Stefan Geyer
Robert Turner *Editors*

# Microstructural Parcellation of the Human Cerebral Cortex

## From Brodmann's Post-Mortem Map to in Vivo Mapping with High-Field Magnetic Resonance Imaging

Springer

# Microstructural Parcellation of the Human Cerebral Cortex

Stefan Geyer • Robert Turner
Editors

# Microstructural Parcellation of the Human Cerebral Cortex

## From Brodmann's Post-Mortem Map to in Vivo Mapping with High-Field Magnetic Resonance Imaging

Springer

*Editors*
Stefan Geyer
Robert Turner
Department of Neurophysics
Max Planck Institute for Human Cognitive and Brain Sciences
Leipzig, Germany

ISBN 978-3-642-37823-2 ISBN 978-3-642-37824-9 (eBook)
DOI 10.1007/978-3-642-37824-9
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013941360



Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

# Preface

A fundamental goal of brain research is to elucidate the functional properties of the structural elements of the brain, at an appropriate organizational scale. One major scientific milestone in this regard was the publication of Korbinian Brodmann's famous map of the cerebral cortex in 1909. This map defines around 40 structural areas in the human cortex based on differences in cytoarchitecture (i.e., size, shape, and topographic arrangement of nerve cells). Subsequent investigators found out that these areas, defined purely anatomically by Brodmann, also correspond to functional entities of the cerebral cortex, so that, for example, Brodmann's area (BA) 4 corresponds to primary motor cortex (M1), and BA 17 to primary visual cortex (V1). Since its publication, Brodmann's map has become a "classic" in the field of neurobiology, and, despite many advances in neuroscience, his nomenclature of cortical areas is still widely used to designate functional regions. Two key problems intrinsic to this mapping strategy, however, are that cytoarchitectonic parcellation requires microscopic analysis of postmortem brain sections and cytoarchitectonic areas vary between individuals in their topography relative to the gyral anatomy of the brain. This means that correlations between microstructure (based on cytoarchitectonic analysis in postmortem brains) and function (based on, e.g., functional magnetic resonance imaging (fMRI) in living brains) have almost always been made probabilistically, with the aid of a computerized brain atlas.

It would be a revolutionary scientific breakthrough if it were possible to map the microstructural correlates of functional activations in the human cortex in a noninvasive and individual-specific way directly in vivo. However, until now, microstructural details of the cerebral cortex have been beyond the resolution of conventional structural MRI, except within the primary visual cortex, where the very prominent Stria of Gennari can relatively easily be detected at the MRI field strength of 3 T. Recently, however, high-field MRI, at a field strength of 7 T and spatial resolution below 0.5 mm, has radically changed this situation by detecting further systematic structural differences within the cerebral cortex. For instance, use of 7 T MRI can resolve the functionally important microanatomical border between primary motor (area 4) and somatosensory (area 3a) cortex in vivo. This opens up the door toward an individual-specific microanatomical brain map with

the enormous potential to make direct correlations between microstructure and function in living human brains.

This brief outline spans an entire century from the publication of Brodmann's postmortem map at the beginning of the twentieth to "in vivo Brodmann mapping" with high-field MRI at the beginning of the twenty-first century. In our book, however, we would like to shed some light also on a few milestones of structural brain mapping that lie between these two "cornerstones". For this reason, the book is divided into three parts.

Part I starts with the world of "classical" cytoarchitectonic brain maps, published in the first half of the twentieth century: the famous parcellation of Korbinian Brodmann (chapter by Guy Elston and Laurence Garey) and the much lesser known map of Constantin von Economo and Georg Koskinas (chapter by Lazaros Triarhou). In contrast to Brodmann, von Economo and Koskinas provide a much more detailed verbal and pictorial description of each area's cytoarchitectonic features. We also bring back to life the almost forgotten myeloarchitectonic map (based on differences in the arrangement of myelinated fibers in preparations stained for myelin sheaths) by Cécile and Oskar Vogt (chapter by Rudolf Nieuwenhuys). Mapping the cortex with high-field MRI shows a renewed interest in myeloarchitecture, since many types of MR image contrast depend on the presence of myelin within the image voxel.

Part II covers more recent approaches that aim at mapping cortical areas noninvasively in living human brains. Bruce Fischl and colleagues use cortical folding patterns to estimate the topography of Brodmann areas in individual brains. Simon Eickhoff and Danilo Bzdok identify functional modules in the cortex in a data-driven fashion by clustering together voxels with similar co-activation patterns and separating them from voxels with different co-activation profiles.

In Part III, we arrive at the second "cornerstone," namely, "in vivo Brodmann mapping" with high-field MRI. The two chapters by Robert Turner argue for the necessity of more realistic functional and structural analysis methods that more effectively exploit the great potential inherent in high-field MRI and, together, should lead to a new understanding of the relationships between structure, function, and connectivity in the living brain. The second chapter also focuses on a discussion about the microstructural origin of the high-field MRI contrast in the cortex. Does it originate from regional variations in the arrangement of cells (cytoarchitecture) or myelin sheaths (myeloarchitecture)? Evidence is provided that the latter (i.e., myelin) is the case. This leads us to the chapter by Nicholas Bock and Afonso Silva on visualizing myeloarchitecture with MRI in the cortex of living marmoset monkeys (*Callithrix jacchus*). We conclude with the first breakthrough in high-field MR mapping in the living human brain (chapter by Stefan Geyer): the detection of the functionally important border between primary motor (area 4) and somatosensory (area 3a) cortex.

January 2013 Stefan Geyer
Leipzig, Germany Robert Turner

# Contents

# Part I
# "Classical" Cyto- and Myeloarchitectonic Human Brain Maps

# Chapter 1
# The Cytoarchitectonic Map of Korbinian Brodmann: Arealisation and Circuit Specialisation

**Guy N. Elston and Laurence J. Garey**

**Abstract** Korbinian Brodmann is best known for his 1909 monograph on comparative localisation of cerebral cortex in a variety of mammals, including man. His "areas" are still widely used to delineate cortical functional regions. He identified "homologous" parts of the cortex in different animals by their structure and produced an "organic" theory of cortex based on anatomical features. He formalised the description of the cortical pattern as being composed of six basic layers, with variations between animals and between areas. He integrated phylogenesis and ontogenesis with observations of adult cortical structure, function and pathology. Later, Brodmann turned to a systematic study of human brains of different races, culminating to a paper on "anthropological" aspects of cortical anatomy in 1913. His work over his short lifetime is a rich source of quantitative information and is of importance for the interpretation of modern imaging studies, particularly involving visual or prefrontal cortex, and the search for a neuroanatomical basis for human consciousness and intelligence. With the advent of new methodologies it has been possible to probe neuron structure at the microscopic level in Brodmann's cortical areas, teasing out and quantifying elements of circuit structure and specialisation. The study of pyramidal cells, the most abundant neuronal type in cortex, has revealed significant and systematic differences in structure and integrative ability among cortical areas, which reflect the physiological characteristics of the neurons and functional complexity. Moreover, comparison of pyramidal cell structure in homologous cortical areas among species reveals different trends among different cortical areas. Pyramidal cell structure in Brodmann's area 17, for example, varies relatively little among primate species whereas pyramidal cells in granular prefrontal cortex are larger, more branched and

G.N. Elston (✉)
Centre for Cognitive Neuroscience, 4562 Sunshine Coast, QLD, Australia
e-mail: guyelston@yahoo.com

L.J. Garey
CH-1166 Perroy, Switzerland
e-mail: l.garey@sunrise.ch

S. Geyer and R. Turner (eds.), *Microstructural Parcellation of the Human Cerebral Cortex*, DOI 10.1007/978-3-642-37824-9_1, © Springer-Verlag Berlin Heidelberg 2013

more spinous in progressively larger prefrontal cortices. Pyramidal cells in prefrontal cortex in man, that region associated with higher cognitive functions, are more complex and integrate more inputs than lower order primates, bridging Brodmann's theories in prefrontal cortex and Cajal's theories on the psychic cell in present day thinking on intelligence.

## 1.1 Korbinian Brodmann: Life and Works

In 1909 Korbinian Brodmann published his "Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues", destined to become a major classic of the neurological world. It still forms the basis for localisation of function in the cerebral cortex. His "areas" are widely used to delineate cortical functional regions by neurologists and experimentalists in various animals (see Garey 1994 for a translation of Brodmann's original monograph).

Brodmann was born in 1868 in Liggersdorf, Hohenzollern and studied medicine, qualifying in 1895. After working with Oskar Vogt in 1896 in the Neurological Clinic in Alexanderbad he turned to neurology and psychiatry, and later studied pathology in Leipzig where, in 1898, he wrote a doctoral thesis on chronic ependymal sclerosis. He then went to the University Psychiatric Clinic in Jena, directed by Otto Binswanger, before transferring to the Municipal Mental Asylum in Frankfurt-am-Main from 1900 to 1901, where he met Alois Alzheimer who inspired an interest in neuroanatomy. In 1901 Brodmann rejoined Vogt and worked with him in Berlin where he began his famous studies on cytoarchitectonics of mammalian cortex, (Brodmann 1903a,b, 1905a,b, 1906, 1908a,b) in the "Journal für Psychologie und Neurologie", and which served as a basis for his 1909 monograph on comparative cortical localisation. In 1910 he moved to Tübingen and was appointed Professor in the Faculty of Medicine. While in Berlin Brodmann had lectured in courses in Munich organised by Emil Kraepelin who forecast an important contribution to neuroanatomical research from architectonics. In 1918 Brodmann received a prestigious appointment to the Psychiatric Research Institute in Munich, where Nissl was working. So he and Nissl began a very promising collaboration, cut short by Brodmann's early death less than a year later.

Before Brodmann, more than a little confusion reigned concerning the structure of the cerebral cortex. In 1858, Theodor Meynert's pupil, Berlin, described six layers in the human isocortex on the basis of variations in cell size and type, including pyramidal and granule cells. Meynert himself, from 1867, subdivided the human cortex into various functional regions. Another important early cortical localisational study was by Vladimir Betz in 1874, in which he described "giant pyramids", in the human motor cortex. In 1878 David Ferrier devoted his Croonian Lecture to cerebral localisation, and before the end of the nineteenth century numerous publications dealt with the laminar pattern of the cerebral cortex, notably by Lewis (1878, 1881), Lewis and Clarke (1878) and Hammarberg (1895). In his monograph of 1909 Brodmann considered these in detail, and pointed out their inconsistencies.

The year 1900 saw the first in the series Ramon y Cajal's studies on human cortex (Cajal 1900–1906), as well as Bolton's treatise on human visual cortex. Brodmann had little respect for Cajal's "erroneous" views on cortical lamination. Grafton Elliot Smith published a detailed atlas of human cortical localisation in 1907, referring to the work of Flechsig, Campbell and Brodmann. In 1905 Alfred Campbell's work on "Histological studies on the localisation of cerebral function" appeared based on human cerebral hemispheres, and those of chimpanzee, orang-utan, cat, dog and pig. In 1953 Constantin von Bonin commented that Campbell's localisation was not as "fine as those of the German school", referring especially to Brodmann's work.

The basis of Brodmann's localisation is the subdivision of the cortex into "areas" with similar cellular and laminar structure. He compared the human cortex with that of several other mammals, including primates, rodents and marsupials. Brodmann's observations integrated concepts of phylogenesis and ontogenesis with his observations of adult cortical structure, function and even pathology. Important support for Brodmann's concepts of functional localisation came from Otfried Foerster's electrical stimulation of human cortex in 1926, work based on Brodmann's structural studies.

Later, Brodmann continued his comparative studies, but his attention turned more toward a systematic study of human brains of different races, culminating in his paper on "anthropological" aspects of cortical anatomy (1913, translated by Elston and Garey 2004). He was not biased in his studies by the prevailing attitude that some human races were "superior" to others. As he states in his text, his motivation was scientific, without ulterior motives. Indeed, Brodmann not only presented data on the cortex of different human races, but also new data from the brains of patients suffering from pathology such as microcephaly, epilepsy, blindness and idiocy. He also presented a wealth of data on granular prefrontal cortex, agranular precentral motor cortex and the primary visual area from a diverse range of primates and non-primates. This paper is a rich source of quantitative information and emphasises the variation in cortical topography in human brains, and is of importance for the interpretation of modern imaging studies, particularly involving visual or prefrontal cortex, and the search for a neuroanatomical basis for human consciousness and intelligence (Sengpiel and Kind 2002; Schoenemann et al. 2005; Elston and Garey 2009).

### *1.1.1 Brodmann's Aims and Results*

The subject of Brodmann's 1909 treatise was histological localisation in the cerebral cortex, related to contemporary physiological or clinical data. He set himself the task of parcellating the cortex according to common anatomical features, such as structurally similar neuronal features. His aim was to identify "homologous" parts of the cortex in different animals by their structure and produce an "organic" theory of cortex based on anatomical features. He excluded consideration of fibre architecture and myelogenesis, although admitting that they were major factors in cortical localisation. Oskar Vogt (1906) had demonstrated cortical

parcellation in man using myeloarchitectonics that was compatible, but more detailed than, Brodmann's cellular localisation. The latter accepted that it could be used to subdivide cytoarchitectonic zones into smaller fields. This was a matter of degree of spatial localisation and not a major divergence. Indeed his colleague, Mauss (1908), confirmed in monkeys an overall agreement with Brodmann's cytoarchitectonic subdivisions.

For Brodmann, cortical cytoarchitectonic localisation was of three types, **elemental** (according to histological elements), **laminar** (according to cell layers) and **topographical** (according to tangentially organised "areas").

**Elemental localisation** depended on neuronal groups of similar structure having similar functions. Brodmann admitted that so far results were not exactly encouraging: "The difficulties in achieving such a subdivision by elements are considerably greater than may appear at first sight. First and foremost we still lack clear criteria for the recognition of anatomically equivalent cellular elements." (Brodmann 1909, Introduction). He stated that perhaps the only good example at that time came from Betz (1874) that the "motor" cortex anterior to the central sulcus was typified by "giant pyramidal" neurons, unlike the "sensory" cortex posterior to the sulcus. However, different cell types (Brodmann distinguished pyramidal cells, spindle cells, granule cells, and stellate cells) were not organised similarly over the whole cortex. They varied widely between areas. He forecast that new techniques would be needed to differentiate particular neurons functionally: "It is possible that later it will be feasible to further differentiate histologically many grossly morphologically similar cell types according to their fine structure. For this, the main necessity is new histological, and particularly staining, techniques that have a specific affinity for functionally related cells or, what amounts to the same, histochemically related cells." This sounds like a plea for not only the sort of histochemistry we know today, but also electron microscopy!

Brodmann equally emphasised the limits of **laminar localisation**. He admitted that he knew little about the significance of individual layers. He returned to his previous example of the layer of Betz giant pyramids saying that their significance remained largely obscure although it must be related to motor function from pathological observations in, for example, amyotrophic lateral sclerosis. "Above all, we have absolutely no proof that this layer represents the only motor component of the cortex, comparable with a specifically sensory one in the granular layers ... Many new observations (electrical stimulation) support the idea that cortical motor activity can be produced without the intervention of this giant pyramidal layer ... Above all, it is clear that the excitomotor zone stretches anteriorly well beyond the extent of this layer". He also gave the example of the stria of Gennari in the visual cortex around the calcarine sulcus, of which the spatial extent was recognisable to the naked eye. Even though this "striate area" was associated with visual activity, or even with specific parts of the retina, Brodmann remained, as always, cautious as to what constituted the "visuosensory element" within the area.

So he concluded that neither elemental nor laminar localisation constituted the whole story. He opted for **topographical localisation** of tangential cortical "areas" of homogeneous intrinsic structure, which involved a knowledge of both their structural elements and their lamination, that is to say their cytoarchitectonics.

### 1.1.2 The Basic Laminar Pattern of the Cerebral Cortex

Brodmann expressed his surprise at the variation in the number of cortical layers described by various authors. In man it varied from five to nine and in other animals between three and ten. "Thus, sometimes completely different layers carry identical names, while on other occasions layers that are anatomically similar, and homologous, are given different names by different authors, although it is a basic prerequisite of scientific logic that similar structures should carry similar names and that homologous patterns should have homonymous designations." (Brodmann 1909, Chap. 1). He supported the idea that the primitive pattern of cortical lamination in all mammals was six-layered, except in certain "rudimentary" cortex, such as in the rhinencephalon and cingulate gyrus. He distinguished two basic cortical patterns. Most of the cortex was **homogenetic**, derived from the embryonic six-layered type, whereas in **heterogenetic** cortex, the six-layered embryonic stage had not been demonstrated. There were two categories of architectonic transformation of homogenetic cortex: **homotypical** (maintaining the same basic six-layered pattern throughout life), and **heterotypical** (no longer having six layers in the mature brain). He cited the description by His (1904) of the original unlayered human cortical Anlage followed by differential growth in thickness, migration of neuroblasts from the "inner plate", and ingrowth of nerve fibres. After the fifth month neuroblasts became organised into layers, with deep layers V and VI first. Finally the cortex entered a six-layered phase over the whole surface, except the small heterogenetic regions.

Brodmann adopted a nomenclature based on previous observations, but which attempted to resolve the many contradictions:

I. *Lamina zonalis* – molecular layer
II. *Lamina granularis externa* – outer granular layer
III. *Lamina pyramidalis* – pyramidal layer
IV. *Lamina granularis interna* – inner granular layer
V. *Lamina ganglionaris* – ganglion cell layer
VI. *Lamina multiformis* – spindle cell layer

Local transformations in this basic six-layered pattern started around the beginning of the seventh month. There could be either a loss of layers, or the formation of sublayers. An example of loss of layers was in agranular cortex, where the inner granular layer (IV) was not present in the mature brain, as in the giant pyramidal "motor cortex". The calcarine "visual cortex" was the best example of subdivision of layers. There was division of the inner granular layer into two cell-dense laminae, a superficial inner granular sublayer (IVa) and a deep inner granular sublayer (IVc), with a cell-poor lamina, the intermediate inner granular sublayer (IVb – the stria of Gennari), between them. Cortical structure could be modified through changes of cell packing density either in the whole depth of the cortex or in a single layer. It could also be modified through changes of cell size or type in one

or more layers. The relative thickness of layers, or the whole cortical thickness, could change.

### 1.1.3 The Comparative Anatomical Basis for the Six-Layered Cortex

Brodmann believed that all mammals had a common primitive six-layered cortex. He used brains from 62 species from all orders of mammals except cetaceans, of which a non-exhaustive list is:

Primates: man, orang-utan, chimpanzee, and various Old and New World monkeys
Prosimians: lemur
Chiropterans: flying fox, pipistrelle
Insectivores: hedgehog, mole
Carnivores: various canines and felines, kinkajou
Pinnipeds: common seal
Rodents: squirrel, mouse, rat, rabbit (although the rabbit would not be considered a rodent now)
Ungulates: hyrax, elephant, pig, goat
Edentates: three-toed sloth
Marsupials: phalanger, kangaroo, wallaby, opossum
Monotremes: echidna

For nine of these he published detailed cortical maps. We shall, however, concentrate on the best known, the human brain map, summarised from his own descriptions. It is noticeable that he was very careful to state when his various areas were easy to differentiate, and when difficult. Regional variations in cytoarchitecture sometimes resulted in sharp borders, sometimes in subtle transitions. He also drew attention to individual differences. Contrary to a widely-held view that his observations on the human brain were from a single case, he often referred to individual differences, and even thanked "Professor Benda for kindly providing human brains".

### 1.1.4 Brodmann's Description of the Human Brain Map

Brodmann "roughly" subdivided the hemispheres of man and gyrencephalic animals into four main lobes, but as he preferred not to speculate on homologies between lobes, especially in non-primates, he described 11 "regions" composed of several individual "areas" (Figs. 1.1 and 1.2). These were: postcentral, precentral, frontal, insular, parietal, temporal, occipital, cingulate, retrosplenial, hippocampal and olfactory (Fig. 1.1).

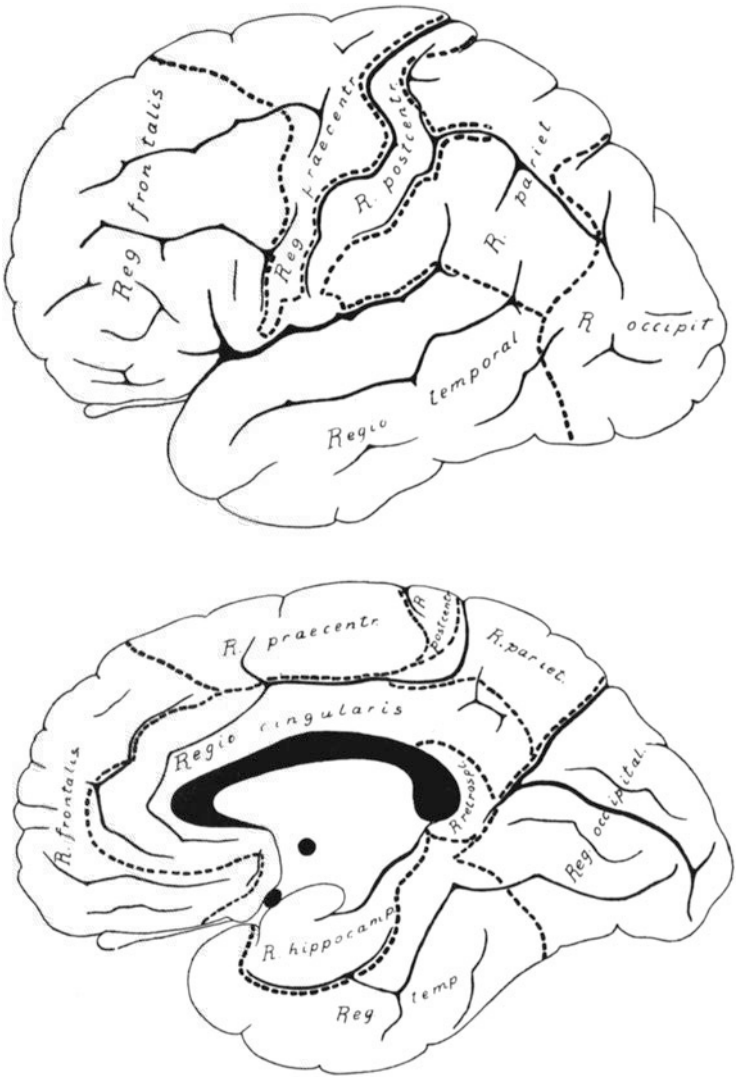


**Fig. 1.1** The human cortical cytoarchtectonic regions (From Brodmann 1909). The olfactory region is not indicated

**The postcentral region** lies directly posterior to the central sulcus and consists mainly of the postcentral gyrus. It is subdivided into four areas: 1, 2, 3 and 43.

**Area 1** – the *intermediate postcentral area* – a strip in the middle of the postcentral region between areas 2 and 3, along the apex of the postcentral gyrus and onto the medial surface, encroaching on the cortex of the central and postcentral sulci.

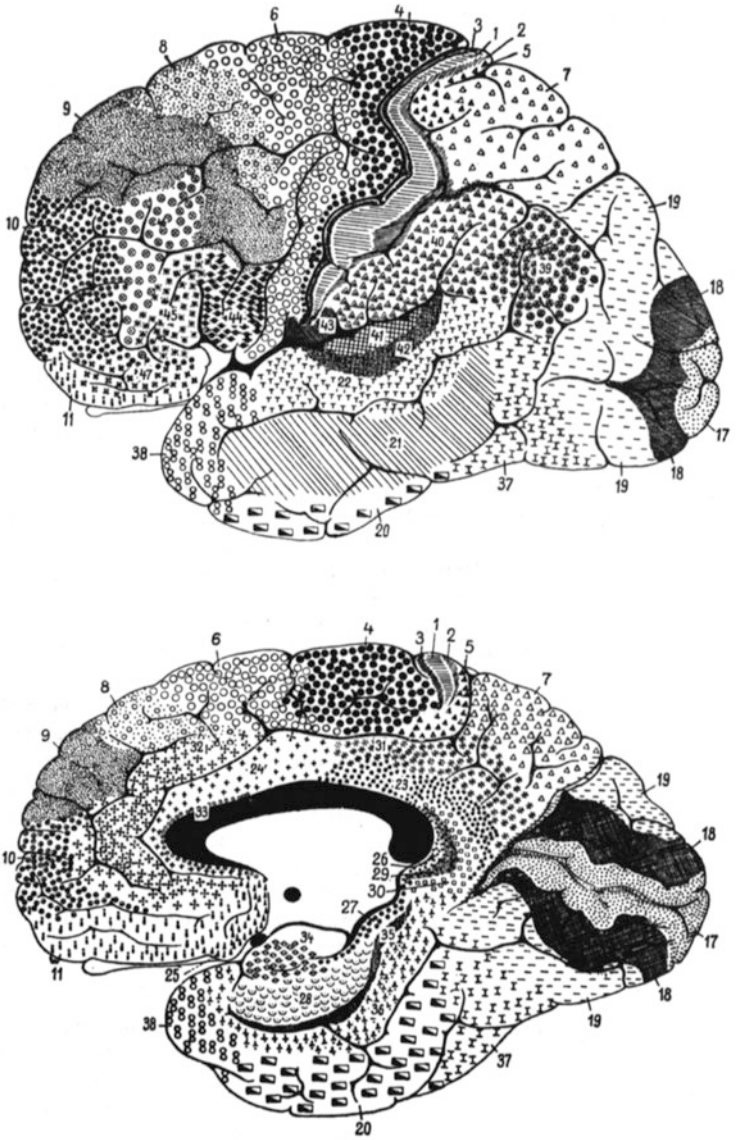


**Fig. 1.2** Cortical areas of the lateral and medial aspects of the human cerebral hemispheres (From Brodmann 1909)

**Area 2** – the *caudal postcentral area* – a narrow strip, mainly on the posterior aspect of the postcentral gyrus (the anterior bank of the postcentral sulcus). Its borders are not always sharp or constant. There are individual differences, as in the sulcal pattern.

**Area 3** – the *rostral postcentral area* – covers the anterior of the postcentral gyrus (the posterior bank of the central sulcus). It has a variable width along the central sulcus. Its border with giant pyramidal area 4 anteriorly is sharp but in some brains its other borders can be less clear. At its medial and lateral ends, area 3 encroaches on the precentral gyrus, pushing area 4 anteriorly.

**Area 43** – the *subcentral area* – is at the junction of the pre- and postcentral gyri at the inferior end of the central sulcus. Its anterior border is sharp and coincides with the anterior subcentral sulcus. It extends into the depths of the Sylvian fissure where it has a distinct boundary with the insular cortex.

**The precentral region** lies directly anterior to the central sulcus and is characterised by the lack of an inner granular layer. Dorsally, its anterior border crosses the precentral gyrus and encroaches on the superior and middle frontal gyri. Its anterior borders are clear but vary between individuals. Its posterior border is well demarcated from the postcentral region, and particularly from area 3, in the central sulcus. Areas 4 and 6 are characterised by the lack of an inner granular layer, and area 4 by the Betz giant cells.

"**Area 4** – the *giant pyramidal area* – is one of the most strikingly differentiated and cytoarchitectonically delimitable structural regions of the whole human cerebral cortex." It is wedge-shaped, along the central sulcus, narrowing from superior to inferior on the precentral gyrus and the adjacent part of the paracentral lobule. Superiorly it includes the whole width of the precentral gyrus but ventrally is restricted to the posterior half of this gyrus. Its borders are variable, especially in the paracentral lobule. There are local and individual differences in the number, size and distribution of giant pyramids: their size and number decrease from superior to inferior. "I must definitely classify as erroneous the idea, proposed by Elliot Smith, that the anterior subcentral sulcus is "a limiting furrow" for area 4".

**Area 6** – the *agranular frontal area* – is broad superiorly, narrowing inferiorly and laterally, and covers the whole vertical extent of the frontal lobe. Medially it occupies the anterior part of the paracentral lobule and the superior frontal gyrus. Laterally, it is on the superior and middle frontal gyri, and further inferiorly the whole precentral gyrus except where it is occupied by area 4.

**The frontal region** is the most extensive of the human cerebral cortex; it includes the frontal lobe anterior to the precentral region, around 20 % of the total cortical area. All its areas contain an inner granular layer. Posteriorly it has a clear boundary with the agranular frontal cortex, and anteriorly extends round the frontal pole. There are eight areas in the human frontal region. Areas 44, 45 and 47 on the inferior frontal gyrus have similarities, and can be termed *subfrontal subregion*. The differences between the others are sometimes difficult to determine.

**Area 8** – the *intermediate frontal area* – is a strip, wide superiorly and narrowing laterally which, like the agranular frontal area (6), crosses from the callosomarginal sulcus on the medial surface onto the lateral surface.

**Area 9** – the *granular frontal area* – is similar to, but more extensive than, area 8. On the lateral surface it stops ventrally near the inferior frontal sulcus.

**Area 10** – the *frontopolar area* – covers the frontal pole. Inferomedially it is demarcated by the superior rostral sulcus.

**Area 11** – the *prefrontal area* – forms the anteroventral part of the frontal lobe on its orbital and medial surfaces, thus including most of the straight gyrus, the rostral gyrus and the anterior end of the superior frontal gyrus.

**Area 44** – the *opercular area* – is a well-differentiated area of the inferior frontal gyrus – Broca's area. There is much variability of the sulci within it.

**Area 45** – the *triangular area* – forms the triangular part of the inferior frontal gyrus. Its caudal border lies in the ascending ramus of the Sylvian fissure, its dorsal border in the inferior frontal sulcus and its rostral border near the radiate sulcus.

**Area 47** – the *orbital area* – shares architectonic affinities with areas 44 and 45 and can be combined with them to form a *subfrontal subregion*.

**Area 46** – the *middle frontal area* – is not clearly distinguishable from neighbouring areas. It includes about the middle third of the middle and the most anterior part of the inferior frontal gyri.

**The parietal region** coincides essentially with the parietal lobe, but inferiorly is difficult to differentiate from temporal and even occipital cortex; it is better distinguishable from the postcentral region at the postcentral sulcus.

**Area 5** – the *preparietal area* – is delimited from neighbouring areas by the presence in layer V of large pyramidal cells almost the size of Betz giant cells, and a thick inner granular layer. Its thickness exceeds that of postcentral cortex. Its structure varies in individual cases, but its position is relatively constant. It begins in the caudal portion of the paracentral lobule, and narrows in the depths of the terminal branch of the callosomarginal sulcus on its rostral bank, extending to the lateral surface of the hemisphere.

**Area 7** – the *superior parietal area* – extends from, medially the subparietal sulcus, laterally the intraparietal sulcus, posteriorly the parieto-occipital sulcus, and anteriorly the superior postcentral sulcus. One can distinguish a division into an anterior and posterior superior parietal area.

**Area 40** – the *supramarginal area* – is ventral to the intraparietal sulcus around the posterior ramus of the Sylvian fissure, on the supramarginal gyrus. Anteriorly it borders the postcentral areas 2 and 43, separated from them by the inferior postcentral sulcus and the posterior subcentral sulcus. It has no sharp boundary with the temporal region (area 22).

**Area 39** – the *angular area* – corresponds to the angular gyrus, widening around the posterior end of the superior temporal sulcus. Its boundaries with the occipital and temporal regions (areas 19 and 37) are ill-defined; its border with the parietal area is formed approximately by the intraparietal sulcus.

**The occipital region** includes the whole occipital lobe, and is divided into three structurally very different areas.

**Area 17** – the *striate area* – is characterised by the calcarine type of cortex which is easily recognisable macroscopically. It is around the calcarine sulcus, and

posteriorly extends a little round the occipital pole onto the lateral surface. Its individual borders are variable, with no relationships to "limiting sulci". The cuneus and the lingual gyrus form part of the striate area to variable extents, depending on the folding of the calcarine sulcus: usually the striate area extends further ventrally from the calcarine sulcus than dorsally. The dorsal striate area retreats entirely from the surface into the depths of the sulcus.

**Area 18** – the *occipital area* – is a ring-like area that surrounds the striate area, more extensively laterally.

**Area 19** – the *preoccipital area* – further surrounds occipital area 18, again especially laterally. Its boundaries are not related to sulci.

**The temporal region** is well delimited and homogeneous, stretching from the posterior margin of the insula over the whole vertical extent of the temporal lobe to the rhinal sulcus or the temporal incisura. It contains several clearly different areas of which certain, such as the transverse gyri, form important subregions of great functional importance.

**Area 36** – the *ectorhinal area* – lies lateral to the rhinal sulcus and represents the first area of the neopallium adjacent to the archipallium, to which area 35 belongs. It is heterotypical with relatively few cells but a massive development of those of layers V and VI. It is the rostral extension of the lingual gyrus.

**Area 37** – *occipitotemporal area*. – is a wide, but poorly circumscribed, transition zone between the adjacent occipital and temporal regions, distinct from preoccipital area 19 and temporal area 20.

**Area 38** – the *temporopolar area* – forms the tip of the temporal lobe, without any clear external delimitation; it fuses laterally with areas 20, 21 and 22, and medially with area 36, and is characterised by its great depth.

**Area 20** – the *inferior temporal area* – corresponds to the inferior temporal gyrus and blends rostrally and caudally with areas 37 and 38 without sharp borders.

**Area 21** – the *middle temporal area* – is situated in the middle temporal gyrus, although not precisely.

**Area 22** – the *superior temporal area* – is well differentiated from areas 20 and 21. Together with the cortex of the transverse gyri of Heschl (1878) (areas 41 and 42) it forms a homogeneous structural region. It was known that the transverse temporal gyri of Heschl had a different structure from most of the temporal lobe. Campbell (1905) differentiated a field within these gyri, his "audito-sensory area", contrasting it with the other temporal gyri, or "audito-psychic area". Elliot Smith (1907), in agreement with this, wrote: "The two transverse gyri of Heschl represent a sharply-defined anatomical area of this cortex", but gave no precise topographical description. The superior temporal area is superficial in the posterior two-thirds of the superior temporal gyrus, the deep part of which is partially occupied by areas 41, 42 and 52. Anteriorly it climbs onto the medial surface of the superior temporal gyrus; posteriorly it reaches the level of the vertical terminal branch of the Sylvian sulcus and blends with the supramarginal area.

**Area 42** – the *lateral (posterior) transverse temporal area* – is medial to area 22, extending obliquely over the superior bank of the superior temporal gyrus,

but partly on the free surface of the gyrus. It forms a well-demarcated crescent along the lateral edge of area 41.

**Area 41** – the *medial (anterior) transverse temporal area* – corresponds to the anterior transverse gyrus. It is bordered medially by the parainsular area 52 from which it is sharply demarcated.

**Area 52** – the *parainsular area* – forms a narrow band on the superior bank of the superior temporal gyrus along the posterior margin of the insula and represents a transitional area between the temporal cortex and the insula.

**The insular region** is distinguishable from surrounding regions by its easily recognisable laminar pattern, including the claustrum. It coincides approximately with the Sylvian fossa, but may encroach on the under surface of the frontal and temporal opercula. Brodmann divided the insula into two halves along the prolongation of the central sulcus, one posterior and granular, the other anterior and agranular, but without attributing numbers to them. Thus, like the central region, the insula is divisible according to the presence or absence of an inner granular layer.

**The cingulate region:** The crescent-shaped cingulate gyrus bordering the corpus callosum is divisible at the level of the central sulcus, like the insula, into a *postcingulate* and a *precingulate subregion*, the former with a distinct inner granular layer, while the latter (except area 32) does not have an inner granular layer. Thus the human cortical surface is divided at the level of the central sulcus into structurally different halves, an anterior agranular and a posterior granular, a trend that is also found in lower mammals.

**Area 23** – the *ventral posterior cingulate area* – is in the ventral part of the posterior half of the cingulate gyrus and lies directly above the corpus callosum. It forms an arc around the splenium as far as the anterior bank of the parieto-occipital sulcus with which it gradually blends. Rostrally it fuses with the agranular precingulate subregion.

**Area 31** – the *dorsal posterior cingulate area* – is in the dorsal portion of the posterior half of the cingulate gyrus and forms an arc around area 23 as far as the parieto-occipital sulcus. There is no clear outer border with area 23 or with the parietal cortex (area 7).

**Area 24** – the *ventral anterior cingulate area* – in the ventral part of the anterior half of the cingulate gyrus next to the corpus callosum. Posteriorly it fuses gradually with a weakly granular transitional zone over the middle of the corpus callosum; anteriorly it extends as far as the rostrum. Its structure changes gradually from posterior to anterior.

**Area 32** – the *dorsal anterior cingulate area* – forms a semicircle around the anterior end of the corpus callosum.

**Area 33** – the *pregenual area* – is formed by a narrow strip of rudimentary cortex hidden in the callosal sulcus. Anteroinferiorly it stretches round the end of the rostrum of the corpus callosum, while posterosuperiorly it extends over the corpus callosum.

**Area 25** – the *subgenual area* – is a small area of cortex inferior to the genu of the corpus callosum. Like the pregenual area it has a rudimentary (heterogenetic) laminar pattern.

**The retrosplenial region** consists of three crescent-shaped areas around the splenium of the corpus callosum. The retrosplenial cortex is partly heterogenetic.

**Area 26** – the *ectosplenial area* – is apposed to the posterior end of the corpus callosum, hidden in the callosal sulcus. It has rudimentary lamination. Laterally it merges without a clear border with Area 29.

In **Area 29** – the *granular retrolimbic area* – there is a unique development of the inner granular layer (IV) and degeneration of layers II and III. It is a narrow semicircular area around the ectosplenial area and lies to a great extent in the depths of the callosal sulcus.

**Area 30** – the *agranular retrolimbic area* – covers the edge of the isthmus of the cingulate gyrus, but also extends a short distance over the anterior bank of the calcarine sulcus. It forms a sort of arc around the other retrosplenial areas. The inner granular layer is degenerated while layers III and V are relatively well developed.

**The hippocampal region** includes the (heterogenetic) cortex between the hippocampal and rhinal sulci.

**Area 27** – the *presubicular area* – lies lateral to the subiculum, separated by a sharp border, as a long, narrow zone along the hippocampal sulcus from the uncus to the tail of the hippocampus just under the corpus callosum.

**Area 28** – the *entorhinal area* – is heterogenetic and lies medial to the rhinal sulcus and covers most of the head of the parahippocampal gyrus.

**Area 34** – the *dorsal entorhinal area* lies mainly medial to the inferior rhinencephalic sulcus.

**Area 35** – the *perirhinal area* – is a narrow band along the rhinal sulcus. The inner granular layer is missing. It forms the border between the archipallium and the neopallium, and it is difficult to decide whether it should be attributed to the one or the other.

**Area 48** – the *retrosubicular area* – is at the caudal end of the perirhinal area (35) and lateral to the presubicular area (27).

### *1.1.5 Brodmann's Arealisation and Circuit Specialisation: The Pyramidal Cell*

Pyramidal neurons are distinguished by their prominent apical dendrite and basal dendritic tree (Fig. 1.3). They comprise some 70–90 % of all neurons in cerebral neocortex (DeFelipe and Fariñas 1992). Pyramidal cells form rich plexuses of connections, often forming intrinsic lattices or patches, within cortical areas.

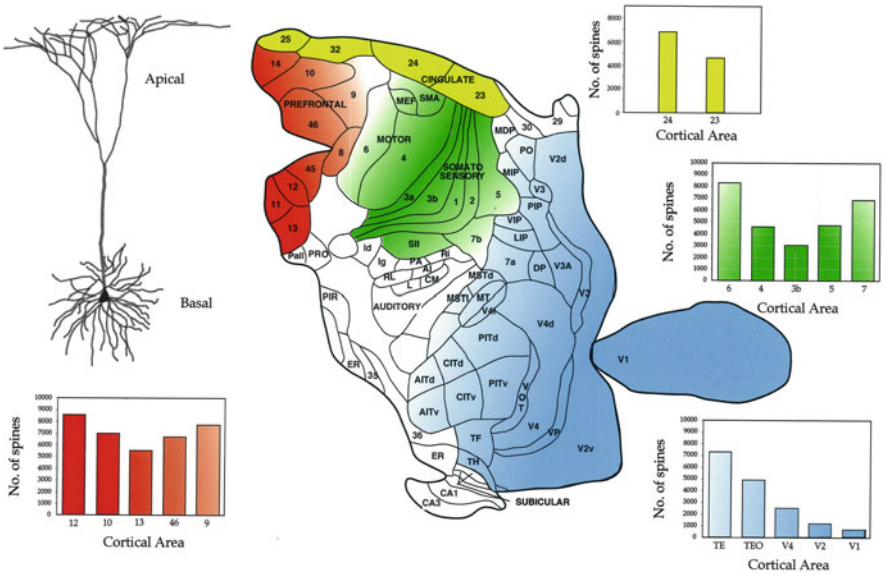


**Fig. 1.3** *Top left*: a typical neocortical pyramidal cell. *Centre*: locations from which neurons were sampled in granular prefrontal (*red*), cingulate (*yellow*), sensorimotor (*green*) and visual (*blue*) cortex of the macaque monkey. *Right*: corresponding bar graphs of estimates of the total number of spines in the basal dendritic trees of layer III pyramidal cells in these areas. As each spine in mature cortex receives at least one excitatory input, differences in the estimates of the number of spines in different populations of cells may be taken as an approximation of numbers of excitatory inputs to these cells. Differences the complexity of the dendritic tree (size, number of branches) may also reflect differences in the integrative abilities of neurons (see Elston 2007 for a review). Note the trend towards more spinous cells with anterior progression from primary sensory areas such as Brodmann's areas 17 (visual) and 3 (somatosensory) into adjacent functionally related cortical areas. In visual cortex, in particular, there is a striking systematic increase in the number of spines on pyramidal cells with progression through a hierarchical series of visual areas, including Brodmann's area 18 (V2), into the temporal lobe. Note also the consistent trend for progressively more spinous cells with progression through somatosensory areas from the central sulcus to the angular gyrus (Data from Elston and Rosa 1998a; Elston et al. 1999a, 2001, 2005a, 2006, 2011; Elston 2000; Elston and Rockland 2002)

They form nearly all cortico-cortical connections, both ipsi- and contralateral, as well as most subcortical connections. Pyramidal cells contain the excitatory neurotransmitter glutamate: their discharge directly facilitates cortical activity, rather than inhibiting it. Arguably, pyramidal cells are the principal neurons of the cerebral cortex, generating nearly all cortically initiated excitation. Different subtypes of pyramidal cells have been reported based on aspects of their morphology, for example, inverted pyramidal cells, those whose axons project into the white matter, and those whose axons are restricted to the grey matter (see Feldman 1984; Nieuwenhuys 1994; Elston and DeFelipe 2002; Valverde 2002 for reviews). In addition, pyramidal cells have been subdivided according to their neurochemical content and receptor subunit profiles (Gabernet et al. 1999; González-Albo et al.

2001; Hof et al. 2001). It has also been proposed that pyramidal cells are not genetically fated to have their characteristic morphology. According to this theory, all variants of spiny neurons, from the typical pyramidal cell to the typical spiny stellate cell, are derived from a common precursor (Valverde 1988). Here we focus on the "typical" pyramidal cell of unknown neurochemical content observed in mature primate cortex. As a prelude to studying specialisations in pyramidal cell structure that have occurred during the evolution of different primate species we first set out how pyramidal cell structure varies among Brodmann's areas in a single species of macaque monkey (*Macaca fasicularis*), and outline how specialisation in cell structure may influence functional capabilities and, in turn, behavioural complexity.

### *1.1.6 Visual Cortex*

The areas of the cerebral cortex that contain neurons involved in some form of visual processing are perhaps the most thoroughly explored in the macaque brain. Prior to the 1970s, most studies were restricted to Brodmann's area 17 (the striate, or primary (V1), visual cortex). Since then there has been an explosion in the number of studies in, and our understanding of, extrastriate visual cortex (Zeki 1969, 1978a) see (Kaas 1995; Rosa 1997; Kaas and Lyon 2001; Kaas and Preuss 2003; Zeki 2003; Rosa and Manger 2005) for reviews. Application of techniques such as electrophysiological mapping and imaging, and the development of specialised tracers, have revealed that visual processing is much more complex than previously thought, involving up to half the cortex and as many as 30 different areas (Fig. 1.3). Various theories have been presented for the existence of so many visual cortical areas, and how visual stimuli are processed by neurons in these areas (see Kaas 1987; Weller 1988; Felleman and Van Essen 1991; Rosa 1997; Kaas 2000 for reviews). In addition, many theories have been proposed regarding the recruitment and interaction of neurons in these different cortical areas during particular visual tasks. Two of the most popular models include the quasi-hierarchical model and the distributed processing model see (Mountcastle 1995) for a review. In the quasi-hierarchical model, visual inputs to cortex are processed through a series of cortical areas. These areas are not necessarily organised into a strict hierarchy, but there is some form of serial processing through select visual areas. In the distributed processing model, visual processing occurs in multiple cortical areas, but not necessarily in any form of hierarchy. That is not to say however, that the two theories are mutually exclusive. Mountcastle (1995), for example, highlighted how hierarchies may exist within a distributed system.

New methods of quantification (Elston and Rosa 1997; Elston 2001) have revealed marked, systematic differences in pyramidal cell structure (and cortical circuitry) in these different visual areas. Briefly, there is a trend for increasingly more complex pyramidal cells with progression from V1 to the second visual area (V2) and parietal visual areas (the lateral intraparietal area, LIP, and

cytoarchitectonic area 7a), and temporal areas (V4, the middle temporal area, MT, cytoarchitectonic areas TEO and TE, and the superior temporal polysensory area, STP) (Elston and Rosa 1997, 2000; Elston et al. 1999a). The increase in the size of the dendritic tree, coupled with a concomitant increase in the number of dendritic branches and spine density, results in a progressive doubling in our estimates of the total number of spines in the basal dendritic trees of pyramidal cells through V1, V2, V4, TEO and TE. The functional implications of these specialisations in pyramidal cell structure in functionally related cortical areas are discussed in detail in the works of Elston (2002, 2007), Jacobs and Scheibel (2002), Spruston (2008) and DeFelipe (2011).

### *1.1.7 Somatosensory and Motor Cortex*

Based on patterns of connectivity, neuronal response properties and, more recently, imaging studies, several theories have been put forward regarding normal function across, and cooperation between, Brodmann's sensorimotor areas (Mishkin 1979; Pons et al. 1987, 1992; Passingham 1997; Geyer et al. 2000). By injecting large numbers of pyramidal cells in some of these different cortical areas it has been possible to demonstrate marked and systematic differences in their size, branching complexity and spine density. More specifically, two trends of increasing morphological complexity have been revealed with progression from the central sulcus to adjacent cortical areas. There is a systematic increase in the size of pyramidal dendritic trees, their branching complexity, and spine density within their basal dendritic trees, with caudal progression from the primary somatosensory area on the posterior wall of the central sulcus (Brodmann's area 3; 3b) to the rostral bank of the intraparietal sulcus (Brodmann's area 5) and the exposed rostral portion of the inferior parietal lobule (Brodmann's area 7; 7b). There is also an increase in the size of the dendritic trees of pyramidal cells, their branching complexity, and the total number of spines within their basal dendritic trees, with rostral progression from the primary motor area on the anterior wall of the central sulcus (Brodmann's area 4) to the exposed lateral portion of the precentral gyrus (Brodmann's area 6 or premotor cortex) (Elston and Rockland 2002). These differences in size, branching complexity and spine density result in appreciable differences in our estimates of the total number of spines in the basal dendritic tree of the average cell in each cortical area (Fig. 1.3).

### *1.1.8 Cingulate Cortex*

A study of the literature reveals little agreement regarding the functions performed in cingulate cortex. Some have attributed higher cognitive and emotional functions to the anterior cingulate cortex and vegetative functions to posterior cingulate