The Prefrontal Cortex:

Its Structure,

Function & Pathology

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THE PREFRONTAL CORTEX

Its Structure, Function and Pathology

Proceedings of the 16th International Summer School of Brain Research, held at the Royal Tropical Institute and the Royal Netherlands Academy of Sciences, Amsterdam (The Netherlands), from 28 August to 1 September 1989

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Preface

The prefrontal cortex has been regarded to be involved in a variety of functions: as the cortex for "higher psychic activity", as the cortex of convergence of cognition and emotion, as being involved in schizophrenia and depression, and as the visceral cortex. The prefrontal cortex is thus on the one hand "attributed the highest integrative faculties of the human mind", whereas others emphasized "the surprising paucity of cognitive deficits" following frontal lesions (Editorial Mesulam, Ann. Neurol., 19, 1986). The prefrontal cortex is therefore an intriguing topic to deal with, given the many different concepts for this part of the cortex.

Over the past decade many new data on the prefrontal cortex have been obtained especially in primates and rodents, thanks to progress in research techniques and an increased interest in this topic. Therefore, the 16th International Summer school of Brain Research, held in Amsterdam in August 1989 (the year of the 80th anniversary of the Netherlands Institute for Brain Research) was entirely devoted to the topic of Prefrontal Cortex. This book is one of the products of this stimulating Summer School. Unfortunately, Professors B. Milner, M. Mishkin and P. Roland were, for several reasons unable to prepare a chapter on their important studies presented during the Summer School.

At first sight, the term prefrontal cortex appears to be illogical: "How can any cortex be in front of the frontal cortex?". This term is still widely used by neurobiologists, since, at present there is no appropriate alternative term. Among alternative terms, the "frontal granular cortex" has been used. This term, however, is not appropriate for many reasons. The cytoarchitectonic criterion implied in the name is not sufficient to define the prefrontal cortex; not only during early development, since the entire frontal lobe of primates *including* the prefrontal cortex is granular, but also in adult animals. There are also *agranular* cortical areas which belong to the prefrontal cortex. The historical origin of the term "prefrontal" has been described elsewhere (I. Divac, IBRO News, 16 (2), 2, 1988). In the classical cortical maps of the human brain we can see that the meaning of the term "prefrontal cortical area" changed during the first decades of this century. Brodmann's area as prefrontalis (conform Smith, 1907) indicates only Brodmann's areas 11 and 12. Also the map of Campbell (1905) names a small rostral cortical area as prefrontal, but this area is different from Brodmann's. Since Walker (1940), the term *prefrontal* cortex defines what we presently consider as prefrontal cortex in primates. On the other hand, even today the borders of the cortical area regarded as prefrontal cortex are under discussion for different mammalian species. In connection with this, the first section describes the present knowledge on the organization of the prefrontal cortex, after the two introductory chapters by Kaas and Parnavelas.

In the second section, developmental and plasticity aspects in rodent and human prefrontal cortex are considered. The third section deals rather extensively with the functional aspects characteristic for the prefrontal cortex in primates, rats and rabbits. In the last section, some topics on dysfunction of prefrontal cortex in rat and human are reviewed, including a historical review on psychosurgery.

This book will therefore be of interest for neuroscientists, neurologists and psychiatrists.

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Organization of Prefrontal Cortical Systems

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Progress in Brain Research, Vol. 85

CHAPTER 1

How sensory cortex is subdivided in mammals: Implications for studies of prefrontal cortex

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Introduction

A general approach toward understanding brain functions is to determine how the brain is subdivided into systems, and then study parts of systems and how they interact. Thus it is initially important to determine with some accuracy what the parts are and how they are interconnected. Prefrontal cortex is an especially intriguing part of the brain because it is obviously expanded in humans, and this expansion undoubtedly accounts for many of our unique mental and behavioral abilities. There is widespread agreement that prefrontal cortex consists of a number of functionally distinct subdivisions, but opinions vary on how this cortex is subdivided in any particular mammalian species, and on how subdivisions of prefrontal cortex compare in various species. This disagreement implies uncertainty, and it would be valuable to obtain accurate and compelling information that could lead to a consensus. However, the issues of how to subdivide cortex and compare species are not specific to prefrontal cortex. Experimental and comparative studies of sensory-perceptual cortex will have the advantage of subdivisions that are denoted by the presence of systematic representations of receptor surfaces, and can provide guidelines, general principles, and basic conclusions that apply to prefrontal cortex. This paper considers conclusions stemming from studies of sensory cortex, and then briefly discusses several proposed subdivisions of the frontal lobe in respect to these conclusions.

The premise of subdividing cortex

A basic premise of Brodmann (1909), Smith (1907), Von Economo (1929), and other early investigators was that cortex is divided into a patchwork of areas or fields, the "organs" of the brain, that perform distinct functions and yet are functionally interrelated. They also believed that because different functions are based on structural variations in cortex, areas must differ in histological appearance, and these differences can be used to distinguish fields. The borders between at least some areas were considered to be sharp, and mammalian species with large brains and more complex behavior, especially humans, were thought to have more areas. All mammals had a number of areas in common, and the number of areas increased in evolution by existing areas (or in some sense, composite areas) subdividing by "differentiating". While these and other early investigators largely agreed on these few principles, they were limited by the techniques of that time to examine brain sections stained for cell bodies or myelinated fibers in order to discover distinctions

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denoting the extents and boundaries of possible subdivisions, and they came to quite different conclusions on how brains are subdivided. Some later investigators, notably Lashley (e.g. Lashley and Clark (1946)) and Von Bonin and Bailey (1961), questioned the assumption that species differ in number of subdivisions and even the validity of the architectonic method. However, it is now clear that cortex is divided into a number of functionally distinct subdivisions or areas, borders are often if not always sharp, species differ in numbers of areas, and areas do differ in architectonic appearances (see Kaas, 1987a, for review). In addition, we are now more aware of the difficulties and potential for error in subdividing cortex. These difficulties both explain why investigators have so often differed in conclusions, and indicate that even current proposals should be evaluated with great caution.

The difficulties of obtaining a comparative understanding of how cortex is subdivided

There are several major reasons why it has been difficult to obtain an accurate portrayal of how cortex is subdivided into areas in different mammals. First and foremost is the enormous scope of the problem. Brains vary greatly in such obvious features as size, shape, and patterns of fissures, and there has been a long time for the evolution of these and other variations. Mammals evolved from therapsid reptiles some 250 million years ago (M.Y.A.), and have formed a number of continuing branches or lines of evolution (see Kaas, 1987b). Prototherian mammals (monotremes) diverged from therian mammals some 200 M.Y.A., metatherian (marsupials) mammals from eutherian (placental) mammals about 150 M.Y.A., and edentates from other eutherian mammals about 120 M.Y.A. The remaining eutherian mammals later divided into 17 or so major orders, largely about 65 M.Y.A. (see Fig. 5 in Kaas, 1987b). Within a given order, especially in primates, the range of obvious brain differences can be considerable. In addition, the rate of brain change can be quite rapid. For example, the evolution of modern human brains from those of one-third the size in Australopithecus occurred within the relatively short time of 3.5 million years.

A second difficulty is that brain subdivisions are usually not obvious. While the specialized functions of some subdivisions of the brain may be based largely on differences in internal organization, other areas may be structurally similar because they mediate basically the same computations, differing largely in what inputs serve as the basis for the computations (see Sur et al., 1988). Whether this is the case or not, many subdivisions of cortex are highly similar in cytoarchitecture, and very difficult to reliably distinguish by differences in appearance using traditional stains. A related problem is that many and possibly most areas of cortex are functionally and structurally heterogeneous (e.g., Livingstone and Hubel, 1988). As a clear example, in all mammals primary visual cortex, V-I or area 17, has a large part activated by both eyes and a small part activated only by the contralateral eye. The binocular portion is notably thicker and is often more conspicuously laminated than the monocular portion. Such structural differences within fields can be mistaken for differences between fields. Thus, Brodmann (1909) mistook the monocular portion of area 17 in squirrels for area 18 (Fig. 1), and the error persists in most descriptions of visual cortex in rodents (see Kaas et al., 1989, for review).

Another difficulty is that brain areas are capable of change in all aspects including appearance. Area 17 or striate cortex was the first recognized area of cortex, and it is perhaps the most distinctive in appearance. Yet, area 17 varies from being rather indistinctly laminated in such mammals as hedgehogs (see Kaas, 1987a) to being conspicuously laminated in tarsiers (e.g., Hassler, 1966). If it were not for the existence of extant species with an area 17 of intermediate degrees of lamination and of a similar position, together with more current and compelling comparative evidence on connections and neural response properties, claims that area 17 is the same area (homologous, stemming

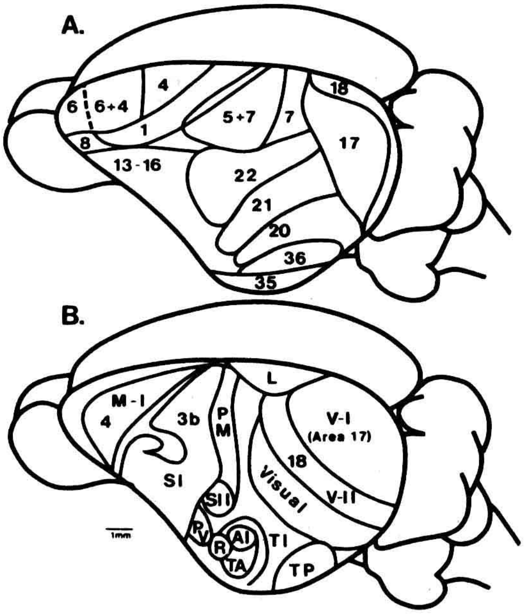

Fig. 1. Different proposals for how cortex is subdivided in rodents (squirrels). (A) Subdivisions of cortex according to the cytoarchitectonic studies of Brodmann (1909). (B) Subdivisions described in recent studies using microelectrode recordings, connection patterns, and architectonics. See Kaas et al. (1989), Luethke et al. (1988) and Krubitzer et al. (1986) for details and references. Note that there is little correspondence between modern and classical views, other than in the parntial overlap of fields designated as primary visual (area 17) and primary motor (area 4) cortex. Brodmann recognized no primary somatosensory or auditory fields in rodents. Modified from Kaas (1989b).

from a common ancestor) in the two mammals would be incredulous. In addition, area 17 has become more laminated in several lines of descent, and ocular dominance columns have evolved independently in area 17 of cats and several groups of primates. Thus, current resemblances in different species may not reflect the ancestral state. It is also possible that a cortical area would change over time to come to resemble another field, creating the likelihood of misidentification. For instance, the primary auditory area, A-I, and the rostral auditory area, R, closely resemble each other in architectonic appearance (see Luethke et al., 1988), and they probably have been confused or, more likely, combined in architectonic studies. However, A-I and R contain separate maps of the cochlea, and have somewhat different connections.

An experimental approach

A logical conclusion is that cortical areas are most reliably defined by multiple criteria (e.g., Campbell and Hodos, 1970; Kaas, 1987a). Thus, the weaknesses and potential for error inherent in one method may be compensated by strengths of another method. A functionally distinct area should have unifying characteristics that distinguish all parts of the area from other areas. Such characteristics may include a host of architectonic and histochemical features reflecting structural specialization, a unique pattern of connections with other parts of the brain as a station in a processing system, a population of neurons with response properties that are distinct from populations in other fields, and specific behavioral defects as a result of deactivation. In sensory systems, areas often contain a systematic representation of a receptor surface (skin, retina, cochlea). Since areas need not be homogeneous in structure or function, subregions and modules within an area may be misidentified as an area. For example, modules in area 17 have different inputs, outputs, histological appearance, and neuron properties (e.g., Livingstone and Hubel, 1988). Nevertheless, these modules clearly are repeating, interacting parts of a larger area. However, there may be regions of cortex where it becomes difficult and perhaps pointless to distinguish modules from areas. In any case, we need to consider many types of evidence in attempts to subdivide cortex, and to weigh information carefully with regard to reliability and power.

In addition to defining areas within a species, it is critically important to evaluate the probability that a given area in one species is or is not homologous (the same area) with an area in another species. Areas are judged to be homologous when the number of observed