Parcellation of Prefrontal Cortical Areas in Mouse and Rat Brain

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Chapter 5

Summary and General Discussion

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In the preceding chapters the cytoarchitectonics of the prefrontal cortex was studied in the ventral/orbital side and on the lateral side of the frontal lobe of the rat (chapter 2), and in all areas of the prefrontal cortex (PFC) in the mouse (chapter 3). The comparative study (chapter 4) examined to what extent prefrontal areas in the mouse differ between the atlases and other publications. The conclusions of these chapters are:

(a) Boundaries between subareas of the PFC can be assessed in rats and mice. (b) The criteria to define boundaries in Nissl stained sections should be based on features consistently observed and well described. (c) For detection of the boundaries between all subareas of the PFC the general cellular staining like Nissl staining is preferred to a histochemical or immunocytochemical staining, which stains specific features of a limited number of cells.

(d) Results of a specific (e.g. immunocytochemical) staining may support the location of a particular PFC subarea boundary defined in a Nissl stained section.

(e) Tracing studies have been important to focus on subdividing PFC regions into PFC subareas. These boundaries are assessable in Nissl stained sections.

(f) The PFC subarea boundaries have been described to facilitate the research and the communication on specific functional properties present.

This chapter will further discuss (1) stainings for PFC area parcellation; (2) differences in rat and mouse PFC areas; (3) to what extent the PFC areas in mouse brain are different in the very new edition of Paxinos and Franklin (2013); (4) the nomenclatures used for the PFC areas in rodents; and finally (5) future developments.

1. Stainings for PFC area parcellation

In cytoarchitectonic studies, generally several factors will influence the delineation of the PFC and its subareas on the surface of the cerebral cortex or in coronal sections through the frontal lobe. These factors are e.g. the use of more than one staining method, the characteristics attributed to

an area in other cytoarchitectonic descriptions, connectivity studies and the number of animals examined within a defined strain of a species. In defining the boundaries of the prefrontal cortex and its subareas in the Figures that are shown in chapters 2 and 3, the characteristics found in the Nissl staining have been the principal source for the determination of boundaries. In addition, the examination of the immunocytochemically and myelin-stained coronal sections supported the results found in the Nissl staining. Thus the additional staining methods confirm the distinction of the areas AId1 and AId2 in Nissl-stained sections of PFC areas in both rat and mouse (chapters 2 and 3), and also the location of area DLO in the rat (chapter 2). The location and size of areas AId1 and AId2, as defined in the mouse PFC (chapter 3), agrees with the location and size of the areas AId and AIv in the immunocyto/myeloarchitectonic study of Paulussen et al. (2011) who used the low-molecular-weight neurofilament protein subunit (NF-L) for staining coronal sections of the mouse PFC. The authors point to the superiority of this staining method over the combined use of the different supporting staining methods employed in our study (Van de Werd et al., 2010). The results of NF-L staining are impressive in their ability to show the myelographic structure and cortical layers in low-power micrographs, as well as fine fibres and the structure of neurons in high-power micrographs. Especially in PFC areas, the NF-L is, however, inferior to the traditional Nissl staining in showing cells in low-power micrographs. In NF-L-stained coronal sections, the distinction of several PFC areas on the medial side of the frontal lobe is not possible. The Nissl staining is superior to additional staining methods as far as it allows viewing all cells without being restricted to a special group of cells. Boundaries that are defined on the basis of the combined results originating from multiple and various methods are more likely to be reproducible /stable and to delineate areas that are reliably functional units. For the evaluation of the prefrontal cortex after experimental procedures [e.g., the effects of cortical or subcortical lesions] the Nissl staining is often preferred for reasons mentioned above. Delineating a boundary in Nissl-stained coronal sections will sometimes

be hampered in case an expected change in a main characteristic of the boundary is not clearly visible, e.g. the difference in layer II of frontal area Fr2 compared with layer II of area ACd is sometimes very subtle. Nevertheless, the description of layer II of the medial precentral area, *PrCm,* as appearing 'lighter, being less densely packed, and more homogeneous than in the anterior cingulate area' (Krettek and Price,1977) agrees well with the description of the corresponding area Fr2 in the studies of Van Eden and Uylings (1985), Van de Werd and Uylings (2008) and Van de Werd et al. (2010). Usually sufficient characteristics are present to delineate boundaries in such a way that they are consistent when repeatedly studied by different examiners and at different times. It is most probable that no single staining method is able to offer a parcellation that presents all possible functional units in the prefrontal cortex as the number of functions attributed to the prefrontal cortex is much higher than the areas distinguished in cytoarchitectonic studies. This view is supported in the review of the myeloarchitectonic studies of the Vogt - Vogt school by Nieuwenhuys (2013), reporting that in the human cerebral cortex some 200 different areas can be found, far more than in the commonly used Brodmann parcellation. Within a delineated area in a complicated structure such as the cerebral cortex no uniform structure can be expected, as is illustrated in layer II of the lateral orbital area LO. The clustering of cells in layer II is clearest in a small part of LO near the boundary with area AId2, but less near the boundary with VLO. In the medial PFC a ventral-dorsal gradually narrowing of layer II can be seen passing different successive areas. In such an area the thickness of layer II is not constant. In order to be able to communicate adequately on the properties of areas it is therefore important that their boundaries are defined on agreed characteristics that are considered to be typical of a particular boundary. Studies of connections reveal that the cytoarchitectonically defined different PFC areas all have a particular set of connections with the thalamus, other cortical areas, basal ganglia, and amygdala (Hoover and Vertes, 2011; Groenewegen and Uylings, 2010; Schilman et al., 2008; Gabbott et al., 2005; Reep et al., 1996; Groenewegen, 1988).

2. Comparison of PFC areas in rat and mouse

When the prefrontal areas on the ventral/orbital and the lateral side of the rat frontal lobe are compared with the prefrontal areas on the same sides of the frontal lobe in the mouse, a different number of prefrontal areas are found. In the rat, the ventral agranular insular area (AIv) is described in the posterior part of the dorsal bank of the rhinal fissure (Van de Werd and Uylings, 2008; Ray and Price, 1992), where it replaces the lateral orbital area that is visible in the part of the ventral/orbital side of the frontal lobe that is rostral to it. In the mouse, this replacement of the lateral orbital area (LO) by the ventral agranular insular area could not be distinguished in a reproducible way (Van de Werd et al.,2010; chapter 3). In the rat, AIv is distinguishable from LO in layer III, which is more cell-sparse in AIv than in LO. In the stereotactic atlas of the mouse brain of Franklin and Paxinos (2008), the ventral agranular insular area (*AIV*) is located on the lateral side of the frontal lobe, corresponding with the location of area AId2 in chapters 2- 4. Thus, *AIV* is defined in this atlas at a different location than AIv in our study (Van de Werd and Uylings, 2008). In addition, the dorsal agranular insular area (*AID*) in this atlas corresponds with area AId1 in chapters 2 - 4.

In the rat, the dorsolateral area (DLO) (Ray and Price, 1992), is cytoarchitectonically differentiated from the dorsal agranular area (AId) by the difference in layer II that is broader in DLO than in AId, by the less densely packed cells in layer III of DLO in comparison with AId and the absence of a deep claustral layer in DLO (Van de Werd, 2008; Chapter 2). DLO is located in front of, and adjacent to, area AId on the lateral side of the frontal pole. In addition to the cytoarchitectonic difference of DLO with AId, Ray and Price (1992) based their distinction of a separate area DLO in the rostral part of the frontal lobe on its distinctive connection with the thalamus. The difference of connections with the mediodorsal nucleus of the thalamus between areas DLO and AId has been demonstrated in anterograde and retrograde tracer experiments (Groenewegen, 1988; Ray and Price, 1992). Area DLO appears to be connected mainly with the ventrolateral caudal

part of the lateral segment of the mediodorsal nucleus (MD), but the dorsal agranular insular area (AId) is mainly connected with the medial segment of MD (Ray and Price, 1992). In the mouse, a differentiation in the cytoarchitecture of AId that would justify the distinction of a separate dorsolateral orbital area DLO on the lateral side of the rostral part of the frontal lobe, is not found (chapter 3 of this thesis; Van de Werd et al., 2010). Connectivity studies are needed to definitely confirm the absence of area DLO in the mouse.

On the ventral/orbital side of the frontal lobe of both rat and mouse three or four orbital areas are usually distinguished. In some groups (e.g. Hof et al., 2000; Franklin and Paxinos, 2008; Paxinos and Franklin, 2013; Paulussen et al., 2011) only one area is defined between the lateral orbital area (LO) and the medial orbital area (MO). This area is called either the ventral orbital area (VO) or the ventrolateral orbital area (VLO). In other studies two areas have been defined, i.e., both VO and VLO, by e.g. Krettek and Price, 1977; Groenewegen, 1988; Ray and Price, 1992; Reep et al., 1996; Van de Werd et al., 2008, 2010. Several authors noted that the orbital prefrontal areas are difficult to distinguish on the basis of only their cytoarchitectonic characteristics (Krettek and Price, 1977; Ray and Price, 1992: Reep et al., 1996). They mention that additional information about their thalamic connections is needed to define these boundaries. Our own studies (Van de Werd and Uylings (2008) and Van de Werd et al. (2010) support the view that a distinction between the orbital areas can be solely based on cytoarchitectonic characteristics if a set of reproducible characteristics is used to define each orbital boundary. The boundary between the orbital areas LO and VLO is mainly defined upon the different aspect of the layers II and III, i.e. the transition of the clustered cell-groups of layer II, sharply separated from the more homogeneous layer III of LO, into the homogeneous columns of cells in layers II and III of VLO. Reep et al. (1996) defined the boundary between LO and VLO mainly upon the difference in their connections with the mediodorsal nucleus (MD) and the submedial nucleus of the thalamus. They report that LO is connected with

the central segment of MD, whereas VLO is supposed to be connected mainly with the submedial thalamic nucleus, and to a lesser degree with the lateral segment of MD. Reep et al. (1996) locate the lateral boundary of VLO in the 'orbital notch', the indentation in the middle of the ventral/orbital side of the frontal lobe, in agreement with the lateral boundary of VLO in Ray and Price (1992), but somewhat more medial than in the studies of Krettek and Price (1977) and Groenewegen (1988). The lateral boundaries of VLO, delineated in chapters 2-4, based on cytoarchitectonic characteristics, are in agreement with the lateral boundary of VLO in Ray and Price (1992) and Reep et al. (1996).

The medial orbital area (MO) as delineated in chapters 2 – 4 and in the studies of Reep et al. (1996), Ray and Price (1992), Uylings and Van Eden (1990), Groenewegen (1988), Krettek and Price (1977) is a small area on the ventral part of the medial prefrontal cortex with a little extension to the ventral/orbital side of the frontal lobe. In the stereotactic atlases of the mouse brain (Franklin and Paxinos, 2008; Hof et al., 2000), area *MO* is larger and reaches, in the rostral coronal sections, halfway the medial prefrontal cortex. Cytoarchitectonically the MO area is distinguished by its localization between the more easily distinguishable ventral orbital area VO on one side, and either the infralimbic area (IL) or the prelimbic area (PL) on the other side. In the rostral part of the frontal lobe, layer II of MO is broad and contains rather evenly dispersed cells, but posteriorly layer II is narrower, contains darker cells and has a sharp border with layers I and II (Van de Werd and Uylings, 2008; Van de Werd et al., 2010). When present, fine cellular columns that involve all layers will be distinctive for MO.

Although the stereotactic atlases of the mouse brain (Franklin and Paxinos, 2008; Hof et al., 2000) do not provide the cytoarchitectonic considerations that led them to delineate the dorsal boundary of area *MO* on the place they did, it can be seen there that layer II, ventral to this boundary, is broad with evenly spread, not very densely packed cells, whereas the aspect of layer II dorsal to this boundary is different inasmuch

here the cells of layer II are more concentrated at the border of layer I, and also as layer II is narrower. In our parcellation, this typical change in the aspect of layer II marks the boundary between the dorsal and ventral part of the prelimbic area (PL).

Contrary to the Franklin and Paxinos (2008) and Hof et al. (2000) parcellations, the localization of the infralimbic area (IL) in rat and mouse is delineated more anteriorly in our studies (Van de Werd and Uylings, 2008; Van de Werd et al., 2010). The homogeneity of all cortical layers in IL distinguishes this area at its dorsal boundary from the prelimbic area (PL) and ventrally from the medial orbital area (MO). In some studies, area *IL* is positioned just posterior to area *MO*, which it suddenly replaces (e.g. Franklin and Paxinos, 2008; Hof et al. 2000; Reep et al., 1996; Swanson, 1992).

The distinction of PFC areas in the frontal pole is difficult in coronal sections because of the small surface and a restricted number of visible cortical layers. This only leaves the characteristics of the superficial cortical layers available and therefore it is partly necessary to extrapolate from more posterior boundaries. In the rat Ray and Price (1992) divided the frontal pole of the rat into two portions, the medial frontal polar cortex, *FPm,* and the lateral frontal polar cortex, *FPl*, based on the different aspect of layer II in *FPm* in comparison with layer II in *FPl* as well as upon a different pattern of connections. Groenewegen (1988) and Uylings and Van Eden (1990) also based the rostral parcellation on connections with the MD, but came to a different rostral parcellation with among others Fr2, ACd and PL, supported by the features of the superficial layers.

3. Changes in the parcellations of Paxinos and Franklin (2013)

In the very recent fourth edition of the stereotactic atlas of the mouse brain (Paxinos and Franklin, 2013), delineations of prefrontal cortical areas (Fig. 1 of this chapter) differ from delineations in the third edition (visible in Figs. 1-11 of chapter 4). As indicated in the introduction of the fourth edition of their atlas, in order to facilitate the comparison of different

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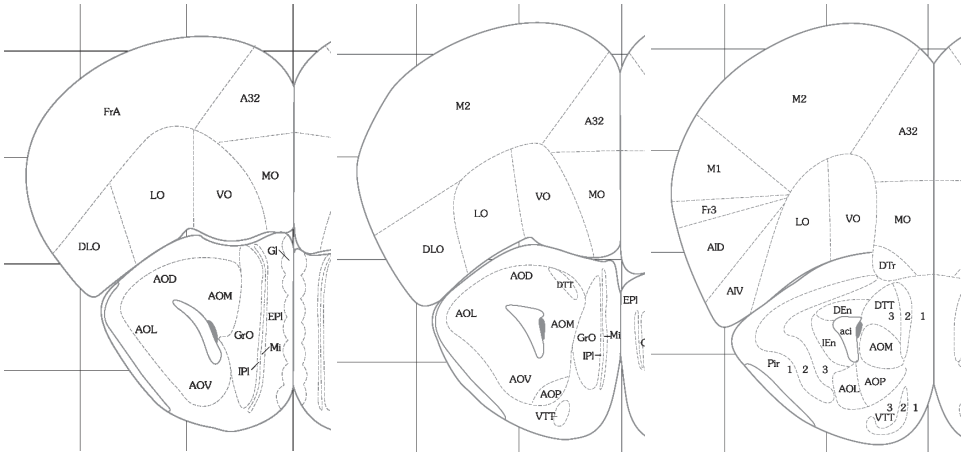
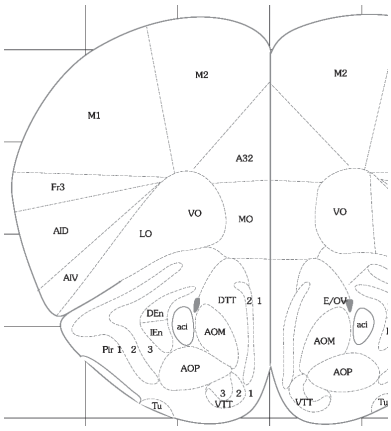
species, the authors adapted the nomenclature of the cingulate areas and the prelimbic and infralimbic areas to the Brodmann nomenclature used in the non-human and human primate (Paxinos and Franklin, 2013). The names of other prefrontal cortical areas have remained the same in both editions. The cingulate areas in the fourth edition generally show some minor changes in size and position in comparison with their size and position in the third edition. As is generally the case in stereotactic atlases the specific reasons for these differences are not specified. For this new fourth edition, the cingulate areas have been parcellated by B.A. Vogt. Therefore, we might assume that Vogt extrapolated his former rat parcellations (Vogt and Peters, 1981; Vogt et al., 2004) into the mouse brain. In the new scheme at Bregma 2.34 mm in Fig. 1 of this chapter (i.e., Fig 3 in Chapter 4), area *Cg1* is taken together with *PrL* into the new area *A32*. In the new scheme at Bregma 2.10 mm, see Fig.1 (i.e. Fig 4 in Chapter 4), however, the former area *Cg1* is included in *M2*, and no longer in *A32*, whereas in the new scheme at Bregma 1.94 mm (i.e. Fig. 5 in Chapter 4) *Cg1* is recognized as a separate entity, now called *A24b*. The former areas *PrL*, *IL* and *DP* have been replaced in the new scheme at Bregma 1.94 mm by areas *A32*, *A24a* and *A25*, respectively, with some change in their mutual boundaries. Area *A25* includes the former dorsopeduncular area (*DP*) and a ventral part of former Franklin and Paxinos' area *IL*. This can be a source of misunderstanding because *A25* will now be easily considered as part of the prefrontal cortex, whereas no tracing studies have indicated until now that *DP* is a part of PFC. A major difference from the former third edition is visible in the parcellation of the medial PFC at new Bregma 1.95 (Fig. 5 in chapter 4). In this figure area *A32* is wedged in between the areas *A24b* and *A24a*. More posteriorly, above the corpus callosum, at Bregma 1.42 mm, areas *A24b* and *A24a* largely conform to former areas *Cg1* and *Cg2* (Fig. 7 in chapter 4). In a comparison of the parcellations of the prefrontal cortex in the two editions of the Franklin and Paxinos atlas (2008 resp. 2013) with the Van de Werd et al. (2010) parcellation (chapter 4), less accordance is found with the new parcellation in the fourth (2013) edition than with

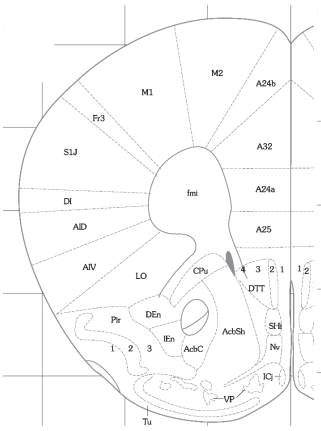
the older parcellation in the third (2008) edition of the atlas. This is best illustrated by comparing the Van de Werd et al. (2010) parcellation (chapter 4, Figs.3-9) with the corresponding new Bregma images presented in Fig.1 of this chapter. The dorsal anterior cingulate area (ACd) and the prelimbic area (PLd–PLv) in the parcellation of Van de Werd et al. (2010) (chapter 4) agree more with the parcellation in the Franklin and Paxinos (2008) edition than with the Franklin and Paxinos (2013) edition. Whether the change in the nomenclature of the cingulate areas and the prelimbic and infralimbic areas in the fourth edition of the Paxinos and Franklin (2013) mouse brain atlas will prove to be really important for the communication between researchers working in the field of the primate brain and those in the field of the rodent brain remains to be seen. The difference in the position of boundaries in the two editions is illustrative of the common problem met in delineating boundaries in cytoarchitectonic studies. As will be discussed in the next paragraph, Lashley and Clark (1946) already called attention to this problem, as was more recently done by Uylings (2007; Botha and Swanson, 2008).



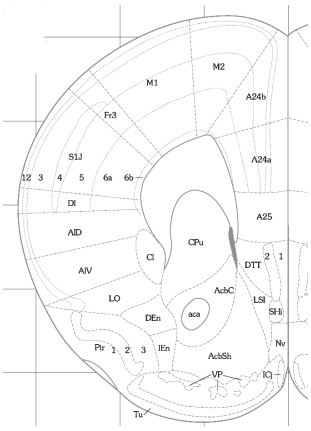
Bregma 2.80 mm Bregma 2.58 mm Bregma 2.34 mm



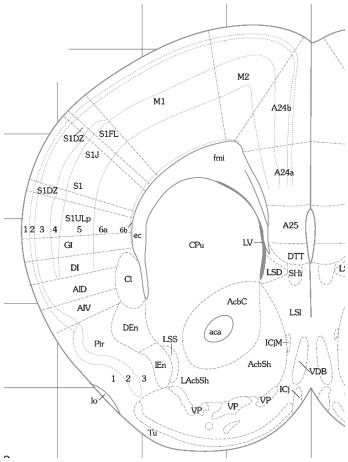
Bregma 2.10 mm



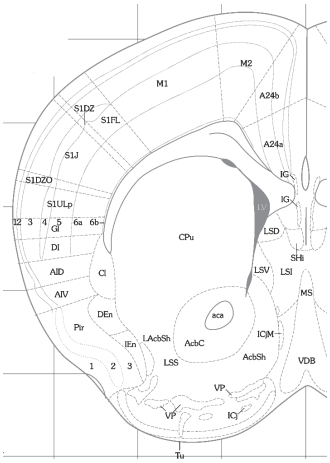
Bregma 1.94 mm



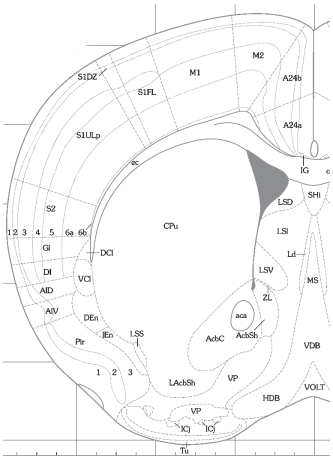
Bregma 1.70 mm



Bregma 1.42 mm



Bregma 1.18 mm



Bregma 0.74 mm

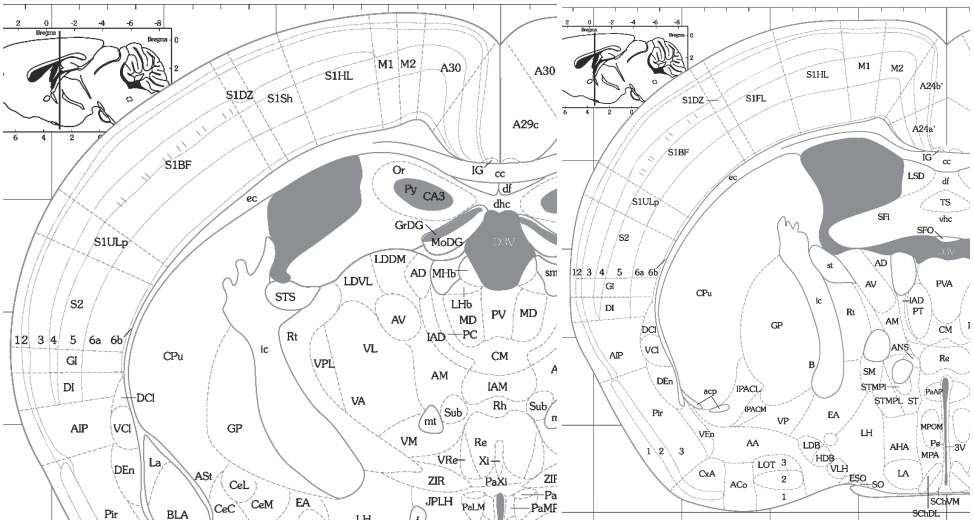


Fig.1. Series of the new schemes from the Paxinos and Franklin (2013) mouse brain atlas,"*The Mouse Brain in Stereotactic Coordinates, Academic Press, Elsevier, N.Y., USA"* corresponding with the series of images from the Franklin and Paxinos (2008) mouse brain atlas, used in the Van de Werd and Uylings study (chapter 4, submitted). Permission granted by Elsevier.

4. Nomenclature of PFC areas in rodents

In the previous paragraph we have seen that even within the same group of authors the same areas (e.g., cingulate areas) have a different size in successive publications.

Another example of this kind of problem is that dorsally to the corpus callosum the boundary between the dorsal and ventral part of the cingulate cortex is defined more dorsally by one group of authors, and more ventrally by another group of authors. In the studies of Krettek and Price (1977), Groenewegen (1988), Zilles and Wree (1995), Palomero-Gallagher and Zilles (2004), Vogt and Peters (1981), and Vogt et al. (2004), this boundary is more ventral than the one in the studies of Franklin and Paxinos (2008), Paxinos and Franklin (2013), Hof et al. (2000), Wree et al. (1983), Swanson (1992), Paulussen et al. (2011). This difference in the

localization of the dorsal and ventral part of the cingulate areas can be explained by the recognition of two different cingulate boundaries in this part of the cingulate region: the boundary between area ACd and area ACv, and within ACv the boundary between ACvd and ACvv in the parcellation of Van de Werd and Uylings (2008) and Van de Werd et al. (2010).

These are two examples of one kind of problem (i.e., boundaries are different) met when studies on cortical areas are compared. Another kind of problem in comparing parcellations of the brain, even in the same species, is that 'the same terms are used for different areas and/or different terms are used for same areas' (Uylings, 2007; Botha and Swanson, 2008). An example of this kind of problem is area AIv. The ventral agranular insular area (AIv) is in some studies restricted to the dorsal bank of the rhinal fissure and/or the dorsal lip of the rhinal fissure (Groenewegen, 1988; Berendse and Groenewegen, 1991; Swanson, 1992; Krettek and Price, 1977), while other studies have located AIv on the lateral side of the frontal lobe ventrally from area AId (Zilles and Wree, 1995; Palomero-Callagher and Zilles, 2004; Paulussen et al., 2011). As a consequence, the type of area, indicated by the term AIv, is quite different for both groups of authors and as a result communication can be confusing.

Furthermore, the nomenclature on the ventral/orbital side of the frontal lobe in rat and mouse appears to be based upon historical grounds instead of the real position of an area. For instance, the ventrolateral orbital area is not located in the lateral half of the ventral side, as the name suggests, but in the medial half of the ventral side of the frontal lobe. It remains to be seen if changing the name into a term that is more in agreement with its location will improve communication about such an area. In the new edition of the Mouse Brain Atlas in stereotactic coordinates, Paxinos and Franklin (2013) have decided to replace the nomenclature for areas of the cingulate region of the mouse by the Brodmann (1909) nomenclature, which was introduced by Brodmann in human and primate cortex and applied by Vogt and Peters, (1981) for the rat cingulate areas. In their study on the 'cingulate cortex and disease models' Vogt et al. (2004)

advocate this change on account of the great relevance of the rat cingulate region in serving as model for human diseases such as schizophrenia, Alzheimer's disease, and chronic pain. They expect that use of the rat version of the Brodmann (1909) nomenclature (Vogt and Peters, 1981) will be of advantage in comparing the effects of changes in the cingulate region in human disease with changes in the rat model of such a disease. The use of Brodmann (1909) nomenclature in rodents, however, runs the risk of suggesting identification of human brain areas as being homologous with rodent brain areas, while rat cortices are not exactly identical to primate cortices (Uylings, 2007; Uylings et al, 2003).

The great variability in cortical boundaries specified in a review of then existing literature brought Lashley and Clark (1946) to a quite pessimistic view on cytoarchitectonical studies. After this publication, cytoarchitectonic studies were considered to be superfluous and misleading for a long period. Zeki (2005) has reviewed the history of the changing appreciation of cytoarchitectonic descriptions during the period 1905 – 2005. Among other things, he pointed out that efforts to combine cytoarchitecture with function have been restored to favor, due to the convincing support for the relation between cytoarchitecture and function coming from highly developed computerized procedures of data processing and from functional brain recording and scanning. Still, the pitfalls in delineating boundaries, expressed in the study of Lashley and Clark (1946) stress the necessity of careful investigations into what characteristics can define a boundary most reliably and reproducibly. In addition, especially when a particular term is used for different regions, it is necessary to specify the criteria by which boundaries are defined.

5. Future developments

Today, especially for the mouse brain, very detailed web-based anatomical information is available. Recent advances in tracing technics, in visualizing cell-specific and genome-wide properties, in automated

collecting and processing of huge amounts of data, and making them accessible for interactive communication, are revolutionizing the research on cytoarchitecture and connections of mouse and rat brain. Hintiriyan et al. (2012) describe the results of exploring the connectivity of the olfactory bulb with other parts of the olfactory region by the use of two non-overlapping co-injections, each with a mixture of an anterograde and retrograde fluorescent tracer. In this manner reciprocal connections are viewed easily and clearly distinguished from one-way connections. The study is part of the Mouse Connectome Project at UCLA, which aims to construct a very detailed connectivity atlas for the whole C57BL/J6 mouse brain. Images are available for interactive use through the online interactive iConnectome in www.mouseconnectome.org. Chung et al. (2011) developed the "Knife-Edge Scanning Microscope Brain Atlas" (KESMBA), a web-based neuroinformatics platform for the visualization of multi-scale, high-resolution images of connective patterns and cells. The scale ranges from the level of the whole brain to the sub-micrometer level without loss of resolution. The images can be customized to the demands of the user by e.g. changing the number of sheets the image is built on, or placing empty sheets between image sheets to enable the choice of thickness of the image and the depth view. Although the images are very sharp and detailed in showing axons as well as cells, the authors admit that it is not yet possible to give an exact assessment of the connectivity in local circuits and that on global scale only 'certain fiber tracts show up prominently in the KESM Golgi data'. The fact that the Golgi stain shows only about 1% of cells has not been found to influence the information negatively. The high resolution of the images enables the distinction of different cell-types and patterns of dendrites and axon bundles. The Allen brain atlas (http://www.brain-map.org) provides a genome-wide 3D gene expression atlas (Markham, 2007; Lein et al., 2007), showing the regions of activity for each of the genes that are active in the mouse brain and also showing the degree of activity by means of different colors. In situ hybridization is used to distinguish those cells in which a particular gene

is active. On a global level the atlas enables the visualization of the density of cells expressing a particular gene in the different regions of the brain as well as, for some genes, their specific location in the cell. Thus e.g., genes involved in synaptic plasticity are found localized in dendrites (Lein et al., 2007). Nissl-stained sections, however, are still needed to link the locations of gene expression with the general anatomy of the mouse brain. The information yielded by the Allen Brain Atlas is likely to advance the knowledge of the relation between structure and function in the brain. In the study of Chung et al. (2011), the existence of various other web-sites in the field of the mouse brain architecture are mentioned: The Mouse Atlas Project (MAP); The Mouse Brain Library (MBL); BrainMaps.org; Whole-Brain Catalog (WBC). The impressive increase in the available tools in brain research, bringing together specialists from many different, highly specialized fields of science will perhaps fulfill the expectation, found in a textbook of neurophysiology (Somjen, 1983) that 'in the future disciplines such as psychiatry and neurology, psychology and neurophysiology will all become a single science'.

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