Parcellation of Prefrontal Cortical Areas in Mouse and Rat Brain

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Chapter 1

General Introduction

The prefrontal cortex (PFC) was initially described by Brodmann (1909; 1912) as a brain region, exclusively present in man and other primates. Later this view changed as a result of the studies of Rose and Woolsey (1948), who demonstrated the existence of a dominant projection of the mediodorsal nucleus (MD) of the thalamus to the prefrontal cortex in rabbit, sheep and cat. In a study of the cortical projections of the mediodorsal nucleus of the thalamus in the rat, Krettek and Price (1977) called attention to the historical development of the definition of the prefrontal cortex (PFC). Referring to studies that demonstrated the increasing growth of the mediodorsal nucleus (MD) of the thalamus in mammals during evolution, they observed that in early studies the prefrontal cortex was assumed to be absent or at most very poorly developed in mammals other than primates. After the description of the PFC in the rat (Krettek and Price, 1977; Van Eden and Uylings, 1985), the PFC was also described in mice (Guldin et al., 1981). Today the PFC in rodents is described as the agranular region in the frontal lobe that is characterized both by a dominant and reciprocal connection with the mediodorsal nucleus (MD) of the thalamus and by the pertinent pattern of connections with the basal ganglia, the cortico-cortical connections and its ‘gating’ position with cholinergic and monoaminergic systems (Uylings and Van Eden, 1990; Uylings et al., 2003). The term ‘gating’ refers here to the PFC in its unique cortical capacity of having direct reciprocal connections with all monoaminergic and cholinergic nuclei that project directly to cerebral cortex regions. The PFC, as a whole, is connected with most parts of the brain, either directly or via relay areas in diencephalon and brainstem. The areas of the PFC are known to have many different, direct axonal connections with other cortical regions, with hippocampus and parahippocampus (Uylings and Van Eden, 1990; Deacon et al., 2003; Schilman et al., 2008; Balu et al., 2009; Parent et al., 2010), the midline and intralaminar thalamic nuclei (Berendse and Groenewegen, 1991), striatum and nucleus accumbens (Berendse et al. 1991; Groenewegen and Berendse, 1994; Wright and Groenewegen, 1995; Groenewegen et al., 1999; Groenewegen and Uylings, 2010), amygdala

(Uylings and Van Eden, 1990; Wright, 1997), hypothalamus (Vertes, 2004; Gabbott et al, 2005), nuclei in the mesencephalon (Uylings and Van Eden, 1990; Gabbott et al., 2005), pontine nuclei (Gabbott et al., 2005),and nuclei in the medulla (Gabbott et al., 2005). The PFC is also involved in many parallel circuits, e.g. the prefrontal – basal ganglia (Groenewegen and Uylings, 2010; Ray and Price, 1992). The PFC is reciprocally connected with all monoaminergic nuclei (Uylings and Van Eden, 1990; Uylings et al., 2003; Douglas et al.,2002; Lidow et al., 2003; Amargós-Bosch, 2004; Dalley et al;, 2004; Vogt et al., 2004; Van Dort et al., 2009; Balu et al., 2009), and with the subcortical cholinergic regions, which project directly to the neocortex (Uylings and Van Eden, 1990; Uylings et al., 2003; Vogt et al., 2004).

The importance of the PFC is, in general, the control of adaptive cerebral activity to changes in the external and internal environment. Many specific functions of the PFC have been studied in detail, such as planning actions (Dalley et al., 2004), controlling the integration of sensorisomatic, motor and autonomic information (Saper, 2004), working memory (Uylings et al., 2003; Dalley et al., 2004; Vertes, 2004), arousal behavior and modulation of wakefulness (Van Dort et al. 2009), freezing as a response to imminent danger (Barrett et al., 2003), acute planning of organization (Dalley et al.,2004), the integration of body functions in order to enable the animal to cope as effectively as possible with changes in the environment that ask for an immediate or short-time executive reaction based upon relevant information processing (Dalley et al., 2004). The functions of the PFC may be distinguished in functions common to all mammals and functions that are typically species-specific. Kolb (1984) and Uylings et al. (2003) coined the term class-common behaviors to denote the principal and general rules common in all PFC functioning, as contrary to the, as they call it, species-typical behaviors. In their study of the effects of cortical lesions on the attentive and affective shifts in mice, Bissonette et al. (2008) refer to the fundamental agreement found for these attentive and affective shifts in the PFC of different species of mammals. A survey of PFC functions can be found in ‘The Prefrontal Cortex’ (Fuster, 2008) and in the review of Miller and Wallis (2012) on the PFC executive function.

Several publications (e.g., Passingham et al., 2002; Lein et al., 2007; Hintiryan et al., 2011; Nieuwenhuys, 2013) emphasize the close relation that exists between anatomical structure and function in the cerebral cortex.

Although many cytological methods are available to delineate subareas in the PFC, the Nissl staining is superior to most other staining methods in visualizing every cell present in the stained region. Immunocytochemical staining and, in general, all staining procedures directed to specific cells offer a restricted, incomplete picture of the cytoanatomy of an area. Such stainings can be helpful for a particular area boundary but not for all boundaries. The study of Paulussen et al. (2011) clearly demonstrates the advantage that the use of the low-molecular-weight neurofilament protein subunit (NF-L) can have in cytoarchitectonic studies, though it does not show all boundaries visible in the Nissl staining. In this thesis attention will be called mainly to the delineation of the boundaries in Nissl-stained coronal sections of the PFC.

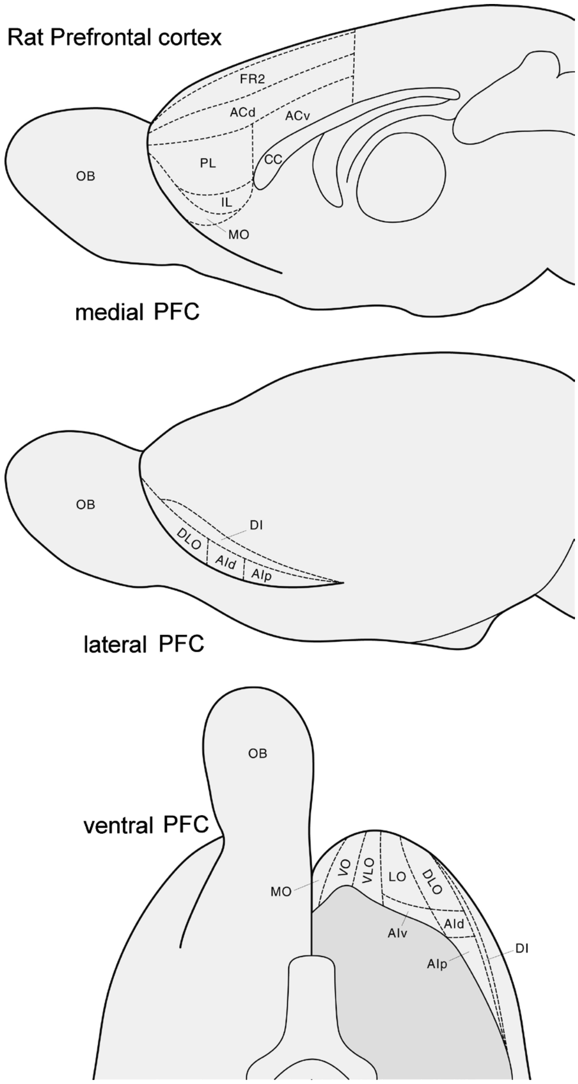

Fig. 1. Schematic view of medial (upper panel), lateral (middle panel) and ventral (lower panel) prefrontal areas in rat brain. For abbreviations of the subareas see chapters 2 and 3.

The relevance of cytoarchitectonic research is in the discrimination of areas that each represents a specific function or a specific group of functions. Cytoarchitectonic parcellation is essential for a stereological analysis of changes in the total number of neurons in particular PFC areas in disease or as result of experiments. To be able to reliably compare the effect that a specific factor may have on the cytoarchitecture of a particular area in different studies, it is important that delineations are made on the basis of the same criteria. A cytoarchitectonic parcellation is also a basis for studies on neuronal connections with injected tracers and on functions by local lesions or (electric) activity patterns. The aim of this thesis is to study how, on the basis of their cytoanatomy, subareas of the PFC are best distinguished. Its approach will be to look for marked changes in the cytoanatomical structure of the different cortical layers, which could indicate a boundary between, anatomically and functionally, different PFC subareas. The cytoarchitectonic changes which have been found and which characterize a particular boundary are used to delineate that boundary in Nissl-stained sections. Attention will be focused on the characteristic structural changes at the boundary, not on the changes that may occur within the area. The PFC consists of 3 regions, i.e. the medial, the lateral and the orbital or ventral PFC (see Fig. 1 for a schematic view of the medial PFC). Each PFC region contains several subareas (see Fig.1). Boundaries between PFC subareas are delineated only in coronal sections as in those sections the results of research are usually made visible. In Chapter 2 (Van de Werd and Uylings, 2008), PFC subareas and boundaries on the ventral and lateral side of the frontal lobe of the rat are studied. Next to the study of Nissl-stained coronal sections of the rat frontal lobe, a number of sections stained by immunocytochemical procedures are studied and compared with the delineations in the Nissl staining of the rat PFC. In Chapter 3, subareas in the medial, ventral, and lateral PFC and their boundaries in the mouse are investigated. Next to Nissl-stained coronal sections, sections stained with antibodies against neurofilaments, acetylcholinesterase, myelin, parvalbumin and calbindin are studied and visible boundaries are compared with boundaries in the Nissl staining. In Chapter 4, the differences and correspondences found in the parcellations of the mouse prefrontal cortex published in stereotactic atlases (Franklin and Paxinos, 2008; Hof et al., 2000) and journal papers (Rose, 1929; Caviness, 1975; Wree et al., 1983) are examined applying the 'Van de Werd et al. (2010)' criteria for parcellation of PFC subareas. Possible causes of the observed differences are discussed. In Chapter 5, the results of the foregoing Chapters will be summarized and discussed. Differences in the parcellation of the prefrontal cortex in the rat when compared with the parcellation of the prefrontal cortex in the mouse will be presented and discussed. Their usability to improve the reliability of delineating boundaries in the prefrontal cortex in rat and mouse will be discussed. The changes in nomenclature introduced in the recently published fourth edition of the mouse brain atlas of Paxinos and Franklin (2013) are compared with the nomenclature in the third edition of the mouse brain atlas of Franklin and Paxinos (2008). In addition, expected developments in cytoarchitectonic methods are discussed.

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