good et al., 2001).

Interhemispheric asymmetry has also been demonstrated in the *sensor and motor cortices*. The primary motor cortex occupies the anterior wall of the central sulcus while the somatosensory cortex is found on the postcentral gyrus. Considering this unique situation with a strong correlation between a macroanatomical landmark and borders of a cytoarchitectonically defined cortical area, the central sulcus was in the focus of numerous studies of interhemispheric differences in the somatosensory and motor system. It was hypothesized that the preferred hand is controlled by a larger cortical region than the non-preferred hand, and that the shape and size of the central sulcus reflect such a structural/functional relationship. The central sulcus was found to be deeper in the right than in the left hemisphere in males and females (Davatzikos and Bryan, 2002), but other studies reported a deeper sulcus in the left, dominant hemisphere in right-handers with an inverse trend in consistent left-handers, and an intermediate position in mixed-handed males (Amunts et al., 1996). The leftward asymmetry was most pronounced in the most dorsal part of the sulcus (Amunts et al., 1996, 2000a; Cykowski et al., 2008). A leftward asymmetry was also found in the lower central and precentral sulci in right-handed subjects (Herve et al., 2006). It can be hypothesized that asymmetry is caused by an increase in the connectivity and neuropil of left motor cortex controlling the coordination of the dominant limb (Amunts et al., 1996). This hypothesis is supported by a recent study, which shows that cortical thickness of the left superior precentral gyrus is up to 15% larger

than that of the right side (Lüders et al., 2006). Studies of the underlying white matter came to conflicting results as well. The pyramidal tract was found to be symmetrical (White et al., 1997), while an earlier study described a left-over-right asymmetry (Yakovlev and Rakic, 1966).

Male, right-handed keyboard players (professional musicians) have a more symmetric central sulcus than controls as demonstrated in an in vivo MR morphometric study (Amunts et al., 1997). Decreased asymmetry was interpreted as a result of lifelong bimanual practice. The loss of leftward asymmetry was found in the upper part of the central sulcus, where the upper limb is represented. Furthermore, the depth of the central sulcus in keyboard players was negatively correlated with the age at which the musicians began bimanual training (Amunts et al., 1997). This convergence of findings suggests that the anatomy of the central sulcus and its asymmetry are part of a lifelong remodeling process.

Asymmetries of the *limbic system* have been described in the hippocampus, the cingulate gyrus, and the amygdala. A rightward volumetric asymmetry of the *hippocampus* was found in a MR study of 61 healthy volunteers (age 6–82 years) after normalization to adjust for intersubject variation in head size; no statistically significant differences were found between different age and gender groups (Li et al., 2007). An earlier study supports this notion about a rightward asymmetry in hippocampal and, additionally, in amygdalar volumes (Szabo et al., 2001), but other studies do not confirm these findings (Bhatia et al., 1993; Narr et al., 2004). Quite contrary, a study based on a deformable hippocampal model and principal component analysis reported a leftward volumetric asymmetry (Kim et al., 2005). Methodical constraints may cause such conflicting data, since the hippocampus is not easy to delineate from the neighboring structures in MR images (Shenton et al., 2001). Formal definitions of the hippocampal borders (e.g., Szabo et al., 2001) differ between the different in vivo MR studies, and do not match the anatomical borders in histological sections. If, for example, the extent of the fascia dentata is taken as an indicator of the rostral border, an underestimation of the rostral extent by a few millimeters may occur (Amunts et al., 2005). There are only a few histological studies of the hippocampal volume, in which different parts of the hippocampus can be unambiguously separated. One histological study has measured the volume of the hippocampus in ten post-mortem brains; volumetric differences between the hemispheres did not reach significance, although there was a tendency of a left-larger-than-right asymmetry (Amunts et al., 2005). This is consistent with an earlier post-mortem observation (Duvernoy and Bourgouin, 1998).

In a recent study of the *cingulate cortex*, MR data of the volume, surface area, and thickness of the cortical mantle were collected in 68 healthy subjects (Wang et al., 2007), excluding the paracingulate gyrus. A significant leftward asymmetry in thickness of the anterior cingulate segment, and a significant leftward asymmetry in the surface area of the posterior segment were found. Another study, however, reported a rightward asymmetry of the anterior cingulate region, which was more frequently found in females than in males (Pujol et al., 2002). The posterior cingulate region did not show an asymmetry. The paracingulate sulcus was found more frequently in the left than in the right hemisphere (Paus et al., 1996). This feature was discussed in the context of the participation of the left anterior cingulated cortex in language processing.

Evidence has been provided for an asymmetry of the *prefrontal cortex* in 137 young adolescents, which may be associated with affective behavior (Whittle et al., 2008). A male-specific, decreased leftward anterior paralimbic cortex volume asymmetry was associated with increased duration of aggressive behavior, and a decreased leftward orbitofrontal cortex volume asymmetry was associated with increased reciprocity of dysphoric behavior. Interhemispheric differences of the prefrontal cortex were also observed in a post-mortem study. The neuronal density, size, and shape were analyzed in Brodmann's areas 9 and 10 in ten control brains (Cullen et al., 2006). The left showed a larger density of neurons than the right hemisphere. Pyramidal neurons of layer III were larger on the left than the right side.

A hemispheric asymmetry in *visual* and *spatial processing* has been shown, whereby this specialization may differ between genders. About one-third of the population is left eye dominant, preferring to use the left rather than the right eye for monocular tasks (Bourassa et al., 1996; McManus et al., 1999). Evidence of lateralization with respect to the (left) word form area and the (right) fusiform face area has been provided. This lateralization is interacting with the spatial frequency of the stimulus (Kanwisher et al., 1997; Cohen et al., 2000; Woodhead et al., 2011).

The spatial covariance between human occipital sulci and functionally defined visual areas using retinotopic mapping has been analyzed (Hasnain et al., 2006). A stronger sulcus-function covariance was found in the left than in the right occipital lobe. The left calcarine fissure covaries with functional areas in both hemispheres, suggesting that it serves as a developmental "anchor" for functional areas in the occipital cortex. These findings support the hypothesis that hemispheric lateralization of function is reflected by the strength of correspondence between cortical surface anatomy and function (Hasnain et al., 2006).

The volumes and cortical thickness of the *primary* (BA17, striate cortex) and *secondary visual cortex* (BA18) as well as the cytoarchitectonic correlate (area hOc5) of V5/MT (Malikovic et al., 2007) were analyzed in a recent cytoarchitectonic study of five male and five female brains (Amunts et al., 2007). Genders differed in interhemispheric asymmetry of hOc5 volumes, and in the right-hemispheric volumetric ratio between hOc5 and BA17. The volumetric asymmetry was accompanied by an asymmetry in surface area of hOc5, but not in its cortical thickness. Volumetric analyses in a sample of post-mortem fetal brains showed that male striate and extrastriate cortices were far more asymmetrical than those in female brains (de Lacoste et al., 1991). Another study described a significant right-larger-than-left volumetric asymmetry of the striate cortex, but failed to demonstrate gender differences (Murphy et al., 1996).

A right-over-left asymmetry of the *planum parietale* (posterior wall of the ascending ramus of the Sylvian fissure) was found in MR images of 106 right-handers and 35 left-handers (Jäncke et al., 1994). Cytoarchitectonically, this region encompasses Brodmann area 40 on the supramarginal gyrus, and area 39 on the angular gyrus (Caspers et al., 2006). A rightward asymmetry has also been described for area PEG in the intraparietal sulcus extending to the angular gyrus (Eidelberg and Galaburda, 1984). In conclusion, structural asymmetry has been reported not only in language and motor areas, where it may underly language dominance and handedness, but also in many if not all other brain regions including the visual cortex, the parietal cortex, and the hippocampus. The degree and direction of asymmetry differ with respect to brain region, handedness, gender, and disease, and both parameters interfere with extrinsic and genetic factors as well as changes during development and aging.

PALEOCORTEX

Olfactory Bulb

The laminar structure and comparative anatomy of the olfactory bulb justify its identification as part of the paleocortex. The human olfactory bulb shows the most extensive regression, both quantitatively and in its laminar pattern, when compared with other primates (Stephan, 1975), but the same principal organization can be demonstrated in the human olfactory bulb as in most mammals.

The most important afferents come from the olfactory epithelium via the fila olfactoria of the first cranial nerve. In animal experiments it has been shown that

recurrent and commissural afferents originate in the diagonal band nuclei, the retrobulbar region and the contralateral bulb and reach the olfactory bulb through the medial olfactory stria and the lateral olfactory tract. The lateral olfactory tract contains ipsilateral efferent fibers from the bulb to the retrobulbar and piriform region, olfactory tubercle, and amygdala (cortical amygdaloid nucleus).

Thus, the olfactory bulb is a cortical area for olfaction both for relay and intracortical modulation. The afferents from basal telencephalic regions modulate, via a complex intrabulbar system of interneurons, the information processing in the olfactory bulb. An accessory olfactory bulb, which is connected with the vomeronasal organ, cannot be found in the adult human brain, in contrast to other mammals (Stephan, 1975).

For a comprehensive description of the human olfactory system see Chapter 34.

Retrobulbar Region (Anterior Olfactory Nucleus)

The retrobulbar region in the human brain has been demonstrated as an equivalent of a paleocortical region in other mammals (Stephan, 1975). The widely used term, anterior olfactory nucleus, is, therefore, misleading, because the human retrobulbar region is a true cortical structure, despite its inconspicuous laminar differentiation. Architectonical regression is a common aspect of the whole olfactory system in the human brain: A two- or three-layered structure recognizable in lower primates is hardly visible in the human brain (Figure 23.2). Also, the delineation of several subareas that is possible in macrosmatic animals is hardly achievable in humans.

The retrobulbar region is located at the place of fusion between the olfactory tract and the hemispheres, immediately rostral of the piriform cortex. It receives its main afferents from the ipsilateral olfactory bulb. At least in the rat, further afferents arrive from the piriform cortex, olfactory tubercle, and amygdala through the medial forebrain bundle and a rostrally directed system of associational fibers (Heimer, 1968, 1972). The projections from the retrobulbar region terminate, after coursing through the medial forebrain bundle, in the olfactory bulb of both sides, and in the ipsilateral piriform cortex, olfactory tubercle, amygdala, mediodorsal thalamic, lateral habenular nuclei, and lateral hypothalamic and supraoptic areas (Lohmann and Lamers, 1967; Ferrer, 1969).

The retrobulbar region is an important station for processing of olfactory information. A destruction of this region leads to *anosmia* or *hyposmia* and is mostly found in connection with impairment of the olfactory bulb.

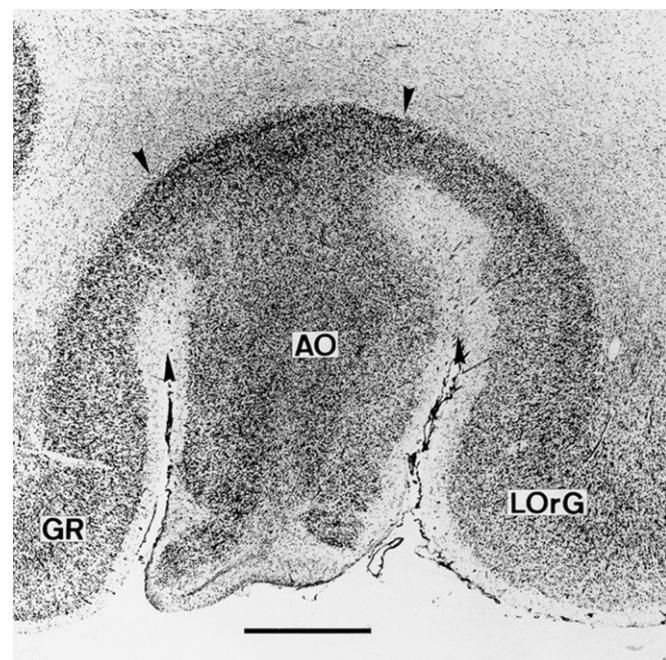


FIGURE 23.2 Coronal section through the human retrobulbar region ("anterior olfactory nucleus," AO) at the basis of the telencephalon. GR, gyrus rectus; LOrG, lateral orbital gyrus. Bar 5 mm. From Zilles, K.: Architecture of the Human Cerebral Cortex. Regional and Laminar Organization In: (Paxinos, G. and Mai, J.K., eds.) The Human Nervous System, 2nd Edition. Elsevier, San Diego, 2004.

Olfactory Tubercle

The olfactory tubercle is located immediately caudal to the retrobulbar region in the anterior perforate substance. This region is also heavily reduced in the human brain when compared with other primates (Stephan, 1975), but the homology with the same region in macrosmatic animals corroborates its classification as a paleocortical region. The three-laminar pattern of other mammals is completely obscured in the human brain. Islands of Calleja can be found within this region (Figure 23.3). For further information about connectivity and function of the olfactory tubercle see Chapter 34.

Piriform Cortex (Area 51 of Brodmann, 1905)

The human (pre)piriform cortex is located between the lateral olfactory tract and the temporal cortex (von Economo and Koskinas, 1925; Rose, 1927; Brockhaus, 1940; Pigache, 1970). According to Allison (1954), this region can be subdivided cytoarchitectonically into a frontal and a temporal area. A three-layered structure is visible (Figure 23.3) with a superficial molecular layer having only a few scattered neurons, a cell-dense second layer, and a less-dense third layer with polymorphic cells. The perikarya in the third layer are the largest.

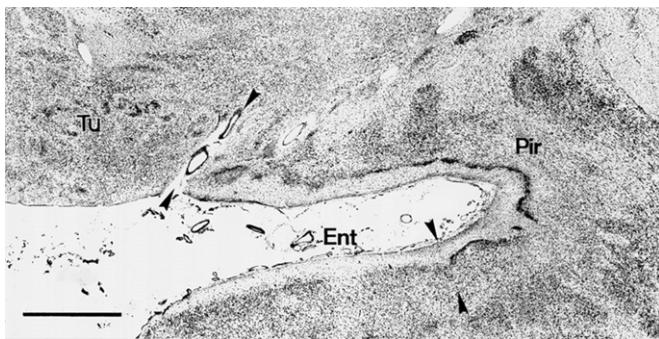


FIGURE 23.3 Coronal section through the human olfactory tubercle (Tu) and (pre)piriform cortex (Pir). The entorhinal cortex (Ent) adjoins the piriform cortex. Bar 2.5 mm. From Zilles, K.: *Architecture of the Human Cerebral Cortex. Regional and Laminar Organization*. In: (Paxinos, G. and Mai, J.K., eds.) *The Human Nervous System*, 2nd Edition. Elsevier, San Diego 2004.

Below this layer a cell-free cleft (*capsula extrema*) is followed by the claustrum. The first layer contains the lateral olfactory tract in the frontal subregion of the piriform cortex.

The afferents to the piriform cortex originate in the olfactory bulb, retrobulbar region, olfactory tubercle, septal region, amygdala, orbitofrontal cortex, and in the contralateral piriform cortex. Commissural fibers originating and terminating in the piriform cortex are found in the anterior commissure. The efferent fibers from the piriform cortex reach all the areas which also have direct afferents from the olfactory bulb (Heimer, 1972; Price, 1973). Additionally, projections to the insular cortex, hippocampus, claustrum, and putamen have been described in many vertebrates (Allison, 1953; Druga, 1971; Hjorth-Simonsen, 1972). It is not clear whether all these experimental results are also valid for the human brain.

The connectivity of the piriform cortex clearly indicates its role as a link between the olfactory and limbic systems. Powell et al. (1965) emphasized the role of the piriform cortex in sexual behavior because of the strong projections to the hypothalamus. For further information about connectivity and function of the piriform cortex see Chapter 34.

Peripaleocortical Region (Area 16 of Brodmann, 1905)

Between the piriform cortex and the laterally adjoining isocortex, a transition zone can be demonstrated that has been called the peripaleocortical claustral region by Stephan (1975). This region is found in close topographical relation to the claustrum and constitutes the rostral transition region to the insular cortex.

Brodmann (1905) described four architectonically different areas (areas 13–16) in the insular cortex with

an increasing complexity in cytoarchitecture. These areas show a rostrocaudal sequence, with the less differentiated area 16 rostrally. Area 16 has a position that compares well with the peripaleocortical claustral region and shows an agranular structure. Although Rose (1929) described many more areas in the human insular cortex, he also delineated a rostral agranular area adjoining the piriform cortex. The most extensive architectonic study of the human insular cortex (Brockhaus, 1940) corroborates these earlier findings. The peripaleocortical claustral region seems to be comparable with the areas ID and TI of von Economo and Koskinas (1925). The laminar pattern of area 16 in humans shows a four-layered type (for further details see Stephan, 1975).

Connections of the peripaleocortical claustral region with the piriform cortex, amygdala, adjoining isocortex, claustrum, and contralateral area 16 have been described in primates (Allison, 1953; Nauta, 1961; Astruc and Leichnetz, 1973). The strong connections with the piriform cortex make an olfactory function of the peripaleocortical insular cortex probable, but a definite statement about the function of area 16 in the human brain is presently not possible.

ARCHICORTEX

The *archicortex* proper is formed by the hippocampus. The adjacent belt-like *periarchicortex* comprises the entorhinal, perirhinal, presubiculum, parasubiculum, retrosplenial, and the subgenual cortex as well as a part of the cingulate cortex. The periarchicortical areas are bordered by a proisocortical belt (Figure 23.1). Both regions represent together with the periarchi- and proisocortical belts of the orbitofrontal, insular and temporopolar regions the *paralimbic cortex (mesocortex)*. Thus, the forebrain contains a “hippocampocentric” (bordering the archicortex) and an “olfactocentric” (bordering the paleocortex) subdivision of the mesocortex (Mesulam and Mufson, 1985; see also “Insular lobe”). The hippocampus can be subdivided into the *retrocommisural hippocampus* (Ammon’s horn, dentate gyrus, and subiculum), the *supracommissural hippocampus* (indusium griseum) and the *precommissural hippocampus*, which is located between the genu of the corpus callosum and the caudal end of the olfactory tract. The hippocampus, entorhinal area, presubiculum, and parasubiculum are described comprehensively in Chapter 24.

Retrosplenial Region (Areas 26, 29, and 30 of Brodmann, 1909)

The retrosplenial region is located in the sulcus corporis callosi immediately behind the splenium of the

corpus callosum (Figure 23.4). It is interposed between the presubiculum and the isocortical areas of the posterior cingulate gyrus. The retrosplenial region can be subdivided into a granular and an agranular part (Rose, 1928). Brodmann (1909) described three areas in the retrosplenial region: the *granular part* (i) comprising area 26 (ectosplenial cortex) and area 29 (granular retrosplenial cortex), and the *agranular part* (ii) or area 30 (agranular retrosplenial cortex). This has been confirmed repeatedly by architectural studies (von Economo and Koskinas, 1925; Braak, 1979b; Armstrong et al., 1986; Vogt, 1995; Vogt et al., 2001).

Although von Economo and Koskinas (1925) have subdivided the retrosplenial region into six different areas (LB₂, LD, LE₁, LE₂, LF₁, LF₂), a careful inspection of the figures shows that only LE₂, LE₁, and LD are comparable with the areas 26, 29, and 30 of Brodmann (1909; cf. also Stephan, 1975); LB₂, LF₁, and LF₂ belong to the supracommissural hippocampus. An architectural analysis of the whole posterior cingulate region

shows a stepwise transition from a simple cortical structure to the elaborated isocortex, i.e. from the supracommissural hippocampus over the areas 26, 29, 30 to the isocortical area 23 (Vogt, 1985; Armstrong et al., 1986; Zilles et al., 1986b; Figure 23.4). Each of the granular or agranular parts can further be subdivided according to Vogt (1993) and Vogt et al. (1995).

The *retrosplenial cortex* (RSC) with the proisocortical areas 29 and 30 is activated during memory and visuospatial processing (Vogt et al., 1987, 2001; Vogt and Lauwers, 2005; Iaria et al., 2007). Recent studies (Vogt et al., 2001) have shown that RSC extends dorsally and rostrally along the callosal sulcus and is not restricted to the most caudal portion of the cingulate gyrus directly behind the splenium as described by Brodmann (1909).

The ectosplenial *area 26* has a primitive laminar pattern comprising a molecular layer, a cell-dense external layer (small pyramidal cells) and an inner layer resembling the neuronal population of layer VI of the isocortex (Braak, 1979b; Vogt et al., 2001).

Area 29, which is buried within the callosal sulcus, shows a four-layered structure in Nissl-stained sections with a molecular layer, a cell-dense external pyramidal layer with small- to medium-sized perikarya ("granular retrosplenial cortex"), an internal pyramidal layer with larger cells, and a polymorphic layer. Near the medial border of area 29 the laminar pattern changes. The external pyramidal layer differentiates into a cell-dense outer and a lighter inner layer (Vogt et al., 2001).

Area 30 encroaches onto the surface of the cingulate gyrus, is dysgranular (Vogt et al., 2001), and shows a further progression of the laminar differentiation. Area 30 has an external pyramidal layer with a less obvious population of small ("granular") perikarya. Thus, this area has been classified as "agranular retrosplenial cortex". However, it shows also the first sign of an internal granular layer between the external and internal pyramidal layers ("dysgranular type"; Vogt et al., 2001). This internal granular layer contains numerous small to medium-sized pyramidal cells, and is, therefore, different from the classical internal granular layer IV of the isocortex (for further details, see Vogt et al., 2001). Area 30 can be classified as proisocortex, since the adjoining area 23 has the typical isocortical structure with six layers.

The connectivity of the retrosplenial cortex further supports the principal subdivision into granular and agranular parts. In the rhesus monkey the main cortical afferents to the granular retrosplenial areas 26/29 originate in the subiculum (Rosene and van Hoesen, 1977), whereas the agranular retrosplenial area 30 does not receive subicular axonal terminals. A main source for cortical afferents to area 30 is the extrastriate visual cortex, whereas these afferents are sparse in areas 26/29. The whole retrosplenial cortex receives afferents from area 24 and the anterior

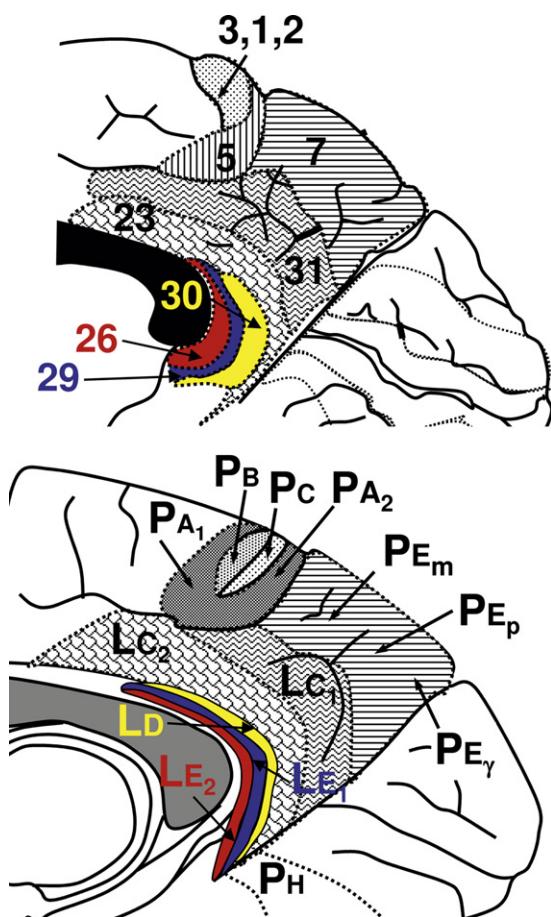


FIGURE 23.4 Posterior cingulate and retrosplenial regions according to Brodmann (1909) (a) and von Economo and Koskinas (1925) (b). Areas 26/LE₂ and 29/LE₁ belong to the allocortex, area 30/LD is part of the proisocortex. Areas 23 and 31 are classified as neocortical regions.

thalamic nuclei. Additionally, the intralaminar, laterodorsal, and lateroposterior thalamic nuclei (Baleydier and Mauguiere, 1980; Vogt et al., 1987), claustrum, diagonal band (Bigl et al., 1982), locus coeruleus, raphe nuclei, and lateral hypothalamus project to this cortical region. The commissural connections are found in the corpus callosum. In the rhesus monkey, the efferent projections of the retrosplenial cortex terminate in the anterior thalamic nuclei, anterior cingulate cortex, and pons (van Hoesen et al., 1993).

Cingulate Region: Transition from Periarchicortex to Isocortex

The largest part of the cingulate gyrus is architectonically iso- and proisocortex. The periarchicortical region of the cingulate region accompanies the supracommissural and precommissural hippocampus.

Brodmann (1908, 1909), Vogt (1910), von Economo and Koskinas (1925), and Rose (1928) published different architectural subdivisions of the cingulate gyrus (Table 23.3). Brodmann (1908, 1909) included in his *subregio postcingularis* the *granular isocortical areas* 23 and 31 (Figure 23.4) of the *posterior cingulate cortex* (Armstrong et al., 1986; Zilles et al., 1986b), in his *subregio praecingularis* the *agranular isocortical areas* 24 and 32 of the *anterior cingulate cortex* (Figure 23.5), and the *periarchicortical areas* 25 and 33 (Figure 23.5). Thalamic afferents in the monkey are differentially distributed over anterior and posterior cingulate areas. The anterior cingulate cortex receives afferents primarily from the paraventricular, reunions, parafascicular, central superior lateral, central densocellular mediodorsal, and limitans nuclei. Further afferents to the cingulate cortex arrive from the substantia innominata, claustrum, raphe nuclei, and locus coeruleus (Vogt et al., 1987). Furthermore, commissural fibers have been described which interconnect the anterior cingulate cortex through the corpus callosum (Showers, 1959; Locke and Yakovlev, 1965). Further afferents arrive from the septum and amygdala (Nauta, 1961). Efferent projections reach the amygdala,

presubiculum, retrosplenial and perirhinal cortex (Baleydier and Mauguiere, 1980; Pandya et al., 1981).

Area 32 shows fully differentiated isocortical structure. Area 24 represents the proisocortical part with a dorsal area medioradiata (MR) and a ventrally adjoining area infraradiata dorsalis (IRd) (for subdivisions of area 24, see Figure 23.5 and Chapter 25). According to Stephan (1975) the rostral part of the periarchicortex is subdivided into an area infraradiata ventralis (area 33 as a rostral prolongation of the taenia tecta) in the sulcus corporis callosi, and an area subgenualis (area 25) accompanying the precommissural hippocampus. The common architectural feature of the periarchicortical areas 25 and 33 is their reduced laminar differentiation.

The relatively simple subdivision of the cingulate cortex into an anterior and posterior subregion is, however, an oversimplification of both the structure and the function of this region. Already Brodmann (1909) had mentioned that his *subregio praecingularis* is not homogeneous and must be further subdivided (see also Braak, 1976a; Vogt and Pandya, 1987; Vogt et al., 2005). Vogt and Vogt (2003) identified two qualitatively distinct regions of the *subregio praecingularis*: the *anterior cingulate cortex* (ACC) and the *midcingulate cortex* (MCC). MCC is characterized by large neurons in layer IIIc and the presence of large layer Vb pyramidal neurons that are not found in other parts of the cingulate cortex.

A further subdivision of the *anterior cingulate cortex* was introduced with a *subgenual* subregion below the genu of the corpus callosum and a *pregenual* subregion rostral and dorsal to the genu (Palomero-Gallagher et al., 2008). The subgenual part encompasses not only area 25, but also the most ventral portions of areas 24, 32, and 33. Area 24 is agranular (lack of granular layer IV) and contains a cell-dense layer Va and a neuron-sparse layer Vb. Three divisions of area 24 based on progressively increasing laminar differentiation were found recently (Palomero-Gallagher et al., 2008): areas 24a, 24b, and 24c. Area 24a abuts area 33 in the callosal

TABLE 23.3 Comparison of the architectural parcellations of the anterior cingulate cortex as described by various authors

Brodmann (1908)	Vogt (1910)	von Econo and Koskinas (1925)	Rose (1928)	Stephan (1975)
32	3, 10, 11, 33–35	FCL, FDL, FEL, FHL	-	-
24	Subregio typica (17–24)	LA ₂	Subregio infraradiata communis (IRB α - δ , IRC α - δ)	Area infraradiata dorsalis (IrD)
	Subregio medioradiata (25–32)	LA ₁	Regio mediorata	Area mediorata (MR)
33	Subregio extrema (10, 15)	LA ₃ , LC ₃	Subregio infraradiata ventralis (IR α - δ)	Area infraradiata ventralis (IrV)
25	Areas 13, 14	FL, FM	Regio subgenualis (Sbga, Sbgp)	Area subgenualis (Sg)

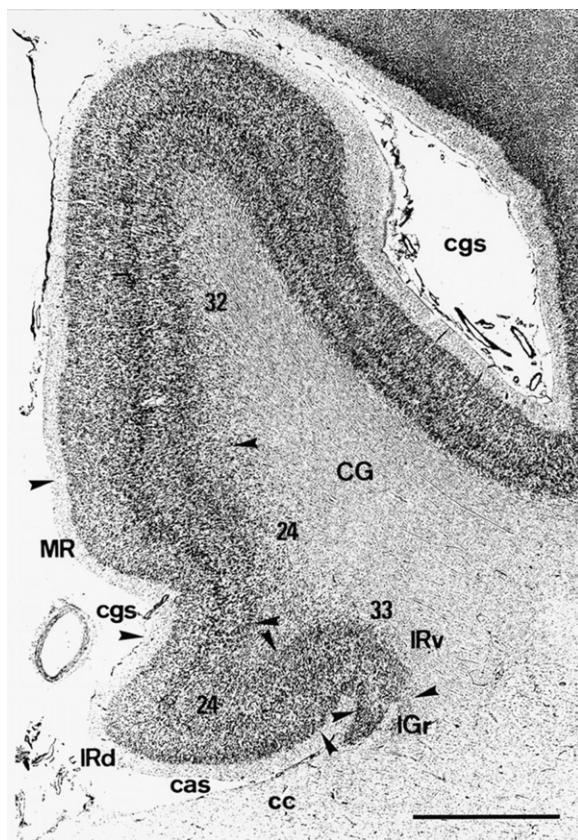


FIGURE 23.5 Horizontal section through the anterior cingulate and rostrally adjoining regions showing the transition from allo- to neocortex. The supracommissural hippocampus IGr (indusium griseum) is bordered by the periarchitectonical area 33 (IRv, area infraradiata ventralis). The adjacent area 24 can be subdivided into a proisocortical part (IRd, area infraradiatadorsalis) and an isocortical part (MR, area mediorata). The isocortical area 32 follows rostrally. cas, sulcus of the corpus callosum; cc, corpus callosum; CG, cingulate gyrus; cgs, cingulate sulcus. Bar 3 mm. From Zilles, K.: *Architecture of the Human Cerebral Cortex. Regional and Laminar Organization In*. (Paxinos, G. and Mai, J.K., eds.) *The Human Nervous System, 2nd Edition*. Elsevier, San Diego 2004.

sulcus, area 24b is between areas 24a and 24c, and area 24c bounds much of area 32 (see Chapter 25).

Area 32 is a dysgranular area between agranular area 24 and granular frontal areas 9, 10, and 12. Area 32 shows a distinct differentiation of layers Va, Vb, and VI in thin and separated layers, a broad layer II and a differentiated layer III with large. The large pyramids of layer III separate area 32 and from area 24. Another difference between these areas is the presence of a thin layer IV in area 32. Further subdivisions of areas 24 and 32 have been identified by analyzing receptor distribution patterns (Palomero-Gallagher et al., 2008).

Area 33 is in the depths of the callosal sulcus and has been referred to as the *pregenual area* (Brodmann, 1909) or *ectogenual cortex* (Braak, 1979a). This region does not end below the genu, but continues along the full caudal extent of area 25. Area 33 is the least differentiated of any

cingulate area. Layers II–III are broad and poorly differentiated, whereas layer V has a few large pyramids, and layer VI is almost non-existent.

Area 25, the subgenual anterior cingulate cortex (ACC), can be subdivided into an anterior (25a) and a posterior (25p) part (Palomero-Gallagher et al., 2009). Area 25a has a narrower and less prominent layer II, but a wider layer III than area 25p. Layer V of area 25a has less but larger SMI32 immunoreactive neurons than 25p. Area 25 is controlling autonomic and endocrine functions, and is activated during negatively valenced emotions. Presently, it plays a major role for explaining the neurobiological basis of depression (Mayberg et al., 2005). Area 25 contains the highest GABA and 5-HT_{1A} receptor densities in the whole cingulate cortex (Palomero-Gallagher and Zilles, 2008).

Afferent fibers to area 25 of non-human primates have been demonstrated from the pole of the temporal lobe (Pandya and Kuypers, 1969) and from areas 7, 21, and 22 (Jones and Powell, 1970). Areas 25, 32, and 24 are interconnected by fibers running tangentially in the molecular layer (Gerebtzoff, 1939; Glees et al., 1950). A further intracingulate connection exists between area 25 and the posterior cingulate cortex, including the retrosplenial region (Showers, 1959). Reciprocal connections have also been described between the prefrontal areas, the posterior cingulate cortex, and the posterior parietal gyri (Vogt et al., 1987).

Electrical stimulation studies have shown that the subgenual part is involved in the inhibition of autonomic responses via activation of area 25 (Burns and Wyss, 1985). The subgenual ACC can participate in affective and autonomic responses via projections of areas 25 and 32 to visceromotor nuclei in the brainstem. The pregenual part of ACC is involved in conditioned emotional learning, vocalizations expressing internal states, assessments of motivational content, and assigning emotional valence to internal and external stimuli (Vogt et al., 2003; Vogt, 2005).

The *midcingulate cortex* (MCC) was further subdivided into an anterior (aMCC), which contains part of the rostral cingulate motor area, and a posterior (pMCC) subregion (Vogt et al., 2003), which contains part of the caudal cingulate motor area. Layer III is less differentiated in aMCC, whereas layer Va is more cell dense in pMCC (Vogt and Vogt, 2003; Vogt et al., 2003, 2005). The amygdala projects to aMCC, but not to pMCC (Vogt and Pandya, 1987). The aMCC is active during fear, and is involved in the reward coding of behavior. pMCC is activated by passive movements (Shima and Tanji, 1998).

The *postcingulate cortex* PCC comprises areas 23 and 31, and is involved in spatial orientation (Olson et al., 1996; Sugiura et al., 2005). PCC can be further subdivided into a dorsal (dPCC) and a ventral (vPCC) part.

Layers II, III, and V of vPCC are densely populated and contain larger pyramids than those of dPCC (Vogt et al., 2005, 2006). Layer III of vPCC is thicker and contains a substantially higher density of neurofilament protein immunoreactive neurons than that of dPCC (Vogt et al., 2005). dPCC supports visuospatial processing and body orientation in space and plays a role in polymodal stimulus-response mapping, whereas vPCC is involved in the assessment of the self-relevance of sensory events and their contexts (Sugiura et al., 2005; Vogt et al., 2006; Ferstl and von Cramon, 2007; O'Hare et al., 2008).

On the basis of these more recent findings, Vogt et al. (2003, 2006) proposed a *four-region model* that integrates architectural, connectional, and functional aspects. Following this model, the cingulate cortex comprises the ACC, MCC, PCC, and RSC regions. MCC is classified as a unique region, and not as a subdivision of ACC. The concept of the four region model has been further supported by receptor architectonic studies (Palomero-Gallagher et al., 2009).

For a comprehensive description of the cingulate region, see Chapter 25.

ISOCORTEX

Frontal Lobe

The isocortex of the frontal lobe can be subdivided cytoarchitectonically into granular (with a clearly visible layer IV; e.g., Figure 23.6), dysgranular (with a weakly developed layer IV; e.g., Figure 23.7), and agranular (lacking layer IV; e.g., Figure 23.10) regions. The primary

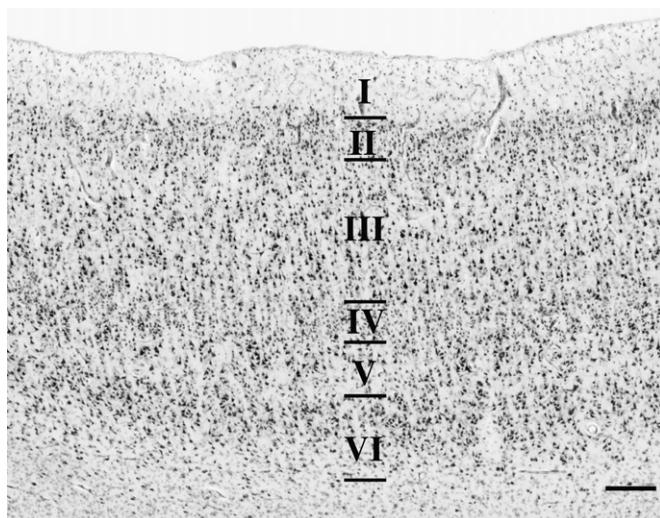


FIGURE 23.6 Horizontal section through Brodmann's (1909) area 10, which belongs to the granular part of the prefrontal cortex. The Roman numerals indicate the six isocortical layers. Bar 200 µm.

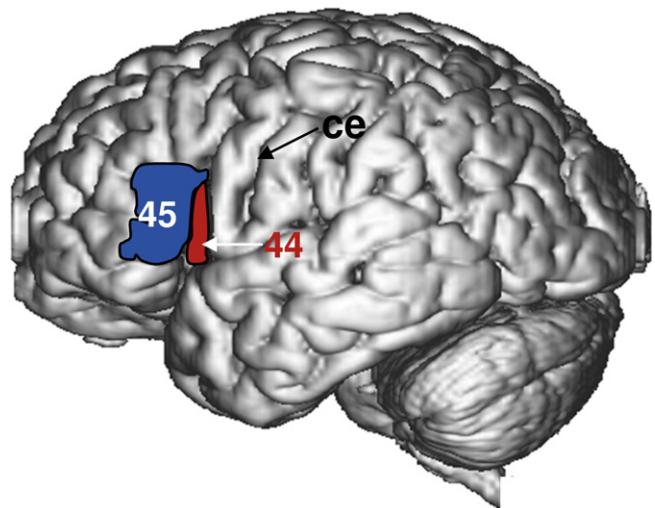


FIGURE 23.7 Areas 44 and 45 in a human brain. The borders of both areas were determined using a quantitative cytoarchitectonic method, which allows an observer-independent definition of the areal borders. ce, central sulcus.

(Brodmann's area 4) and non-primary (Brodmann's area 6) motor areas are agranular, Brodmann area 44 of Broca's speech region is dysgranular, the lateral prefrontal region is granular (except a dysgranular transitional region (Brodmann's area 8) between the motor and prefrontal cortex), and the medial prefrontal cortex (Brodmann's areas 24 and 32) is agranular. Broca's region can be further subdivided into anterior and posterior, i.e. Brodmann's areas 45 and 44 (Figures 23.7, 23.8, and 23.35). According to Brodmann, the granular (lateral) prefrontal region can be further subdivided into a dorsolateral (Brodmann's areas 9, 10, and 46) and a ventro-orbital part (Brodmann's areas 11, 12, and 47). The medial prefrontal cortex comprises the isocortical part of the anterior cingulate region. For a cortical map see Figure 23.35. For comparison of different cytoarchitectonical terminologies in the frontal lobe see Table 23.4.

A detailed architectonical study of the human frontal lobe has been published by Sanides (1962). This author delineates about 60 areas, which can be classified into cortical zones of different architecture (Figure 23.9). His frontal motor zone (FmZ) resembles areas 4 and 6. The proisocortical zone (PrO) is an agranular cortex and corresponds to area 24. The dorsal and ventral paralimbic zones (PlZd, PlZv) are agranular to dysgranular regions and may be equivalents of area 32. The fronto-opercular zone (FoZ) resembles areas 44, 45, and 47. The granular paraopercular zone (PoZ) corresponds to area 46, the paramotor zone (PmZ) to areas 9 and 8, the granular frontopolar zone (FpZ) to area 10, and the granular orbitomedian zone (OmZ) to areas 11 and 12.

Hopf (1956), Ngoyang (1934), Strasburger (1937), and Vogt (1910) have presented more detailed cyto- and myeloarchitectonical studies of the human frontal lobe.

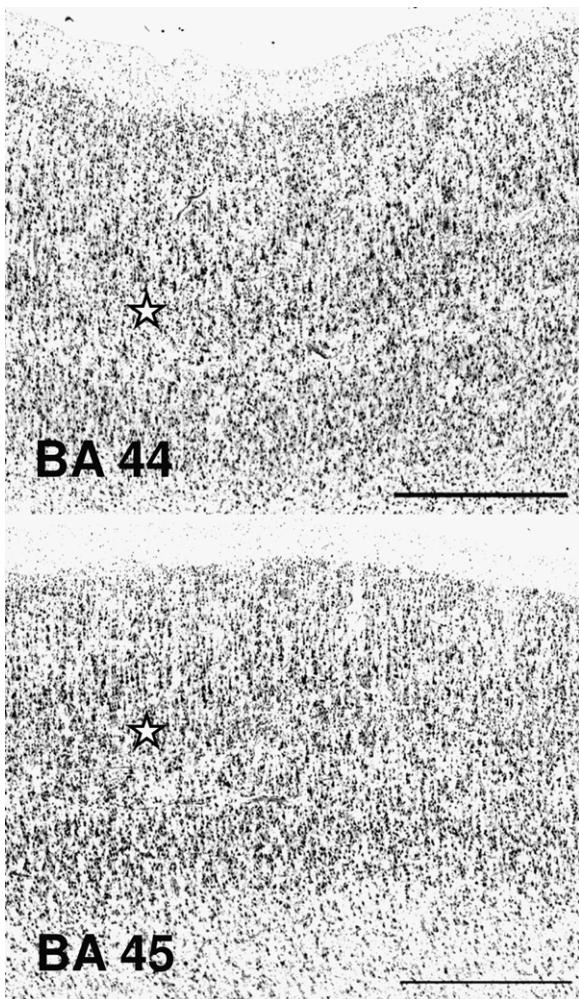


FIGURE 23.8 Cytoarchitecture of the dysgranular areas 44 and 45. Layer IV is labeled by asterisks. Bar 1 mm. From Zilles, K.: *Architecture of the Human Cerebral Cortex. Regional and Laminar Organization In:* (Paxinos, G. and Mai, J.K., eds.) *The Human Nervous System, 2nd Edition.* Elsevier, San Diego, 2004.

Prefrontal Region

The prefrontal cortex contains a larger granular and a smaller dysgranular part (Walker, 1940; Goldman and Schwartz, 1982; Goldman-Rakic, 1984; Schwartz and Goldmann Rakic, 1988; Selemon and Goldman-Rakic, 1988; Cavada and Goldman-Rakic, 1989a, 1989b; Fuster, 1989; Preuss and Goldman-Rakic, 1990; McGuire et al., 1991; Petrides and Pandya 1999). The inner granular layer in the prefrontal cortex is most obvious in its rostral part (Brodmann area 10: Figure 23.6), whereas the more caudal part shows a transition to the dysgranular type (area 8) with a visible, but less remarkable inner granular layer. The granular part is unique in primates and reaches its largest expansion in humans (Preuss and Goldman-Rakic, 1991; Semendeferi et al., 2001). For subdivisions of the prefrontal cortex of non-human primates see Paxinos et al. (2000).

A detailed study of the human prefrontal granular areas 9 and 46 (Rajkowska and Goldman-Rakic, 1995a, 1995b) demonstrates cytoarchitectonic differences between both areas and the intersubject spatial variability of the areal borders. Area 9 extends along the middle third of the superior frontal gyrus and adjacent regions of the middle frontal gyrus. Area 46 is partially or completely surrounded by area 9 on the middle frontal gyrus. Rajkowska and Goldman-Rakic (1995b) clearly describe the lack of correlation between macroscopical landmarks (fundi of gyri, etc.) and areal borders and emphasize the considerable intersubject variability of the borders of these areas. Lamina IV is wider and contains more densely packed neuronal cell bodies in area 46 than in area 9; the sublamination of layers III and V is more differentiated in area 9 than in area 46. Area 46 is less myelinated than area 9.

The prefrontal cortex of primates receives major thalamic input from the mediodorsal nucleus, with the magnocellular part of this nucleus projecting to the ventro-orbital, and the parvocellular part to the dorsolateral prefrontal areas (Kievit and Kuypers, 1977; Divac et al., 1978; Goldman, 1979; Goldman, 1981; Fuster, 1989). Important cortical afferents to the prefrontal cortex in non-human primates arrive from various cortical areas of the same (ipsilateral associational) and of the opposite hemisphere (callosal connections) (Pandya et al., 1971a, 1971b; Goldman and Nauta, 1977a, 1977b; Jacobson and Trojanowski, 1977a, 1977b; Kunzle, 1978; Cavada and Goldman-Rakic, 1989b; Preuss and Goldman-Rakic, 1989). The callosal connections are reciprocally organized (Goldman and Schwartz, 1982; Schwartz and Goldman-Rakic, 1988; McGuire et al., 1991). Cortical afferents to the dorsolateral prefrontal cortex originate in the parietal (Petrides and Pandya, 1984; Cavada and Goldman-Rakic, 1989b), and premotor cortices (Barbas and Pandya, 1987; Lu et al., 1994; Pandya and Yeterian, 1998). Contrastingly, the ventral prefrontal cortex receives its input from the temporal cortex (Webster et al., 1994; Bullier et al., 1996; Pandya and Yeterian, 1998). Ventral and dorsal parts of the prefrontal cortex are interconnected (Barbas, 1988; Pandya and Yeterian, 1998; Petrides and Pandya, 1999). The temporal pole and the anterior insula project to the ventro-orbital part of the prefrontal cortex, which in turn is connected with the amygdala, basal forebrain, and the magnocellular part of the mediodorsal thalamic nucleus (Mesulam and Mufson, 1982, 1985; Goldman-Rakic and Porrino, 1985; Pandya and Yeterian, 1985; Barbas and DeOlmos, 1990).

A major part of the prefrontal efferents projects to the striatum (Selemon and Goldman-Rakic, 1985). Further details on the connection can be found in Goldman and Nauta (1977a), Kunzle (1975) and Johnson et al. (1968). Other efferents end in the dorsal thalamus

TABLE 23.4 Comparison of various classification schemes of the human cerebral cortex*

Brodmann (1909)	Campbell (1905)	Smith (1907)	von Economo and Koskinas (1925)	Bailey and von Bonin (1951)	Sarkisov et al. (1955)
3, 1, 2	Postcentral Intermediate postcentral	Postcentralis, Postcentralis A Postcentralis B	PA,PB,PC,PD	Koniocortex Parakoniocortex	3, 1, 2
4	Precentral	Praecentralis A	FA	Agranular giganto-pyramidal	4
5	Intermediate postcentral and parietal	Postcentralis B	PA ₂	Parakoniocortex	-
6	Intermediate precentral	Praecentralis B	FB	Agranular, Dysgranular	6
7	Parietal	Parietalis superior A, Parietalis superior B	PE	Homotypical	7, 7a
8	Frontal	Frontalis B, Frontalis superior anterior	FC	Dysgranular	8
9	Frontal	Frontalis A, Frontalis B	FD	Dysgranular	9
10	Prefrontal	Frontalis A, Frontalis B Frontalis C, Praefrontalis	FE	Homotypical	10
11	Prefrontal	Praefrontalis	FG,FH	Homotypical, Juxtaallocortex	47
12	Prefrontal	Praefrontalis B	FH	Homotypical	12
17	Visuosensory	Striata	OC	Koniocortex	17
18	Visuropsychic	Parastriata, Peristriata, Temporalis occipitalis	OB	Parakoniocortex	18
19	Temporal, and Visuropsychic	Peristriata, Temporalis occipitalis	OA	Homotypical	19
20	Temporal	Temporalis inferior	TE	Homotypical	20
21	Temporal	Temporalis medius	TE	Homotypical	21
22	Auditopsychic	Temporalis superior	TA,TB	Homotypical	22
23	Limbic C	Callosus A	LC	Homotypical	23
24	Limbic A	Callosus B, Callosus C	LA ₁ ,LA ₂	Mesocortex	24
25	Limbic B	Callosus D	FL,FM	Juxtaallocortex, Mesocortex	25 24

26	Limbic C	Parasplenialis	LE ₂	Allocortex	—
27	Limbic C	Subiculum (S), Hippocampus (H)	HD	Allocortex	—
28	Olfactory	Pyriformis	HB,HC	Allocortex	—
29	Limbic C	Parasplenialis	LE ₁	Allocortex	—
30	Limbic C	Parasplenialis	LD	Homotypical	31
31	Limbic C	Callosus A	LC	Homotypical	31
32	Frontal	Frontalis D	FC,FD,FE,FH	Juxtaallocortex	32
33	Limbic A	Callosus C	LA ₃ ,LC ₃	Mesocortex	—
34	Olfactory	Pyriformis	HA	Allocortex	—
35	Olfactory	Subiculum (S), Hippocampus (H)	TG,TH	Juxtaallocortex	—
36	Temporal	Paradentatus	TG;TH	Juxtaallocortex	20
37	Temporal	Paratemporalis	PH	Homotypical	37
38	Temporal	Temporalis polaris	TG	Dysgranular	20/38, 21/38 22/38
39	Temporal	Parietalis inferior A, parietalis inferior B, Parietalis occipitalis	PG	Homotypical	39
40	Temporal	Parietalis inferior B and C,	PF	Homotypical	40
41/42	Auditosensory	Temporalis superior	TC,TB	Koniocortex Parakoniocortex	—
43	Unlabeled area	Frontalis inferior, postcentral A postcentral B	FB,PF	Dysgranular, Homotypical	43
44	Intermediate precentral	Frontalis inferior B,	FCBm	Dysgranular	44
45	Intermediate precentral	Frontalis inferior	FD γ	Homotypical	45
46	Frontal	Frontalis B, frontalis inferior	FD	Homotypical	46
47	Intermediate precentral	Orbitalis	FF	Homotypical,	47

* The classification schemes of various authors are compared with Brodmann's (1909) parcellation of the human cortex. Since the areal maps of the authors show incompletely matching patterns, often only parts of the areas are included in one Brodmann area.

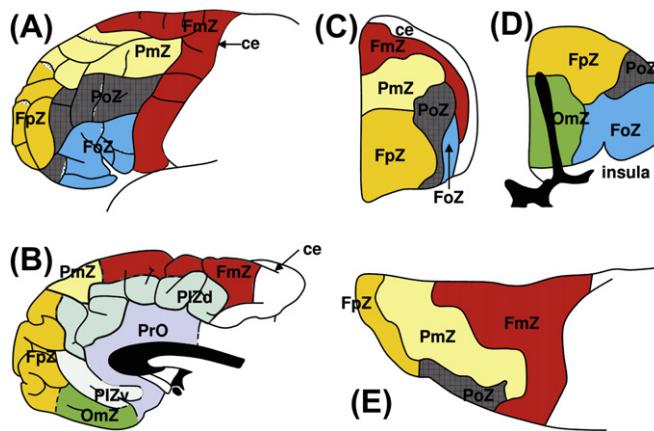


FIGURE 23.9 Areal map of the frontal lobe modified from Sanides (1962) in (A) lateral, (B) medial, (C) frontal polar, (D) basal and (E) dorsal views. ce, central sulcus; FmZ, frontal motor zone; FoZ, frontoopercular zone; FpZ, frontopolar zone; OmZ, orbitomedian zone; PIZd, dorsal paralimbic zone; PIZv, ventral paralimbic zone; PmZ, paramotor zone; PoZ, paraopercular zone; PrO, proisocortex.

(Goldman, 1979) and the superior colliculus (Goldman and Nauta, 1976). The dorsolateral prefrontal cortex is connected to the pulvinar, through which it can influence the cingulate and multi- as well as unimodal sensory areas (Goldman-Rakic and Porrino, 1985). Various other cortical and subcortical areas are further targets of the prefrontal efferent fibers (Selemon and Goldman-Rakic, 1988).

Studies in non-human primates (Goldman and Nauta, 1977b; Goldman-Rakic, 1984) have shown a remarkable columnar organization of the prefrontal cortex that is based on vertical units of neurons with special input-output relations and intrinsic synaptic connections. These columns are organized by alternating columns of ipsilateral and callosal corticocortical connections (Goldman and Schwartz, 1982). A two-dimensional reconstruction of the columns in frontal section reveals a distribution in the form of stripes, which can bifurcate and show cross linkages and blind endings. The columns have a width of 300–700 µm and extend across all cortical layers. Since this structural pattern can be found in a variety of mammals (Goldman-Rakic, 1984) its existence in the human cortex is highly probable. The large increase in gyration (Zilles et al., 1989) and surface (Brodmann, 1912) of the human prefrontal cortex during evolution is, therefore, associated with an increasing number of cortical columns. While the interdigitating columnar pattern is shown for callosal and ipsilateral corticocortical systems, the same pattern has also been found for the cells constituting the efferent fibers for these connections (Schwartz and Goldman-Rakic, 1984). Thus, afferent terminals and efferent cell bodies of the same system are found in identical columns.

Since the corticocortical connections are only one part of the input and output of the prefrontal cortex, the corticostriatal and corticothalamic projections have been analyzed with respect to columnar organization. For both systems, a compartmentalization has been demonstrated. The corticothalamic neurons projecting to the mediodorsal nucleus form regularly spaced clusters in layer V of the prefrontal cortex. A further example of the modular organization in the primate prefrontal cortex is given by the efferents to the parahippocampal gyrus and the presubiculum (Goldman-Rakic, 1984).

The prefrontal cortex is a major anatomical substrate of various cognitive processes. The dorsolateral prefrontal cortex plays an important role in mnemonic encoding of visual space (Funahashi et al., 1989). The columnar segregation of afferent systems may be the prerequisite for the various associative functions of this region. A great number of columns with different, well-segregated connections may allow for an even greater number of associative combinations by interaction between different columns. Destroying parts of the prefrontal lobe leads to disturbances of initiative and planning of activities, emotional status, social behavior, and memory functions (Milner and Petrides, 1984; Selemon and Goldman-Rakic, 1988; Sawaguchi and Goldman-Rakic, 1991). Destruction of the most rostrally and basally located areas leads to restlessness and hyperactivity (Jacobsen, 1935) and autonomic and emotional reactions (Kaada, 1960). Reduction of intellectual ability and ethical standards are immediately apparent phenomena after bilateral destructions of the human prefrontal cortex (Brodal, 1969). The orbito-prefrontal cortex is active during processing social behavior and judgment of the social consequences of actions (Fletcher et al., 1995; Frith and Frith, 1999; Moll et al., 2002). Additionally, visual object categorization is correlated with neural activity in the orbito-prefrontal cortex (Vogels et al., 2002).

Atrophy of the frontal cortex is found in Pick and Alzheimer disease. Prefrontal leucotomy, a neurosurgical intervention introduced by Moniz (1936), has frequently been performed in the past in an attempt to cure symptoms of various mental disorders (schizophrenia, obsessions, etc.). Leucotomy has induced a controversial debate about the ethical problems involved with this procedure, because aside from influencing the symptoms of mental disorders, it severely changes personality.

More specific data about the function of granular prefrontal areas in the human brain is provided by imaging studies. A region comparable with the dorsal part of area 10 (Brodmann, 1909) shows the highest metabolism and regional cerebral blood flow in conscious, wakeful subjects. These signs of activity ("hyperfrontality") disappear during sleep. Discrimination of tone sequences,

mental calculation, and object categorization are associated with an increase in neuronal activity in this region. Working memory, learning, detection, association, discrimination, recognition, anticipatory tuning, regulation of attention and abstraction are subserved by the granular prefrontal cortex. In summary, this part of the iso-cortex controls and regulates the operation of different sets of other cortical areas, i.e. it is active whenever tasks require organization by the brain itself (for review, Roland, 1993).

Recent functional imaging work shows a considerable segregation of the neural correlates of emotion, episodic memory retrieval, and working memory. The left dorsolateral areas seem to subserve monitoring operations during memory tasks, rostral and ventrolateral areas of both hemispheres are contributing to retrieval and cue-specific episodic memory retrieval operations, and the left ventro-posterior as well as the bilateral dorso-posterior regions of the prefrontal cortex are subserving phonological and generic working memory operations, respectively (Cabeza et al., 2002). The hippocampal and parahippocampal regions are active both during episodic memory retrieval and working memory. The medial prefrontal cortex plays a general role in emotion processes (for review see Phan et al., 2002).

Area 8 represents the dysgranular part of the prefrontal cortex. Sanides (1962) has delineated a paromotor zone PmZ (Figure 23.9) which has a similar location, but probably also includes parts of area 9. The FC area (Figure 23.37) of von Economo and Koskinas (1925) seems to have a larger size than Brodmann's area 8. More recent functional observations have identified a frontal eye field in primates (Bruce and Goldberg, 1984), including humans (Roland, 1984), which is in good agreement with the ventrolateral part of area 8. Although earlier observations questioned the functional identification of area 8 as the frontal eye field, it has been demonstrated in a comparable region of non-human primates that this part of the dysgranular prefrontal cortex contains cells responsive to visual stimuli which discharge before saccadic eye movements and in anticipation of saccadic behavior (Bruce and Goldberg, 1984). The saccadic direction is elicited in specific cell columns. Excitation in neighboring columns leads to different directions. As stated above, callosal and acallosal bands alternate (Goldman-Rakic, 1984), horizontal eye movements are controlled by acallosal columns, while vertical movements are controlled by callosal columns.

Clinical reports in humans suggest presaccadic activity in area 8 with metabolic activation during ocular fixation, pursuit eye movements, and various visual discrimination tasks (for review, see Roland, 1984). A dominance of the right frontal eye field is found when non-verbal signals are analyzed.

For a comprehensive description of the prefrontal cortex, see Chapter 26.

Anterior Cingulate Region

Areas 24 and 32 constitute the proisocortical and iso-cortical parts of the anterior cingulate region. The agranular area 24 has been subdivided into several subareas in humans, monkeys, and rats (Matelli et al., 1985, 1991; Vogt, 1993; Vogt et al., 1995). Subarea 24d occupies the most caudal and dorsal part of human area 24. It is followed rostrally by subarea 24c' at the level of the anterior commissure, and by subarea 24c at the level anterior to the genu of the corpus callosum. Subareas 24d, c', and c represent the dorsal subregion of area 24. Subareas 24b' and b constitute the intermediate subregion, and subareas 24a' plus 24a the ventral subregion (Vogt et al., 1995), which is buried in the callosal sulcus (for figures and further details see Chapter 25). The anatomical correlate of the functionally defined human cingulate motor area (CMA; Paus et al., 1993) comprises subarea 24d as caudal cingulate, and subareas 24c' and c as rostral cingulate motor areas (Zilles et al., 1995, 1996b; Roland and Zilles, 1996a). The motor function of the cingulate cortex has convincingly been demonstrated by microstimulation of the monkey cortex (Luppino et al., 1991). It is presently not clear to what extent human area 32 or parts of it must also be interpreted as part of CMA.

CMA sends efferent fiber to the primary motor cortex (area 4) and the spinal cord (Luppino et al., 1994). CMA appears to be activated during self-paced movements and controls the execution of motor responses (Paus et al., 1993; Naito et al., 2000). Vocalization and fear reactions also seem to be controlled by CMA. Ablation of areas 24 and 32 leads to increased tameness and reduction of social contacts in animals, together with a lowered performance in delayed alternation tasks (Glees et al., 1950; Divac, 1971).

For a comprehensive description of the cingulate region, see Chapter 25.

Broca's Language Region

The caudal part of the left inferior frontal gyrus has been shown to represent a language region (Broca, 1861; Penfield and Rasmussen, 1950; Roland, 1984) in 95% (Branche et al., 1964) of right- and left-handers. A destruction of the dominant Broca area is accompanied in most cases by a loss of fluent speech and agrammatism, though language comprehension may not be affected. Detailed functions of Broca's region were examined by authors using different verbal tasks and functional imaging (Mazziotta and Mettner, 1988; Petersen et al., 1988, 1990; Mazoyer et al., 1993; Petrides et al., 1993; Frackowiak, 1994; Buckner et al., 1996; Fox et al., 1996; Paulesu et al., 1996; Zatorre et al., 1996;

Amunts et al., 2004b), and electrical stimulation (Penfield and Rasmussen, 1950; Ojemann, 1991). The homologous region in the right hemisphere is involved in prosodic aspects of speech (Botez and Wertheim, 1959) and the detection of syntactic errors (Bradvik et al., 1991; Nichelli et al., 1995).

Areas 44 and 45 (Figure 23.7) are the cytoarchitectonical correlates of Broca's region (Brodmann 1909, 1914; Amunts et al., 1999). Macroscopically, both areas are located bilaterally in the opercular (area 44) and triangular (area 45) region of the inferior frontal gyrus. Both areas reach the adjoining lower surface of the frontal operculum. An incipient inner granular layer (with an increasing granularity from caudal to rostral) is found in the areas 44 and 45 (Brodmann, 1909; Sanides, 1962; Amunts et al., 1999; Figure 23.8). Layer IV of area 45 is still less clearly visible compared with the rostrally adjoining lateral prefrontal areas. Thus, the cortex of Broca's speech region can be classified as dysgranular (Amunts et al., 1999). Further descriptions of cyto- and myeloarchitectonic aspects were published by Knauer (1909), von Economo and Koskinas (1925), Stengel (1930), Riegele (1931), Kononova (1949), Strasburger (1938), and Rabinowicz (1967). Considerable differences in the extent, location, and sizes of areas 44 and 45 are evident between the different maps, and the architectonic features were reported to be highly variable among subjects (Kononova, 1935; Amunts et al., 1999, 2004a). It is still a matter of discussion whether or not cytoarchitectonic features are associated with functional lateralization of speech (Galaburda, 1980; Scheibel et al., 1985; Simonds and Scheibel, 1989; Hayes and Lewis, 1995, 1996). The functional segregation between areas 44 and 45 is presently not clear. In some neuroimaging studies, functional activation covered both areas (Demonet et al., 1992; Hinke et al., 1993; Mazoyer et al., 1993; Hirano et al., 1996; Heim et al., 2005), but in others activation was found to be restricted to area 44 or area 45, or to parts of both areas, or distributed over areas 44 and 6 (Sergent et al., 1992; Fox et al., 1996; Herholz et al., 1996; Paulesu et al., 1996; Kim et al., 1997). These ambiguous results regarding the precise anatomical location of neural activity may be caused not only by differences between the actual tasks in the different observations, but also by differences in spatial resolution of the various functional imaging techniques. Furthermore, the warping of functional imaging data to anatomical atlases without architectonically defined borders of cortical areas and without considering the degree of intersubject variability of the borders are further confounding factors.

A quantitative cytoarchitectonic study (Amunts et al., 1999) provided not only a 3-D representation of the microscopically defined borders of areas 44 and 45, but also population maps of these areas based on a sample

of ten (five males and five females) human brains. The cytoarchitectonically defined borders of both areas did not consistently coincide with the sulcal pattern. Thus, macroscopical landmarks are not reliable indicators of these borders. Although the volume of area 44 varies considerably between subjects, the volume of area 44 was larger on the left than right side in all ten brains. All five male and three of the female brains had higher cell packing densities on the left than on the right side (Amunts et al., 1999). These morphological asymmetries of area 44 may represent a correlate of the functional lateralization of speech production (Galaburda, 1980). An ontogenetic study in six female and five male brains indicated a left-over-right asymmetry in the volume of area 45 in the male group (Uylings et al., 1999). Further studies on a larger number of male and female subjects are needed to substantiate morphological asymmetries in Broca's region.

Major input to Broca's region arrives through cortico-cortical fibers of the arcuate fascicle, which originates in Wernicke's area of the temporal lobe, but other fiber tracts are also found in close vicinity to Broca's region and may terminate. Efferents from areas 44 and 45 terminate in the face region of the primary motor cortex. Broca's region controls the complex motor pattern of neuronal assemblies in the face region of area 4, which in turn command the motor cranial nerve nuclei for the muscle activity during vocalization.

A series of studies report a possible architectonical homology (Petrides and Pandya, 1994; Rizzolatti et al., 1996b, 1998) between Brodmann's areas 44/45 in the inferior frontal opercular part of the human brain (Brodmann, 1909; Amunts et al., 1999) and the frontal premotor area F5 in monkeys (Matelli et al., 1985, 1986, 1991). Area F5 contains mirror neurons (Di Pellegrino et al., 1992; Rizzolatti et al., 1996b), i.e. neurons which are not only active during grasping, but also during the observation of another monkey performing the same action. Area F5 is, therefore, active during matching of observed and executed actions. Observation of actions and motor imagery tasks (Grafton et al., 1996; Rizzolatti et al., 1996c; Kramps et al., 1998; Parsons and Fox, 1998; Iacoboni et al., 1999; Binkofski et al., 2000) as well as imitation of target-directed actions are correlated with neuronal activity in the opercular part of the human inferior frontal gyrus (Koski et al., 2002). Thus, functional similarities between the human opercular cortex of the inferior frontal gyrus and the monkey area F5 have been observed.

Recent architectonic studies of the macaque and the human brain shed new light onto the cortical segregation of this region, and the transition between the prefrontal language and motor regions, in particular. Evidence was provided that areas 44 and 45 can further be subdivided based on their function, connectivity,

and/or cytoarchitecture. For example, it was demonstrated that the dorsal and ventral parts of areas 44 are differentially activated during observation and imitation of actions (Molnar-Szakas et al., 2005); others found activations during an imagery of movement task in the ventral, but not the dorsal part of area 44 (Binkofski et al., 2000). Area 45 was subdivided into a more anterior and more posterior part using the width of layer II as a criterion, as well as differences in their connectivity (Petrides and Pandya, 2009). A recent receptorarchitectonic study investigating the distribution pattern of receptors of different neurotransmitter systems (glutamate, GABA, acetylcholine, norepinephrine) reported a much more complex segregation of Broca's region and its transition to the premotor cortex including several new areas in the depths of the precentral and inferior frontal sulci (Amunts et al., 2010). These findings agree with recent studies of the ventral premotor region in the macaque cortex, where F5 has been segregated into different parts (Nelissen et al., 2005; Belmalih et al., 2009; see also Chapter 27).

Primary Motor Cortex

Area 4 of Brodmann (1909) is the best candidate for the functionally defined primary motor cortex. Area 4 is agranular (Brodmann, 1903a; Marin-Padilla, 1970) and contains the giant Betz pyramidal cells (Figure 23.10). This cortical area is comparable with caudal parts of the precentral area of Campbell (1905) (Figure 23.33), caudal parts of the area precentralis A of Smith (1907) (Figure 23.34), area FA γ of von Economo and Koskinas (1925) (Figure 23.37), and the frontal ganglionic core of Braak (1980) (Figure 23.11) (cf. Table 23.4).

Brodmann's (1903b) definition of the caudal border of area 4 (by the lack of an inner granular layer; see Figure 23.10A) from the caudally adjoining area 3a (Figure 23.12) in the fundus of the central sulcus has been widely accepted. The rostral border of area 4 was under dispute, because here Brodmann's (1903b, 1909) parcellation is based exclusively on the presence of Betz cells in area 4 and their absence in area 6 (compare Figure 23.10A,C). Most of the papers critically discussing Brodmann's delineation of the border between area 4 and area 6 are based exclusively on the drawing of his famous map (Brodmann, 1909). Here, area 4 seems to cover larger parts of the free surface of the precentral gyrus. One must understand, however, the limitations inherent in schematic representations and read the detailed description of area 4 in Brodmann's original paper of 1903a (see also Zeki (1979) for a discussion of the misuse of Brodmann's schematic drawing in other cortical regions). Area 4 is described in Brodmann's first article (1903a) as a wedge-shaped field which is very tiny on the laterobasal side and covers only the rostral

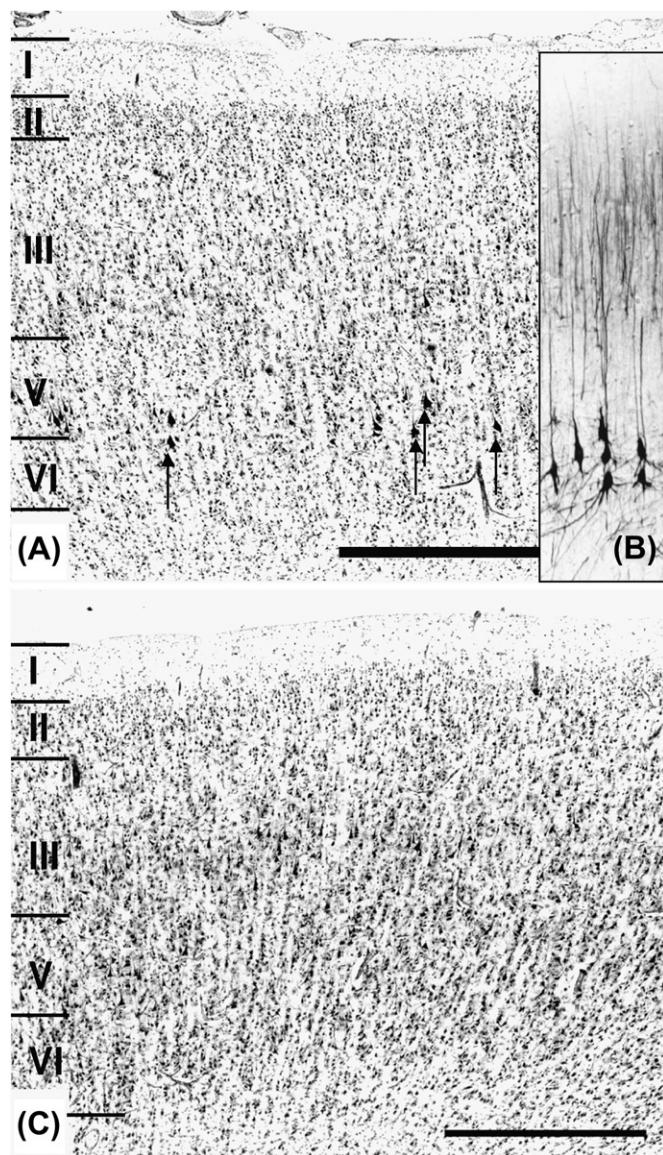


FIGURE 23.10 Cytoarchitecture of Brodmann's (1909) agranular areas 4 (A, B) and 6 (C). (A) Nissl-stained section of area 4. The arrows indicate several Betz cells in layer V. (B) SMI-32 stained section of the macaque area 4 with prominently stained Betz cells. (C) Nissl-stained section of area 6. Bar 1 mm. From Zilles, K.: *Architecture of the Human Cerebral Cortex. Regional and Laminar Organization In:* (Paxinos, G. and Mai, J.K., eds.) *The Human Nervous System, 2nd Edition.* Elsevier, San Diego, 2004.

wall of the central sulcus. That means that area 4 does not spread over the free cortical surface of the precentral gyrus to a considerable extent, but is buried in the central sulcus. Also, the broad part of area 4 on the paracentral lobule of the medial hemispheric surface shows no major differences when compared with more recent observations (Geyer et al., 1996, 2000c). Brodmann (1903a) described other characteristics of area 4 and the Betz cells (large cortical thickness, inconspicuous lamination pattern, low cell density, no clear boundary

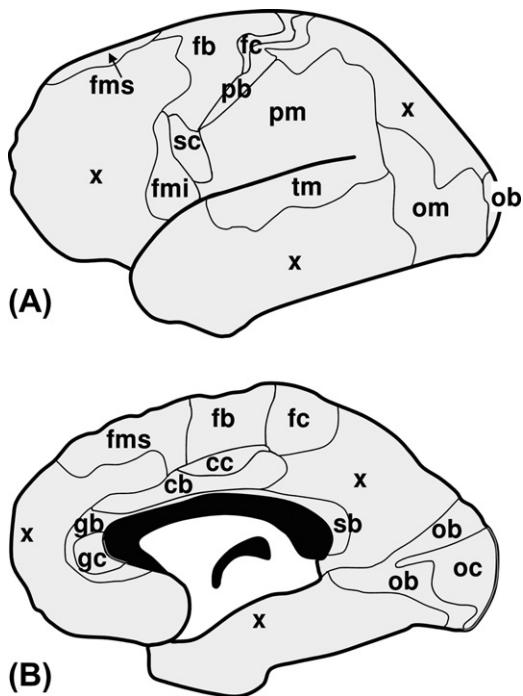


FIGURE 23.11 Cortical map based on pigmentoarchitectonical observations of Braak (1980) in (A) lateral and (B) medial views. cb, cingulate belt; cc, cingulate core; fb, frontal belt; fc, frontal core; fmi, frontal magnopyramidal region inferior part; fms, frontal magnopyramidal regions superior part; gb, genual belt; gc, genual core; ob, occipital belt; oc, occipital core; om, occipital magnopyramidal region; pb, parietal belt; pm, parietal magnopyramidal region; sb, splenial belt; sc, subcentral region; tm, temporal magnopyramidal region; x, cortical regions not parcellated. From Zilles, K.: *Architecture of the Human Cerebral Cortex. Regional and Laminar Organization In: (Paxinos, G. and Mai, J.K., eds.) The Human Nervous System, 2nd Edition. Elsevier, San Diego, 2004.*

between layer VI and white matter, decreasing size of Betz cells along the mediolaterobasal extent). Recently, Geyer et al. (1996) could demonstrate – by combining quantitative cytoarchitectonical mapping and transmitter receptor distributions with functional imaging data – the posterior and anterior borders of area 4, its intersubject variability and motor function, and a subdivision of area 4 into a rostral subarea 4a and a caudal subarea 4b. This subdivision is supported by functional data showing differential modulation of the neural activity in both subareas by attention to action (Binkofski et al., 2002).

Area 4 receives afferent fibers from both subcortical sources (caudal part of the ventrolateral and rostral part of the ventroposterolateral thalamic nuclei) and cortical sources (for details see Chapter 27). A major efferent pathway of area 4 is part of the pyramidal tract. However, area 4 is not the only cortical source of the pyramidal tract fibers. The non-primary motor and the primary and secondary somatosensory cortices represent additional sources (Minckler et al., 1944; Kuypers,

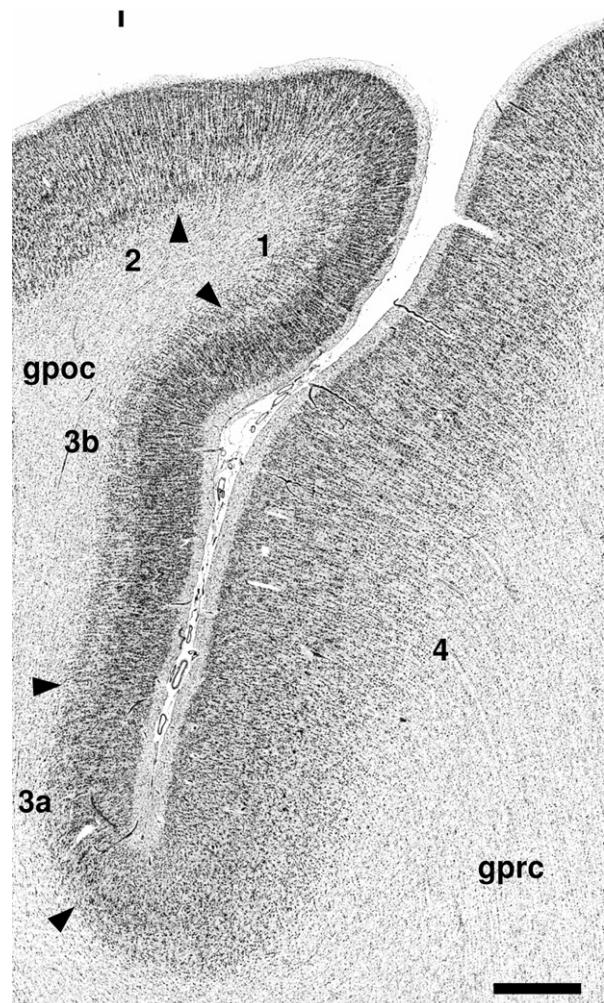


FIGURE 23.12 Horizontal, cell body-stained section through the human precentral (gprc) and postcentral (gpoc) gyri with the agranular motor area 4, the transition zone area 3a, and the granular somatosensory areas 3b, 1, and 2. Bar 1 mm.

1958; Brodal, 1969). About 30% of pyramidal tract fibers originate from large, medium-sized, and small pyramidal cells in layer V of area 4. Whereas the volume of area 4 does not differ between the left and right side, the volume of this part of the pyramidal tract originating in area 4 is significantly larger in the left than right hemisphere (Rademacher et al., 2001c). This left-over-right asymmetry of a part of the pyramidal tract may be related to the left-hemispheric dominance for handedness in more than 90% of the population (Gilbert and Wysocki, 1992). The axons terminate in motor nuclei of cranial nerves (corticuclear tract), in pontine nuclei (corticopontine tract), and on α -motoneurons, interneurons, and (via interneurons) on γ -motoneurons of the spinal cord (corticospinal tract). Area 4 controls the activity of both proximal and distal muscle groups, but only the motor activity of distal muscles is impaired after destruction of the lower corticospinal tract.

One of the most conspicuous aspects of organization in the primary motor cortex is its somatotopy. The studies of Penfield and Rasmussen (1950) have shown the representation of the various parts of the body in the motor cortex. The contralateral foot is found on the medial surface of the hemisphere followed by the leg and trunk around the upper margin of the hemisphere. A considerable large cortical area is covered by the hand representation in the upper half of area 4 on the lateral surface of the hemisphere. The site of the motor hand representation is visible in axial sections by a Ω-like protrusion of the precentral gyrus towards the central sulcus ("hand-knob") (Yousry et al., 1997). The lower half of area 4 is occupied by the cortical representation of the face and especially the lips, tongue, pharynx, and larynx muscles.

The Betz cells differ from the other pyramidal cells of area 4 by their morphology (Scheibel and Scheibel, 1978). They show not only the major apical dendritic stem and typical basal dendrites, but numerous additional dendrites originating from the whole circumference of their cell bodies (see also Figure 23.10B).

Non-Primary Motor Cortex

Brodmann (1909) described the border between the primary motor cortex (area 4) and the rostrally adjoining non-primary motor cortex which is represented in his map by a single cortical field, Brodmann area 6. The distinction between these areas is based on the presence of Betz cells in layer V of area 4, cells which are not found in area 6 (Figure 23.10C). However, this finding is a problematic criterion for the precise definition of the border between both areas. Wise (1985a, 1985b) emphasized the difficulties of separating the Betz cell population from other pyramidal cells by using cell body size as the criterion. This is corroborated by Braak and Braak (1976), who used the histochemical method of lipofuscin staining ("pigmentoarchitectonics") to identify Betz cells. These cells show a vast agglomeration of lipofuscin granules in their perikarya not visible in other pyramidal cells of layer V. According to these results, the size distribution of Betz cell perikarya shows a wide overlap with that of large- and medium-sized pyramidal cells. Therefore, the identification of the border between areas 4 and 6 is difficult when based exclusively on Nissl-stained sections and the criterion of cell size. Consequently, the true Betz cell area (frontal core in Figure 23.11) delineated by Braak (1979a, 1980) on the basis of pigmentoarchitectonical features is different from Brodmann's area 4 published in his famous map (Brodmann, 1909). The lateroventral part of the frontal core is completely buried in the central sulcus. According to the map in Figure 23.11, which is a simplified presentation of the detailed results of Braak's (1980) architectonical studies, Brodmann (1909) may have

overestimated the extent of area 4. The area FAγ (see Figure 23.37) of von Economo and Koskinas (1925) resembles more closely the frontal core area of Braak and area 4 as delineated by Geyer et al. (1996). Therefore, the architectonical delineation of the border between areas 4 and 6 needs further elaboration. The border between area 6 and the adjoining prefrontal areas is defined by the appearance of an inner granular layer (layer IV) in prefrontal areas, which is lacking in the non-primary motor cortex. However, this criterion is not easy to recognize in Nissl-stained section.

The second feature of Brodmann's (1909) area 6, its appearance as a single cortical field, has been questioned by architectonical observations in human brains (Vogt, 1910; Strasburger, 1937; Sanides, 1962; Braak, 1976a, 1980). Comparative anatomical and functional studies substantiate the architectonical and functional segregation of area 6. Such observations in humans and non-human primates strongly support the concept of the non-primary motor cortex as being composed of two major regions, the premotor and the supplementary motor cortex (for review see Geyer et al., 2000c). This subdivision corresponds only partly with the frontal belt and cingulate core areas (Figure 23.11), which have been delineated by Braak (1976a, 1979a, 1980). The premotor and supplementary cortices can be further subdivided by architectonical and functional criteria both in non-human primates and humans (Penfield and Welch, 1951; Roland et al., 1980; Matelli et al., 1986, 1989, 1991, 1998; Wiesendanger and Wiesendanger, 1984; Wise and Strick, 1984; Wiesendanger et al., 1985; Wise, 1985a, 1985b; Barbas and Pandya, 1987; Rizzolatti et al., 1988, 1990, 1996a, 1996b, 1996c, 1998; Luppino et al., 1990, 1991, 1993, 1994, 1999; Paus et al., 1993; Tanji, 1994; Tanji and Shima, 1994; Sanes et al., 1995; Stephan et al., 1995; Zilles et al., 1995, 1996b; Matelli and Luppino, 1996; Picard and Strick, 1996; Roland and Zilles, 1996a; Geyer et al., 1998, 2000a, 2000c; Schubotz et al., 2010). A detailed description of the functional and connectional aspects of the complete motor cortex is given in Chapter 27.

Parietal Lobe

The human parietal lobe consists of the *postcentral* and *parietal regions* (Brodmann, 1909). The *postcentral region* comprises the postcentral gyrus, parts of the paracentral lobule mesially, and parts of the operculum Rolandi ventrolaterally. The *parietal region* contains the superior and inferior parietal lobules separated by the intraparietal sulcus, the most posterior part of the paracentral lobule, and the mesial extent of the superior lobule down to the subparietal sulcus and to the parieto-occipital sulcus. For a detailed description see Chapter 28.

The maps of Brodmann (1909) and von Economo and Koskinas (1925) still dominate the present concepts on the cytoarchitectonical organization of the human parietal cortex (Figure 23.13A–D). Brodmann's map strongly influenced the parcellation scheme of Sarkisov et al. (1955) (Figure 23.39A,B), which differs only by minor details from his map. More recent studies (Bailey and von Bonin, 1951; Pandya and Seltzer, 1982a, 1982b; Eidelberg and Galaburda, 1984) further developed the Economo-Koskinas concept. However, all these cytoarchitectonic maps do not reflect the high degree of functional segregation in the parietal

cortex revealed by neuroimaging studies in the human brain (Dong et al., 2000; Fink et al., 2000a, 2000b, 2001a, 2001b; Weiss et al., 2000; Bremmer et al., 2001; Inoue et al., 2001; Grefkes et al., 2002; Gurd et al., 2002). Furthermore, numerous anatomical and functional (Seltzer and Pandya, 1980; Matelli et al., 1986, 1998; Luppino et al., 1990, 1993, 1999; Colby and Duhamel, 1996; Galletti et al., 1997; Rizzolatti et al., 1997; Bremmer et al., 2000; Cavada, 2001; Matelli and Luppino, 2001) observations in the monkey also demonstrate a much higher degree of areal differentiation than that presented in Brodmann's (1909) maps of the human or monkey cortex. Thus, the parietal cortex is still an architectonically insufficiently explored region of the human cerebral cortex. For a recent parcellation of the macaque parietal cortex, see Gregoriou et al. (2006), Rozzi et al. (2006, 2008), and Paxinos et al. (2000).

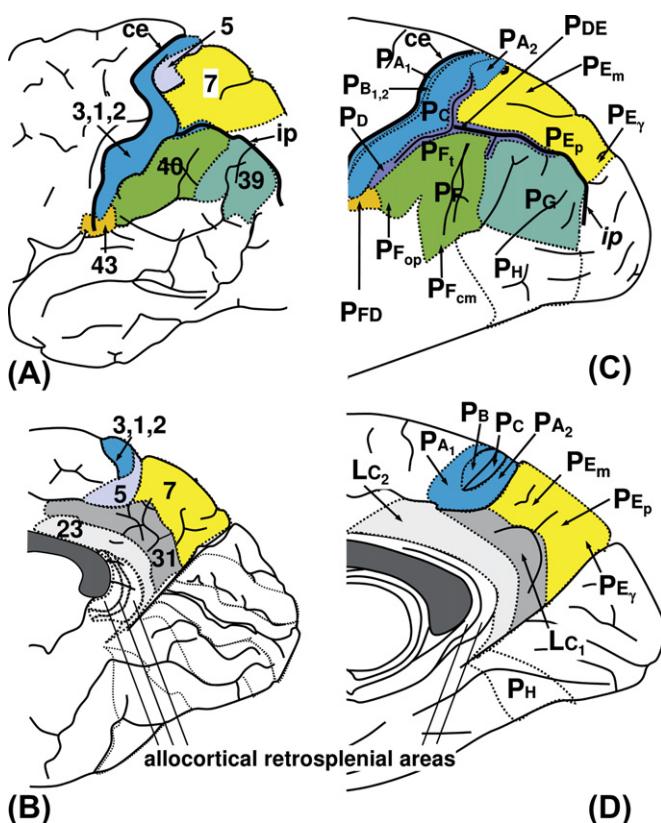


FIGURE 23.13 Cytoarchitectonic maps of human parietal areas. Figure 23.13A (lateral view) and Figure 23.13B (medial view) are modified after the map of Brodmann (1909); Figure 23.13C (lateral view) and Figure 23.13D (medial view) are modified after von Economo and Koskinas (1925). ce, central sulcus; ip, intraparietal sulcus; LC₁, area cingularis posterior ventralis; LC₂, area cingularis posterior ventralis; PA₁, area postcentralis gigantopyramidalis sulcal part; PA₂, area postcentralis gigantopyramidalis (paracentral lobule); PB₁, area postcentralis oralis granulosa; PB₂, area postcentralis oralis simplex; PC, area postcentralis intermedia; PD, area postcentralis caudalis; PDE, transition zone between areas PE and PD; PE_m, area parietalis superior magnocellularis; PE_y, area parietalis superior parvocellularis; PE_y, area parietalis superior posterior gigantopyramidalis; PF, area supramarginalis; PF_{cm}, area supramarginalis magnocellularis columnata; PFD, transition zone between areas PF and PD; PF_{op}, area parietalis tenui corticalis opercularis; PF_t, formatio supramarginalis tenuicorticalis; PG, area angularis; PH, area parietalis basalis; PHO, area parietalis basalis limes occipitalis.

Postcentral Region

Brodmann (1909, 1910) divided the postcentral region into four architectonically related areas, i.e. areas 3, 1, 2 (according to their anterior-posterior sequence; Figures 23.13A,B), and area 43 on the operculum Rolandi, whereas von Economo and Koskinas (1925) defined six areas, i.e. PA₁, PA₂, PB₁, PB₂, PC, PD (Figure 23.13C,D) and one subarea PC_y (not shown). For a comparison of the different nomenclatural systems see Table 23.5.

The fundus of the central sulcus is a landmark of the architectonical border between the motor area 4 and the most rostral postcentral area 3a (Figures 23.12 and 23.14A,B) in most human brains. In some cases, however, this border can be found in the posterior wall of the precentral gyrus or the anterior wall of the postcentral gyrus. Furthermore, a small region displaying a mixture of the cytoarchitectonical characters of areas 4 and 3 can be found at the bottom of the central sulcus, the anterior part of the paracentral lobule, and the posterior part of the operculum Rolandi. This transitional region was identified by von Economo and Koskinas (1925) as their area PA₁ (Figure 23.13C,D) and later called area 3a (for review see Jones and Porter, 1980). The remaining and larger part of area 3 is the primary somatosensory area 3b (Figures 23.12–23.14), which corresponds to von Economo's and Koskinas' areas PB₁ and PB₂. Area 3b has a conspicuous layer IV with small granular neurons invading layer III. Thus, area 3b is a typical koniocortex, i.e. a heterotypical six-layered isocortex with a distinct and wide layer IV (Figure 23.14B,C). The koniocortical type is found in all primary sensory areas of the human brain. The subdivision of area 3b into PB₁ and PB₂ by von Economo and Koskinas was based on the stronger invasion of layer III of PB₁ by small granular cells compared to the reduced granularization of layer III in PB₂.

TABLE 23.5 Comparison of different architectonical parcellation schemes of the human parietal cortex

Brodmann (1909) cytoarchitecture	von Economo and Koskinas (1925) cytoarchitecture	Eidelberg and Galaburda (1984) myeloarchitecture	Vogt (1911) myeloarchitecture	Flechsig (1920) myelogenetic
1	PC	-	70	2
2	PD	-	71	-
	PDE	-	(86?), (87?)	13
(3b)	PB ₁ , PB ₂	-	69	2
(3a)	PA ₁	-	67	-
5	PA ₂	-	75	-
7	PE _m , PE _p , PE _γ	PE	83, 85	16, 21
23	LC ₂	-	(76–82)	33
26	LF ₁	-	-	-
	LE ₁ , LE ₂	-	(91–96)	6
	LD	-	(91–96)	-
31	LC ₁	-	(76–82), 84	33
39	PG	PG, PEG	90	34
40	PF, PF _v , PF _{cm}	PF, PFG	88, (86?), 89	19
43	PFD	-	72	-
opercular	PF _{op}	-	73, 74	-

Area 3b is followed posteriorly by intermediate postcentral area 1 (Figures 23.12 and 23.14C,D), which corresponds to von Economo's and Koskinas' *area PC* (Table 23.5). Area 1 reaches as a narrow strip (PC_γ of von Economo and Koskinas) the caudal part of the paracentral lobule on the mesial hemispheric surface and borders ventrolaterally to area 43. The cytoarchitecture of area 1 shows a homotypical six-layered isocortex with large pyramidal cells in deeper layer III and a less conspicuous layer IV when compared with area 3b. Thus, area 1 fits into the general cytoarchitectonic feature of other unimodal sensory areas, e.g. area 18 or area 42 of the visual or auditory cortex, respectively. Subarea PC_γ differs from PC by its very large pyramidal cells in layer V, and from area PA₂ by its better developed layer IV.

Area 1 is followed caudally by the postcentral area 2, which corresponds to von Economo's and Koskinas' *area PD* (Figures 23.12 and 23.13C; Table 23.5). It is difficult to delineate area 2 from area 1, because both areas belong to the homotypical six-layered isocortex and contain large pyramidal cells in deeper layer III (Figure 23.14D). Recently, the border between area 2 and 1 was demonstrated by using a quantitative cytoarchitectonical technique and receptor architectural analysis (Geyer et al., 1997, 1999, 2000b; Grefkes et al., 2001). It was also demonstrated that area 2 is involved in somatosensory tasks of varying complexity

(Naito et al., 1999, 2005; Bodegård et al., 2000a, 2000b, 2003; Young et al., 2003). Von Economo and Koskinas (1925) emphasized that PD can be differentiated from areas of the superior parietal lobule by numerous pyramidal-like cells in deeper layer VI of PD. In contrast to Brodmann (1909), but in accordance with von Economo and Koskinas (1925), it was demonstrated by Grefkes et al. (2001), that area 2 does not extend to the mesial hemispheric surface. Von Economo and Koskinas (1925) described a transition region between PD and PE, their area PDE. It continues on the upper and lower bank of the intraparietal sulcus (Figure 23.13C). Thus, the intraparietal part of PDE can be compared with Brodmann's caudal part of area 2 in the intraparietal sulcus (Brodmann, 1909) and the "visuo-sensory band β" of Smith (1907). For a comprehensive description of the somatosensory system, see Chapter 30.

The subcentral area 43 (Brodmann, 1909) is located lateroventrally at the basis of the postcentral gyrus, approximately between the anterior and posterior subcentral sulci on the operculum Rolandi (Figure 23.13A). It extends for a considerable distance along the depth of the Sylvian fissure. The most probable candidate for a comparable area in von Economo's and Koskinas' map is their area PFD (Figure 23.13C). Considering its location and extent, area 43 or parts of it may be candidates for the functionally defined second somatosensory

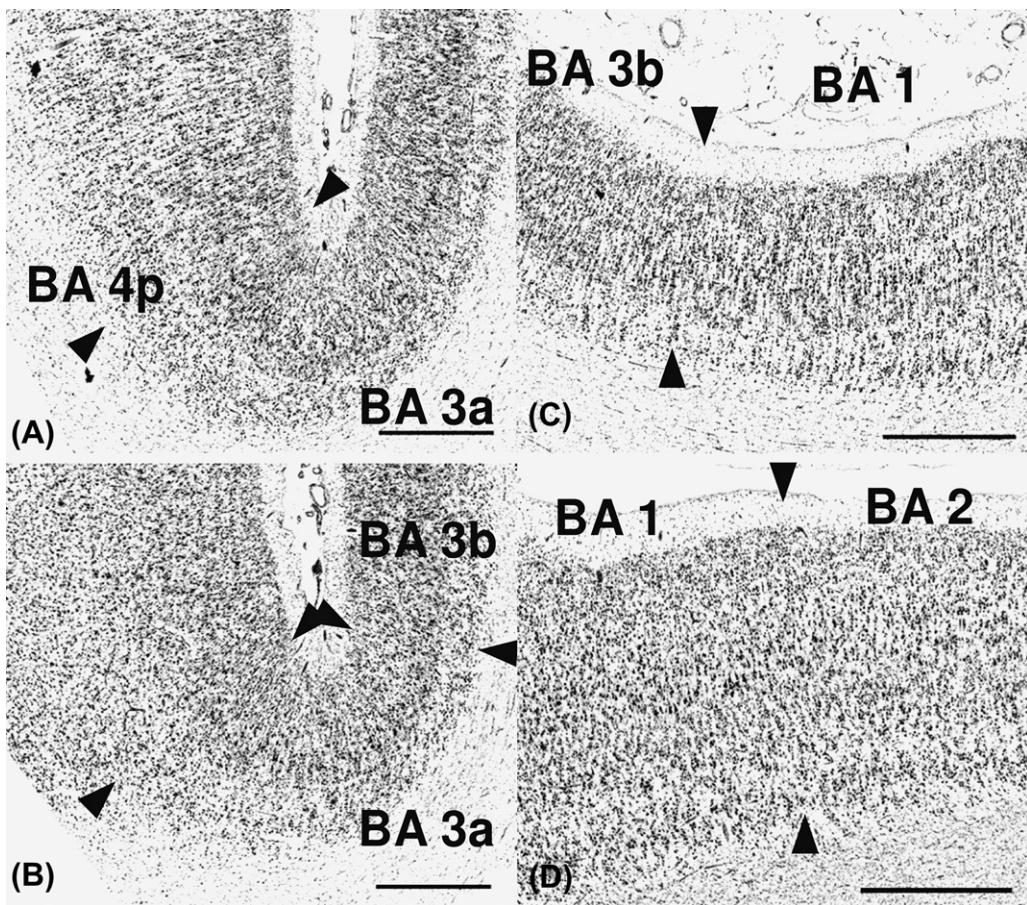


FIGURE 23.14 Cytoarchitecture of the areas 3a (a, b), 3b (b, c), 1 (c, d) and 2 (d) of the human postcentralgyrus. Bars 1 mm. From Zilles, K.: Architecture of the Human Cerebral Cortex. Regional and Laminar Organization In: (Paxinos, G. and Mai, J.K., eds.) The Human Nervous System, 2nd Edition. Elsevier, San Diego 2004.

cortex. Recently, Eickhoff et al. (2006a, 2006b, 2006c, 2006d; 2007a) identified several cytoarchitectonic areas in the parietal operculum, which are not described in the classical cytoarchitectonic maps, but probably comprise the anatomical correlates of the functionally defined second somatosensory cortex SII and other functional areas (e.g., vestibular, gustatory).

Parietal Region

A complete architectonic map of the human parietal region compatible with the extensive regional segregation demonstrated by functional imaging is presently not available. Surprisingly, the practically forgotten myelo- and cytoarchitectonic studies by Vogt (1911), Gerhardt (1940), and Batsch (1956) indicate a much higher architectonical heterogeneity of the cortical organization than represented in the classical maps. Thus, we will briefly present here these forgotten maps, which may be of interest on the background of the high degree of functional segregation demonstrated by recent neuroimaging studies.

According to Brodmann (1908, 1909) and von Economo and Koskinas (1925), the parietal region comprises the four architectonical areas 5, 7, 39, and 40, or the 12 areas PA₂ (originally listed by von Economo and Koskinas as part of the postcentral region), PDE, PE, PE_m, PE_p, PE_γ, PF, PF_t, PF_{op}, PF_{cm}, PF_m, and PG, respectively (Figure 23.13). The major part of the basal parietal region PH of von Economo and Koskinas (1925) is located at the occipito-temporal transition zone, and belongs to the functionally defined visual cortex. This area will be described below in the section about the temporal lobe.

A major controversy concerning the architectonic organization arose from Brodmann's maps (Brodmann, 1909) of human and monkey parietal cortex (Figure 23.15). Area 5 of monkeys covers the complete superior parietal lobule, and area 7 the complete inferior parietal lobule. Contrastingly, in the human cortex areas 5 and 7 are found in the superior parietal lobule, whereas the inferior parietal lobule contains the "human-specific" areas 39 and 40. Vogt (1911) subdivided the superior lobule into areas 5a and 5b, and the inferior

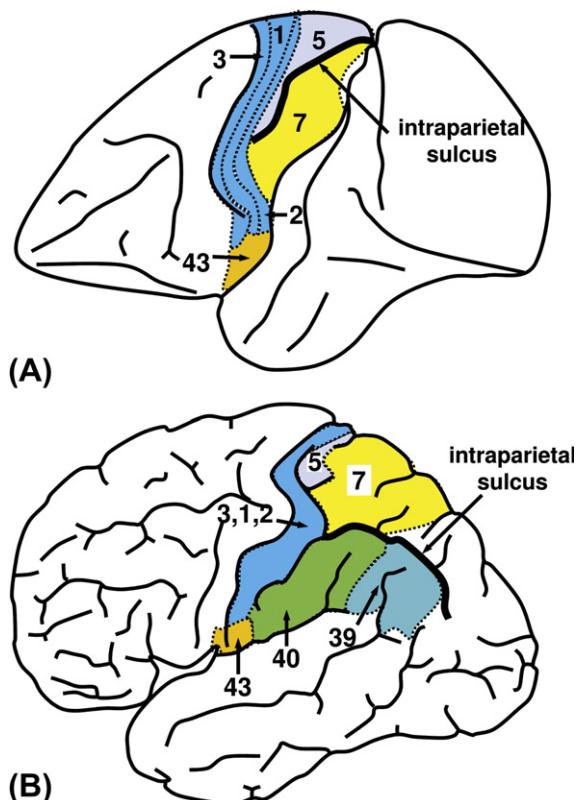


FIGURE 23.15 Areal pattern of the parietal cortex in the macaque (A) and human (B) brains after Brodmann (1909). According to these maps, the intraparietal sulcus has a different position relative to area 7 in the human compared to the macaque brain.

lobule into areas 7a and 7b. Area 7a includes parts of Brodmann's areas 39 and 40, 7b represents the most rostral part of area 40. Area 5 of Brodmann is a small part of the areas 5a and 5b of Vogt and Vogt (1926), which are covered almost completely by Brodmann's area 7.

Superior Parietal Lobule

The *parareptial area 5* was classified by Brodmann (1909) as part of his parietal region, but von Economo and Koskinas (1925) identified their comparable area PA₂ as part of the postcentral region (Figure 23.13). PA₂ shows extraordinarily huge pyramidal cells in layer V (Figure 23.16), which are comparable to the giant Betz cells of area 4. However, in sharp contrast to area 4 a conspicuous layer IV is visible in PA₂. Area 5 extends from the posterior part of the paracentral lobule to the rostral bank of the calloso-marginal sulcus, and continues laterally between the superior part of the postcentral sulcus and the anterior border of area 7. Scheperjans et al. (2005a) could subdivide area 5 into three areas by using regional and laminar differences in multiple transmitter receptor distributions. Based on these molecular data and the cytoarchitecture (2008a, 2008b) within BA 5, they suggested a subdivision into the medial area

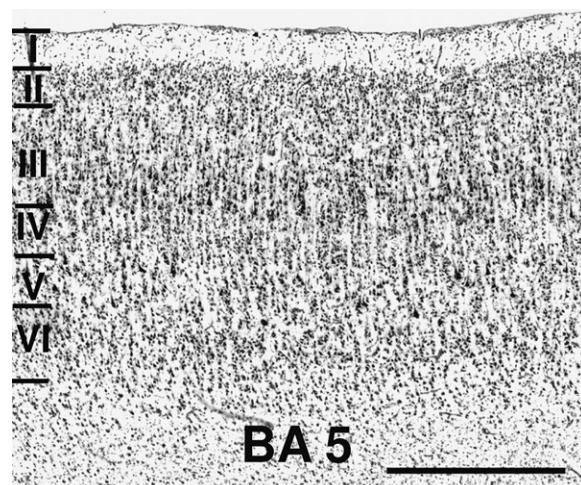


FIGURE 23.16 Cytoarchitecture of area 5 of the human parietal cortex. Bar 1 mm. From Zilles, K.: Architecture of the Human Cerebral Cortex. Regional and Laminar Organization In: (Paxinos, G. and Mai, J.K., eds.) *The Human Nervous System*, 2nd Edition. Elsevier, San Diego 2004.

5M, lateral area 5L, and area 5Ci in the region around the cingulate sulcus. BA 5 is therefore a heterogeneous cortical region, with a receptor expression pattern similar to the adjoining higher-order somatosensory, multimodal parietal, or cingulate regions. Human BA 5 constitutes, therefore, a higher-order cortical area, clearly distinct from the primary somatosensory and motor cortex.

The *superior parietal* (Brodmann, 1909) area 7 occupies most of the lateral superior parietal lobule and of the medial precuneus (Figure 23.13A,B). A comparable location was described by von Economo and Koskinas (1925) for their PE areas (Figure 23.13C,D and Table 23.5).

PE is characterized by a sharply delineated band of conspicuously low cell packing density corresponding to deeper layer V (layer Vb), whereas the borders of this band are blurred in the inferior parietal areas 39 and 40. Further cytoarchitectonic criteria are provided by the generally smaller cells of inferior parietal lobule areas when compared with PE. PE was further subdivided into the anterior area PE_m, with a more pronounced magnocellular appearance compared to the posterior relatively smaller celled area PE_p. The border between PE_m and PE_p is marked approximately by the superior parietal sulcus. According to von Economo and Koskinas (1925), a transitional area PDE (or PED) is located between areas PD and PE. PDE extends into the intraparietal sulcus. A further subdivision was described in the most posterior part of PE_p, the gigantopyramidal area PE_γ. The larger part of this area is found on the anterior wall of the parieto-occipital sulcus. PE_γ is characterized by widely spaced, very large, but slim pyramidal cells in layers IIIc and V.

A detailed parcellation of the superior parietal lobule based on the distribution of transmitter receptors and cytoarchitectonic mapping was proposed by Schepersjans et al. (2005b, 2008a, 2008b). In addition to the three areas in BA 5 (5L, 5M, 5Ci; see above), four areas were identified in BA 7 (7PC, 7A, 7P, 7M), and one in the anterior intraparietal sulcus (hIP3). These areas are possible structural correlates of functional segregations within the human superior parietal lobule.

Inferior Parietal Lobule

The *angular area* 39 (Brodmann, 1909) corresponds broadly to the angular gyrus. Von Economo's and Koskinas' (1925) *area PG* is the equivalent to Brodmann's area 39 (Figure 23.13 and Table 23.5). PG is found posteriorly of the sulcus of Jensen, below the intraparietal sulcus, above area PH, and rostrally to the occipital cortex, which differs from PG by widely spaced larger pyramidal cells in lower layer IIIc, a conspicuously lighter and smaller layer V, and a more cell dense and smaller layer VI. The cytoarchitecture of PG takes an intermediate position between area PE of the superior parietal lobule and area PF of the supramarginal gyrus. Layer III of PG is smaller than that of PE, layer V of PG appears lighter than its layer VI, and its overall cell size is smaller than in PE but larger than in PF.

The *supramarginal area* 40 (Brodmann, 1909) corresponds approximately to the supramarginal gyrus. Von Economo and Koskinas' equivalent to area 40 is *area PF* (Figure 23.13 and Table 23.5). PF occupies the rostral part of the inferior parietal lobule, is found on the posterior part of the operculum Rolandi and the operculum parietale, and reaches approximately to Jensen's sulcus. Von Economo and Koskinas (1925) did not find sharp borders between PF and adjacent areas, but identified transitional areas (PF_t, PF_{op}, PF_m, and PF_{cm}) that are highly variable in cytoarchitecture and size (for architectonic details of these transitional areas see Caspers et al., 2006, 2008). The major part of PF consists of relatively small neurons in all layers. Layers V and VI display a similarly low cell density, layers II and IV are wide, and a conspicuous, fine columnar arrangement of cells is visible. In contrast to the occipital areas, the cortex of PF is wider (2.5–3.6 mm). The temporal areas differ from PF by a higher cell density in layers V and VI. For a more detailed description of the cytoarchitecture of the inferior parietal lobule see Chapter 28.

Neither Brodmann (1909) nor von Economo and Koskinas (1925) provided a cytoarchitectonic parcellation of the cortex in the *intraparietal sulcus*. In monkeys, however, several areas (e.g., anterior intraparietal area AIP (Sakata et al., 1995, 1997), lateral intraparietal area LIP (Andersen et al. 1990), medial intraparietal area MIP (Colby et al., 1988), posterior intraparietal area PIP (Colby et al., 1988), ventral intraparietal area VIP

(Maunsell and van Essen, 1983; Ungerleider and Desimone, 1986; Colby et al., 1993), the area PEIp (Rizzolatti et al., 1998; Matelli and Luppino, 2001), V6A (Gallelli et al., 1996, 1999)) were found in the intraparietal sulcus and at its junction with the parieto-occipital sulcus. These areas are intensively connected with the frontal premotor and occipital cortices. Thus, it can be assumed that the human intraparietal sulcus is also subdivisible into numerous, probably comparable, cytoarchitectonic areas.

Recently, Choi et al. (2006) found two cytoarchitectonic areas hIP (human IntraParietal)1 and hIP2 in the anterior part of the intraparietal sulcus (Figure 23.17), which may be the anatomical correlates of the functionally identified areas VIP and AIP (Bremmer et al., 2000; Grefkes et al., 2002, 2004). Schepersjans et al. (2008a, 2008b) have delineated a third area hIP3. The functional properties of this area are presently not understood.

The connectivity of human posterior parietal areas is described in Chapter 28. Posterior parietal lesions in humans lead to apraxia and extinction (lesion of the left hemisphere) as well as neglect (lesions of the right hemisphere) (Balint, 1909; Denny-Brown et al., 1952; Luria, 1959; Tyler, 1968; Sirigu et al., 1995; Vallar, 1998, 2001; Mesulam, 1999; Freund, 1987, 2001; Driver et al., 2001; Fink et al., 1997, 2000a, 2001b, 2001c). Lesions of the angular gyrus in the dominant hemisphere (areas PF and PG) lead to finger agnosia (inability to recognize, distinguish, and name one's fingers or those of other persons), pure agraphia, right-left disorientation, and dyscalculia (inability to recognize the value of a number). These symptoms were summarized as Gerstmann syndrome (Gerstmann, 1930).

The maintenance of a spatial reference system for goal-directed movements seems to be a major function

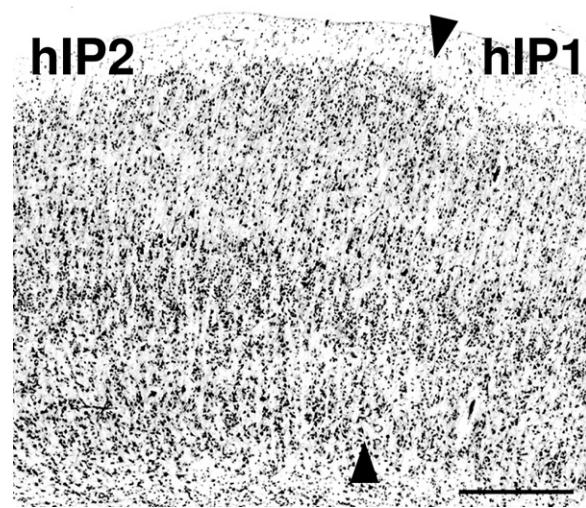


FIGURE 23.17 Cytoarchitecture of the parietal areas hIP1 and hIP2 in the intraparietal sulcus. Bar 1 mm.

of the posterior parietal region. This function is a prerequisite for important human activities, i.e. tool use and conceptualization of actions. Recent functional imaging and other mapping studies (Roland and Zilles, 1994, 1996a, 1996b, 1998; Zilles et al., 1995, 1997; Geyer et al., 1996; Larsson et al., 1999; Naito et al., 1999, 2000; Bodegård et al., 2000a, 2000b, 2003; Ehrsson et al., 2000; Bremmer et al., 2001) demonstrate that areas in the inferior parietal lobule and intraparietal sulcus were activated during imagining (Jeannerod, 2001) and executing (Binkofski et al., 1999), grasping (Decety et al., 1994; Grafton et al., 1996), evaluation of the possible motor significance of sensory stimuli ("motor intention irrespectively of the likelihood of providing a response"; Toni et al., 2001), perceptually based decisions and prospective action judgment (Parsons et al., 1995), action observation (Buccino et al., 2001), and visual presentation of graspable objects (Chao and Martin, 2000).

In a recent event-related fMRI study, the contribution of the parietal–temporal– premotor circuit to sensorimotor transformations was analyzed "where behavior is guided by rules rather than objects or places" (White and Wise, 1999; Passingham and Toni, 2001; Toni et al., 2001). It could be shown that (i) activation of the posterior parietal cortex can be correlated with motor intention, (ii) that of the premotor cortex with movement preparation, and (iii) that of the posterior part of the superior temporal gyrus with the extraction of contextual and intentional cues during goal-directed behavior. Finally, it has been shown that the superior posterior parietal cortex of the human brain is a multimodal region implicated in task switching, even when no visual or spatial component is part of the task (Gurd et al., 2002).

Forgotten Maps of the Human Parietal Cortex

Detailed cyto- (Gerhardt, 1940) and myeloarchitectonic (Vogt, 1911; Batsch, 1956) parcellations of the human parietal lobe are available. Vogt (1911) proposed a map of the human parietal cortex displaying 28 different myeloarchitectonic areas. However, these three studies of the Vogt-School are practically forgotten. Here, a brief review of the detailed maps (Figures 23.18–23.20) will be given (see Table 23.5 for comparison with other nomenclatures).

Major criteria in the myeloarchitectonic studies are interareal differences in the length, thickness, and spacing of the radial fiber bundles, the visibility or lack of the Kaes-Bechterew stripe, i.e. tangentially oriented myelinated nerve fibers in the most superficial part of layer III, the visibility or lack of the outer and inner Baillarger stripes, i.e. tangentially oriented myelinated nerve fibers in layer IV and deeper layer V, respectively, and the merging or separation of the outer and inner Baillarger stripes (Figure 23.21).

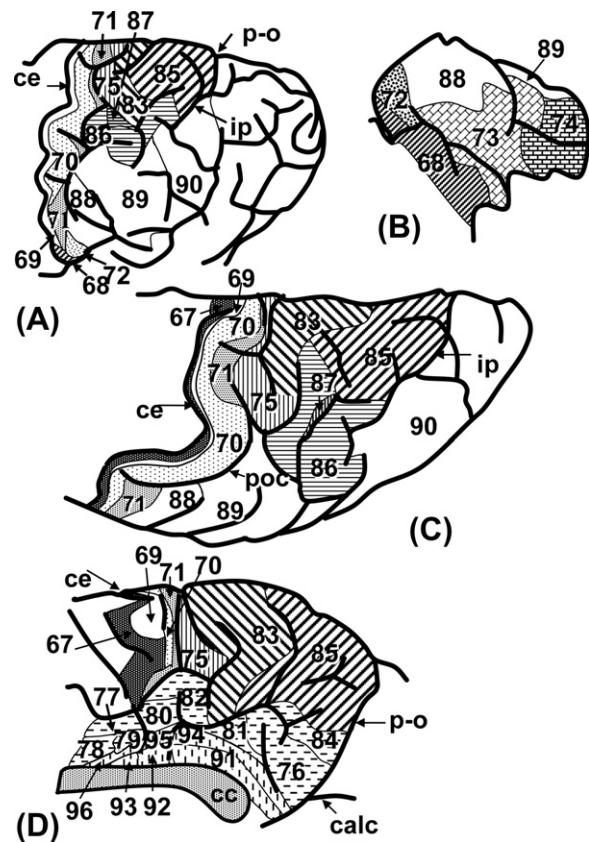


FIGURE 23.18 Myeloarchitectonic map of the human parietal cortex (modified after Vogt, 1911). A, lateral view; B, surface of the parietal operculum; C, dorsal view; D, mesial view. calc, calcarine sulcus; cc, corpus callosum; ce, central sulcus; ip, intraparietal sulcus; p-o, parieto-occipital sulcus; poc, postcentral sulcus. The Arabic numerals indicate the myeloarchitectonic areas, which are not identical with the numerical scheme of Brodmann.

The parcellation in the maps of Vogt (1911) and Batsch (1956) is well comparable. Differences between both maps are only found when the sizes of equivalent areas are compared between the studies. This, however, is not surprising, since the sizes of equivalent cortical areas in different brains show a considerable degree of intersubject variability (Geyer et al., 1996, 1999, 2000b; Roland et al., 1997; Zilles et al., 1997; Amunts et al., 1999, 2000b; Grefkes et al., 2001; Rademacher et al., 2001b; Caspers et al., 2006, 2008; Choi et al., 2006; Schepersjans et al., 2008a, 2008b). Thus, the two myeloarchitectonic studies provide a concordant map of the human parietal cortex. The myeloarchitectonic maps are further supported by the cytoarchitectonic observations of Gerhardt (1940). This study provides an even more detailed map; however, the parcellation was based on only one hemisphere. Only the major areas of this cytoarchitectonic map are reproduced here (Figure 23.19), and show an areal pattern very similar to those observed by Vogt (1911) and Batsch (1956) in their myeloarchitectonic

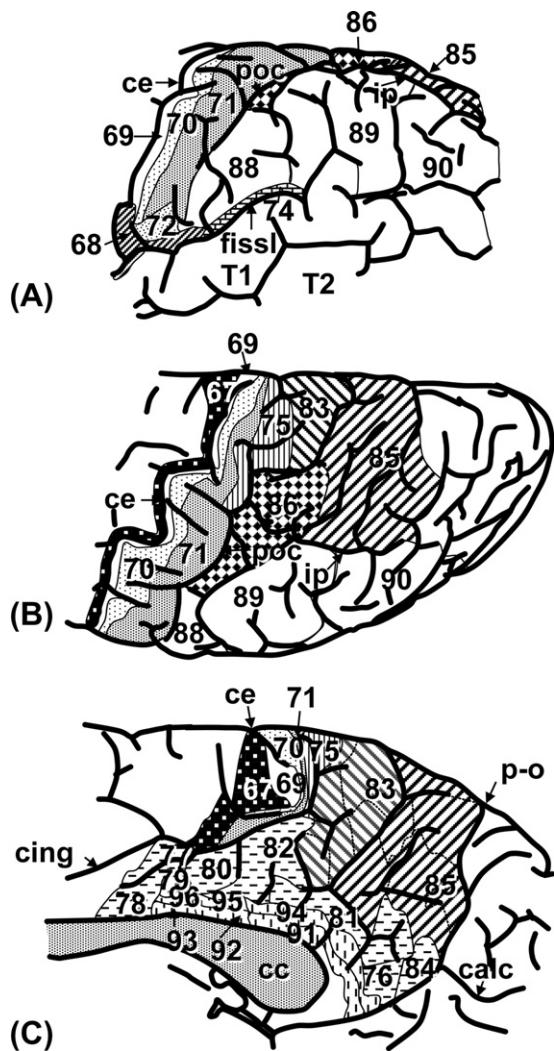


FIGURE 23.19 Cytoarchitectonic map of the human parietal cortex (modified after Gerhardt, 1940). A, lateral view; B, dorsal view; C, mesial view. calc, calcarine sulcus; cc, corpus callosum; ce, central sulcus; fissl, lateral fissure; ip, intraparietal sulcus; p-o, parieto-occipital sulcus; poc, postcentral sulcus; T1, superior temporal gyrus; T2, inferior temporal gyrus. The Arabic numerals indicate the cytoarchitectonic areas of Gerhardt, which are not identical with the numerical scheme of Brodmann but comparable to the myeloarchitectonic classification of Vogt as shown in Figure 23.18.

studies. These three studies indicate that the areal parcellations of Brodmann (1909) and von Economo and Koskinas (1925) do not give a sufficiently complete picture of the architectonical organization in the human parietal lobe.

Temporal Lobe

The temporal lobe consists of a large number of cortical areas differing in structure (isocortical to allocortical) and function (unimodal auditory, unimodal visual, multimodal association). The superior (transverse gyri,

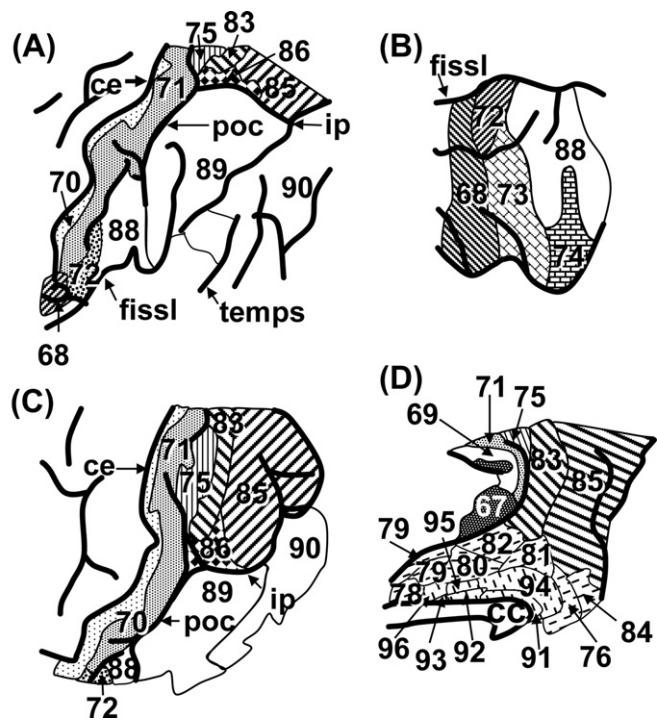


FIGURE 23.20 Myeloarchitectonic map of the human parietal cortex (modified after Batsch, 1956). A, lateral view; B, surface of the parietal operculum; C, dorsal view; D, mesial view. cc, corpus callosum; ce, central sulcus; fissl, lateral fissure; ip, intraparietal sulcus; poc, postcentral sulcus; temps, superior temporal sulcus. The Arabic numerals indicate the myeloarchitectonic areas of Batsch, which are not identical with the numerical scheme of Brodmann but comparable with the myeloarchitectonic classification of Vogt as shown in Figure 23.18.

anterior part of the planum temporale) and dorsolateral (superior temporal gyrus) zone of the temporal lobe contains various isocortical areas, which are the structural correlates of the unimodal auditory cortex and the Wernicke region. The visual and multimodal isocortical areas of the inferior lateral and ventral zones of the temporal lobe (medial and inferior temporal gyri, fusiform (= lateral occipito-temporal) gyrus, rostral part of the lingual (= medial occipito-temporal) gyrus) are summed up here as the inferotemporal zone. It is followed most medially by allocortical regions, which comprise the most medial, multimodal zone of the temporal lobe. This latter zone consists of the periallocortical entorhinal, perirhinal, parasubiculum, and presubiculum areas as well as the hippocampus (dentate gyrus, Ammon's horn, subiculum) and the small cortical part of the amygdala. The polar zone of the temporal lobe (Brodmann's area 38) consists of a multimodal region with an isocortical to proisocortical architecture and was interpreted as part of the paralimbic belt by Mesulam (1998).

The most detailed anatomical studies of the human temporal isocortex are based on myeloarchitectonic

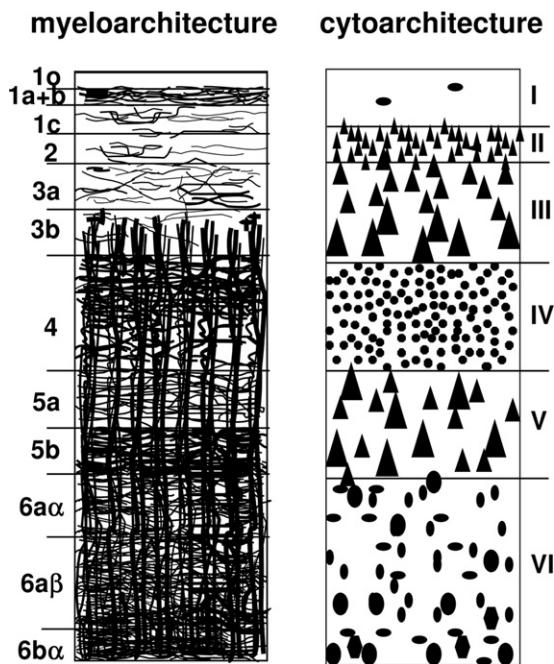


FIGURE 23.21 Schematic drawing of the myelo- and cytoarchitectonical lamination patterns in the human isocortex. Arabic numerals indicate the cortical layers in myelin-stained sections, Roman numerals indicate the cortical layers in cell body-stained sections. The myelinated fibers are running vertically or horizontally to the surface of the cerebral cortex. Only a few fibers are obliquely oriented. The vertical fiber bundles contain myelinated *axons* and are called “radial fibers”. This term may give rise for confusions, since the same term is used for vertically oriented *glial* fibers in the fetal brain. The thickness, length and packing density of the myelinated fiber bundles are important criteria for myeloarchitectonic parcellations. The horizontally oriented fiber bundles also contribute as important criteria to the myeloarchitectonic studies. The most superficial horizontal fiber bundle is the Exner-stripe in layer 1a+b, followed by the Kaes-Bechterew-stripe in layer 3a, the outer Baillarger-stripe in layer 4 and the inner Baillarger-stripe in layer 5b.

observations (Hopf, 1954, 1955, 1968). Seven major regions were identified, which were further subdivided into 20 subregions and 60 cortical areas. Figure 23.22 provides an overview of the different regions as described by Hopf (1954). A detailed comparison of the parcellation by Hopf (1954, 1955, 1968) with the cytoarchitectonic studies of Smith (1907), Brodmann (1909), and von Economo and Koskinas (1925), however, reveals considerable differences (cf Table 23.6). Braak’s (1978) pigmentoarchitectonical observations (Figure 23.23) are also at variance with all the other studies. Thus, it is presently not possible to provide a conforming and sufficiently detailed architectonical map of the human temporal isocortex, which reconciles the different earlier parcellation schemes.

Despite these controversies in details, general aspects of the architectonical segregation of the temporal

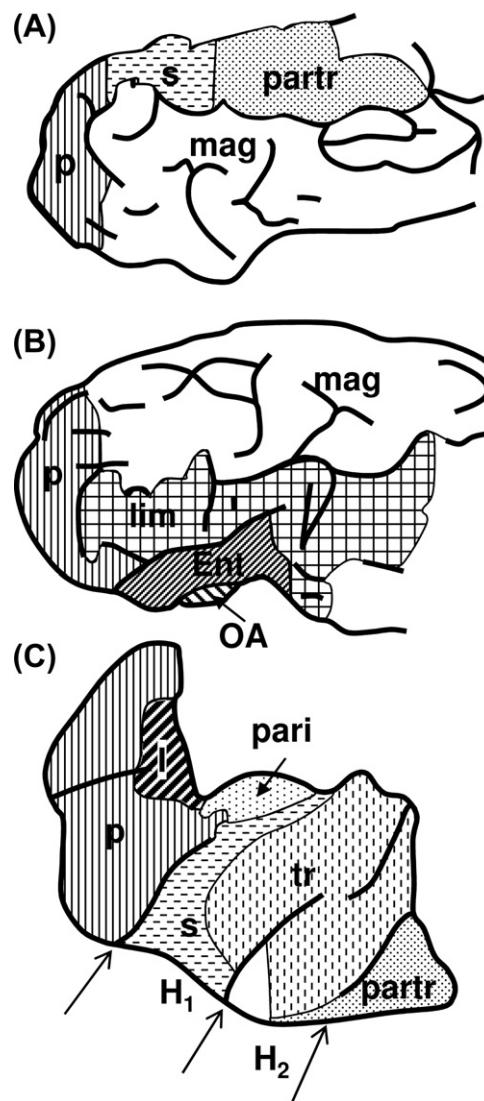


FIGURE 23.22 Areal map of the temporal lobe (A, lateral view; B, basal view; C, dorsal view) based on the myeloarchitectonical observations of Hopf (1954). Ent, Entorhinal area; H₁, first transverse gyrus of Heschl; H₂, second transverse gyrus of Heschl; I, insular region; limregio temporalis limitans; mag, regio temporalis magna; p, regiotemporopolaris; pari, regio temporalis parainsularis; partr, regio temporalis paratransversa; s, regio temporalis separans; tr, regio temporalis transversa.

isocortex are evident. The human temporal lobe comprises three main iso- or proisocortical regions: (i) a proisocortical polar (Brodmann’s temporopolar area 38) together with a mediobasal (Brodmann’s ectorhinal area 36 on the rostral prolongation of the lingual gyrus and adjacent parts of the parahippocampal gyrus) proisocortical region (p and lim in Figure 23.22). The cortex of these regions is very poorly myelinated and is part of the paralimbic region of Pandya and Seltzer (1982b) and Mesulam (1998), (ii) a large isocortical region on the middle temporal gyrus (Brodmann’s middle temporal

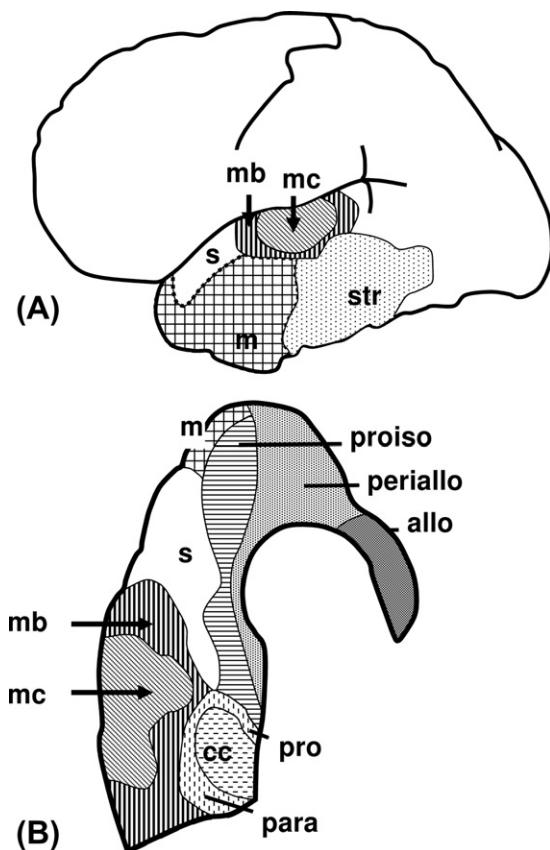


FIGURE 23.23 Areal map of the temporal lobe (A, lateral view; B, dorsal view) based on the pigmentoarchitectonical observations of Braak (1978). allo, allocortex; cc, koniocortical core area; m, area temporalis magna; mb, magnopyramidal temporal belt; mc, magnopyramidal temporal core; para, posterior part of the parakoniocortex; periallo, periallocortex; pro, prokoniocortex; proiso, proisocortex; s, area temporalis simplex; str, area temporalis stratiformis.

area 21), inferior temporal gyrus and fusiform gyrus (Brodmann's inferior temporal area 20 and occipito-temporal area 37), which is also poorly myelinated (mag in Figure 23.22), and (iii) an isocortical region on the superior and transverse temporal gyri and the planum temporale (Brodmann's area 42 and superior temporal area 22; s and ptr in Figure 23.22), which surrounds rostrally, laterally and posteriorly the primary auditory area 41. The cortex of this region is rich in myelinated fibers. The ptr region projects to the premotor cortex, the s and m regions to the prefrontal cortex according to Pandya's and Seltzer's (1982b) studies in the rhesus monkey. The ptr, s, and m regions project also to the paralimbic association cortex, parts of which are represented by the p region of Hopf (1954).

A small proisocortical region, immediately adjacent to the insular cortex, poor in myelinated fibers and of small cortical width (pari in Figure 23.22), is architectonically defined as Brodmann's parainsular area 52.

This latter area is part of the temporal paralimbic cortex of Mesulam (1998) and of a proisocortical stripe (Figure 23.23) described by Braak (1978).

Auditory Cortex

The human auditory cortex consists of various unimodal areas located on the dorsal surface of the temporal lobe and the superior temporal gyrus. A conspicuous architectonic feature of the auditory cortex is its high content of myelinated fibers (Hopf, 1954, 1955, 1968) and the arrangement of neuronal perikarya in distinct vertical columns ("organ pipes" and "rain shower" formations of von Economo and Koskinas, 1925). The average column width and the interval between columns in all temporal auditory areas are smaller in the right than in the left hemisphere (Seldon, 1981).

The principal structure of the connectivity of the auditory cortex supports the concept of three parallel streams of areas running in a rostrocaudal direction as proposed by Pandya (1995). The medial stream is represented by the parainsular cortex, the interposed (core) stream occupies the supratemporal plane, and the most lateral stream is located on the superior temporal gyrus. The areas of each stream have feedforward connections originating in layer III of one area and terminating in layer IV of the rostrally adjacent area. The feedback connections originate in the infragranular layers and terminate in layer I. The areas of the most medial and most lateral streams are connected with the prefrontal multimodal association areas and limbic areas. Additionally, the areas of the most lateral stream show a detailed connectivity according to their rostrocaudal sequence. The most rostral areas of this stream are connected with the orbital and medial prefrontal regions, the intermediate group with the lateral prefrontal areas, and the caudal group with the caudal part of the prefrontal cortex. The areas of the intermediate stream are connected with the ventral nucleus of the medial geniculate body, whereas the areas of the medial and lateral streams are connected with the magnocellular and dorsal nuclei of the medial geniculate body, pulvinar, dorsomedial, and intralaminar thalamic nuclei.

Magnetic resonance imaging (Binder et al., 1994; Strainer et al., 1997; Schmid et al., 1998; Talavage et al., 1999) and magnetoencephalographic (Romani et al., 1982; Hari et al., 1984; Pantev et al., 1995; Langner et al., 1997) studies have demonstrated auditory functions such as the response to pure tones and to acoustic frequency patterns which map onto the medial two-thirds of the Heschl gyrus. A considerable function-depending plasticity of the representation in the auditory cortex was also demonstrated (Pantev et al., 1998; Rauschecker, 1999; Pienkowski and Eggermont, 2011).

Primary Auditory Cortex (Core Region)

The cytoarchitectonical areas 41 of Brodmann (1909) and TC of von Economo and Koskinas (1925) (Figures 23.35 and 23.37) represent the putative cytoarchitectonical correlates of the human primary auditory cortex. The neurons are tuned to pure tones and pitch. Several studies demonstrated a tonotopic organization of the primary auditory cortex with responses to low-frequency stimuli originating more laterally and high-frequency stimuli originating more medially (Hari et al., 1984; Lauter et al., 1985; Yamamoto et al., 1992; Tiitinen et al., 1993; Reite et al., 1994; Pantev et al., 1995; Verkindt et al., 1995; Howard et al., 1996; Talavage et al., 1997; Bilecen et al., 1998). Area 41 has the typical koniocortical structure of primary sensory areas. Area 41 is located deep in the Sylvian fissure on the temporal transverse gyrus (Heschl) gyrus, and is surrounded caudo-laterally by the secondary auditory area 42, rostrally and laterally by areas 22 and 42, and medially by the area 52.

Braak's (1978) "granulous core field" (demonstrated by his pigment-staining technique), was identified as putative primary auditory cortex (Figure 23.23), but covers only the rostral half of the first transverse gyrus of Heschl. Thus, his anatomical correlate of the primary auditory cortex seems to be smaller than shown in the classical maps of Brodmann (1909) and von Economo and Koskinas (1925). Galaburda's and Sanides' (1980) temporal koniocortex (primary auditory cortex) shows also a much greater rostrocaudal extent compared with Braak's (1978) granulous core field. However, a considerable intersubject variability in size and shape of the transverse gyrus(i) has to be considered (Steinmetz et al., 1989; Penhune et al., 1996; Thompson et al., 1996; Leonard et al., 1998). This makes a straightforward comparison between different maps difficult. Moreover, the maps of Brodmann (1909), von Economo and Koskinas (1925), and Braak (1978) do not allow – because of their schematic 2-D representation – a reliable spatial transformation into a stereotaxic system.

Recently, Morosan et al. (2001) and Rademacher et al. (2001a, 2001b) published a cytoarchitectonical map of the primary auditory cortex. Since their maps are transformed into a 3-D reference system, the intersubject variability of this cortical area was defined by presenting probability maps, and the auditory function of the subareas could be corroborated using functional imaging (Johnsrude et al., 2000). Most importantly, Morosan et al. (2001) and Rademacher et al. (2001a, 2001b) demonstrated that the borders of the cytoarchitectonically defined primary auditory cortex cannot be assigned reliably to macroscopically visible landmarks of the Heschl gyrus. Since this lack of coincidence between the borders of architectural areas and

macroscopical landmarks was found also in other cortical regions (Rademacher et al., 1992; Zilles et al., 1995, 1996b, 1997; Geyer et al., 1996, 1997, 1999, 2000b; Roland and Zilles, 1996b, 1998; Amunts et al., 1999, 2000b), this finding seems to be a general caveat for any attempt to infer the position of cytoarchitectonical borders from macroscopical landmarks.

In contrast to Brodmann (1909), other authors identified two or more areas representing the primary auditory cortex (Economo and Koskinas, 1925; Sarkissov et al., 1955; Galaburda and Sanides, 1980; Rivier and Clarke, 1997; Morosan et al. 2001). Morosan et al. (2001) subdivided their primary auditory area Te1 (equivalent to Brodmann's area 41) into the three subareas Te1.1 (caudomedial), Te1.0 (central), and Te1.2 (rostrolateral) using an observer-independent, quantitative cytoarchitectonic technique (Schleicher et al., 1999).

A detailed description of the primary auditory cortex is given in Chapter 36.

Secondary Auditory Cortex (Belt Region)

Brodmann's (1909) area 42 (Figure 23.35) and von Economo's and Koskinas' (1925) area TB (Figure 23.37) are the putative architectonical correlates of the secondary auditory cortex. Area 42 is less granular (clearly visible but the less densely populated and smaller layer IV) when compared with area 41. Area 42 of Brodmann (1909) has correlates in the maps of Braak (1978) and Galaburda and Sanides (1980), which are named as pro- and parakoniocortical areas. Braak's (1978) pro- and parakoniocortical areas (putative secondary auditory cortex) surround completely the core field (putative primary auditory cortex). Area 42 (and area 22) contains phonological representations of words (Howard et al., 1992; Binder et al., 1994; Price and Giraud, 2001).

Stimulation by longer sound durations leads to an activation of a field in the most lateral part of the Heschl gyrus which may correspond at least to parts of Brodmann's area 42 or the parakoniocortical field of Rivier and Clarke (1997). This field shows a mirror tonotopic organization (medio-lateral low- to high-frequency gradient; Engelien et al., 2002) compared with the primary auditory cortex (latero-medial low- to high-frequency gradient).

A detailed description of the secondary auditory cortex and further unimodal auditory areas is given in Chapter 36.

Planum Temporale

The cortex on the superior temporal plane caudal to the first transverse gyrus and extending to the end of the lateral (Sylvian) fissure is defined as *planum*

temporale. The left planum was found to be larger than its equivalent in the right hemisphere in most cases of a large human sample (Geschwind and Levitsky, 1968; Galaburda et al., 1978a, 1978b; Steinmetz et al., 1989; Jäncke and Steinmetz, 1993). Von Economo and Horn (1930) interpreted this gross anatomical asymmetry as a larger extent of the left auditory “association” cortex.

In contrast to the anatomically defined term “planum temporale”, the term “Wernicke region” is functionally (Wernicke, 1874) and not anatomically defined. Thus, the planum temporale is *not* identical with the Wernicke region. The precise position of the architectonic borders of Wernicke’s region (Wernicke, 1874), however, is presently not known. This multimodal language area covers more brain regions than the planum temporale of the superior temporal gyrus (Aboitiz and Garcia, 1997; Grabowski and Damasio, 2000). This area is commonly related to the most posterior part of area 22 (Brodmann, 1909), to area TA₁ of von Economo and Koskinas (1925), or to area Tpt (Galaburda and Sanides, 1980). Tpt (Figures 23.24, 23.25) includes posterior and lateral temporal regions in which lesions cause Wernicke’s aphasia. Tpt was larger on the left side in all four cases measured (Galaburda et al., 1978a) with relative differences between both sides showing an enormous variability between 14 and 626%.

Braak (1978) delineated magnopyramidal regions with large pyramidal cells in the lower part of layer III, which adjoined laterally the belt region of the auditory cortex (mb and mc in Figure 23.23). He considered these regions as the structural basis of Wernicke’s

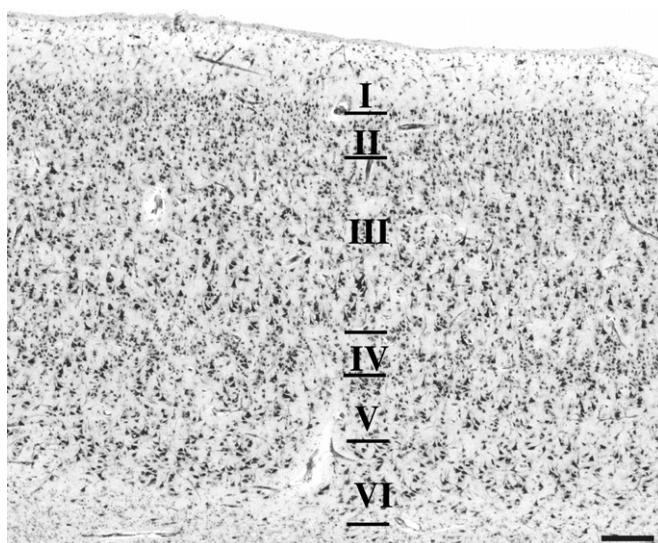


FIGURE 23.24 Coronal section through the upper bank of the superior temporal sulcus with area Te4 (the lower Brodmann area 22). The Roman numerals indicate the six isocortical layers. Bar 250 μm.

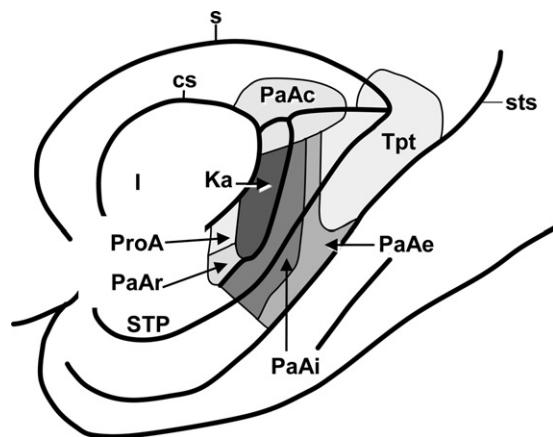


FIGURE 23.25 Areal map of the temporal lobe (lateral view, with a schematic opening of the insula) based on the cytoarchitectonical observations of Galaburda and Sanides (1980). cs, circular sulcus; I, insular cortex; Ka, koniocortex; PaAc, caudal parakoniocortex; PaAe, external parakoniocortex; PaAi, internal parakoniocortex; PaAr, rostral parakoniocortex; ProA, prokoniocortex; s, Sylvian fissure; STP, superior temporal plane; sts, superior temporal sulcus; Tpt, temporoparietal area.

region. The magnopyramidal regions are surrounded by three isocortical areas on the rostromedial (“area temporalis simplex”; s in Figure 23.23), rostralateral (“area temporalis magna”; m in Figure 23.23), and posterolateral sides (“area temporalis stratiformis”; str in Figure 23.23).

The classical myeloarchitectonic maps (Vogt and Vogt, 1919; Beck, 1930; Hopf, 1954, 1955) indicate that a posterior part of Brodmann’s area 22 may contribute to Wernicke’s region. The putative myeloarchitectonical homolog of Wernicke’s region is the area tpartr.p of Hopf (1954). This area is characterized by relatively densely packed myelinated fibers, the lack of the Koenig-Behnert stripe (Figure 23.21), and darkly stained outer and inner Baillarger stripes, which seem to merge to one broad stripe. In contrast, the auditory belt region has a lower fiber density than the Wernicke region, especially in layer III.

A more detailed description of the planum temporale is given in Chapter 36.

Inferotemporal Zone

The inferotemporal zone consists of the areas 21, 20, and 36 (Brodmann, 1909). Brodmann’s area 37 is located between the temporal, parietal, and occipital lobes (Figure 23.35), and is included here as a further area of the inferotemporal zone.

Parts of these four areas belong to the multimodal association cortices, other parts are higher-order unimodal visual and auditory cortices (Mesulam, 1998). Brodmann’s middle temporal area 21, inferior temporal area 20, and occipito-temporal area 37 can be classified

TABLE 23.6 Comparison between different areal maps of the temporal lobe with the myeloarchitectonic map of Hopf (1954)

Hopf (1954)	Smith (1907)	Brodmann (1909)	von Economo and Koskinas (1925)
Regio temporalis (= p)	Area temporopolaris (rostral part)	38	TG
Regio temporalis (= s)	Area temporalis superior	22, 41, 42	TA, TC, TB, TD
Regio parainsularis (=pa)	?	52	medial parts of TB and TD
Regio temporalis transversa (=tr)	Area temporalis superior	41, 42	TC, TB
Regio temporalis paratransversa (=ptr)	Area temporalis superior	22	TA
Regio temporalis magna (= m)	Area temporalis media, Area temporalis inferior, Area paratemporalis	21 20 37	TE TE PH
Regio temporalis limitans (= l)	Area temporopolaris (posterior part), Area paradentata	35, 36 35, 36	TH, TF TH, TF

as typical six-layered homotypical isocortex, whereas area 36, which is found at the transition between the iso- and allocortex on the parahippocampal gyrus, shows modifications of this cortical type. At least parts of area 36 can be classified as proisocortex.

The cortex of areas 20 and 21 is very thick, almost as wide as the motor cortex. Layer III is relatively small and its cell packing density is very low. Layer IV is also very thin, and the cells are arranged in vertical columns. The deeper layers V and VI are very wide. Layer V contains large pyramidal cells (Figure 23.24). Since areas 20 and 21 are difficult to separate by cytoarchitectonic criteria, von Economo and Koskinas (1925) classified both areas as one cortical region, Regio temporalis propria TE. The only criterion for a parcellation of this region into the subareas TE₁ and TE₂ seems to be the somewhat larger size of the pyramidal cells in layer III of TE₁ compared with TE₂. Equivalencies with the cortical terminologies of other authors are given in Tables 23.4 and 23.6.

Brodmann's ectorhinal area 36 (Figure 23.35) is not only poor in myelinated fibers, but also shows a lower overall cell packing density compared with the adjacent isocortical area 20.

According to von Economo and Koskinas (1925) and more recent architectonic and functional imaging studies (for review Zilles and Clarke 1997), Brodmann's area 37 is not a homogeneous cortical area. Some parts of area 37 are probably multimodal (Mesulam, 1998), others are higher-order unimodal visual areas (e.g., V5/MT; see Chapter 37). On the lateral cortical surface, area 37 covers posterior parts of the middle and inferior temporal gyri and anterior parts of the middle and inferior occipital gyri. Thus, area 37 is approximately comparable to the area paratemporalis of Smith (1907) (Figure 23.34) and the area PH of von Economo and Koskinas (1925) (Figure 23.37; Table 23.6). It consists of small radial cell columns in layers III and IV, a narrow layer IV,

and hardly delineable layers V and VI caused by relatively small cells in layer V. PH shows a sharp border between cortex and white matter. Von Economo and Koskinas (1925) emphasize that the cytoarchitecture of PH is not homogeneous. It displays characteristics of the temporal, parietal, and occipital cortices depending on the actual position within PH. Parts of area 20 on the inferior temporal gyrus and at least the parts of area 37 on the fusiform gyrus belong to the "ventral stream" (Ungerleider and Mishkin, 1982; Mishkin et al., 1983) of the visual cortex. The parahippocampal gyrus (containing area 36), and the fusiform gyrus (containing parts of area 20) are found to be activated by attention to shape (Corbetta et al., 1990). Activations of meaningful speech have been found in the middle and inferior temporal gyri (Price, 2010). Emotional face-specific clusters were identified in regions known to be involved in face processing, including anterior fusiform gyrus and middle temporal gyrus (Sabatinelli et al., 2011).

In conclusion, the inferotemporal zone of the human cerebral cortex – as defined here – is a region where auditory, language, visual, auditory memory and multimodal functions are represented (Nakamura et al., 2000; Munoz-Lopez et al., 2010). This high degree of functional segregation supports the assumption of a parallel, much more detailed architectonical segregation than presently shown by the available maps with only four areas.

Occipital Lobe

Most of the visual cortical areas are found in the occipital lobe, but visual stimuli elicit cortical activations also in the temporal and parietal lobes. Thus, the functionally defined visual cortex is considerably larger than the occipital lobe. All visual areas together constitute more than half of the human isocortex.

TABLE 23.7 Architectonic subdivisions and nomenclature of the human striate and extrastriate visual cortex

	Striate cortex	Extrastriate cortex	
Campbell (1905)	Visuo-sensory	Visuo-psychique	
Brodmann (1909)	Area 17	Area 18	Area 19
Smith (1907)	Area striata	Area parastriata	Area peristriata
Vogt and Vogt (1919)	Area 17	Area 18	Area 19 (19a, 19b)
Flechsig (1920)	Area 8	Area 23	Areas 15, 16, and 28
von Economo and Koskinas (1925)	OC	OB (OB γ ; OB Ω)	OA (OA ₁ , OA ₂ , OA _m)
Filimonoff (1932–3)	Area 17	Area 18	Area 19
Bailey and von Bonin (1951)	Koniocortex	Parakoniocortex	
Sarkisov et al. (1955)	Area 17	Area 18	Area 19
Braak (1977–80)	Striate area	Parastriate area	Peristriate area

Brodmann (1909) proposed a tripartition of the occipital lobe with area 17 as primary visual cortex V1, and areas 18 and 19 as unimodal higher visual fields (Figure 23.35). A similar parcellation with areas OC, OB, and OA was published by von Economo and Koskinas (1925; Figure 23.37), Filimonoff (1932) and Sarkisov et al. (1955; Figure 23.39). Von Economo's and Koskinas' area OC (area striata) corresponds to Brodmann's area 17, OB (area parastriata) to area 18, and OA (area peristriata) to area 19 (for comparisons between the nomenclatures used by the different authors see Table 23.7). Braak (1977) subdivided area 19 into numerous areas in his pigmentoarchitectonical studies of the human brain. These areas cover the occipital lobe and extend into the parietal and temporal lobes (Figure 23.26).

Brodmann's (1903b, 1909) cytoarchitectonical delineation of area 17 is unanimously accepted. Also the location and architectonic features of his area 18 could be corroborated using quantitative cytoarchitectonical techniques (Amunts et al., 2000b). Filimonoff (1932) and Amunts et al. (2000b; see Figure 23.28) described the high intersubject variability of the borders of areas 17 and 18. Brodmann's concept of an architectonically homogeneous area 19, however, is not supported by axonal tracing and electrophysiological studies in non-human primates (for a recent map of the macaque occipital cortex, see Paxinos et al., 2000), and does not match the results of functional imaging studies and retinotopic mapping, in particular. Area 19 is not a homogeneous area, and thus, the use of the term "area 19" is not justified anymore. Area 19 and the rostrally adjacent visual regions must be further subdivided both structurally (Braak, 1980) and functionally (Tootell et al., 1998; Georgieva et al., 2009; Kolster et al., 2010),

since they differ in cytoarchitecture, transmitter receptor distribution patterns (Eickhoff et al., 2007b, 2008; Zilles and Clarke, 1997) and functional properties (see Figure 23.27).

The vast majority of extrastriate areas in the human brain, however, are defined by various functional

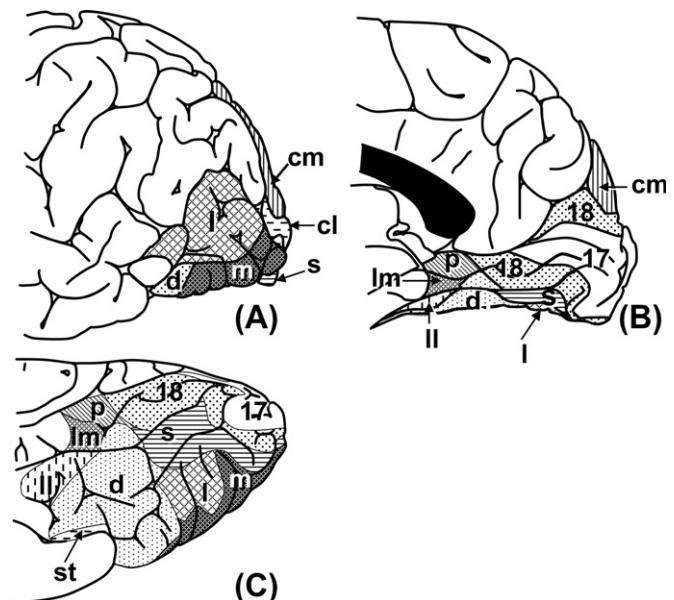


FIGURE 23.26 Areal map of the occipital lobe (A, lateral; B, medial; and C, basal views) based on the pigmentoarchitectonical observations of Braak (1977). cm, Area peristriata cunealis medialis; cl, area peristriata cunealis lateralis; d, area peristriata densopyramidalis; l, area peristriata latopyramidalis; ll, area peristriata limitans lateralis; lm, area peristriata limitans medialis; m, area peristriata magnopyramidalis; p, area properstriata; s, area peristriata simplex; st, area peristriatastriformis; 17, area 17; 18, area 18.

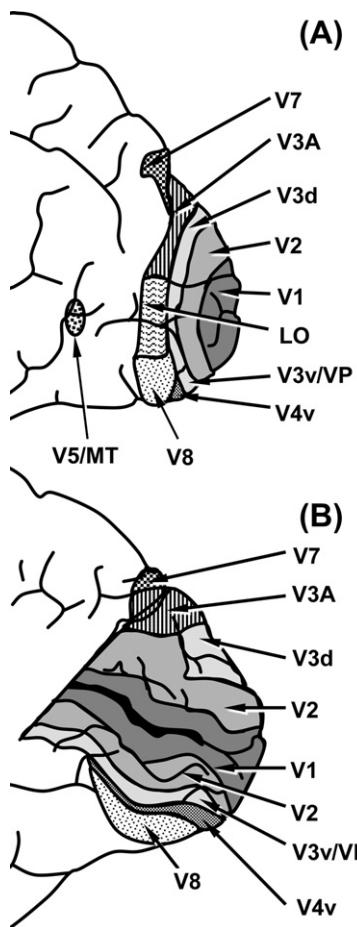


FIGURE 23.27 Areal map of the human visual cortex (A, lateral; B, medial views) adopted from Tootell et al. (1998).

criteria. The retinotopic mapping (Kolster et al., 2010) has been proven to be particularly powerful for the functionally based identification. A comprehensive description of the functional maps is, however, beyond the scope of the present chapter. In addition to area 17, we will describe here only those extrastriate areas which have been cytoarchitectonically characterized and delineated.

Primary Visual Cortex

Area 17 of Brodmann (1903b, 1907, 1909, 1910, 1912) represents the primary visual cortex V1 (Figures 23.26–23.31). It extends from the occipital pole over the total length of the calcarine sulcus. It is the major target of the optic radiation and represents the entire contralateral visual hemifield plus a smaller part of the ipsilateral hemifield. The major part of area 17 receives input from both eyes (binocular part) with the central part of the visual field at the occipital pole. The upper half of the visual field is represented in the lower wall of the calcarine sulcus and adjacent parts of the cortical surface, whereas the lower half

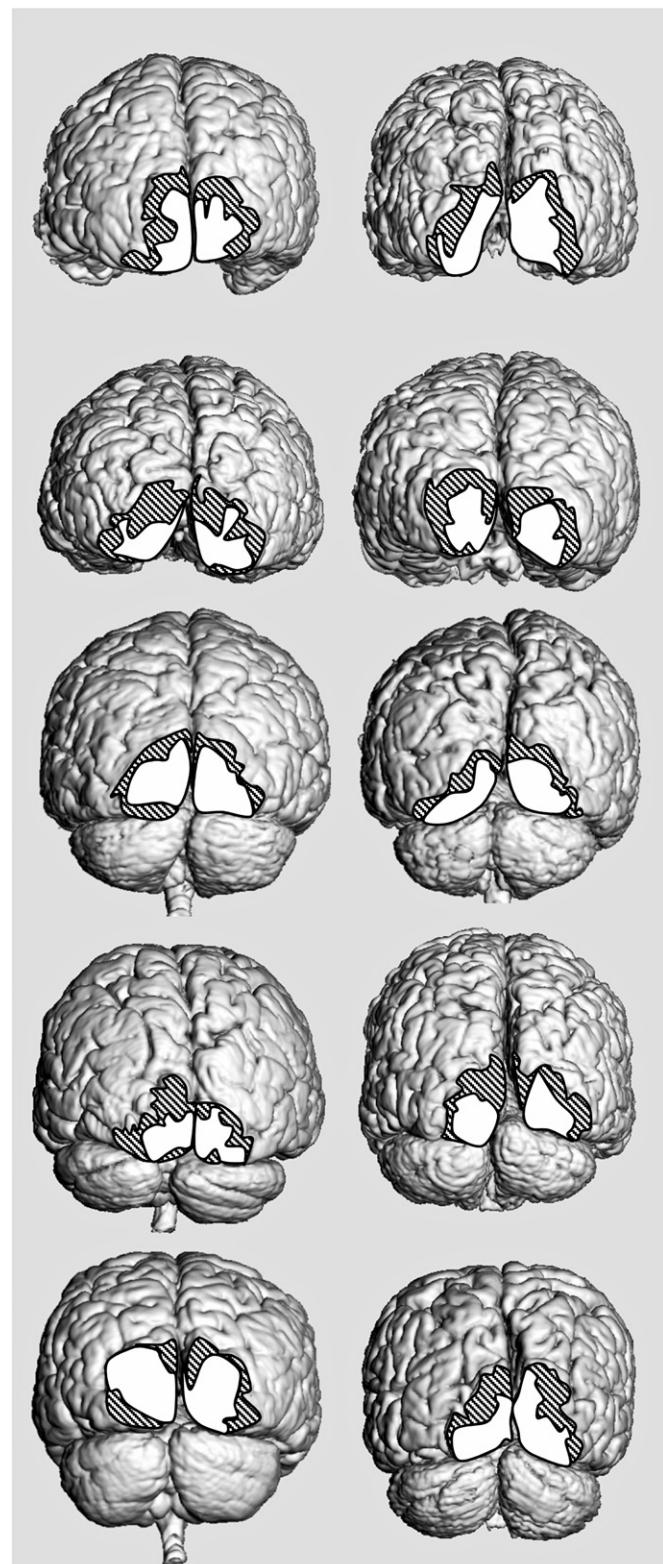


FIGURE 23.28 Intersubject variability of the primary visual cortex V1 (Brodmann's area 17) and the secondary visual area V2 (Brodmann's area 18) in ten human brains (modified from Amunts et al., 2000b). V1, white area, V2, hatched area.

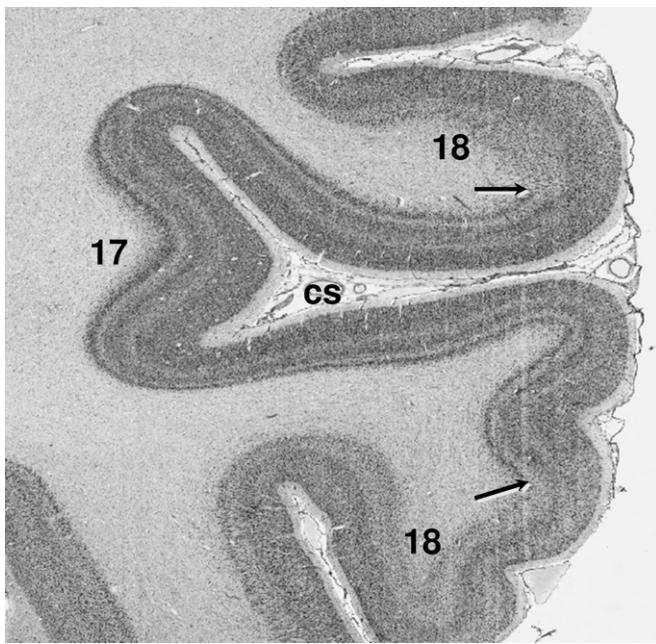


FIGURE 23.29 Cytoarchitecture of area 17 and 18. The arrows mark the borders between the areas 17 (V1) and 18 (V2). cs, calcarine sulcus.

of the visual field is projected to the upper wall and adjacent parts of the cortical surface. The horizontal meridian is located in the fundus of the calcarine sulcus. The vertical meridian is located at the border between areas 17 and 18.

Area 17 shows the most differentiated laminar structure of all isocortical areas in the human brain (Figures 23.29 and 23.30A). It is characterized by a prominent, tripartite layer IV with the sublayers IVA-C. Layer IVC can be further subdivided into layers IVC α and IVC β . Most of the parvocellular afferents from the lateral geniculate body terminate in sublayer IVC β (E. Braak, 1982). Layer IVC α is a target of the magnocellular afferents. Layer IVA of New World and Old World monkeys is characterized by a thin cytochrome oxidase-rich band in layer IVA, which is caused by parvocellular terminals (Wong-Riley, 1994). Humans and chimpanzees lack this band in layer IVA of V1 (Horton and Hedley-White, 1984; Preuss et al., 1999). In contrast to non-human primates, human layer IVA shows a conspicuous immunoreactivity of antibodies against non-phosphorylated neurofilaments (NPNF) and an extracellular proteoglycan distributed in mesh-like bands, as well as a dense irregular staining of calbindin (indicating most probably the presence of GABAergic inhibitory interneurons) in the territories between the mesh-like bands of layer IVA (Hendry and Carder, 1993; Preuss et al., 1999; Preuss and Coleman, 2002). Since the NPNF and the antibody-specific matrix proteoglycan are preferentially or exclusively expressed in the magnocellular pathway (Hof and

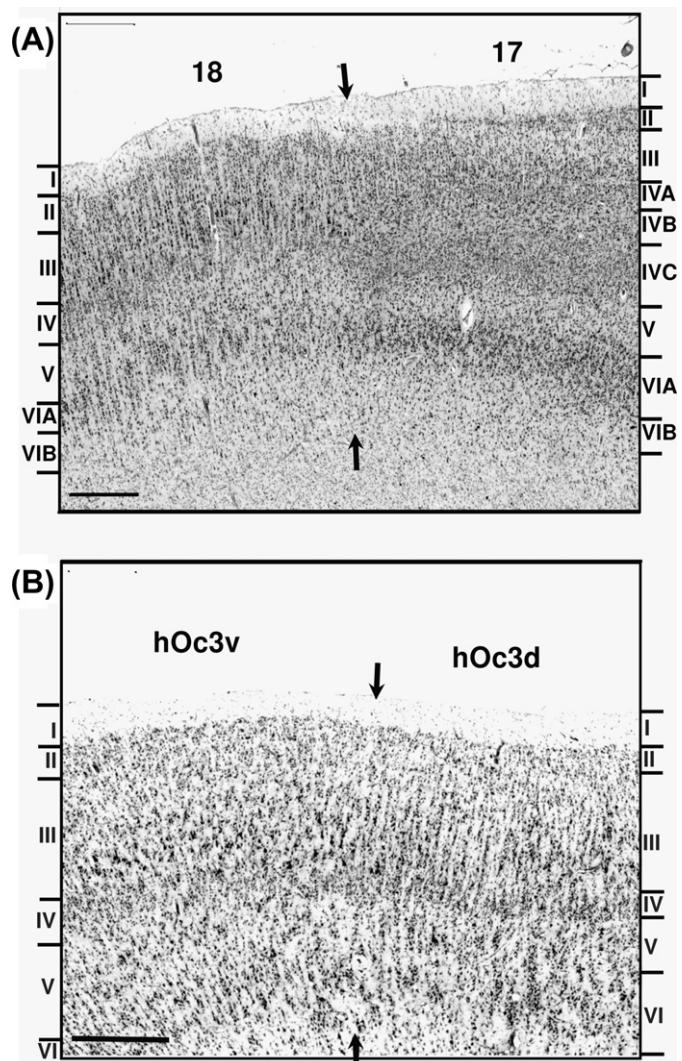


FIGURE 23.30 Cytoarchitecture of areas 17 and 18 (A) and the dorsally and ventrally adjacent extrastriate areas hOc3v and hOc3d in the occipital lobe (B) (Rottschy et al., 2007). The two extrastriate areas are parts of what Brodmann has labeled as “area 19”. Roman numerals indicate the different layers, arrows – cytoarchitectonic borders. Bar 0.5 mm.

Morrison, 1995; Preuss et al., 1999; Preuss and Coleman, 2002), a considerable reorganization of the magno- and parvocellular pathways in human layer IVA occurred during the evolution of the human brain compared with monkeys and apes. Layers III and V contain (beside larger pyramidal cells) numerous small neurons which elicit the visual impression of an extremely high “granularization” of the koniocortical area 17. Layer V with its low cell packing density is easily distinguishable from layer VI. Further details of the differentiated laminar structure of human area 17, ultrastructure, ontogeny, and quantitative aspects have been described by E. Braak (1982), H. Braak (1976b, 1977), Brodmann (1903b), von Economo and Koskinas (1925), Filimonoff

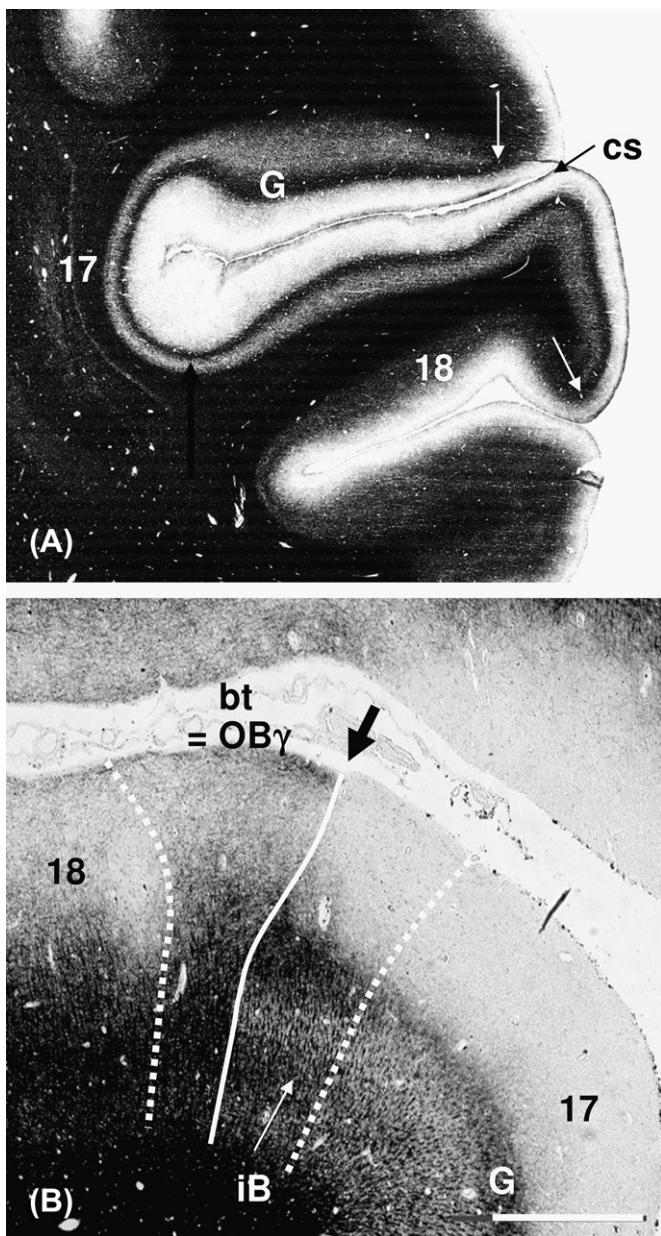


FIGURE 23.31 Myeloarchitecture of the human visual cortex at the border region between area 17 and area 18. The myeloarchitecture of area 17 is characterized by the prominent stripe of Gennari (Figure 23.31A). Figure 23.31B shows the various myeloarchitectonic changes at the border region. bt, border tuft; cs, calcarine sulcus; G, stripe of Gennari; iB, inner stripe of Baillarger; OB γ , limes parastriatusgigantopyramidalis of von Economo and Koskinas (1925). The white arrows and the large black arrow indicate the border between area 17 and area 18. Bar 1 mm.

(1932), Garey (1984), Haug (1958), Horton and Hedley-White (1984), Preuss et al. (1999), Preuss and Coleman (2002), and Zilles et al. (1986a).

The border between areas 17 and 18 is very distinct. A myelin-dense layer (stripe of Gennari) occurs only in area 17, and stops abruptly at the border between area

17 and area 18 (Figure 23.31A). At this site, layer IV of area 17 becomes considerably thinner and the subdivision of layer IV into the three sublayers IVA-C stops at the border to area 18 (Figure 23.30A). A small zone with a very light layer V is found at the beginning of area 18. The neurons in this zone are less densely packed than in the remaining part of this area. Layer IV is the broadest layer in area 17, whereas layer III is the most prominent layer in area 18. The packing density of cell bodies is generally higher in area 17 than in area 18. Thus, more space for dendrites, axons, and synapses is available in area 18 compared with area 17. The border region between areas 17 and 18 is characterized myeloarchitectonically by two small subareas (Lungwitz, 1937; Sanides and Vitzthum, 1965a, 1965b), one belongs to area 17 and the other to area 18. The “border tuft” subarea (“Grenzbüschel”) of Sanides and Vitzthum (1965a, 1965b) contains a distinct bundle of densely packed radial fibers (bt in Figure 23.31B) and belongs to area 18. Very large pyramidal cells, “giant cells”, are visible in layer III of this subarea. Thus, the border tuft subarea shows similarities to area OBy (Figure 23.31B) as described by von Economo and Koskinas (1925). It adjoins a small subarea (“Randsaum”) of Sanides and Vitzthum (1965a, 1965b), which belongs to area 17. This subarea is characterized by the appearance of the inner Baillarger stripe (iB in Figure 23.31B), which is only found in this border zone, but not in the major part of area 17. The border region of area 17 with the prominent inner stripe of Baillarger and the bt region of area 18 together are probably the architectonical correlates of the representation of the vertical meridian. This zone is the target of many callosal fibers, and bridges equivalent points of the visual field on both sides of the vertical meridian (Shoumura et al., 1975; Clarke and Miklossy, 1990; see also Chapter 37). The visualization of callosal axonal terminals provides useful anatomical criteria for the delineation of extrastriate areas, because callosal fibers are concentrated in border regions of many visual areas (Van Essen et al., 1982; Clarke and Miklossy, 1990).

Extrastriate Visual Cortex

The visual areas outside the striate area 17 are summarized as extrastriate areas. More recent anatomical and physiological observations have clearly demonstrated a higher number of extrastriate visual areas than assumed in the tripartite models of Brodmann and other earlier investigators. Kolster et al. (2010) describe 18 extrastriate areas based on the retinotopic mapping using fMRI in the human brain. The frequently used functional nomenclature of the visual cortex (subdivisions into V1, V2, V3, etc.) is introduced here, whenever the comparability between

functional and architectonical parcellations is demonstrated or highly probable.

AREA V2

Area 18 of Brodmann (1909) is the architectonical equivalent of the functionally defined cortical field V2 (Figures 23.27–23.31). It is a 1.0–3.4 cm wide cortical belt above and below V1. Its surface is 1.7 times larger than that of V1 (Tootell and Taylor, 1995). The representation of the visual field in area 18 differs from that in area 17, where adjacent loci of the visual field are also located as neighboring sites in V1. In V2, the horizontal meridian is located at the rostral border of V2; this topographical transformation leads to representation of the upper and lower quadrants of the visual field in separate, not adjacent, cortical places. Also, the normal point-to-point mapping of the visual field in the cortex is disrupted in V2 (for review, Tootell et al., 1998).

V2 is a homotypical isocortical area. Layer II and the upper part of layer III are difficult to separate. The size of the pyramidal cells of lower layer III is increased compared with V1 (Clarke, 1994b). Very large cells in deep layer III are frequently found in the border region to V1 (Figure 23.30). Layer IV of V2 is thinner than in V1, but thicker than in the other visual areas. The contrast in cell density between layers V and VI is not as distinct as in V1. The columnar arrangement of cells increases from V1 to V2 and from here to the other visual areas.

The clearly visible inner Baillarger stripe is a characteristic myeloarchitectonic sign of V2 (Clarke, 1994b). In flattened myelin-stained sections of human V2 additional and alternating dark and light stripes are visible. The respective stripes have a distance of 6–8 mm (Tootell and Taylor, 1995). The dark or light stripes of myelin-stained sections, however, are not identical with the stripes and interstripes visible in cytochrome-oxidase (COX)-stained sections (Burkhalter and Bernardo, 1989; Hockfield et al., 1990). The thick COX-stripes of area V2 show a conspicuous immunoreactivity of the antibody Cat-301 against an extracellular matrix proteoglycan (Hendry et al., 1984, 1988; Hockfield et al., 1990). This proteoglycan is indicative of the magnocellular pathway of the human visual system. It is also present in the magnocellular layers of the lateral geniculate body, layer IVA of V1 (see above), and in area V5/MT (see below).

V2 receives massive input from area 17 and has reciprocal connections with many extrastriate areas. Layers III and IV of V2 and of other extrastriate areas receive also a major input from the pulvinar. The reciprocal connections from the extrastriate visual areas to the pulvinar originate in layer V (for review see Felleman and van Essen, 1991). Cells in layer VI of area 17, V2 and further extrastriate areas give rise to a pathway descending to the lateral geniculate body.

Human V2 is activated during shape discrimination (Gulyás and Roland, 1994) by a task similar to illusory contour tasks, which reveal V2 activation in monkeys (Peterhans and von der Heydt, 1989; von der Heydt and Peterhans, 1989). V2 and other extrastriate areas (e.g., V4) are activated by color discrimination tasks (Gulyás and Roland, 1991, 1994). V2 is also active during visual recall of real objects (Le Bihan et al., 1993). Thus, V2 is not only a region of basic perception, but is also activated during the performance of complex perceptual, cognitive, and mnemonic tasks (e.g., face and word processing; Halgren et al., 1994).

AREA V3

This area is located immediately adjacent to V2 (Sereno et al., 1995; Tootell et al., 1995a) on the mesial and lateral surfaces of the occipital lobe (Figure 23.27). Initially, V3 has been identified as a cortical area containing a single, complete representation of the contralateral hemifield (Sereno et al., 1995). Dynamic form perception (Zeki, 1990a) and high-contrast selectivity (Tootell et al., 1995a) were described as further functional characteristics of V3. The precise extent and organization of V3, however, are a matter of controversies (Kaas and Lyon, 2001; Van Essen et al., 2001; Zeki, 2003; Orban et al., 2004). The arguments are based on retinotopy as an important argument in defining a distinct visual “area” (Tootell et al., 1998; Kolster et al., 2010). V3 has been conceptualized as part of a “third visual complex” with the representation of the lower visual field in its more dorsal part V3d, and with the upper visual field representation in its more ventral and posterior part VP. A representation of the entire visual field, however, was observed in a large region (ventrolateral posterior area VPL) of non-human primates, which includes VP (Rosa and Tweedale, 2000). A large dorsomedial complex DM has also been proposed, which contains V3d and adjoining regions. In this concept, DM represents the entire visual field (Lui et al., 2006). In non-human primates, other authors define the dorsal part of V3 as a separate visual area V3d (Burkhalter and Van Essen, 1986; Felleman et al., 1997; Tootell et al., 2003) and identify a ventral portion of V3 as a distinct area V3v or VP (ventroposterior area) (Figure 23.27), because both areas differ in their connectivity patterns, and VP contains more color-sensitive neurons compared with V3d. VP shows a lighter myelin staining compared with dorsal V3 (Clarke and Miklossy, 1990; Zilles and Schleicher, 1993; Clarke, 1994b). The dorsal and ventral parts of V3 also differ with respect to the laminar distribution (glutamatergic AMPA and NMDA-receptors, adrenergic α_1 and α_2 receptors, serotonergic 5HT_{1a} receptors) and density of receptor-binding sites (including GABA_A and benzodiazepine receptors for GABA and cholinergic M₁ and M₃ receptors; Eickhoff

et al., 2008). That is, the findings provided by anatomical studies support the notion of (at least) two independent areas in the V3 region. Consequently, V3d would be part of the dorsal stream (Ungerleider and Mishkin 1982; Ungerleider and Haxby, 1994) connecting V1 with the posterior parietal cortex. VP would be part of the ventral stream connecting to the inferotemporal cortex. Rostrally to V3d an area V3A has been identified, which does not immediately adjoin V2. V3d together with V3A are activated during processing of global motion (Brad-dick et al., 2001). The V3a complex has been defined based on studies of retinotopic mapping, and consists of four components (V3A, V3B, V3C, V3D), whereby the latter two abut V7 (Georgieva et al., 2009). The cytoarchitectonic correlates of these areas, however, have not yet been identified. Recent cytoarchitectonic studies showed that two extrastriate areas, hOc3v and hOc4v, are ventrally adjacent to area 18 (V2) (Rottschy et al., 2008), which seem to correspond to functionally defined areas VP and V4v (Wilms et al., 2010).

Although it is problematic to compare the schematic drawings of classical cytoarchitectonic maps with 3-D functional imaging data, area V3 is topographically best comparable with the major part of the parvocellular posterior peristriate area OA₁ of von Economo and Koskinas (1925). OA₁ shows a very small layer I. Layers II and III are difficult to separate, and layers III and V contain small pyramidal cells. Layer VI consists of particularly coarse cell columns. Nevertheless, the cyto- and myeloarchitectonical identification of the V2/V3 border by pure visual inspection is very difficult because of the high degree of microstructural similarity between both areas (Clarke, 1994b). Only recently, quantitative cyto- and receptorarchitectonical criteria enabled the observer-independent definition of this border (Amunts et al., 2000b; Eickhoff et al., 2007b, 2008).

A model of the organization of the V3 complex based on the regional distribution of neurotransmitter receptors is proposed here, in which the undisputed hierarchical difference between V2 and V3 is augmented by a distinction between the dorsal and ventral parts of these areas, that is, their upper and lower visual field representations. This dorsoventral asymmetry is then continued within the presumed upper and lower field representations of the subsequent areas V3A and V4.

AREA VP

Human area VP is bordered posteriorly by V2 and dorsally by V3d on the lateral hemispheric surface, and medially by V2 on the mesial surface (Figure 23.27). VP has been tentatively delineated by cyto- and myeloarchitectonic features (Clarke and Miklossy, 1990; Zilles and Schleicher, 1993). It lacks large pyramidal neurons in both layers III and V, whereas adjacent V2 has large pyramids in layer III and adjacent area V4

in III and V. VP is weakly myelinated, and both striae of Baillarger are absent. It differs also by its light COX staining from the adjacent, darkly stained areas V2 and V4 (Clarke, 1994a). Quantitative receptorarchitectonical criteria enabled recently the identification of VP/V3v (Eickhoff et al., 2008).

Human areas VP/V3v and V4 appear to be interconnected with the inferior part of medial pulvinar, while V5/MT is interconnected with the lateral pulvinar (see Table 6 in Zilles and Clarke, 1997).

AREA V3A

Human area V3A extends consistently below and above the lateral occipital sulcus (Tootell et al., 1997) on the mesial and lateral hemispheric surface (Figure 23.27). V3A adjoins the extrastriate visual areas V7 and LO rostrally, and area V3d posteriorly (Van Essen 2002). The borders of V3A, as determined by retinotopic mapping, show a considerable inter-subject variability and cannot be reliably correlated with macroscopical landmarks. Sufficiently detailed cytoarchitectonical descriptions of this area are presently not available, but a recent receptorarchitectonical study (Eickhoff et al., 2008) could demonstrate the border between V3d and the rostrally adjoining area V3A.

AREA V4

The cortex of the lingual and fusiform gyri seems to play an important role in color perception, since lesions of this region cause achromatopsia (Meadows, 1974; Damasio et al., 1980; Rizzo et al., 1992; for review Zeki, 1990b), and functional imaging as well as electrophysiological observations demonstrate activation by color (Lueck et al., 1989; Corbetta et al., 1991; Zeki et al., 1991; Gulyás and Roland, 1991, 1994; Allison et al., 1993; Sakai et al., 1995; Sereno et al., 1995) and shape (Corbetta et al., 1991). Thus, this region has been suggested to be the human correlate of the monkey V4, which is populated by color-, space-, and shape-responsive neurons (Desimone and Schein, 1987; Desimone and Ungerleider, 1989; Zeki, 1990b; Schiller and Lee, 1991; Heywood et al., 1992; Walsh et al., 1993; De Yoe et al., 1994). Presently, however, it is controversially discussed whether this human V4 in the fusiform gyrus represents the equivalent of the monkey V4 (Meadows, 1974; Walsh et al., 1993; Zeki, 1993; Ungerleider and Haxby, 1994; Heywood et al., 1995).

The putative human V4 is located on the posterior part of the fusiform gyrus and abuts the rostral border of the putative human VP (Sereno et al., 1995). The position and extent as well as the architecture of the area peristriata magnopyramidalis of Braak (1977) make this pigmentoarchitectonically well-defined cortical region to a candidate for human V4. V4 contains large

pyramidal cells in layers III and V, and shows an intense COX staining. Both criteria allow a delineation of this area from VP (Clarke, 1994a). The myelin density is well above average in human and monkey V4 (Zilles and Clarke, 1997).

A ventral area V4v – separable from V4 – has been identified by using fMRI (Sereno et al., 1995) or fMRI in combination with cytoarchitectonic maps (Wilms et al., 2010). This area adjoins the ventral half of the anterior border of VP (Figure 23.27). This border represents the vertical meridian, whereas the horizontal meridian is found at the anterior border of V4v. Human V4v contains the upper visual field as in monkeys with a non-mirror image representation of the visual field.

AREA V5/MT

For the first time, area V5/MT was identified by functional and anatomical studies in the superior temporal sulcus of non-human primates (Allman and Kaas, 1971; Zeki, 1974, 1980; Van Essen et al., 1981; Maunsell and Van Essen, 1983, 1987; Albright, 1984; Fiorani et al., 1989; Born and Tootell, 1992).

PET and fMRI studies demonstrated a comparable area in the human brain activated by moving visual stimuli and during visual motion aftereffects (Corbetta et al., 1990, 1991; Zeki et al., 1991, 1993; Watson et al., 1993; Dupont et al., 1994; Cheng et al., 1995; Tootell et al., 1995a, 1995b). This area is located close to the level of the AC-PC line and posterior to the contact of the ascending limb of the inferior temporal sulcus with the lateral occipital sulcus (Watson et al., 1993). Kolster et al. (2010) localized the human MT/V5 which is found in a region between the lateral, anterior, and inferior occipital sulci. In parallel with monkey data, a retinotopic organization of human V5/MT was reported (Huk et al., 2002; Georgieva et al., 2009; Kolster et al., 2010). An even more characteristic feature of V5/MT in the monkey is the direction specificity, i.e. preference for one direction of moving visual stimuli (Zeki, 1974; Van Essen et al., 1981). This property was recently demonstrated by functional imaging (Heeger et al., 1999; Huk and Heeger, 2002) and focal electrical stimulation also for the human V5/MT area (Blanke et al., 2002).

The putative anatomical correlate of human V5/MT is a relatively small, heavily myelinated area (Clarke and Miklossy, 1990; DeYoe et al., 1990, 1994; Tootell and Taylor, 1995). No comparable cortical area is found in the cytoarchitectonic maps of Brodmann (1909) and Sarkisov et al. (1955), but recently a cytoarchitectonic probability map of human V5 was published and successfully compared with functional data from fMRI and MEG experiments (Wilms et al., 2005; Barnikol et al., 2006; Malikovic et al., 2007). Von Economo and Koskinas (1925) show a lateral area OAm (Figure 23.37),

which has a position approximately comparable with that of V5/MT, but the schematic presentation of their maps does not allow a direct comparison with functional imaging data. Flechsig's area 16 (subangular gyrus; Flechsig, 1920; Figure 23.36), however, was proposed to be a good candidate for V5/MT (Watson et al., 1993), since it is not only found in a location (Clarke, 1994a; Tootell and Taylor, 1995) comparable to the functional site, but was also described as a heavily myelinated area (Flechsig, 1920). Destruction of this area leads to akinetopsia, i.e. visual motion blindness where a patient is not able to recognize moving stimuli in his visual field, although other functions of the visual system are completely intact (Zeki, 1991; Zihl et al., 1991; Mesulam et al., 1994).

Although human V5/MT receives a major input from layer IVB of V1 and from V2 (Felleman and Van Essen, 1991), human V5/MT is activated by moving bar also in a completely hemianopic patient with a lesion in area V1 (Barbur et al., 1993). The patient was consciously aware of the nature and direction of the stimulus. Thus, the input to V5/MT may bypass V1, and arrive directly from the lateral geniculate body (Benevento and Yoshida, 1981; Fries, 1981; Yukie and Iwai, 1981) and/or indirectly via the superior colliculus and the pulvinar (Benevento and Fallon, 1975; Keating, 1980; Pasik and Pasik, 1982; Standage and Benevento, 1983). Direct evidence for a component of directional motion discrimination bypassing human V1 comes from transcranial magnetic stimulation of V1 and V5/MT (Beckers and Zeki, 1995). The inactivation of V5/MT abolishes the motion perception and causes akinetopsia, whereas V1 inactivation had only marginal effects.

Insular Lobe

The insular cortex of the adult human brain is buried in the depth of the lateral fissure and covered by the frontal and parietal opercula as well as the temporal lobe. Its outer borders are demarcated by the circular sulcus of Reil. Its superior limiting segment defines the border to the frontoparietal operculum, and its inferior limiting segment is the border to the supratemporal plane of the superior temporal gyrus (Figure 23.32). The surface of the insula is subdivided by a central sulcus, which separates a posterior from an anterior part. The central sulcus does not precisely coincide with the cytoarchitectonical subdivision into granular and agranular cortex, but runs through the dysgranular part of the insula.

The anterior part is interconnected with the amygdala and the ventromedial thalamic nucleus. The posterior part of the insula is reciprocally connected with the cortical areas of the parietal operculum, particularly

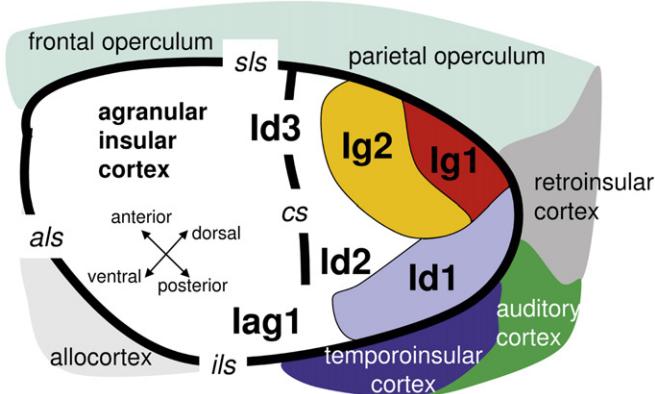


FIGURE 23.32 Schematic drawing of the principal organization of the human insular cortex. als, anterior limiting sulcus; cs, central sulcus; ils, inferior limiting sulcus; lag1, insular agranular area; Id1, insular dysgranular area 1; Id2, insular dysgranular area 2; Id3, insular dysgranular area 3; Ig1, insular granular area 1; Ig2, insular granular area 2; sls, superior limiting sulcus.

with the secondary somatosensory cortex, and with the ventral posterior inferior nucleus of the thalamus.

Mesulam and Mufson (1985) described a radial organization of the insular cortex which surrounds the posterior part of the allocortical (pre)piriform cortex by three belt regions.

The first belt consists of an agranular region characterized by a superficial pyramidal cell layer and an inner cell layer. The inner granular layer IV is completely

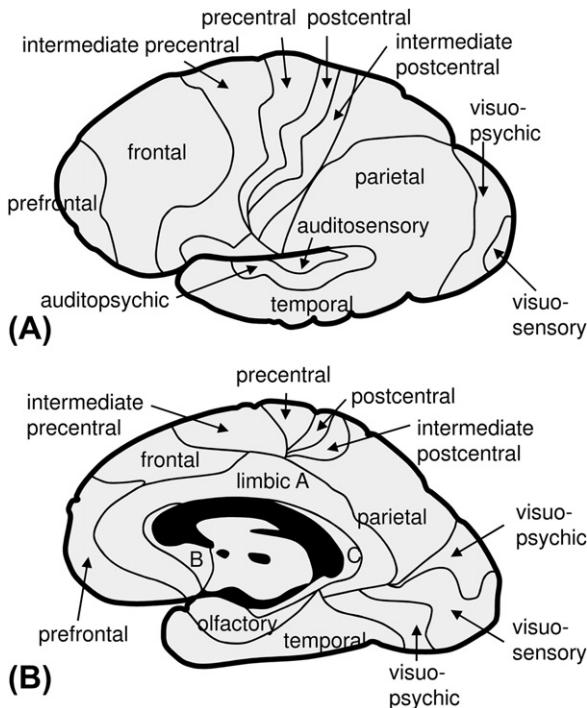


FIGURE 23.33 Areal map of the human cerebral cortex in (A) lateral and (B) medial views after Campbell (1905). For comparisons with other cortical maps, see Tables 23.4 and 7.

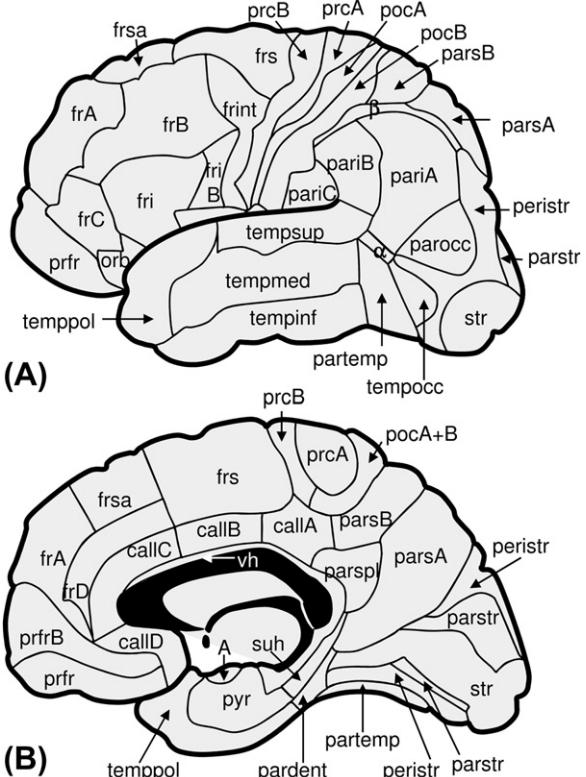


FIGURE 23.34 Areal map of the human cerebral cortex in (A) lateral and (B) medial views after Smith (1907). A, amygdala; α , visuo-auditory band (probably area V5 of present functional nomenclature); β , visuo-sensory band; callA, area callosa A; callB, area callosa B; callC, area callosa C; callD, area callosa D; frA, area frontalis A; frB, area frontalis B; frC, area frontalis C; frD, area frontalis D; frs, area frontalis superior; frsa, area frontalis superior anterior; fri, area frontalis inferior; fri B, area frontalis inferior posterior; frint, area frontalis intermedia; orb, area orbitalis; pardent, area paradentata; pariA, area parietalis inferior A; pariB, area parietalis inferior B; pariC, area parasylvia; parsA, area parietalis superior posterior; parsB, area parietalis superior anterior; parspl, area parasplenialis; parstr, area parastriata; partemp, area paratemporalis; peristr, area peristriata; pocA, area postcentralis A; pocB, area postcentralis B; prcA, area praecentralis A; prcB, area praecentralis B; prfr, area praefrontalis; prfrB, area praefrontalis B; pyr, area pyriformis; str, area striata; suh, subiculum hippocampi; tempol, area temporopolaris; tempinf, area temporalis inferior; tempmed, area temporalis media; tempocc, area temporo-occipitalis; tempsup, area temporalis superior; vh, vestigia hippocampi (hippocampus supracommissuralis). For comparisons with other cortical maps, see Tables 23.4, 6 and 7.

lacking, layer II is difficult to identify. The anterior insula of both sides plays a key role when human self-awareness is experienced (Craig, 2009, 2010).

The second belt is a dysgranular region, characterized by the presence of an inconspicuous inner granular layer IV. Layers V and VI are also not clearly demarcated. The dysgranular region has common borders with the orbitofrontal and temporopolar regions, and can be subdivided into several cytoarchitectonical areas (Kurth et al., 2010a, 2010b; Figure 23.32). The transition

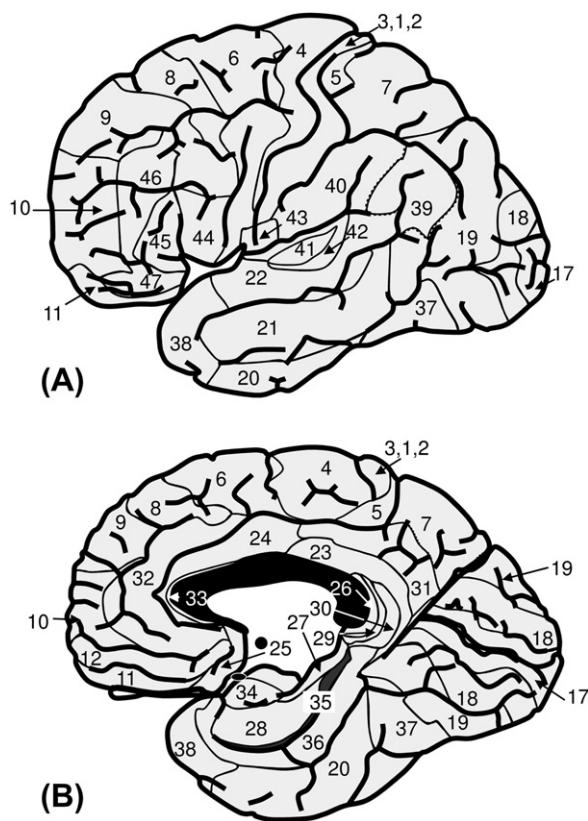


FIGURE 23.35 Areal map of the human cerebral cortex in (A) lateral and (B) medial views after Brodmann (1909, 1910, 1912, 1914). 1, area postcentralisintermedia; 2, area postcentraliscaudalis; 3, area postcentralisrostral; 4, area gigantopyramidalis; 5, area praeparietalis; 6, area frontalisagranularis; 7, area parietalis superior; 8, area frontalisintermedia; 9, area frontalisgranularis; 10, area frontopolaris; 11, area praefrontalis; 12, not explained by Brodmann; 17, area striata; 18, area occipitalis; 19, area praeoccipitalis; 20, area temporalis inferior; 21, area temporalis media; 22, area temporalis superior; 23, area cingularis posterior ventralis; 24, area cingularis anterior ventralis; 25, area subgenualis; 26, area ectosplenialis; 27, area praesubcircularis; 28, area entorhinalis; 29, area retrolimbica (retrosplenialis) granularis; 30, area retrolimbica (retrosplenialis) agranularis; 31, area cingularis posterior dorsalis; 32, area cingularis anterior dorsalis; 33, area praegenualis; 34, area entorhinalisdorsalis; 35, area perirhinalis; 36, area ectorhinalis; 37, area occipitotemporalis; 38, area temporopolaris; 39, area angularis; 40, area supramarginalis; 41, area temporalis transversamedialis; 42, area temporalis transversalateralis; 43, area subcentralis; 44, area opercularis; 45, area triangularis; 46, area frontalis media; 47, area orbitalis; 52, area parainsularis. For comparisons with other cortical maps, see Tables 23.3–23.7.

between the agranular and dysgranular insular cortex in the caudal-most part of the dorsal insula, reacts not only to pure taste stimuli but also to other intra-oral stimuli. It likely plays a role in taste and flavor perception as well as in feeding regulation (Small, 2010).

The outermost and most posterior belt is a granular region with clearly visible inner (layer IV) and outer (layer II) granular layers, a differentiation of layer III into sublayers, and a clear demarcation of layer V from layer VI. The granular belt shows also the highest degree

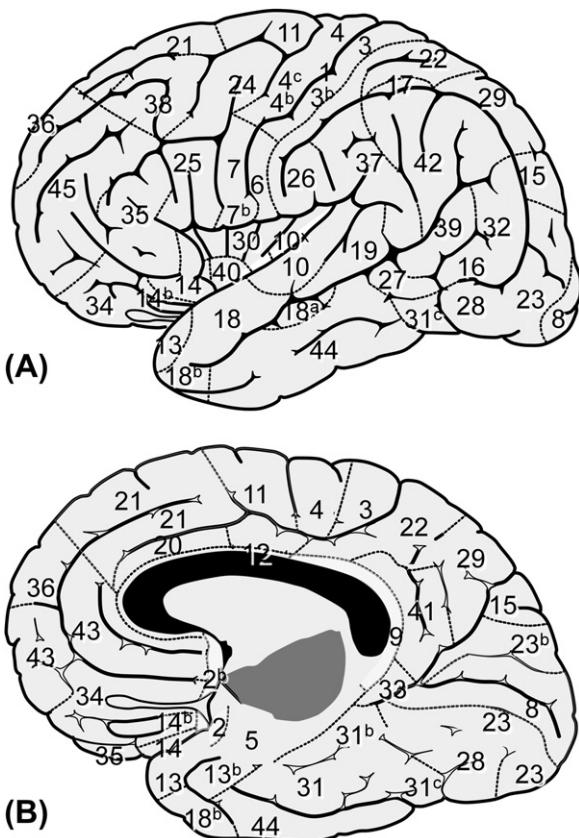


FIGURE 23.36 Areal map of the myelogenetic areas after Flechsig (1920) in the human cerebral cortex (A, lateral; B, medial view). The numbers of the areas describe the sequence of myelination during fetal and early postnatal stages. The cortical regions with first signs of myelination before birth are Flechsig's primordial areas (areas 1–16), between birth and the end of the 6th postnatal week are his intermediate areas (17–28), and after the beginning of the second postnatal month are his terminal ("association") areas (29–45). For comparisons with other cortical maps, see Tables 23.5 and 23.7.

of myelination of all insular regions with a clearly visible outer stripe of Baillarger. The granular part can be subdivided into two cytoarchitectonic areas Ig1 and Ig2 (Kurth et al., 2010a, 2010b).

The dorsal posterior insula contains the primary cortical sensory representation of temperature and pain in humans (Craig et al., 2000; Garcia-Larrea et al., 2010). Probably, this region resembles the cytoarchitectonic area Ig1 (Kurth et al., 2010a, 2010b).

CORTICAL MAPS OF THE HUMAN BRAIN: PAST, PRESENT, FUTURE

Numerous cyto- and myeloarchitectonic studies have been performed during the first half of the 20th century (Brodmann, 1903a, 1903b, 1905, 1908, 1909, 1910, 1912, 1914; Campbell, 1905; Smith, 1907; O. Vogt, 1910, 1911; C. Vogt and O. Vogt, 1919, 1926, 1956; Flechsig, 1920;

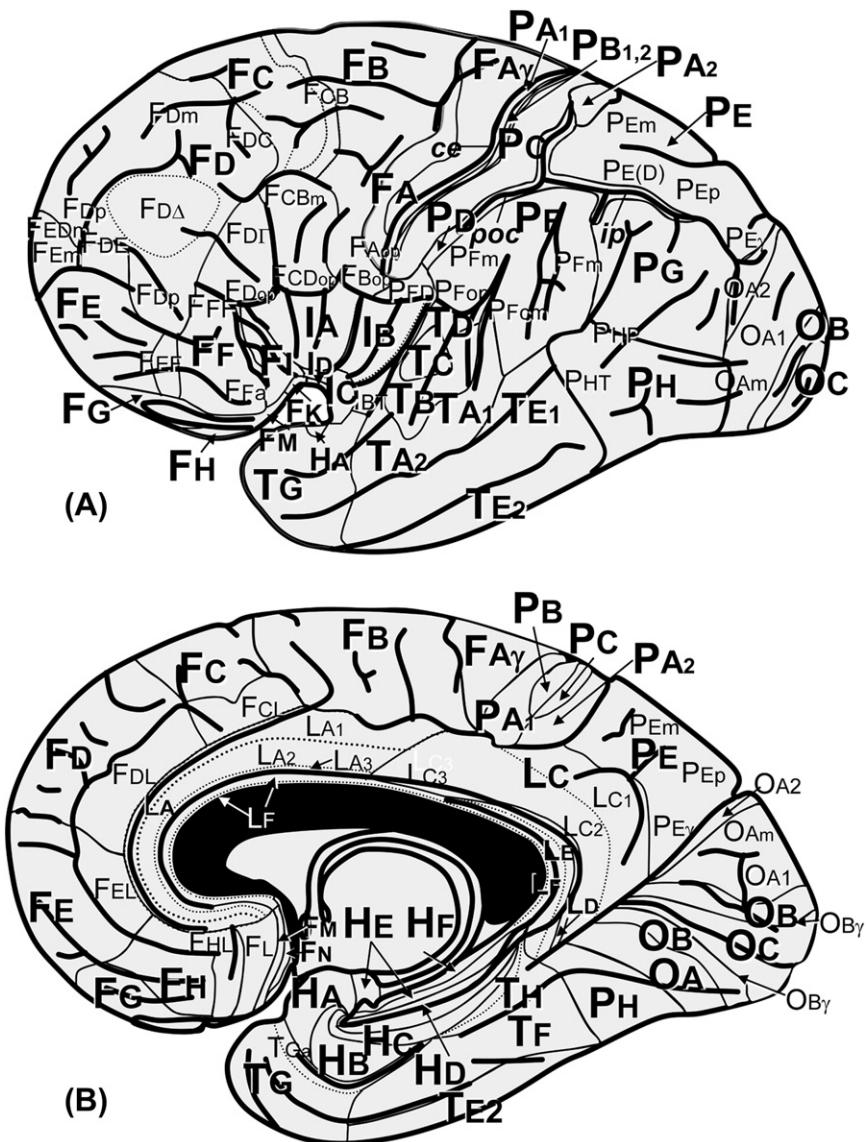
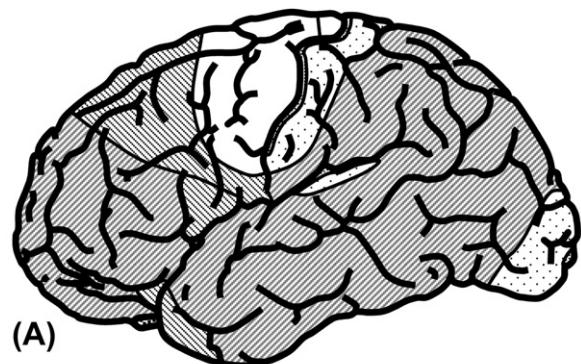


FIGURE 23.37 Areal map of the human cerebral cortex in (A) lateral and (B) medial views after von Economo and Koskinas (1925). For comparisons with other cortical maps, see Tables 23.3–23.7.

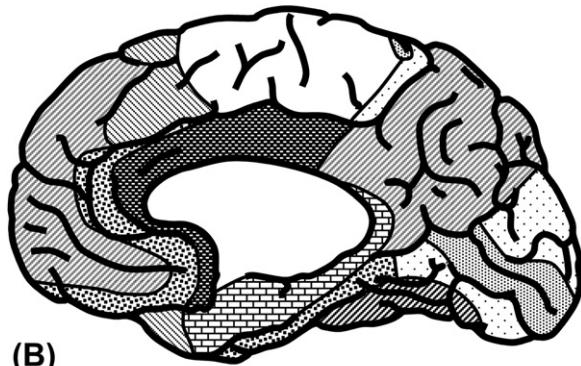
von Economo and Koskinas, 1925; Rose, 1926, 1927, 1928, 1929; Beck, 1928, 1930; Stengel, 1930; von Economo and Horn, 1930; Riegele, 1931; Filimonoff, 1932, 1947; Ngowyang, 1932, 1934; Kreht, 1936; Lungwitz, 1937; Strasburger, 1937, 1938; Brockhaus, 1940; Gerhardt, 1940; Bailey and von Bonin 1951; Hopf, 1954, 1955, 1956; Sarkissov et al., 1955; Batsch, 1956). The common goal of all these studies was the generation of a detailed and reliable map of the human cerebral cortex, which represents its regional inhomogeneity in cyto- and/or myeloarchitecture and its segregation into numerous structural and functional areas.

After more than 100 years of research, however, the architectonical parcellation of the human cerebral cortex is still not finished but a work is in progress (Zilles and Amunts, 2010). This statement is supported by a comparison between the classical maps, e.g. published by Bailey

and von Bonin (1951), Brodmann (1909), Campbell (1905), Flechsig (1920), Sarkissov et al. (1955), Smith (1907), and von Economo and Koskinas (1925), which shows a sufficiently comparable areal pattern only in some cortical regions, while the delineations differ markedly in other regions (Figures 23.33–23.39). The reasons for this sometimes considerable disagreement between different observers are found in the morphological complexity of the human cerebral cortex, the architectonical similarity of numerous isocortical areas, particularly in the multimodal association regions, the interindividual variability of architectonic features (none of these maps is based on a larger sample or defines the range of variability between different individuals), the relatively simple methodical approach based on pure visual inspection of only Nissl- or myelin-stained sections, and the strong influence of the



(A)



(B)

	homotypical
	koniocortical
	parakoniocortical
	dysgranular
	agranular
	mesocortex
	juxtaallocortex
	allocortex

FIGURE 23.38 Areal map of the human cortex in (A) lateral and (B) medial views after Bailey and von Bonin (1951). For comparisons with other cortical maps, see Tables 23.4 and 23.7.

observer's criteria on delineations and definitions of areas. None of these objections denies that the classical maps, particularly Brodmann's and von Economo's and Koskinas' maps represent pioneering work; however, the above-listed problems can only be solved if a novel approach to architectonics is introduced which uses various staining techniques as well as objective, observer-independent, and quantitative image analysis procedures and statistically testable criteria (Zilles et al., 1982, 1986a, 1986b, 1995, 2002; Schleicher et al., 1999, 2005; Amunts and Zilles, 2001; Amunts et al., 2002; Toga et al., 2006; Zilles and Amunts, 2010).

Furthermore, all the classical studies do not allow a direct comparison with 3-D data sets of functional imaging studies, which is a great obstacle for establishing architectonical/functional correlations. Therefore, an important aspect of present and future architectonic studies is the comparability of the microstructural data and areal borders with the results of functional imaging studies in the same spatial reference system (Rademacher et al., 1993, 2001a, 2001b, 2001c; Geyer et al.,

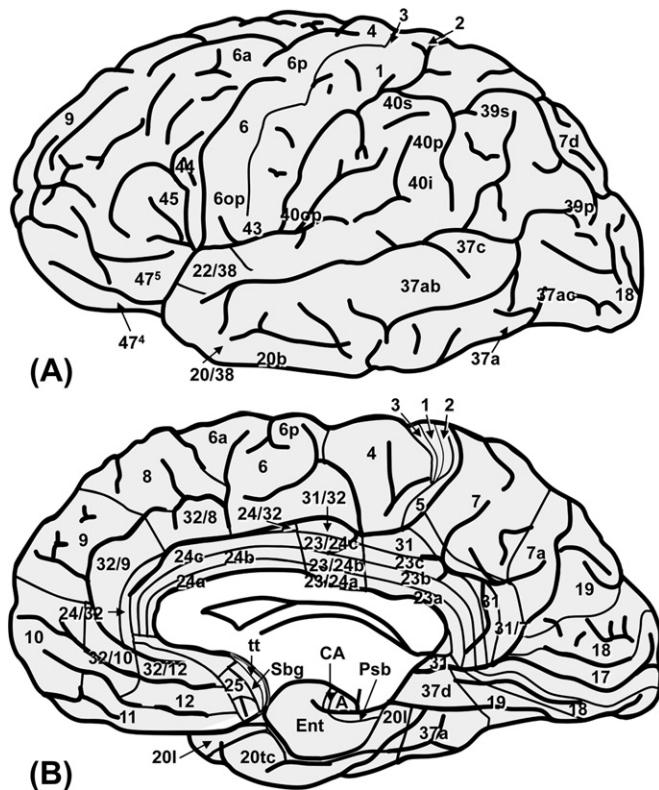


FIGURE 23.39 Areal map of the human cortex in (A) lateral and (B) medial views after Sarkissov et al. (1955). The nomenclature follows Brodmann's scheme (see legend of Figure 23.35), and introduces self-explaining symbols for subparcellations and transition zones. A, amygdala; CA, Ammon's horn; Ent, entorhinal area; Psb, presubiculum area; Sbg, subgenual area; tt, taeniae (precommissural hippocampus). For comparisons with other cortical maps, see Tables 23.4 and 23.7.

1996, 1999, 2000b; Zilles et al., 1997, 2001, 2002; Amunts et al., 1999, 2000b, 2002, 2007; Amunts and Zilles, 2001; Grefkes et al., 2001; Mazziotta et al., 2001a, 2001b; Morosan et al., 2001; Eickhoff et al., 2005, 2007c; Zilles and Amunts, 2009). Since the interindividual variability of the architectonical organization is a challenge for correlations of structure and function, the novel concept of probabilistic maps has been introduced (Roland and Zilles, 1994, 1996a, 1996b, 1998; Roland et al., 1997; Amunts et al., 2000b). Probabilistic brain mapping has meanwhile developed into a multi-site international effort (Mazziotta et al., 2001a, 2001b; Toga et al., 2006).

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