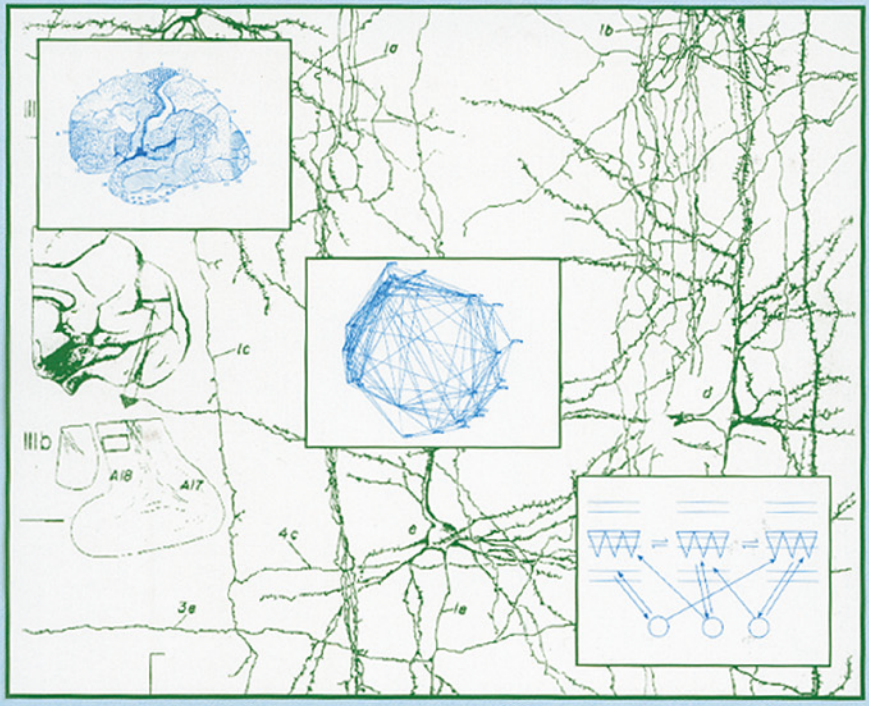
Cortical Areas: Unity and Diversity

Edited by: Almut Schüz and Robert Miller



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Cortical Areas:
Unity and Diversity

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Cortical Areas: Unity and Diversity

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PREFACE

Since the time when Bell and Magendie first showed the different functions of dorsal and ventral roots of the spinal cord, idea that different functions can be identified with different locations in the central nervous system has been central to attempts to understand the brain. The possibility that different *psychological* functions might in some way "reside" in different locations of the cerebral cortex was also an attractive idea, even when scientific study of the cerebral cortex was in its earliest infancy, as shown by the popularity of phrenology in the first half of the nineteenth century. This possibility came to have a firmer empirical basis in the latter half of that century, as a result of the studies of neurologists such as Broca, Wernicke and others. Development of ideas of cortical localization of function was given further impetus by results of cortical stimulation experiments, and, in the early twentieth century, from the study of cortical cytoarchitectonics. Nowadays, a localizationist view of the cortex is also favoured by the widespread use of functional imaging techniques.

Throughout this long history, an alternative perspective has been advocated periodically, placing emphasis of the fact that many psychological functions appear not to be localized in specific cortical regions, or if they are associated with particular cortical areas, these areas are multiple, and distributed, rather than single and discrete. In the lesion studies of memory conducted by Lashley it was even concluded that functional loss depends more on the size of the lesions, rather than its exact location. A modern expression of this perspective comes from some of those using functional imaging methods, who are also concerned with widely distributed functions, and document networks of several cortical areas activated together when particular psychological functions are employed. Modern morphological work on the cerebral cortex, to which one of us has contributed also fits into this alternative tradition, cortical connectivity being described and analysed in terms of broad statistical constraints which might generalize across the whole neocortical mantle.

These two perspectives might seem antithetical, but this is appearance rather than reality. It is not a contradiction to believe that some functions have a strict association with particular cortical areas, while others are based on more widely-distributed cortical regions. Which of these two perspectives emerges as prominent in an experiment depends on the way the experimenters frame their questions.

In the chapters below, many aspects of this complex topic are explored. These include the actual evidence that the cortex can be subdivided into morphologically different areas, the correlation between such parcellation and patterns of connectivity of various sorts, the degree to which there is nevertheless an underlying uniformity to the cortex, generalizing across areas and between species, the functional equivalence of different areas, as well as the large-scale patterning of cortical functioning, and the overall integration of cortical

functions by interplay with other forebrain structures. all these issues have been discussed many times in the past. However, we believe it is timely to revisit them, and thus to put some of these long-standing debates in the context of modern evidence about the structure and function of the cerebral cortex.

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1 Introduction: Homogeneity and Heterogeneity of Cortical Structure: A Theme and its Variations

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The cortex is subdivided into anatomically recognizable areas. This phenomenon, though described in detail nearly a century ago, is still difficult to grasp precisely. The local differences in structure are subtle enough to have evoked debates which still continue about the exact definition of a cortical area, the number of areas, the exact location of their borders and the comparability of areas between species. It depends on the context whether one considers the cortex as a more or less homogeneous structure, or rather emphasizes its heterogeneity. In view of the very different tasks in which the cortex is involved, such as sensory processing of different modalities, learning, long-term planning, decision taking, movement or human speech, one may be impressed by the relative homogeneity of the overall structure of the cortex, both within and between species. If, on the other hand, one compares the cerebral cortex to the cerebellar cortex, which shows no signs of local differences in architectonics, the heterogeneity of the structure of the cerebral cortex is striking.

Both aspects have to be explained: the fact that the cortex can perform a large variety of tasks on the basis of a more or less uniform structure, as well as the reasons for the local variations in structure. The homogeneous aspects, the "theme" of cortical structure, indicate that some common denominator can be found for the whole spectrum of tasks in which the cortex is involved. The heterogeneous aspects, the "variations" superimposed upon the theme, may point the way to relevant parameters for local variations in cortical function.

Much knowledge has accumulated concerning both aspects during the last few decades. New anatomical methods and the enormous developments in electrophysiology have increased our understanding of the basic structure and function of the cortex, and they have also added a large amount of detailed knowledge about individual cortical areas. It therefore seems timely to revisit the work of Brodmann (1909), Vogt (1910, 1911), von Economo and Koskinas (1925), Flechsig (1920) and others, on the basis of these new developments, and to make a new effort to better understand the anatomical differences in terms of function. We will see that this effort will lead us deep into crucial questions of information processing in the cortex.

OUTLINE OF THE BOOK AND BASIC QUESTIONS

The topic of cortical areas can be approached in different ways. Fascinating insights into the role of cortical areas have come from the analysis of the various processing stages

within one modality, in particular in the visual system, as detailed in the work by Hubel and Wiesel (e.g. 1977), Zeki and co-workers (e.g. Zeki, 1993), Oram and Perrett (1994), Gauthier and Logothetis (2000), and others. Another approach is based on a comparison between the various sensory systems, as in the volumes edited by Woolsey (1981a,b, 1982) and by Peters and Jones (1985a,b, 1986). The present book follows that line. It does not concentrate on one particular modality, but is concerned with the entire cortex, including a comparison between areas dealing with different modalities. The main emphasis is on anatomy, but with the aim of rising above the descriptive level as far as possible, to reach a better understanding of the role of cortical areas in general. This is why we have also included a few chapters based on other techniques such as electrophysiology and experimental surgery.

The book is divided into several parts, by grouping the chapters according to their main topic. The division is, however, not a strict one: Some topics come up in various chapters, viewed from different vantage points. Following the five parts, we have therefore included a *Discussion Chapter* in which we try to pull together threads from the preceding parts.

Part I attempts to provide a better grasp of the local differences in architechtonics, by way of more recent methods, or by way of a new look at the classic methods. It deals with questions like the following: Do cortical maps derived with different histological methods agree with each other? In other words, do the various histological methods basically describe the same map, though perhaps with different precision, or are there several maps independently superimposed onto each other (chapters by Hellwig, Amunts *et al*., Rademacher)? How do maps differ between individual brains, and how is this variation related to that of gyri and sulci (Rademacher, Seitz)? How do the anatomical maps relate to functional mapping (Seitz)? This latter chapter leads us towards the long-standing topic of debate between localization *vs* distribution of function.

Part II focusses on another crucial question with respect to information processing: How can the structural variations described in architectonic maps be interpreted as variations in *connectivity*? Differences and similarities in *intracortical connectivity* are dealt with in the chapters by Jacobs and Scheibel and by Levitt and Lund, but are also adressed in some chapters of the other sections (Hellwig, Valverde *et al*., Pallas, and Shipp). The *relationship between thalamus and cortical areas* is treated by Cusick. Differences and similarities between areas with respect to *cortico-cortical long-range connectivity* are dealt with in the chapter by Kaas, but are also touched upon in the various chapters in Part V.

In Part III, the questions of mapping and of connectivity come up again in the comparison between species (Valverde *et al*.) and between iso- and allocortex (Miller and Maitra).

Part IV takes up another crucial question: Is the cortex, in principle, a largely equipotent network in which the inputs from different modalities could be exchanged? This question is related to two other important questions: (1) What role does the thalamic and/or sensory input play in shaping the structure of a cortical area (Pallas); and, (2) as pointed out in the same chapter, in what respects does sensory processing differ at all in different modalities? To a certain extent, an apparent equipotentiality of the cortex may be simply due to the fact that there are basic similarities in information processing between different sensory modalities. These questions are dealt with in the chapters by Pallas, Dinse and Schreiner.

Part V discusses integration between cortical areas, as well as the segregation of functions, as determined by the cortico-cortical long-range system (Young, Shipp). This leads us to the question of hierarchical *vs* parallel processing in the cortex and to the topic of feature extraction and feature combination. The chapter by Miller deals with the integrative role of the thalamus, the basal ganglia and the hippocampus for cortical functions. In these chapters, the term "unity" in the title of the book gets a somewhat different meaning from that in the other parts in which it was used in the sense of "uniformity" in structure or "universality" in function. In this last section, the term "unity" may be understood as the integration of different parts of the cortex involved in a particular task, thinking perhaps of the various regions which light up in functional imaging during a particular task.

BASIC CONNECTIVITY OF THE CORTEX AND LOCAL VARIATIONS

Homogeneous aspects of cortical structure are those which are common to all cortical areas, both within and between mammalian species, such as the existence of layers, similar input and output organization to – and from – subcortical structures, and the orthogonal orientation of pyramidal cells with respect to the layers. In order to offer some starting point for a discussion of the role of cortical areas, I will briefly summarize some of the homogeneous features of cortical connectivity from which one can draw conclusions about the basic function of the cortex (Braitenberg, 1974, 1978a; Braitenberg and Schüz, 1998). The following list is based on quantitative anatomical studies from our own laboratory (e.g. Braitenberg, 1978b, 1986; Schüz and Palm, 1989; Schüz and Demianenko, 1995) as well as on those by Sholl (1956), Cragg (1967), Scheibel and Scheibel (1968), Valverde (1971), Foh *et al*. (1973), Wolff (1976), Winkelmann *et al*. (1977), Peters (e.g. Peters and Feldman, 1976; Peters and Kara, 1985), Beaulieu and Colonnier (1985), Braak and Braak (1986), White (1989) and others.

1. The neurones in the cortex are mainly connected to other cortical neurones. Input and output connections with subcortical neurones contribute only a small percentage to the synapses of cortical neurones (see also chapter by Young, this volume).
2. The majority of neurones in the cortex are of one type, the pyramidal cells.
3. They are excitatory, and form an extensive network mainly among themselves. Inhibitory interneurones are loosely interspersed and contribute only about 11% of the synapses.
4. Each pyramidal cell projects to, and gets input from thousands of other neurones, but makes usually only one or few synapses with any one of them.
5. Most pyramidal cells make both short-range connections in their immediate vicinity via axon-collaterals, and long-range connections somewhere else in the cortex via the main axon traversing the white matter.
6. The pyramidal cells are connected with each other mainly via dendritic spines. Much speaks in favour of the assumption that the spines are structural specializations which are particularly suited for regulating the strength of synapses and thus have to do with plasticity and learning (for review see Horner, 1993; for recent experimental evidence see Engert and Bonhoeffer, 1999).

The definition of pyramidal cells adopted by our group does not put emphasis on the shape of the cell body or the dendritic tree, but more on the presence of spines and the existence of a long-range connection, in accordance with the definition of the Class I cells used by Globus and Scheibel (1967). Such a definition of this class of cells has received further support from electronmicroscopical studies (summarized in Peters and Jones, 1984). The class comprises the excitatory neurones of the cortex, and, in addition to their main group (the pyramidal cells of older classifications), also includes spiny neurones without an apical dendrite (even though a subpopulation of those does not participate in the long-range system; see Valverde *et al*., this volume).

The fact that each pyramidal cell is connected to thousands of other neurones makes it very unlikely that the genetic instruction for cortical wiring reaches down to the level of connectivity between individual neurones. Genetic instruction can be assumed to be limited to the determination of neuronal types and the approximate distribution of projections, i.e. to the determination of *probabilities* of connections (Sholl, 1956; Cragg, 1967; Braitenberg, 1978a).

Although this does not allow us to say anything about the connectivity between individual neurones, the shape and location of dendritic and axonal trees will tell us something about the connectivity between neuronal populations. The ramifications of axons and dendrites reflect the location of synapses on a neurone quite faithfully: Synapses are distributed throughout dendritic trees (with some well-known gradients; e.g. Globus and Scheibel, 1967; Marin-Padilla, 1967; Valverde and Ruiz-Marcos, 1969; Kunz *et al*., 1972) and—as far as it is known—also throughout unmyelinated axonal ramifications (Amir *et al*., 1993; Hellwig *et al*., 1994). This suggests that the neurones tend to make synapses with the neuronal processes, they meet in the neuropil without too much selectivity. This view is supported by other anatomical data which suggest a statistical connectivity between cortical neurones (summarized in Braitenberg and Schüz, 1998; Schüz, 1992). Moreover, although some neuronal populations do show interesting deviations from a purely statistical connectivity (Johnson and Burkhalter, 1997; for evidence for both selectivity and non-selectivity, see White, 1989), complete selectivity has only been shown for one type of non-pyramidal cell, the chandelier cells, which seem to connect only to pyramidal cells (see data collected by White, 1989). Thus, whatever the details of the rules which decide that a synapse is established between two individual neurones (be it only a question of "who hits onto whom" in the crowd of cell processes or beyond that some developmental or activity-dependent selectivity), the shapes, densities and locations of dendritic and axonal trees can be taken as an indicator of the network structure at any given place.

To a large extent, the architectonic differences, as seen for example in the Nissl picture, may reflect local differences in the density and shape of dendritic and axonal ramifications, i.e. local variations in the statistics of the connectivity between neurones (see also the chapter by Hellwig). For example, in a region or layer in which pyramidal cells have loosely ramifying dendritic trees, individual axons may have a lower chance of hitting a particular dendritic tree more than once than in case of more densely ramifying dendrites. Thus, looseness of dendritic trees entails a higher degree of convergence, while density of dendritic ramifications correlates with the strength of coupling between neurones. The diameters of dendritic trees reflect the size of the sampling area of a neurone. In topographically organized areas, the co-existence of small and large dendritic trees has been related to our ability to shift attention from the details of a scene to large-scale figures (Braitenberg, 1984), while the lateral spread of axonal trees may be related to receptive

field size, or even to the size of the region from which a receptive field can be influenced (Gilbert and Wiesel, 1994).

Figure 1.1 shows two examples from a simulation study, in which the spread of excitation was investigated as a function of the shapes of dendritic and axonal trees in a given area

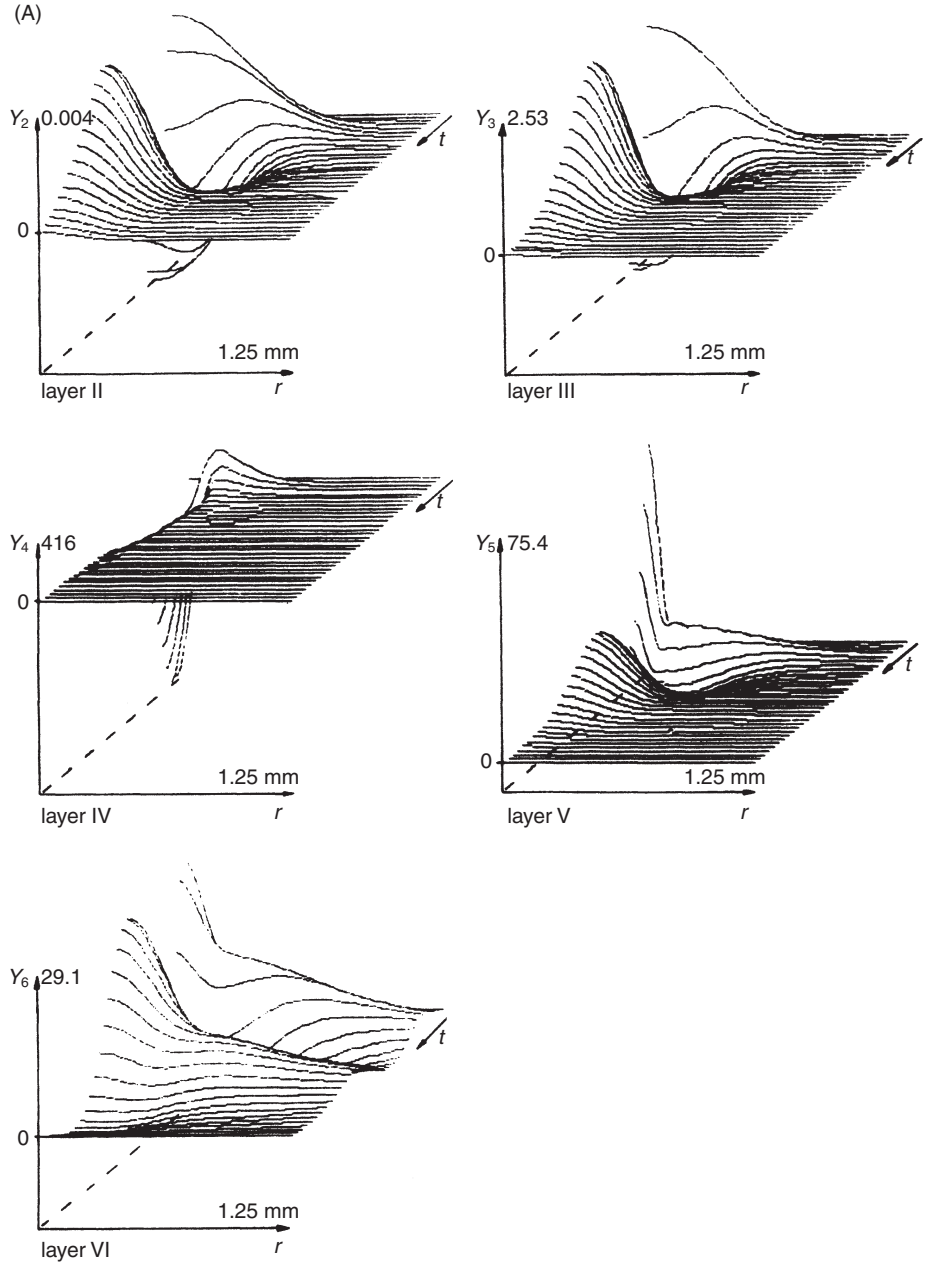

Figure 1.1. Continued

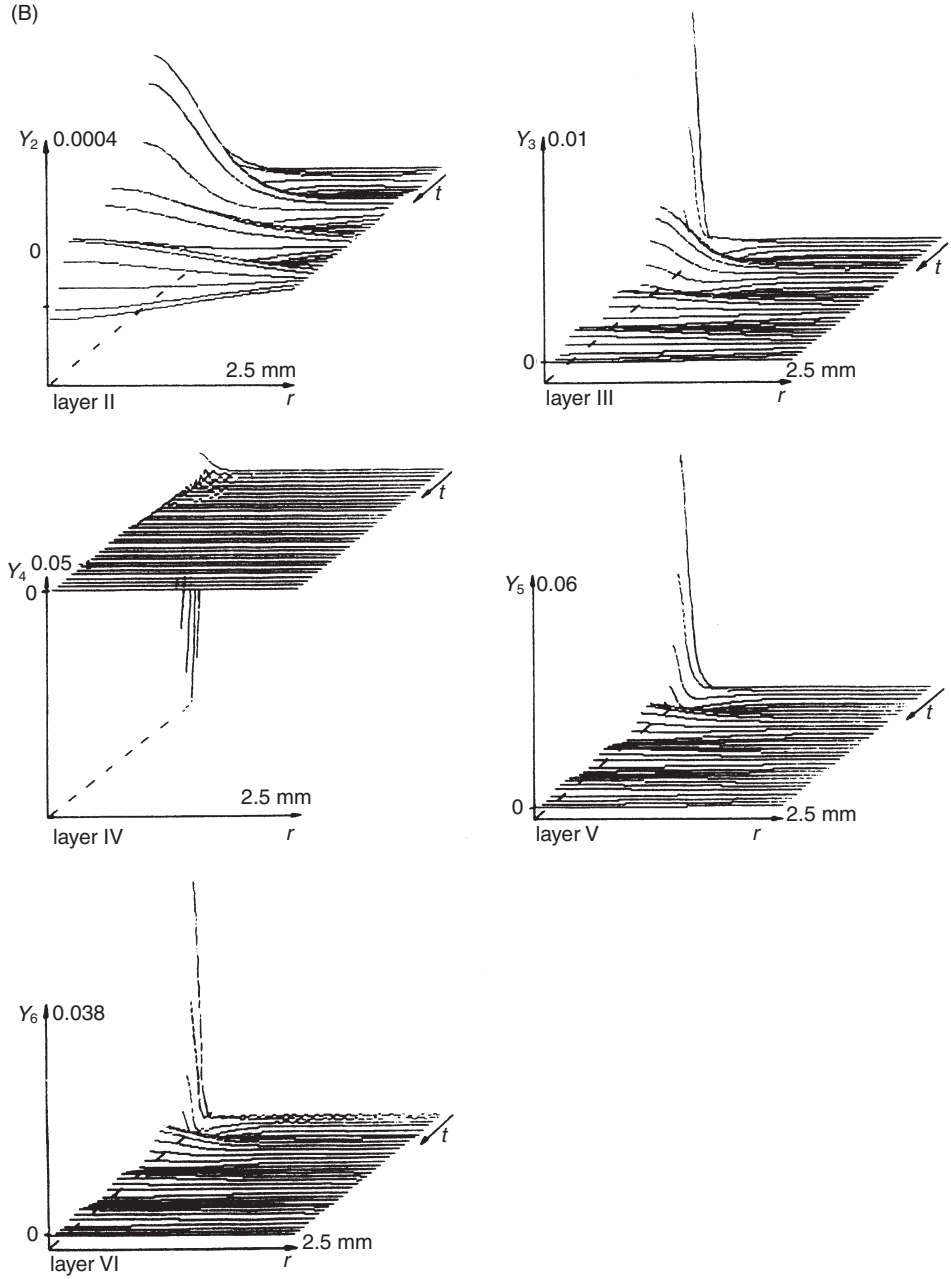

Figure 1.1. Two examples from a simulation study, showing the spread of activity in space (along a radius *r*) and time (*t*) in layers II to VI and its dependence on the shape of axonal and dendritic trees. In both cases, layer IV is stimulated by a short impulse at time zero (hindmost line). Time varies from 0 to 100 msec, activation (*y*-axis) is indicated in arbitrary units. In (**A**) a cortical area is assumed in which pyramidal cells have relatively wide apical dendritic trees and short recurrent axon collaterals (to layers above the cell body); in (**B**) narrow apical dendrites were assumed and long recurrent collaterals. Reproduced with permission from Krone *et al.* (1989). Further examples can also be found in Fuentes *et al.* (1996).

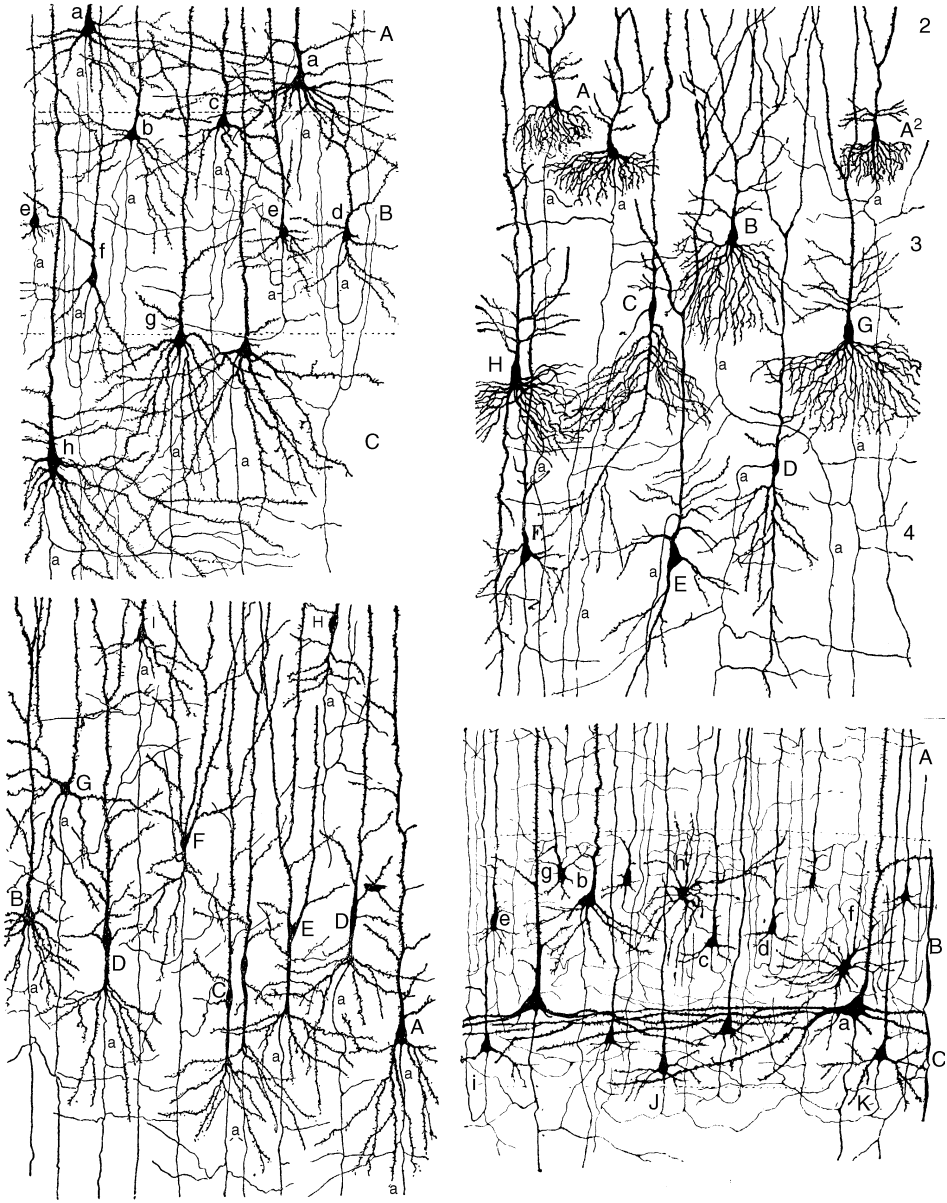

Figure 1.2. Examples of the variability of dendritic trees of pyramidal cells in different cortical areas, collected from the book by Ramón y Cajal (1911). Reproduced with permission from Braitenberg and Schüz (1989).

(Krone *et al*., 1989). Figure 1.2 shows typical shapes of dendritic trees for some cortical areas, collected from the book by Ramón y Cajal (1911). Various chapters in the present book (Hellwig, Jacobs and Scheibel, Levitt and Lund, Valverde *et al*.) will treat the topic of local variations in the geometry of dendritic or axonal trees and their functional significance in more detail, a point which will be taken up again in the discussion chapter.

THE BASIC FUNCTION OF THE CORTEX

Why are the points listed above worth emphasizing among the many others which one could mention? The answer is that they make much sense in connection with an old theory of cortical function, the theory of cell assemblies first proposed by Hebb (Hebb, 1949; Braitenberg, 1978a; Palm, 1982). Hebb postulated that the "units of cognition" consist of groups of neurones, defined by the strength of their mutual connections. The individual neurones of such a group could be scattered over the cortex, but should be more strongly connected to each other than to other neurones. According to Hebb, such "cell assemblies" are the result of learning, based on the strengthening of synapses between neurones which are often active together. Such coincidence of neural activity indicates correlated events in the outside world, such as the coherent properties of an object, or the relation between objects and their names. Repeated common activity of neurones stands for the various basic concepts, a child has to learn about the world. A concept has been learned when the synapses between the members of a cell assembly have become strong enough to enable a subset of the cell assembly to ignite the whole set. The theory also postulates that individual neurones can be members of several cell assemblies, representing similar properties of different concepts, such as for example same colour of different objects.

This theory implicitly makes requirements on the structure of the cortex, some of which Hebb could not have known at the time he was writing, but which nevertheless fit the situation in the cortex remarkably well, as we know today. What is needed, is a network consisting of a large number of neurones of the same kind, each of which is "waiting" for activity in common with that in other neurones. In order to form cell assemblies, they should be connected via excitatory synapses, and these should be modifiable in strength. In order to be prepared for as many constellations of common activity as possible, each neurone should be connected to as many other neurones as possible. Connections between distant regions of the cortex should also be present in order to enable the brain to learn correlations in which different modalities are involved.

These properties characterize the basic structure of the cortex, as shown above (Braitenberg and Schüz, 1998). Indeed, it is important to note that the cortex is the only one amongst the major parts of the brain in which this particular combination of properties is realized (Figure 1.3). The most striking point is that the cortex is the only large network in the brain which consists mainly of excitatory connections between its principal neurones. In the other large parts of the brain the majority of neurones are either connected into an inhibitory network, as in the basal ganglia (Somogyi *et al*., 1981; Miller and Wickens, 1991) or they do not form a network directly among themselves, but rather relay a certain input to a certain output in a feedforward manner, such as in the relay nuclei of the thalamus (Steriade *et al*., 1990; Miller, 1996) or in the cerebellar cortex (Braitenberg *et al*., 1997). Therefore, the kind of learning proposed by Hebb, and often referred to by the term associative learning, could not be realized within these other parts of the brain, but can very well be in the cortex. Thus, being a particularly efficient learning device may indeed be the particular basic function of the cortex. Overlapping of neurones between cell assemblies could provide the basis for the sequencing of the learned items into "trains of thoughts", sentences and new ideas (Braitenberg, 1978a). This again would be difficult to realize in an inhibitory network. Hence, if we ask "what can the cortex do better than other parts of the brain?", the answer is "the cortex is specialized for detecting, incorporating and dealing with correlations". Clearly, on a very basic level, dealing with all kinds of

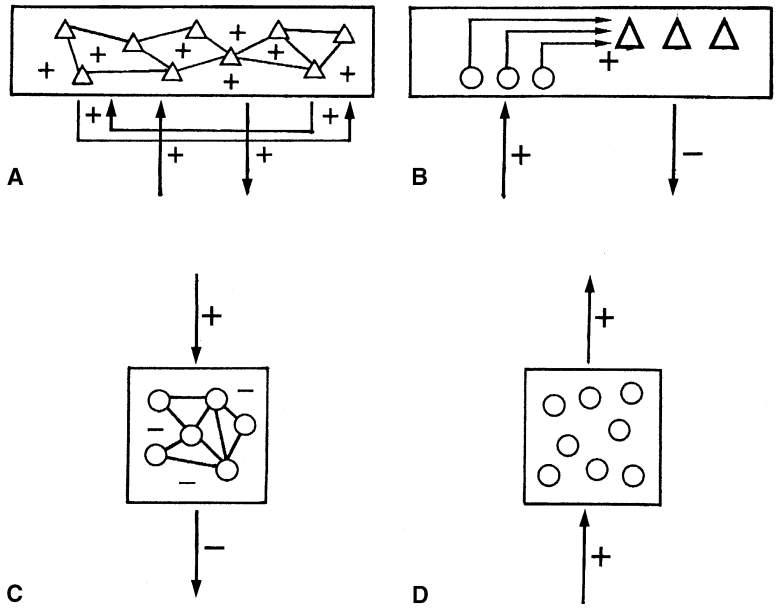

Figure 1.3. Basic features of the connectivity in the cortex (A), the basal ganglia (B), the cerebellar cortex (C) and the thalamus (D). The cortex is characterized by excitatory feedback connections, both in its short-range and its long-range system. The principal neurones in the basal ganglia form a network, similar to the neurones in the cortex, but with inhibitory connections. In the cerebellar cortex, the vast majority of the neurones, the granular cells, are excitatory, but are not connected among themselves. As in (B) and (D) feedback connections within the cerebellar cortex are inhibitory. Also in the thalamus (D) the excitatory relay neurones seem not to form direct connections among themselves. Modified with permission from Schüz (2001).

correlations can certainly be regarded as a common denominator for all higher cognitive functions. The chapter by Pallas will give interesting experimental evidence for the discrepancy between the cortex and the thalamus in adapting to new correlations in the sensory input.

If one starts out from this basic view of the cortex, a guideline for reading this book might be the following question: *"What are the different kinds of correlations the cortex is exposed to from the different sensory or cortico-cortical inputs, and how do the local variations in sructure improve the ability of the cortex to deal with them?"*

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Part I

THE EMPIRICAL STATUS OF CORTICAL MAPS

2 Cyto- and Myeloarchitectonics: Their Relationship and Possible Functional Significance

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In the human cerebral cortex, a number of cortical areas can be distinguished by anatomical methods. Two classical types of cortical parcellation have been described, based on cyto- and myeloarchitectonics. In cytoarchitectonics, the definition of areas relies on variations in the sizes and packing densities of cell bodies. Myeloarchitectonic parcellation is based on the layering, the distribution and the amount of intracortical myelinated fibres. It is shown here that cyto- and myeloarchitectonics are closely related. Two simple assumptions are sufficient to transform quantitative cytoarchitectural data into the corresponding myelin picture. The rules linking cyto- and myeloarchitectonics seem to be essentially uniform throughout the neocortex. It is also well known that characteristic functional specializations can be attributed to cortical areas. However, beyond the localization of function, the functional significance of areal variability in the cortex is largely unclear. For instance, it remains to be clarified why certain areal adaptations of the basic cortical network seem to be particularly appropriate for the execution of specific tasks. It is argued that this issue will only be understood when the wiring schemes of each area are known. Since it is difficult to infer connectivity patterns from cyto- and myeloarchitectonics, their significance for a functional interpretation of cortical anatomy seems to be limited. The paper suggests, however, possible strategies that may allow one to describe cortical architectonics in terms of connectivity.

KEYWORDS: areas, connectivity, cytoarchitectonics, human cerebral cortex, myelin, myeloarchitectonics

1. INTRODUCTION

It has been known for a long time, i.e. since the discovery of the stripe of Gennari in the primary visual cortex (Gennari, 1782), that the cerebral cortex is not uniform. A number of histological methods allow one to distinguish cortical areas which are defined by characteristic variations of the basic cortical architecture. Interestingly, this anatomical parcellation of the cortex is not merely descriptive, but is somehow related to cortical function. Different types of information (visual, auditory, motor, etc.) are processed in different cortical areas. As yet, this relation between structure and function has been elucidated mainly in just one respect: Certain functions can be *localized* in certain areas. Reaching this conclusion is an important achievement, useful, for example, for a clinical neurologist who can associate symptoms in a patient with lesions visible in a CT scan. However,

localization of function is not the whole story. Knowing *where* a certain type of information is processed does not explain *how* this is done. The functional significance of areal variations in the cortex will not be understood until the *mechanisms* of information processing as well as its localization can be related to cortical anatomy. For instance, it would be interesting to know why a piece of cortex that is involved in motor control looks like the motor area, and not like the primary visual cortex.

The present paper will not be able to solve this problem. However, it will consider two classical approaches in cortical parcellation, cyto- and myeloarchitectonics, and discuss whether a functional interpretation is possible beyond the mere localization of function.

1.1. Cytoarchitectonics

In cytoarchitectonics, cortical areas are defined on the basis of cell body stains such as the Nissl stain. Cortical parcellation relies on variations in the sizes and packing densities of neurones leading to characteristic patterns of layering (Figure 2.1). The most prominent maps of the human cerebral cortex worked out on the basis of cytoarchitectural observa-

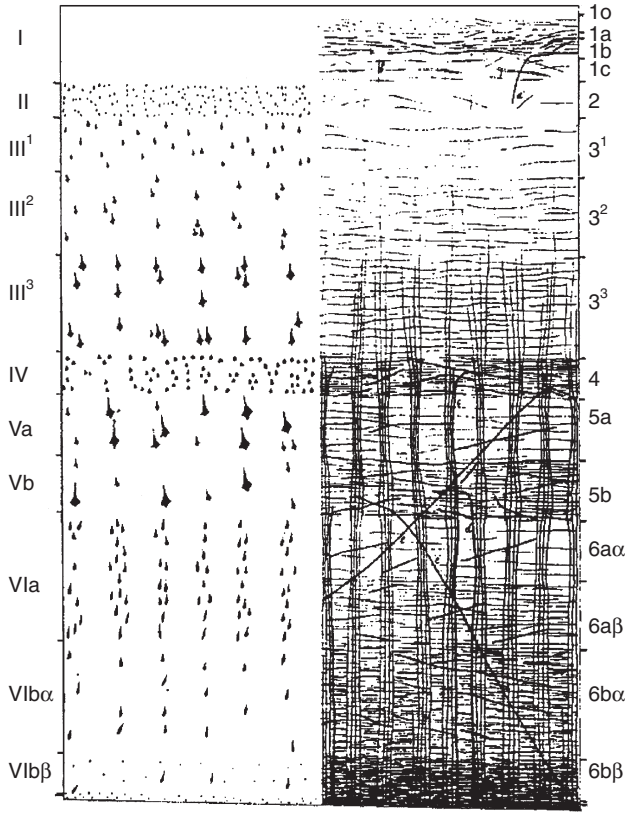

Figure 2.1. Schematic drawing of a piece of association cortex: cytoarchitectonics (left) and myeloarchitectonics (right). The stripes of Baillarger correspond to the horizontal bands of myelinated fibres in layers 4 and 5b. From Vogt and Vogt (1919).

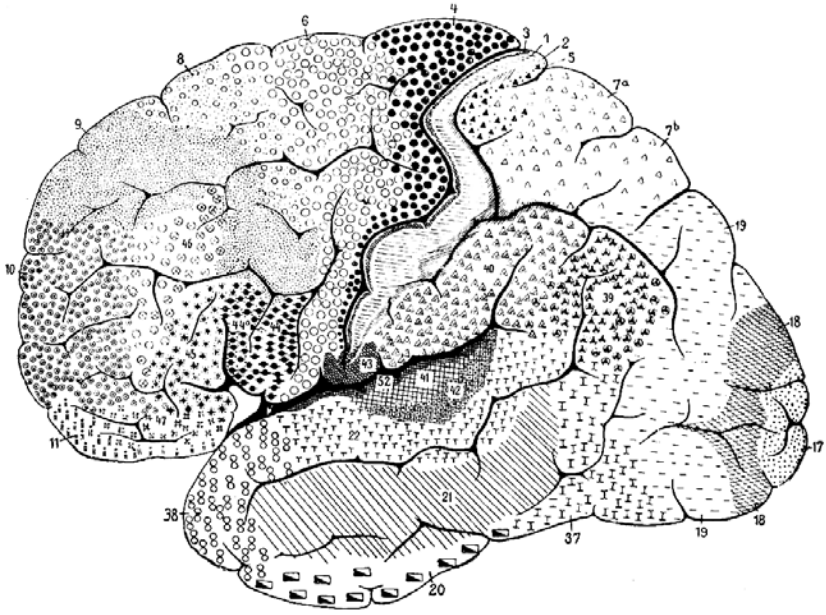

Figure 2.2. Brodmann's map (1909) of the human cerebral cortex (lateral view).

tions are those by Brodmann (1909) (Figure 2.2) and von Economo and Koskinas (1925) (see Figure 3.1(B) in chapter by Amunts *et al*., this volume). It is not the aim of this paper to present all the anatomical details of each area. These can be found in the monographs by Brodmann and von Economo mentioned above as well as in a more recent treatise by Braak (1980) which combines cyto- and myeloarchitectural observations with studies on the pigmentoarchitectonics of the human cerebral cortex. However, in order to give a basic idea of the cytoarchitectural organization of the neocortex, some general principles should be mentioned. Following a suggestion by von Economo and Koskinas (1925) the different cortical areas can be collected into larger groups. Most areas, in particular the association areas, show the typical six-layered cortex schematically illustrated in Figure 2.1. They are referred to as *homotypical*. Areas in which six layers cannot be clearly discerned are called *heterotypical*. They come in two forms. First, there is the *agranular* cortex in which layers 2 and 4 with small, densely packed neurones are not well developed. Examples for the agranular cortex are the Brodmann areas 4 and 6, i.e. the motor and premotor areas (Figure 2.2). The second type of heterotypical cortex is the *granular* cortex, which is characterized by strongly developed layers 2 and 4 with many densely packed, small neurones. This type of cortex is mainly found in the primary sensory cortices, e.g. in the Brodmann areas 17, 41 and 3 (primary visual, auditory and somatosensory cortex).

1.2. Myeloarchitectonics

The myeloarchitectonics of the human cerebral cortex, based on the layering, the distribution and the amount of intracortical myelinated fibres, has been described in detail by Vogt and his co-workers (e.g. Vogt, 1910, 1911; Vogt and Vogt, 1919; Strasburger, 1937;

Hopf, 1954; Batsch, 1956). Myelin preparations show three types of intracortical fibres (Figure 2.1): (1) radial fibres (vertical to the cortical surface), (2) oblique fibres, and (3) horizontal fibres (parallel to the cortical surface). The horizontal fibres are particularly useful for cortical parcellation. In most areas they form two conspicuous horizontal bands, the so-called stripes of Baillarger (Baillarger, 1840), which are usually located in layers 4 and 5b respectively (Figure 2.1). The stripes of Baillarger vary from area to area. Again, it is not the aim of this paper to describe the areal variability of myeloarchitectonic patterns in detail. The reader is referred to the papers by Vogt and his co-workers mentioned above as well as to the treatise by Braak (1980). However, some general remarks can be made. The *homotypical* cortex, as it was defined for cytoarchitectonics, usually exhibits both stripes of Baillarger. In some regions, such as the frontal and temporal pole, or areas located medially in the interhemispheric cleft, only the outer stripe of Baillarger may be discernible. In the *heterotypical agranular* cortex the stripes of Baillarger are concealed in a dense feltwork of fibres, either completely as in the primary motor cortex or partially as in the premotor cortex where only the outer stripe of Baillarger is visible. In the *heterotypical granular* cortex two myelin patterns can be distinguished. On the one hand, there is the primary visual cortex with its conspicuous band of horizontal myelinated fibres in layer 4b, the so-called stripe of Gennari. On the other hand, in the primary somatosensory cortex or the primary auditory cortex both stripes of Baillarger are present, the inner one being distinctly more prominent than the outer one.

It is also interesting to consider the areal variability of the *total amount of myelin* in the cortex. The degree of myelination diminishes with increasing distance from the primary areas. It is particularly low in the region of the frontal and temporal pole as well as in areas located medially in the interhemispheric cleft.

1.3. Cyto- and Myeloarchitectonics: Different Aspects of the Same Underlying Cortical Network?

Before discussing possible functional implications of the areal variability described by cyto- and myeloarchitectonics, it seems worthwhile to consider whether there is a relation between patterns of cell bodies and patterns of myelinated fibres. Finding such a relation may elucidate aspects of the underlying cortical network. According to Brodmann (1909), maps of the human cerebral cortex based on either cyto- or myeloarchitectonics are essentially identical. This is corroborated by Sanides' monograph (1962) on the frontal lobe of the human brain. Here, the investigation of a series of sections alternatively stained by a cell body and a myelin stain yielded only one map of areal diversity in the frontal cortex. Thus, there seems to be a close relationship between cyto- and myeloarchitectonics in the sense that they obviously reflect different aspects of the same underlying cortical network. However, what is the nature of this relation? Inspection of Figure 2.1 reveals that an answer to this question is by no means obvious. While the outer stripe of Baillarger, situated in layer 4, corresponds to densely packed, small cell bodies, the inner stripe of Baillarger, located in layer 5b, coincides with less densely packed, large cell bodies.

Braitenberg (1962, 1974) put forward a hypothesis as to how cyto- and myeloarchitectonics might be related. He suggested that horizontal intracortical myelinated fibres, i.e. those fibres forming the stripes of Baillarger, correspond mainly to local axonal ramifications of pyramidal neurons, the most frequent cell type in the cerebral cortex (Braitenberg,

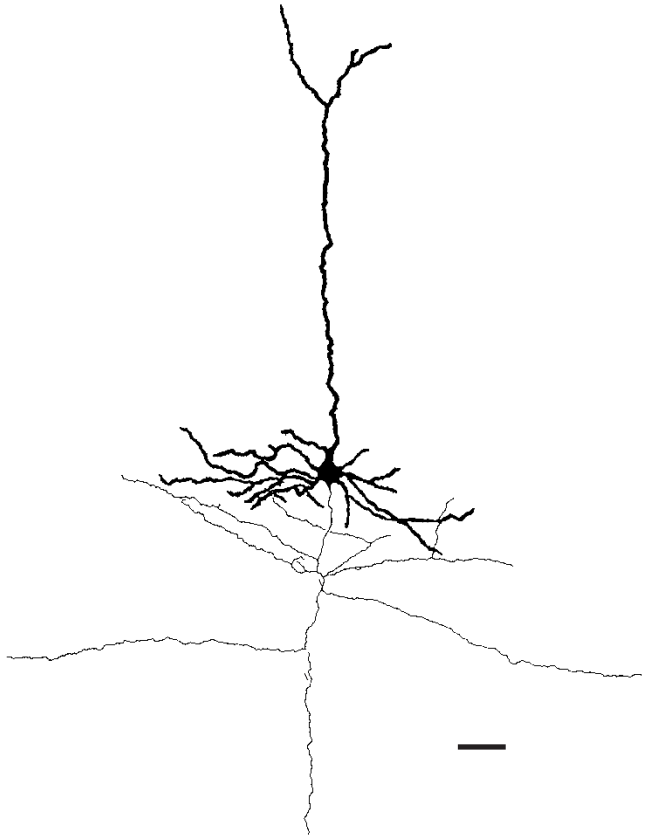

Figure 2.3. Camera lucida drawing of a Golgi-stained pyramidal cell in the cerebral cortex of the mouse. A number of horizontally directed axon collaterals originate slightly below the cell body. Bar, 50 µm.

1978; Braitenberg and Schüz, 1998). The bulk of horizontal axon collaterals of pyramidal cells leave the descending main axon 200 to 300 µm below the cell body (Figure 2.3) (cf. Cajal, 1911; Gilbert and Wiesel, 1979, 1983; Landry *et al.*, 1980; Martin and Whitteridge, 1984; DeFelipe *et al.*, 1986; Schwark and Jones, 1989). The pyramidal cells which in the majority of areas are most conspicuous in layers 3 and 5 would thus produce two maxima of horizontal fibres. These maxima, shifted downwards relative to layers 3 and 5 by 200 to 300 µm, could account for the two stripes of Baillarger. The assumption that horizontal myelinated fibres in the cortex consist mainly of local axonal ramifications of pyramidal cells (and not of thalamic or cortico-cortical afferent fibres) is supported by degeneration and tracer studies (Le Gros Clark and Sunderland, 1939; Fisken *et al.*, 1975; Creutzfeldt *et al.*, 1977; Gatter and Powell, 1978; Colonnier and Sas, 1978; Levitt *et al.*, 1993). Starting out from Braitenberg's hypothesis, Hellwig (1993) showed in a computational study that, provided quantitative data on the cell body picture of a certain area are given, two simple assumptions are sufficient to predict correctly the corresponding myelin picture. Part of this work is reviewed in the following section.

2. SIMPLE RULES RELATE THE CYTO- AND MYELOARCHITECTONICS OF THE HUMAN CEREBRAL CORTEX: UNIFORMITY IN AREAL DIVERSITY

2.1. Cytoarchitectural Data

It was the aim of Hellwig's study (1993) to compute myelin pictures from quantitative data on the cytoarchitectonics of different areas. Cytoarchitectural data were taken from the treatise on the human cortex by von Economo and Koskinas (1925) which contains detailed descriptions of all areas. Three types of data were considered: (1) layer thicknesses; (2) neurone sizes in each layer (specified as the width of a cell body); (3) the volume density of neurones in each layer (specified as numbers of neurones per 0.001 mm^3).

2.2. Two Basic Assumptions

Two basic assumptions were used to transform von Economo's cytoarchitectural data into myelin pictures:

2.2.1. First assumption

Large neurones contribute more to the intracortical myelin content than small ones. This relation can be represented by the sigmoid curve in Figure 2.4. The assumption is hypothetical, but was inspired by observations on Nissl, myelin and Golgi stained sections through human and non-human cortices.

2.2.2. Second assumption

The average distribution of horizontal axon collaterals of pyramidal neurones can be quantified by the histogram of Figure 2.5. This histogram is derived from a Golgi study on pyramidal cells in the rat visual cortex by Paldino and Harth (1977). It was used as a model of the distribution of horizontal axon collaterals with respect to the cell body. Only one modification was introduced for the computations: the histogram was scaled to the

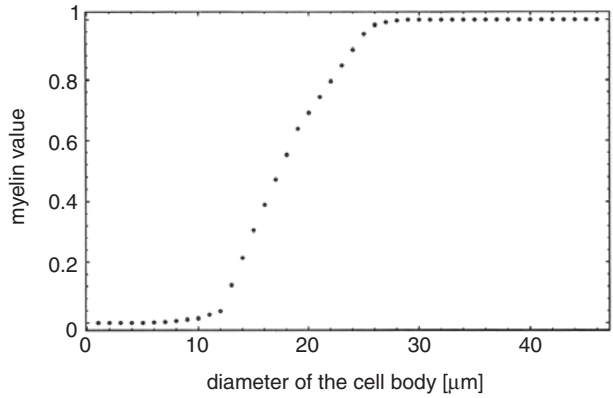

Figure 2.4. A hypothetical curve that transforms the diameter of a neurone's cell body into a "myelin value".

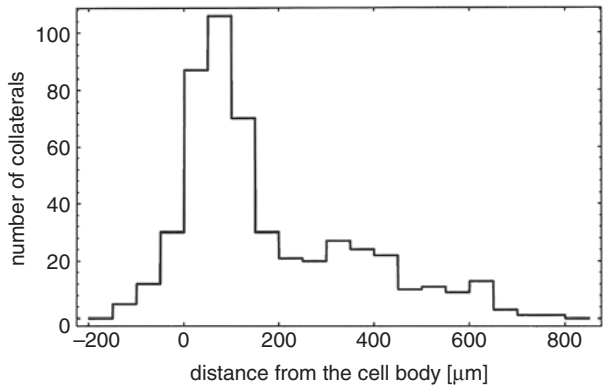

Figure 2.5. Modified diagram from a study by Paldino and Harth (1977) on pyramidal neurones in the rat visual cortex. Distances (vertical to the cortical surface) between the endpoints of axon collaterals and the cell body were measured (positive distances: below the cell body; negative distances: above the cell body). Note that the bulk of collaterals is located below the cell body.

thickness of each area. Note that the second assumption concerns only pyramidal neurones. For the computation this means that the few neurones in layer 1 which are all of the non-pyramidal type (e.g. Peters and Kara, 1985) were discarded. In addition, below layer 1, where the non-pyramidal neurones account for only about 15% of the whole neurone population (Peters and Kara, 1985; Braak and Braak, 1986; Braitenberg and Schüz, 1998), all neurones were considered as pyramidal cells.

2.3. Procedure and Results

In all, 14 neocortical areas were chosen for this study. They comprise areas focussed on by many investigators, and include the motor cortex, the primary sensory areas or the speech centres. Moreover, they give a fair impression of the variability of myeloarchitectonic patterns across the human neocortex. Here, the results of just three areas are presented, the Brodmann areas 4, 7 and 17. The architecture of area 7, a field in the parietal association cortex, is paradigmatic for the homotypical cortex. Area 4 (primary motor cortex) and area 17 (primary visual cortex), on the other hand, represent the two extremes of the heterotypical cortex (Nissl sections shown in Figure 2.6a).

Myelin pictures were computed in two steps. First, using data from von Economo and Koskinas (1925), the average size of neurones in each layer was transformed into a myelin value by means of the curve in Figure 2.4. The myelin value was then multiplied by the corresponding number of neurones per unit volume. The procedure yields, for each layer, a single value which can be considered as the layer-specific contribution to the population of horizontal myelinated fibres (Figure 2.6b).

In the second step of the computation, it was taken into account that myelin is distributed along axonal arborizations. This was done by convolving the diagrams in Figure 2.6b with the histogram of Figure 2.5. This simply provides for shifting the myelin into the appropriate position (Figure 2.6c).

The densities of myelin thus obtained were represented as shades of grey (Figure 2.6d) in order to facilitate comparison with real myelin preparations (Figure 2.6e). The simulated

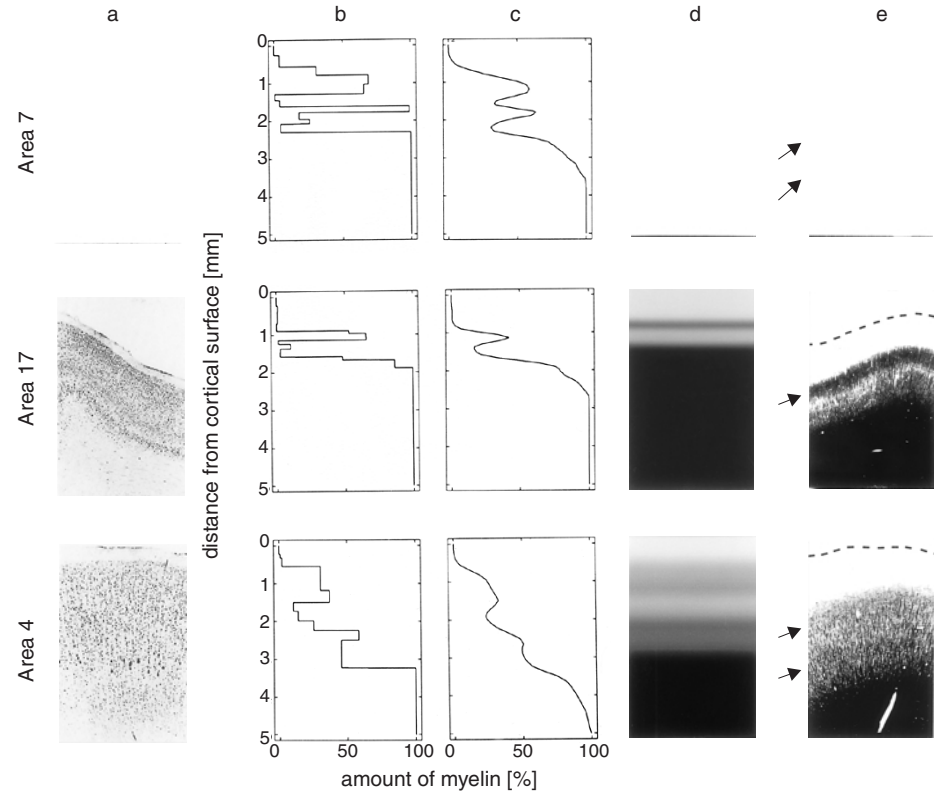

Figure 2.6. Computation of myelin pictures for areas 4, 7 and 17 and comparison with real myelin preparations. (a) Nissl pictures. (b) First step of the computation: the layer-specific amounts of myelin are shown as a function of the cortical depth. (c) The second step of the computation: the diagrams of Figure 2.6b are convolved with the histogram of Figure 2.5. (d) Figure 2.6c, transformed into shades of grey. (e) Real myelin preparations. Bar, 1 mm.

myelin pictures are remarkably close to the real ones. In area 7, both stripes of Baillarger are visible, in agreement with Vogt's (1911) original description. In area 17 only one band of myelinated fibres is conspicuous, the so-called stripe of Gennari (cf. Vogt and Vogt, 1919). In area 4 the comparison between simulation and reality is complicated by the fact that the myeloarchitectonic patterns differ in two subfields. The simulation is close to the anterior part of area 4 where, according to Vogt (1910), only the outer stripe of Baillarger is visible, while the inner one grades into the white matter.

2.4. Conclusion

The findings presented above support the assumption that the stripes of Baillarger consist mainly of horizontal axon collaterals of pyramidal cells. The two assumptions relating cyto- to myeloarchitectonics apply also to the other areas investigated in Hellwig's study (1993). This suggests that the distribution of horizontal axon collaterals of pyramidal neurones and the principles of their myelination are remarkably similar in different areas. Thus, there is obviously both diversity and unity in the cortex. Despite areal variability,

the rules linking cyto- and myeloarchitectonics seem to be essentially uniform throughout the neocortex.

3. CAN CYTO- AND MYELOARCHITECTONICS BE INTERPRETED IN FUNCTIONAL TERMS?

3.1. Connectivity and Function

A functionally or computationally relevant description of cortical anatomy will focus on the *connectivity* between neurones. It is obvious that the wiring scheme in the cortex strongly influences how information is processed. Considering the enormous number of synapses in the cortex, connectivity certainly has to be described in a statistical way. The cortical wiring scheme can probably be adequately grasped by parameters such as connection probabilities, number of synapses involved in a connection, the amount of divergence and convergence or the relative importance of short- and long-range connections. Once these parameters are known, one should be able to specify the connections of an arbitrarily selected neurone to other neurones in the cortex in a probabilistic way.

Braitenberg and Schüz (1998) have described the basic machinery of the mouse cortex on the basis of a statistical analysis of its components. To some extent, these data can be extrapolated to the human cerebral cortex. However, it is still largely unclear how the basic cortical wiring scheme varies from area to area. This leads to the question discussed in the next section: Can the variability of the connectivity scheme in different areas of the human cerebral cortex be inferred from cyto- and myeloarchitectonics and does this lead to a better understanding of the mechanisms of information processing in these areas?

3.2. Discussion

In cytoarchitectonics, the local variations of size and packing density of cell bodies are used for cortical parcellation. The number of synapses on cell bodies is small, rarely exceeding 200 (Peters and Kaiserman-Abramof, 1970; White and Rock, 1980; Müller *et al.*, 1984). This is not much compared to the overall number of synapses carried by a cortical neurone: about 8000 in the mouse and about 40 000 in the human cortex (Braitenberg and Schüz, 1998). In other words, a method that stains the cell bodies of a neurone cannot be very helpful for elucidating cortical connectivity. Connections are predominantly located in the neurophil, i.e. in those parts of the cortical tissue that remain unstained in cell body preparations.

Nevertheless, a few general statements about connectivity can be made, since the size of a cell body is positively correlated to the length of its dendritic arborizations (Bok, 1959). For instance, small perikarya which are densely packed indicate that the dendritic processes are relatively short, thus occupying only a small volume. This applies to layer 4 of the primary sensory areas where the thalamic afferents arrive. The dense packing of cell bodies points to a local preprocessing of the incoming thalamic information.

Some layers contain large cell bodies which are not so densely packed, e.g. layers 3 and 5 in Figure 2.1. This indicates large and richly ramified dendritic trees, i.e. information is sampled from a relatively extended piece of cortex. Pyramidal neurones in layers 3 and 5 are the origin of important long-range projections to other cortical or subcortical structures.

Their large dendrites seem to ensure that the information which is projected contains a relatively general overview of cortical activity, and not some specialized data about the processes in small cortical patches.

Beyond this, cytoarchitectonics does not tell us much about patterns of dendritic or axonal arborizatons which carry the bulk of synapses and are thus most important for cortical connectivity. In this respect, myeloarchitectonics might be more interesting because it shows patterns of intracortical fibres.

The main function of myelin is probably to increase conduction velocities. However, it is doubtful that this is an important property for all *intracortical* axonal fibres. Many of them are so short that the actual conduction times are within the range of a few milliseconds, even if the whole variability of conduction velocities encountered in the nervous system is taken into consideration. This is unlikely to be significant (Hellwig, 1993). An important function of intracortical myelin might be its ability to insulate axonal fibres, in the sense that myelinated segments of axonal ramifications are unable to form synapses. This is an interesting property of myelin, since it means that myelination imposes a spatial structure on axonal trees: in some places they are capable of interacting with other neurones, in others they are not.

The distribution of myelin over the axonal tree is probably not random. The time course of maturation in the primary visual cortex of the cat suggests that myelination is related to early learning processes. In the first postnatal weeks, there is a period of extraordinary plasticity in the visual cortex, the so-called critical period. Plasticity, for example the susceptibility to the effects of monocular deprivation, is high until some time between the sixth or eighth week after birth (Hubel and Wiesel, 1970; Olson and Freeman, 1980). On the level of pyramidal neurones this period is characterized by the emergence and refinement of axonal arborizations (Callaway and Katz, 1990). By pruning of inappropriate axon collaterals, axonal ramifications are formed in which long horizontal axonal fibres give off clusters of axon collaterals that preferably contact certain target regions, namely columns of similar orientation preference (Gilbert and Wiesel, 1989). The process of shaping axonal trees is experience-dependent (Löwel and Singer, 1992). Axonal arborizations attain an adult appearance by the end of the critical period, i.e. about 7 weeks after birth (Callaway and Katz, 1990). Interestingly, this is the time when myelination starts. The first myelinated fibres in the primary visual cortex of the cat appear by the end of the sixth postnatal week, myelination is moderate until the end of the eighth week, and then undergoes an enormous, almost explosive increase (Haug *et al.*, 1976).

In conclusion, two processes seem to coincide at the end of the critical period in the visual cortex of the cat: the termination of the experience-dependent shaping of axonal branching patterns and the onset of myelination. Observations on individual pyramidal cells suggest that the myelinated parts of axonal trees are mainly those horizontal fibre segments that interconnect clusters of collaterals (DeFelipe *et al.*, 1986) (Figure 2.7). Thus, myelin would insulate predominantly axonal segments which failed to establish functional relations with other cortical neurones during the critical period. In other words, myelin would be a sort of memory trace, a tool to store information about early learning processes.

The interpretation of myelin as a memory trace by which early experiences are fixed may explain why the overall amount of myelin is higher in the heterotypical areas, i.e. in the primary motor and sensory cortices, than in the homotypical association cortex. The primary areas are in a close relation to the outside world, and a repertoire of information

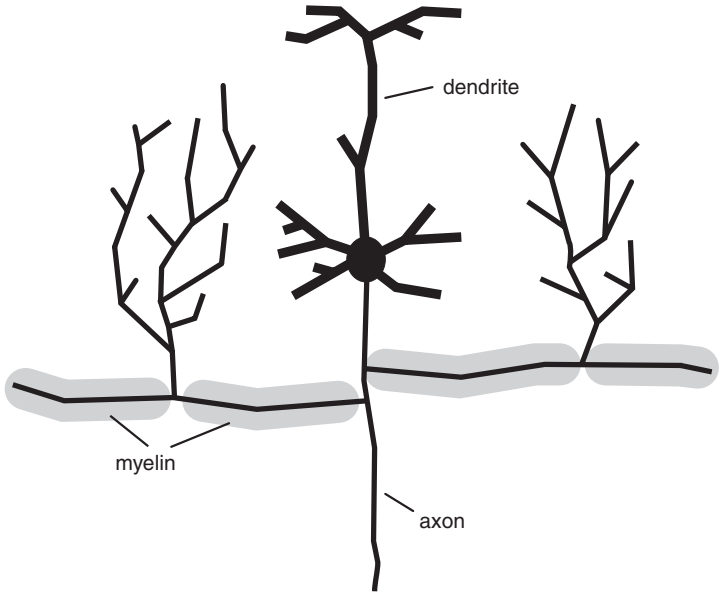

Figure 2.7. Schematic drawing of a cortical pyramidal cell. Long myelinated horizontal axon collaterals emanate below the cell body and give off clusters of non-myelinated collaterals.

processing steps fixed by early experiences may be an efficient way to deal with ever-recurring standard tasks. In the association cortex the tasks to be expected are less predictable. Thus, a less rigid wiring scheme may be useful in which associations of all kinds can be learned. In this context, it is also interesting to note that the onset of myelination is much earlier in the primary areas than in the association cortex (Flechsig, 1920, 1927). All in all, it is, however, most difficult to interpret areal variability as revealed by myeloarchitectonics in functional terms. This is mainly due to the fact that myelin preparations, although showing axonal fibres, do not reveal the cortical wiring scheme, since those axonal fibre segments are stained that, insulated by myelin, are unable to contact other neurones. In a way, myelin preparations display the "negative" of intracortical connectivity.

3.3. Outlook

It is an important task for neuroanatomists (and for neuroscientists in general) to relate structure to function. As far as the parcellation of the cortex into areas is concerned, this goal has been achieved mainly in one respect: Certain functional specializations can be attributed to certain areas. However, beyond the *localization* of function, the functional interpretation of areal variability in the cortex is largely unclear. In particular, it remains to be clarified why areal adaptations of the basic cortical network seem to be particularly appropriate for the execution of specific tasks. For instance, one wonders why the structure of the motor cortex is obviously useful for the control of movements, but not for other tasks such as the processing of visual information. In other words, the relation between the *mechanisms* of information processing and the areal variability of cortical anatomy is

unclear. This is due to the fact that the connectivity patterns in each area are largely unknown. As pointed out above, cyto- and myeloarchitectonics are not very helpful in this respect.

How can variations of wiring schemes in different areas be elucidated? Knowing the variability of neuronal arborizations in different areas would in itself be helpful. Unfortunately, this type of information is scarce. For the human cortex, one of the main sources is still Cajal's (1911) treatise on the nervous system, which yields some qualitative, but no quantitative data on the variability of Golgi-stained neurones in different areas. More recent material is reviewed in this book in chapters by Jacobs and Scheibel (2002) and Valverde *et al*. (2002). In all, studying the architectonics of the cortex as revealed by Golgi or similar methods is still a worthwhile research program.

An approach by which the local connectivity between pyramidal neurones in a given area can be quantitatively estimated has been suggested by Hellwig (2000). Pyramidal neurones in layers 2 and 3 of the rat visual cortex were intracellularly stained and three-dimensionally reconstructed using a computer-based camera lucida system. In a computer experiment, pairs of pre- and postsynaptic neurones were formed and potential synaptic contacts, i.e. spatial contacts between axons and dendrites, were calculated. For each pair, the calculations were carried out for a whole range of distances (0 to 500 µm) between the pre- and the postsynaptic neurone, in order to describe cortical connectivity as a function of the spatial separation of neurones. It was also possible to differentiate whether neurones were situated in the same or in different cortical layers. The data thus obtained were used to compute connection probabilities, the average number of contacts between neurones or the frequency of specific numbers of contacts. It could be shown by comparison with independent data that the local cortical connectivity between pyramidal neurones estimated in this way was a good approximation to reality. In principle, this approach can be extended to other layers as well as to other areas. This makes it possible to investigate cortical architectonics in terms of connectivity.

The interpretation of functional processes in cortical areas will certainly be promoted by knowledge about the underlying wiring scheme. However, data on connectivity could also be important in another context: They could actually be used to build artificial neuronal networks with a biologically realistic structure. In such networks, the areal variability of information processing could be studied. Thus, describing cortical architectonics in terms of connectivity would not just be an analytic undertaking, but could also serve as a basis for a synthetic approach.

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3 Architectonic Mapping of the Human Cerebral Cortex

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The classical cyto- and myeloarchitectonic maps of the human cerebral cortex considerably influenced the concept of localization of function. Presently, these maps serve as anatomical references in functional imaging studies. However, the classical maps suffer from drawbacks such as the highly observer-dependent definition of areal borders; the fact that they present only a single aspect of architectonic organization of the cortex (e.g. only cytoarchitecture), and the lack of information on intersubject variability of location and size of a cortical area in a spatial reference system. Recent methodological progress in computerized image analysis of histological specimens, the introduction of markers which reflect various architectonic aspects of cortical organization (e.g. receptor autoradiography), and the development of warping techniques to compensate for intersubject variability of brain structure in 3D made it possible to overcome these drawbacks. We propose a new concept of architectonic mapping which is based on: (i) a definition of areal borders by using multivariate statistical analysis, and not by highly subjective judgements; (ii) a quantitative analysis of similarity and dissimilarity in architecture between cortical areas; and (iii) a multimodal characterization of cortical organization based on cyto-, myelo- and receptor-architectonic mapping. The comparison of architectonic maps with functional imaging data in a common standard reference space allows, for the first time, a direct analysis of correlations between structure and function in the living human brain, and provides new insights into the architecture of the cerebral cortex.

KEYWORDS: architecture, brain mapping, human cerebral cortex, intersubject variability, transmitter receptors

1. INTRODUCTION

The classical cytoarchitectonic maps of the human cerebral cortex published by Brodmann (1909), Campbell (1905), Elliot Smith (1907), von Economo and Koskinas (1925) and the Vogts (Vogt and Vogt, 1919) have recently gained considerable attention, since they present mandatory structural data for the microanatomical interpretation of functional imaging data. These maps, however, do not fulfil the requirements of an anatomical reference system for functional human brain mapping. For instance, they present only schematic, simplified drawings of a single, individual brain or hemisphere in a two-dimensional view without any descriptions of the intersubject variability of cortical architecture. The same is true for more recent architectonic maps, e.g. by the Russian school (Sarkisov *et al*., 1949),

Sanides (1962, 1964), Bailey and von Bonin (1951) and Braak (1979). Moreover, these maps differ between each other with respect to the number, location and extent of cortical areas (Zilles, 1990).

Campbell subdivided the human cerebral cortex on the basis of cell body- and myelin-staining into 14 regions, amongst them precentral, frontal, visuo-sensory, and the audito-psychic areas (Campbell, 1905). Elliot Smith studied the regional and laminar distribution of myelinated fibers in unstained sections, and proposed a different map containing about 50 areas (Elliot Smith, 1907). Nowadays, the most widely used map is that of Brodmann, which relies on extensive studies of cell body-stained (Nissl-stain) histological sections (Brodmann, 1903, 1905, 1908, 1909). He subdivided the cortex on the basis of cytoarchitectonic criteria into approximately 40 cortical areas. Unfortunately, he never described his criteria for parcellation of most of the areas in sufficient detail. This is true in particular for so-called higher associative areas like areas of the prefrontal cortex, posterior parietal lobe, and of the inferior temporal cortex.

Brodmann's schematic surface drawing of an architectonic map was used by Talairach and Tournoux as basis of the architectonic parcellation in their stereotaxic atlas (Talairach and Tournoux, 1988). They simply transferred Brodmann's areas to their own brain atlas by trying to identify corresponding sulcal patterns in both brains, assuming a strong association between the sulcal pattern and borders of cortical areas. Such an association, however, was already doubted by Brodmann. He mentioned that "... a schematic drawing can reflect only the major spatial relationships, and therefore, precise topographical associations[1] cannot be considered in general or only in a distorted manner; this is true in particular for all those cortical regions which have borders in the neighborhood of sulci and those regions which are located in the depth of such a cortical region" (Brodmann, 1908).

The basis of Brodmann's research was the working hypothesis that the cerebral cortex is composed of numerous cortical areas, each of them characterized by a distinct cyto-architecture and function. Following this concept, the cytoarchitecture of a cortical area should be more or less constant within a cortical area, but changes considerably at its border. For example, Brodmann's area 4 was conceptualized as the anatomical equivalent of the primary motor cortex which guides voluntary movements (Fritsch and Hitzig, 1870) and Broca's region was regarded as the anatomical correlate of the functionally defined center of speech (Broca, 1861). Although for the vast majority of cortical areas such as microstructural-function relationship could not be rigorously tested at that time, both Brodmann and Campbell took architectonic localization of function for granted. The strict localizationist approach culminated in a map of the human cortex of Kleist (1934) in which complex functions were assigned to a distinct cytoarchitectonic area. Brodmann's area 18 (for instance) was associated with visual attention, perception of spatial position, and eye movements toward the upper and lower visual field. Brodmann himself did not represent such an extreme localizational concept (Brodmann, 1909). In order to avoid a confusion of histological data and unproven evolutionary and functional speculations, he created his system of a "neutral" nomenclature by numbering different cytoarchitectonic areas mainly according to their dorso-ventral sequence. Older studies (Vogt and Vogt, 1919) and more recent electrophysiological studies in nonhuman primates have demonstrated that the basic idea of Brodmann was true: Neurones with similar receptive fields and

[1] i.e. between sulci and areal borders [Au].

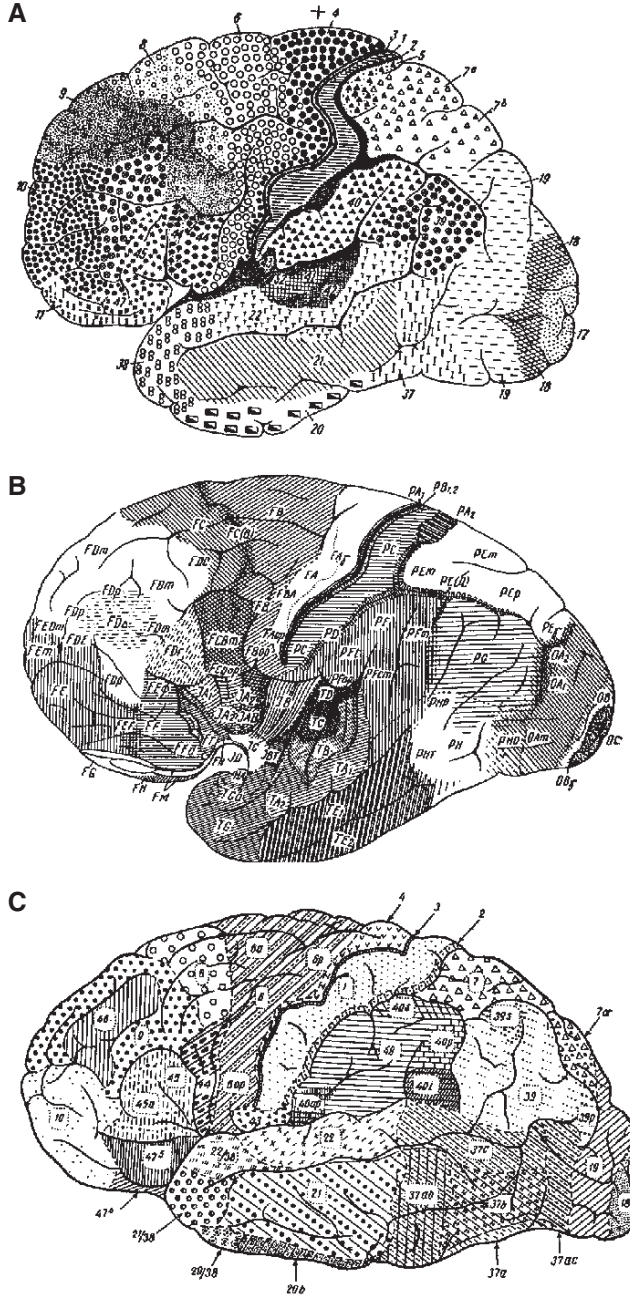

Figure 3.1. Cytoarchitectonic maps of the lateral surface of human brain adapted from [**A**] Brodmann (1909), [**B**] von Economo and Koskinas (1925) and [**C**] the Russian school (Sarkisov *et al*., 1949). Cytoarchitectonic areas are marked by different hatches and classified according to Brodmann's nomenclature by Arabic numerals [**A, C**] or according to that of von Economo and Koskinas by letters and numerals [**B**]. Note differences in sulcal pattern as well as in shape and extent of the areas (e.g. in the frontal lobe with respect to areas 45, 9 and 46; compare **A** with **C**).

response properties lie within the same cytoarchitectonic area, as found when the same brain is sectioned and cell-stained following recording experiments, and correlations are sought between penetration sites and the cytoarchitectonic pattern. Conversely, response properties of neurones change across cytoarchitectonic borders (Luppino *et al.*, 1991; Matelli *et al.*, 1991; Tanji and Kurata, 1989).

Although later studies extended and supplemented the maps of Brodmann and Campbell, they followed the concept of a cortical area implied by these maps. von Economo and Koskinas (1925) introduced an even more complex subdivision of the human cortex into cortical areas with regional peculiarities (= subareas). They defined cortical areas on the basis of their topography (frontal, parietal, occipital, etc.), and in terms of their cytoarchitecture and local peculiarities. As an example, area F*A*g is characterized by its location in the frontal lobe ("F"), an agranular cytoarchitecture ("*A*") with giant pyramidal cells ("γ"). Area F*CB*, e.g. has common features of area F*B* and F*C*, etc. Discussion of this concept, however, raised controversy in the scientific community. von Economo and Koskinas applied quantitative criteria (e.g. size of cells, thickness of layers) in order to provide a more precise characterization of a cortical area, to formalize the cytoarchitectonic description of cortical areas, and to make it more independent of the experience of the observer. Finally, the Russian school published another map of the human cerebral cortex which was, however, based mainly on Brodmann's approach. Additionally, they tried to overcome one of the unsolved problems of Brodmann's map, i.e. the neglect of intersubject variability. Their atlas considered intersubject variability in the extent and position of cortical areas by analyzing a sample of dozens of hemispheres (Filimonoff, 1932; Kononova, 1935, 1938; Sarkisov *et al.*, 1949).

The increasing number of available architectonic atlases revealed a further problem of architectonic mapping. Although all the cytoarchitectonic maps were based on the same concept of a cortical area as an architectonically distinct and homogeneous region, and all were the result of the same methodical approach, their areal patterns do not match, for example, with respect to the number of cortical areas, their relationship to sulci and gyri, as well as to the neighbouring cortical areas. Even if we compensate for interindividual differences in the macroscopical anatomy of the brains, numerous differences between the maps can hardly be explained. Thus, in the frontal lobe, area 46 has a common border with areas 44 and 45 in Brodmann's map (Brodmann, 1909), but this border is absent in the map of the Russian school, since here area 9 separates completely area 46 from 44 and 45 (Sarkisov *et al.*, 1949). In a more recent study, transitional areas were defined which exhibited mixed architectonic features of areas 46 and 45 (Rajkowska and Goldman-Rakic, 1995b). Considerable differences between the maps can also be found with respect to the anterior border of area 4, the extrastriate visual cortex, and the parietal cortex, where Brodmann found only a few areas, but recent observations revealed a much higher number of areas.

What might be the reasons for differences between the maps? One reason concerns differences in parcellation criteria of the different observers. The most important criteria used in all studies are the density and size of nerve cells, their distribution within cortical layers, the absolute and relative thicknesses of cortical layers, the radial and horizontal arrangement of neurones, the presence of special cells (e.g. giant Betz cells of Brodmann's area 4), and locally specific subdivisions of layers into sublayers (e.g. the subdivision of layer IV of Brodmann's area 17 into sublayers IVA–C). For the vast majority of cortical areas, not only one, but a whole complex of criteria is used for its definition. Very often,

these criteria are weighted relative to each other, in a different way by each observer. In addition, the criteria are sometimes difficult to formalize objectively. This can be illustrated by the example of such a "simple" area as Brodmann's area 4. Typical for this area are giant pyramidal cells in layer V (Betz cells), which were discovered by Betz as characteristic cells of the motor area of man, chimpanzee, other primates and dog (Betz, 1874). However, how big is a Betz cell? The height of these cells may vary between different individuals from 60–120 µm, their width from 30–60 µm. Moreover, comparably large-sized cells can be found outside area 4 in the area postcentralis gigantopyramidalis (von Economo and Koskinas, 1925). Furthermore, the distance between single Betz cells increases towards subarea 4a (Geyer *et al*., 1996; Zilles *et al*., 1995). Thus, the border between area 4 and the rostrally adjoining area 6 is difficult to define on the basis of the Betz cells-criterion. If giant pyramidal cells are defined not by their absolute size, but by their relative size (i.e. comparison with cells in neighbouring areas), such cells can be also found in layers III and V of areas 44 and 45, in the extrastriate visual cortex and in the temporal cortex (Bailey and von Bonin, 1951). Consequently, a reliable definition of area 4 requires not only this, but also additional criteria, e.g. the absence of an inner granular layer.

Bailey and von Bonin further followed this line of discussion and asked if there is any objective basis for a detailed cytoarchitectonic map at all. They came to the final conclusion that "... vast areas are so closely similar in structure as to make any attempt at subdivisions unprofitable, if not impossible". As a consequence, their cytoarchitectonic map is based only on a parcellation into a few main types of cortical regions: regions with numerous granular cells (koniocortex), without granular cells (agranular cortex), with large pyramids in layer III, and the allocortex, as well as 4 combinations between these main types. In contrast to the previously mentioned maps of Brodmann and others, their map does not show sharp borders but gradual transitions between areas (Bailey and von Bonin, 1951).

The question arises about which cortical map is the most appropriate. Is it that of Bailey and von Bonin with 8 subdivisions, that of Campbell, Brodmann and the Russian school with about 20 to 40 subdivisions, or that of von Economo and Koskinas with about 100 areas and subareas? One way to answer this questions may be the combination of cytoarchitectonic mapping with other architectonic mapping techniques (multimodal mapping). Flechsig was the first to gave a detailed subdivision of the neocortex into 40 cortical areas by his myelogenetic method, i.e. by studying the heterochronous development of myelination in the white matter immediately below the cortex during foetal and early postnatal periods (Flechsig, 1898). The Vogts and their co-workers subdivided the human cortex on the basis of myeloarchitectonic criteria (distribution and density of myelinated axons within the cortex) into more than 150 fields (Lungwitz, 1937; Riegele, 1931; Strasburger, 1938; Vogt and Vogt, 1919; Vogt, 1919). Their map and the underlying nomenclature were quite complex and difficult to verify for other observers. This might be one reason why it did not reach general acceptance in subsequent years. More recent methods of cortical mapping, e.g. by immunohistochemistry (Bidmon *et al*., 1997; Campbell and Morrison, 1989; Hendry *et al*., 1994; Tootell and Taylor, 1995; Zilles *et al*., 1991c), histochemistry (Burkhalter and Bernardo, 1989; Clarke, 1994; Wong-Riley *et al*., 1993), pigmentoarchitecture (Braak, 1977, 1979) and regional and laminar distribution of different transmitter receptor binding sites (Dietl *et al*., 1987; Jansen *et al*., 1989; Zilles and Clarke, 1997; Zilles and Schleicher, 1995; Zilles *et al*., 1988, 1991d) proved to be valuable alternatives in architectonic research. Most importantly, the maps based on different histological and histochemical techniques frequently show a perfect spatial coincidence of

many areal borders, thus corroborating the position of an areal border by multimodal imaging. Moreover, since a single receptor may not reveal all borders demonstrated by other markers, this finding can be used to define a family of neurochemically related areas by studying the regional pattern of one transmitter receptor, and comparing its distribution with the maps revealed by other receptors or by cytoarchitecture. We think that such a multimodal concept of cortical mapping improves and supplements classical cytoarchitectonic analysis.

We will show below, that the architectonic analysis of any histological or histochemical specimen can also be improved considerably by using quantitative measurements and statistically testable image analysis procedures:

(i) Borders between cortical areas can be identified by observer-independent statistical analysis of local changes in cytoarchitecture (Schleicher *et al*., 1999). We will illustrate this approach in cytoarchitectonic specimens, although it can also be applied to receptor architectonic and myeloarchitectonic specimens (Zilles and Schleicher, 1993).
(ii) We will present a method for quantifying cytoarchitectonic differences between cortical areas. This method defines the similarity or dissimilarity between cortical areas in terms of numerical distance measures. Using this approach, it can be tested statistically whether differences in cytoarchitecture (or any other architecture) are significant. Furthermore, it allows one to test the long-standing hypothesis of the gradual, rather than distinct character of the majority of cytoarchitectonic borders (Bailey and von Bonin, 1951).
(iii) In contrast to previous cortical maps which were based on only one technique, multimodal architectonic analysis will be performed. We will discuss the correspondence and differences of architectonic borders which are revealed by receptor autoradiography of numerous different receptor binding sites, as well as by cytoarchitecture. Human striate and extrastriate areas, as well as Brodmann's areas 44 and 45 (Broca's region) will serve as examples for multimodal mapping of the cerebral cortex.
(iv) We will conclude with some perspectives on the application of these maps in a three-dimensional probabilistic atlas system.

2. OBSERVER-INDEPENDENT DEFINITION OF CYTOARCHITECTONIC BORDERS

One of the key features of the neocortex is its organization in layers running parallel to the pial surface. Cortical layers differ by their absolute and relative widths and cell densities. The laminar pattern of a cortical area is represented by its sequence of layers, varying in cell density. Our observer-independent approach to the definition of cortical borders considers these architectonic features. It is based on the assumption that each area has a unique, homogeneous laminar pattern, which distinguishes it from those of neighbouring cortical areas. Several methods have been applied in the past for quantifying the laminar pattern. An early approach was described by Hudspeth and colleagues (1976). They analyzed optical density profiles to describe the distribution of staining intensity across cortical layers in the human primary visual cortex. Although the optical density is an easy and fast measurable parameter, it has the major disadvantage of being sensitive to differences in staining intensity of nerve cells (and of the background) in different brains and sections.

For technical reasons, such differences are almost inevitable in histological specimen. Variations in intensity are influenced by factors like age, clinical history, cause of death, *post mortem* delay, autopsy conditions, and histological techniques (Blinkov and Glezer, 1968; Haug, 1980; Skullerud, 1985; Vierordt, 1893).

Based on this experience, we used the volume density of nerve cells in order to quantify the laminar pattern, a parameter with a long tradition in quantitative neurobiology (Haug, 1956; von Economo and Koskinas, 1925). It has the advantage that, within reasonable limits, it is not affected by either staining, or anisotropy (Weibel, 1979). The volume density of nerve cells was estimated as the areal fraction of all stained cellular profiles in square measuring fields of 20–30 µm and defined as gray level index (GLI) ranging from 0% to 100% (Schleicher and Zilles, 1990). Other stereological parameters (e.g. the numerical density) are also available, but we focussed on the volume density since this robust stereological parameter can be automatically estimated from existing histological series in large samples. This parameter is highly correlated with the volume density of neurones, since the density of endothelial and glial cells does not vary systematically throughout the cortical layers (Wree *et al*., 1982). Using a computerized image analyzer, the GLI was measured in cortical regions of interest (Figure 3.2). GLI images were achieved from which GLI profiles (= density profiles) reaching from the border between layers I and II to the border between cortex and white matter were extracted. The shape of these density profiles describes quantitatively the laminar pattern, i.e. the cytoarchitecture of a cortical area. Dissimilarities between cortical areas and their laminar patterns were reflected by differences in shape of the density profiles. The shape of a profile was numerically described by a set of ten features: the mean of the amplitude (i.e. the mean GLI; *meany.o*), the center of gravity in the x-direction (*meanx.o*), the standard deviation (*sd.o*), the skewness (*skew.o*), the kurtosis (*kurt.o*), and the analogous parameters for the first derivative of each profile (*meany.d, meanx.d, sd.d, skew.d, kurt.d*). Features are based on central moments (Dixon *et al*., 1988) of the original density profile, and on its first derivative, by treating the profile as a frequency distribution, whereby the cortical depth is the x-value and the GLI is the frequency value at that x-value. Features were normalized in order to weight them equally. Some features can be interpreted directly in terms of cytoarchitecture: the mean GLI increases with increasing density of cell bodies. The feature *meanx.o* will be smaller than 50% if the supragranular layers have a higher GLI than the infragranular layers. Vice versa, if the infragranular layers show more densely packed cell bodies than the supragranular layers, the *meanx.o* will be shifted to a value greater than 50%.

Multivariate statistical analysis was then used in order to quantify differences in shape between profiles. The Mahalanobis distance *D* was used as a multivariate measure of differences in shape between neighbouring profiles for detecting cytoarchitectonic borders (Schleicher *et al*., 1998, 1999). The basic idea was that profiles are more or less similar in shape within a cortical area (homogeneity criterion), and the shape changes abruptly at the border of two neighbouring areas (Schleicher *et al*., 1995). In order to detect the position of the border, cortical regions of interest were covered by a sequence of equidistant density profiles (Figure 3.2A). The Mahalanobis distance was then calculated between two neighboring sets (= blocks) of profiles (Figure 3.2C). If these two blocks belong to one and the same area, the Mahalanobis distance was small, since differences in the laminar pattern between these two groups of profiles were small. *Vice versa*, if these two blocks were located exactly at opposite sides of a cortical border, the Mahalanobis distance was maximal since differences in the laminar pattern of these two groups of profiles were

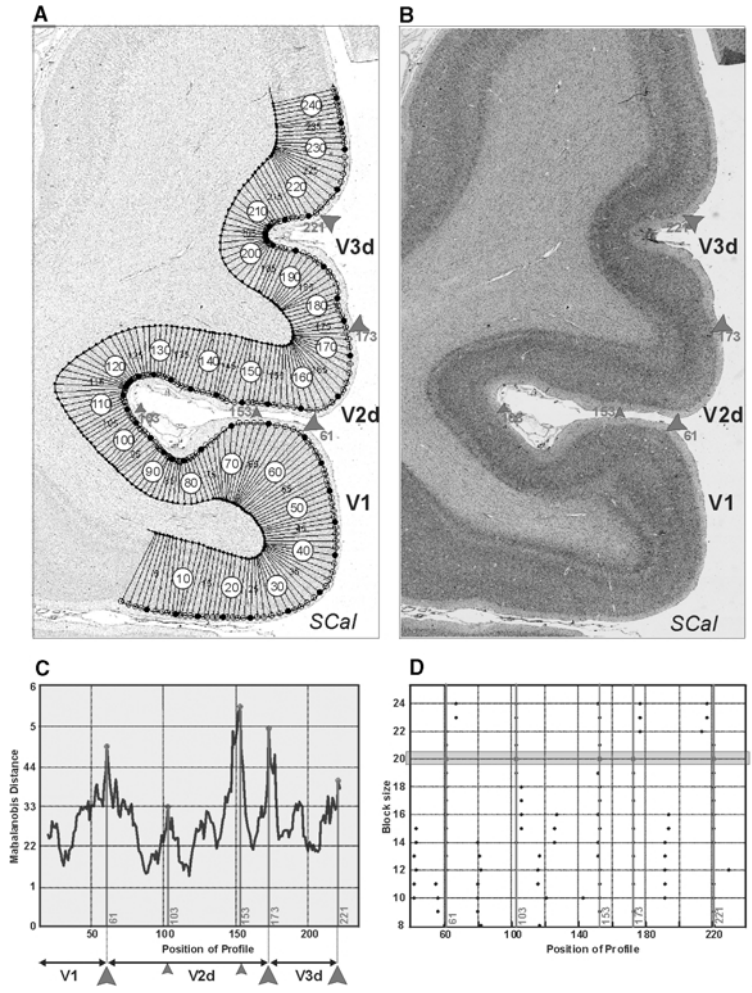

Figure 3.2. Observer-independent definition of cytoarchitectonic borders of the visual cortex. The GLI as a measure of neuronal packing density (Wree *et al*., 1982) was obtained in a histological section stained for cell bodies (Zilles and Schleicher, 1980; Zilles *et al*., 1986; Amunts *et al*., 2000; Schleicher and Zilles, 1990). As a result, a GLI image [**A**] was produced, in which each pixel corresponds to a GLI value measured with a spatial resolution of 25 µm. Light pixels correspond to a low packing density, dark pixels to a high density. The cortical region of interest was covered by a sequence of profiles, indexed consecutively from 1 to 242 [**A**]. Each profile quantifies the course of the GLI from the border between layers I and II to the border between the cortex and the white matter (along a line perpendicular to the cortical surface). A multivariate distance measure, the Mahalanobis distance *D*, was calculated (Schleicher *et al*., 1998) [**C**]. *D* is a measure of difference in profile shape between neighbouring blocks of profiles; e.g. *D* at the position of profile 20 was calculated as the difference in shape between profiles 1–20 and profiles 21–40 [**C**]. Since 20 profiles of one block were compared with 20 profiles of the neighbouring block, the block size in this case was 20. *D* was calculated for different block sizes ranging from 8 to 24 [**D**]. The dots mark the positions of significant Mahalanobis distances for each block size and each position of the profile. For block size 20, significant distances were obtained from the graph of [**C**]. Significant values of the Mahalanobis distance are marked by red circles and lines. In this histological section, borders were quantitatively defined between areas V1 and V2d (large arrowhead at position 61), within area V2d (small arrowheads at positions 103 and 153), and between areas V2d and V3 (large arrowhead at position 173), and transferred to the original histological section [**B**]. The border between areas V1 and V2d corresponds to the border between Brodmann's areas 17 and 18, that between V2d and V3 to the border between Brodmann's areas 18 and 19 (Amunts *et al*., 2000; Gattass *et al*., 1981; Newsome and Allman, 1980; Newsome *et al*., 1986; Zilles and Clarke, 1997). *Scal*—Sulcus calcarinus. (*see Color Plate 1*)

large. After the calculation of the Mahalanobis distance for the two adjacent blocks of profiles, both blocks were shifted simultaneously by ≈128 µm (i.e. by the width of one profile) to the next position. In this manner, the Mahalanobis distance was calculated continuously for all sequential positions of all possible blocks of profiles in the region studied (Figure 3.2C). Distances were calculated for different block sizes ranging from 8 to 24 profiles per block (Figure 3.2D). They were calculated between blocks of profiles, and not between single profiles, in order to improve the signal to noise ratio. A subsequent Hotelling's T^2 test (with a Bonferroni correction of the p-values) was applied for testing the significance of each value of the Mahalanobis distance. Borders were defined at those positions of profiles where the following criteria were fulfilled. The Mahalanobis distance D is significant (Hotelling's T^2-test; $\alpha = 5\%$), positions with significant D were stable across different block sizes and could be followed up through neighboring histological sections.

In the histological section shown in Figure 3.2, the Mahalanobis distance reaches significant values at the areal borders between areas V2d and V1 at position 61, and between areas V2d and V3 at position 173. Within area V2, the distance shows local maxima at positions 103 and 153. In our sample, internal subparcellations of V2 were associated with the presence or absence of large pyramidal cells in deep layer III. Borders within area V2 have been described in the past by several authors using cytoarchitectonic criteria (Amunts *et al*., 2000; von Economo and Koskinas, 1925), myeloarchitecture (Lungwitz, 1937; Sanides and Vitzthum, 1965a,b) as well as on the basis of cytochrome oxidase staining (Burkhalter and Bernardo, 1989; Clarke, 1993; Clarke and Miklossy, 1990; Gattass *et al*., 1997; Lewis and Olavarria, 1995; Merigan *et al*., 1993; Tootell and Taylor, 1995).

Thus, this approach not only confirms borders between well known cytoarchitectonic areas according to Brodmann's map, but it also detects new subdivisions. A further example is the subdivision of Brodmann's area 4 into an anterior and a posterior part (Geyer *et al*., 1996). Recently, areas 3a and 3b were confirmed in cytoarchitectonic specimens (Geyer *et al*., 1999) using this method. These areas were first mentioned by Brodmann (1909) and later explicitly described by the Vogts in their myeloarchitectonic map (Vogt and Vogt, 1919).

3. HOW DIFFERENT ARE TWO CORTICAL AREAS IN THEIR CYTOARCHITECTURE?

Whether a cortical region is homogeneous in architecture and thus constitutes a single cortical area or, alternatively, consists of two or more cortical areas, has been a matter of controversy between different observers. Consequently, the different cortical maps display a different number of cortical fields. The number reaches from 8 (Bailey and von Bonin, 1951) to more than 100 (von Economo and Koskinas, 1925; Vogt and Vogt, 1919). The analysis of interareal differences in cytoarchitectonics becomes even more complicated due to intersubject variability in architecture of the same cortical area in different brains. Cytoarchitectonic variability has been described since the early days of architectonic research (Kononova, 1938; von Economo and Koskinas, 1925). Other authors mentioned it as "considerable", but the degree of variability was not quantified. Intersubject variability in microstructure makes it often difficult or even impossible to detect reliably subtle differences in cytoarchitecture between areas. Finally, the statement of whether several

cortical areas are more similar (or different) in cytoarchitecture cannot be verified by using pure visual inspection.

Thus, analysis of interareal differences has to be based on measurements. Most studies in the past relied on the measurement of single morphometric parameters within a certain sample, e.g. the dendritic length (Hayes and Lewis, 1996; Huttenlocher, 1979), cell sizes (Blinkov and Glezer, 1968; Hayes and Lewis, 1996; von Economo and Koskinas, 1925), the layer thickness (Amunts *et al*., 1995; Harasty *et al*., 1996; Zilles *et al*., 1986), the sizes of cortical areas, subcortical structures and fibre bundles (Andrews *et al*., 1997; Filimonoff, 1932; Geyer *et al*., 1999; Haug, 1987a; Kononova, 1935, 1938; Rajkowska and Goldman-Rakic, 1995b; Stensaas *et al*., 1974). Stereological parameters have also been applied successfully (Brody, 1955; Gundersen *et al*., 1988; Haug, 1984, 1987a,b; Henderson *et al*., 1980; Pakkenberg and Gundersen, 1997; Schmitz *et al*., 1999; Terry *et al*., 1987; West, 1993; Zilles *et al*., 1986). Altogether, these parameters represent important, quantitative data of cortical microstructure. However, they often reflect only a single aspect of cortical microstructure (e.g. cell density) and do not consider that the cortex is a layered structure with local changes in cell density, size and number within cortical layers and sublayers. In a more recent study on the human frontal lobe, several cytoarchitectonic parameters of areas 9 and 46 were analyzed (Rajkowska and Goldman-Rakic, 1995a,b). Hereby, a three-dimensional counting method (Williams and Rakic, 1988) was applied to measure total cortical and relative laminar thicknesses, neuronal packing density per $0.001\,mm^3$ in individual cortical layers, and sizes of neuronal somata in selected cortical layers. The analysis of these morphometric parameters revealed differences between both areas in the thickness of layer IV, in the packing density of neurones as well as in the size distribution of neurones. The authors concluded that objective cytometric methods can clearly distinguish two adjacent areas within the human prefrontal lobe. In this study, different morphometric parameters were treated and interpreted separately.

It is also possible to combine cytoarchitectonic parameters and to analyze them by multivariate statistical analysis. Such an approach has been used by us in defining areal borders (see above). The multivariate approach offers the advantage that different morphometric parameters can be normalized by compensating for different scales and can be combined into one feature vector. The feature vectors are then used in a comprehensive statistical test. In addition, multivariate analyses (e.g. discriminant analysis) take into account the correlations – often high – between parameters and offer procedures to detect those parameters which contribute most to the dissociation between areas.

We illustrate this multivariate approach and discuss its implication for a group of five cortical areas: Brodmann's areas 6, 44, 45, V1 and V2. These areas were selected by the following considerations:

(i) The terms *Broca's region* and *Broca's area* are based on functional concepts. They are used inconsistently with respect to cytoarchitecture. It is widely accepted that areas 44 and 45 constitute Broca's region (Aboitiz and Garcia, 1997; Amunts *et al*., 1999; Kononova, 1949; Petrides and Pandya, 1994; Roland, 1993; Uylings *et al*., 1999), but the terms Broca's region and Broca's area are also applied for areas 44, 45 and 47 (Riegele, 1931; Vogt, 1910), as well as for area 44 only (Galaburda, 1980; von Economo and Koskinas, 1925). In some recent functional imaging studies, Broca's region (or area) refers to a cortical region which includes area 44 and, sometimes, adjacent area 6 (Paulesu *et al*., 1993; Petrides *et al*., 1993). Recent fMRI studies

have provided evidence that the posterior part of Broca's region, area 44, and the homologue region of the right hemisphere might be involved in imagery of movement (Binkofski *et al*., 1999, 2000). This would associate area 44 functionally with area 6. Originally, the definition was based on gross macroscopical markers, i.e. by gyri and sulci (Broca, 1861; Herve, 1888). In this context, we wanted to check whether areas 44 and 45 can be grouped together on the basis of cytoarchitectonic similarity.

(ii) If areas 44 and 45 constitute Broca's region, they should be more similar in cytoarchitecture to each other than to neighboring cortical areas, e.g. to the adjacent ventral part of area 6.

(iii) It was expected that areas 44 and 45 would differ even more from areas V1 and V2 than from area 6, because V1 and V2 belong to the visual cortex and are characterized by a completely different organization of their input and output, reflected by different laminar patterns.

(Dis-)similarities between these areas were quantified by calculating a multivariate distance measure between the density profiles in these areas. Profiles were obtained from cytoarchitectonic areas 6, 44, 45, V1 and V2 of ten human *post mortem* brains (Amunts *et al*., 1999, 2000). Fifteen to thirty profiles were obtained from three randomly selected sections of each area, hemisphere and brain. Thus, a total of about 3000 profiles were processed. Ten features were extracted from each of the profiles, as described above, for the definition of borders. In contrast to the latter approach, the Euclidean distance (and not the Mahalanobis distance) was used as multivariate distance measure. The advantage of the Euclidean distance for this type of analysis is that it is more sensitive in detecting the dissimilarity in architecture between cortical areas. i.e. the Euclidean distance measures the absolute distance between two centroids of the ten-dimensional space (= dissimilarity between areas), whereas the Mahalanobis distance depends not only on this distance, but also on the variability within an area. Thus, the Mahalanobis distance becomes smaller with increasing variance (Schleicher *et al*., 2000).

The Euclidean distance was calculated in each individual brain for all ten possible combinations of two areas from the areas 44, 45, 6, V1 and V2 (= *interareal differences*). It was also calculated between profiles from corresponding areas of the left and the right hemisphere (= *interhemispheric differences*). Corresponding distances were averaged across the whole sample size. Multidimensional scaling (Systat® for Windows, Version 9, SPSS, USA) was applied for data reduction and visualization of distances between the cortical areas. *Interhemispheric differences* were tested statistically against differences between randomly selected profiles from one and the same area. The results are shown in Figure 3.3.

The analysis showed a high degree of similarity in cytoarchitecture of areas 44 and 45. Both areas differed considerably from areas 6 as well as V1 and V2 (large distances between the centroids). Area 6 showed shorter distances to areas 44 and 45 than to V1 and V2, which may correspond to the close topographical and functional relationship between areas 44/45 and 6. On the basis of the cytoarchitectonic similarity of areas 44 and 45, these data provide an anatomical argument to combine areas 44 and 45, but not 44 and 6 into a region. Based on classical cytoarchitectonic descriptions, area 44 (which is dysgranular) takes a transitional position between area 45 (which is granular) and area 6 (which is agranular). This relationship is kept in the arrangement of the centroids in the graphs.

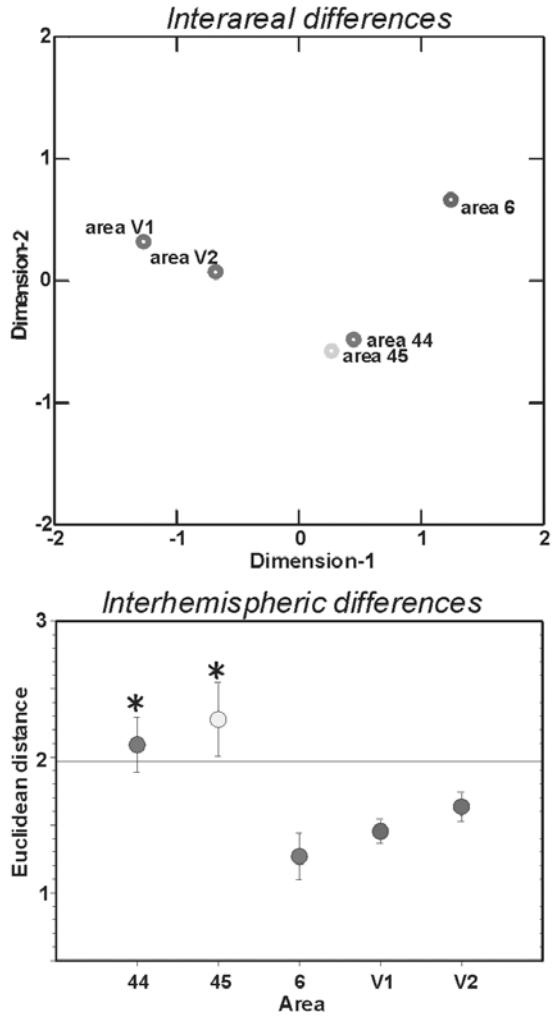

Figure 3.3. Dissimilarities of Brodmann's areas 44, 45, 6, as well as areas V1 and V2 based on quantitative cytoarchitecture (K. Amunts, unpublished observations). Euclidean distances were calculated as multivariate measures of dissimilarity between profiles of different cortical areas (= *interareal differences*) and of the two hemispheres of one and the same area (= *interhemispheric differences*). Euclidean distance is based on features, which characterize the shape of the profiles of an area (see text). Multidimensional scaling was applied for visualization of *interareal differences* and for data reduction to a two-dimensional plane defined by dimension-1 and dimension-2 (Schleicher *et al*., 2000). The larger the dissimilarity in cytoarchitecture between two areas, the larger the distance between them in the graph. Error bars indicate standard errors. Results in this **upper graph** quantify *interareal differences* of the left hemisphere. Whereas areas 44 and 45 were found to be very similar in cytoarchitecture, both areas differed considerably from area 6 as well as from visual areas V1 and V2.

Interhemispheric differences in cytoarchitecture (**lower graph**) were significant (marked by an asterisk) for areas 44 and 45, but not for areas 6, V1 and V2. The line marks the level of intersubject variability in cytoarchitecture. It was calculated as the average Euclidean distance between corresponding areas across different subjects (i.e. the distances in shape within the sample of 10 brains between all areas 44, all areas 45, etc. were calculated and then averaged across the brains and areas). The analysis supplemented previous findings on asymmetry in volume of area 44 (Amunts *et al*., 1999) and demonstrates that cytoarchitectonic asymmetry in areas 44 and 45 might be a microstructural correlate of brain lateralization and dominance for language, in particular.

Finally, interhemispheric distances between corresponding areas of both hemispheres were significant for areas 44 and 45, but not for areas 6, V1 and V2. That is, areas 44 and 45 revealed significant left/right differences in cytoarchitecture. Thus, in addition to asymmetry in volume of area 44 which was reported previously (Amunts *et al*., 1999; Galaburda, 1980), interhemispheric asymmetry was demonstrated at a microstructural level. This cytoarchitectonic asymmetry may contribute to the functional phenomenon of cerebral lateralization and dominance for language, in particular.

Information obtained from analysis of interareal differences might be applied for creating hierarchies and families of cortical areas, as described for the cortex of nonhuman primates (Fellemann *et al*., 1997; Fellemann and Van Essen, 1991; Gattass *et al*., 1997; Hubel and Wiesel, 1972; Kaas, 1989; Kötter and Sommer, 2000; Nakamura *et al*., 1993; Peterhans and von der Heydt, 1993; Stephan *et al*., 2000; Xiao *et al*., 1999; Zeki, 1978; Zilles and Clarke, 1997).

Multivariate distance analysis has been applied to detect interhemispheric cytoarchitectonic differences of the motor cortex (Amunts *et al*., 1996), its developmental changes (Amunts *et al*., 1997), interareal, interhemispheric and intersubject differences of Broca's region (Amunts *et al*., 1999), as well interareal differences in receptor architecture of the mesial motor and premotor cortex in the macaque (Geyer *et al*., 1998) and of the human the somatosensory cortex (Geyer *et al*., 1997, 1999). A quantitative analysis of interareal differences in cytoarchitecture is also relevant for detecting architectonic differences between normal and pathologically altered cortical tissue. Finally, the criterion of similarity in architecture might be valuable with respect to a comparative analysis of homologies between humans and non-human primates (Petrides and Pandya, 1994).

4. MULTIMODAL MAPPING – CORRESPONDENCES AND DIFFERENCES BETWEEN CYTOARCHITECTONIC AND RECEPTOR ARCHITECTONIC BORDERS

Architectonic analysis using multivariate statistics can be even more decisive when they incorporate other modalities of architecture, e.g. receptor architecture. The comparisons of receptor- and cytoarchitectonic maps provided evidence that in several cortical regions receptor architecture reveals similar architectonic parcellations as compared to cytoarchitecture. We will present here recent data from our analysis of the human visual cortex for discussing the correspondence between cytoarchitectonic and receptor-architectonic parcellation schemes.

Numerous observations on the regional and laminar distribution of transmitter receptors in the human primary (V1) and secondary visual cortex (V2) have been published. Reports on receptors in other extrastriate areas are rare. (For an overview see Zilles and Clarke, 1997). This is due to the facts, that (i) human extrastriate areas are difficult to identify in cytoarchitectonic sections, (ii) the classical architectonic maps of the human occipital lobe show a much less detailed parcellation than corresponding maps of nonhuman primates, and (iii) receptor architectonics of the human occipital lobe require extraordinary large cryostat sections of unfixed, frozen brains, which are difficult to handle. Our own observations in nonhuman primates and human *post-mortem* brains, as well as recent data from the literature, provide evidence that receptor architectonic mapping is a promising approach to human brain mapping (Bonaventure *et al*., 2000; d'Argy *et al*., 1988; Geyer *et al*., 1997,