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Architectonic Mapping of the Human Brain beyond Brodmann

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Brodmann has pioneered structural brain mapping. He considered functional and pathological criteria for defining cortical areas in addition to cytoarchitecture. Starting from this idea of structural-functional relationships at the level of cortical areas, we will argue that the cortical architecture is more heterogeneous than Brodmann's map suggests. A triple-scale concept is proposed that includes repetitive modular-like structures and micro- and meso-maps. Criteria for defining a cortical area will be discussed, considering novel preparations, imaging and optical methods, 2D and 3D quantitative architectonics, as well as high-performance computing including analyses of big data. These new approaches contribute to an understanding of the brain on multiple levels and challenge the traditional, mosaic-like segregation of the cerebral cortex.

Introduction

Korbinian Brodmann subdivided the cerebral cortex into numerous areas based on regional differences in the distribution, density, shape, and size of cell bodies, i.e., the cytoarchitecture (Brodmann, 1909). Although not proven at that time, he was convinced that each cortical area subserves a certain function within a larger network. In present neuroimaging studies, Brodmann's schematic drawings of cortical maps are still frequently used references to register functional activations to anatomical structures, although his map does not match more recent anatomical and functional data in many brain regions (Zilles and Amunts, 2010), and new approaches are mandatory (Amunts et al., 2014b).

Brain mapping based on the regional distribution of cortical areas is a valuable concept beyond the generation of an atlas. It is a way to understand cortical organization by integrating in vivo structural and functional imaging data and post mortem high-resolution cytoarchitectonic observations in a common reference space (Amunts et al., 2007, 2014b; Mazziotta et al., 2001; Roland et al., 1997; Roland and Zilles, 1994). This attempt to compare architectonic and functional data has a long history and goes back to Cecile and Oskar Vogt (Vogt and Vogt, 1919) who collaborated with the neurosurgeon Otfried Förster (Foerster, 1931). They performed electrophysiological mapping in patients and monkeys and compared the independently achieved architectonic and functional results in both species to understand the functional role of architectonically defined areas (Vogt and Vogt, 1926) (Figure 1). Their approach conceptually foresees the development of brain mapping during the last decades (Table 1).

In the present review, we will focus on recent developments in mapping the microscopical organization of the human cerebral cortex, which not only is based on new methods and tools for observer-independent parcellations, but also includes the novel concept of probabilistic mapping. It will also review available as well as potential future strategies of multimodal and multiscale approaches from areas to cells and molecules. Starting with Brodmann's idea about structural-functional relationships at the level of cortical areas and its relationship to myeloarchitecture, we will argue that intra-areal organization is more heterogeneous than classical cortical maps suggest. Consequently, it requires a new definition of the concept of a "cortical area" as central element of cortical segregation. We will highlight and discuss the impact of recent developments in quantitative cytoarchitectonics and probabilistic mapping of cortical areas, as well as novel methods to specifically label cellular and molecular components of cortical architecture including "whole-brain approaches." Finally, we will discuss the potential of and the challenges on modern optic and computational methods for a deeper understanding of cortical organization, including its complex fiber architecture and structural connectivity.

Cytoarchitectonic, Myeloarchitectonic, and Myelin Density Maps

The spatial distribution pattern of neuronal cell bodies is called cytoarchitecture, and that of myelinated nerve fibers represents the myeloarchitecture (Brodmann, 1909; Vogt and Vogt, 1919; Von Economo and Koskinas, 1925; Zilles et al., 2015a, 2015b). Distinct layers of cell bodies (parallel to the cortical surface) and myelinated fibers (vertically, horizontally, and obliquely oriented) can be identified in the cerebral cortex. Cell bodies are also vertically arranged, thus forming (mini)columns (Buxhoeveden et al., 2000; Schlaug et al., 1995; Schleicher and Zilles, 2005).

Most regions of the human cerebral cortex have a six-layered architecture (isocortex), with the notable exception of the motor cortex, which does not show a clearly recognizable layer IV in adult brains (Brodmann, 1909). Non-isocortical (i.e., allocortical) regions have more (e.g., entorhinal cortex) or less (e.g., hippocampus) layers than the isocortex. Regionally specific

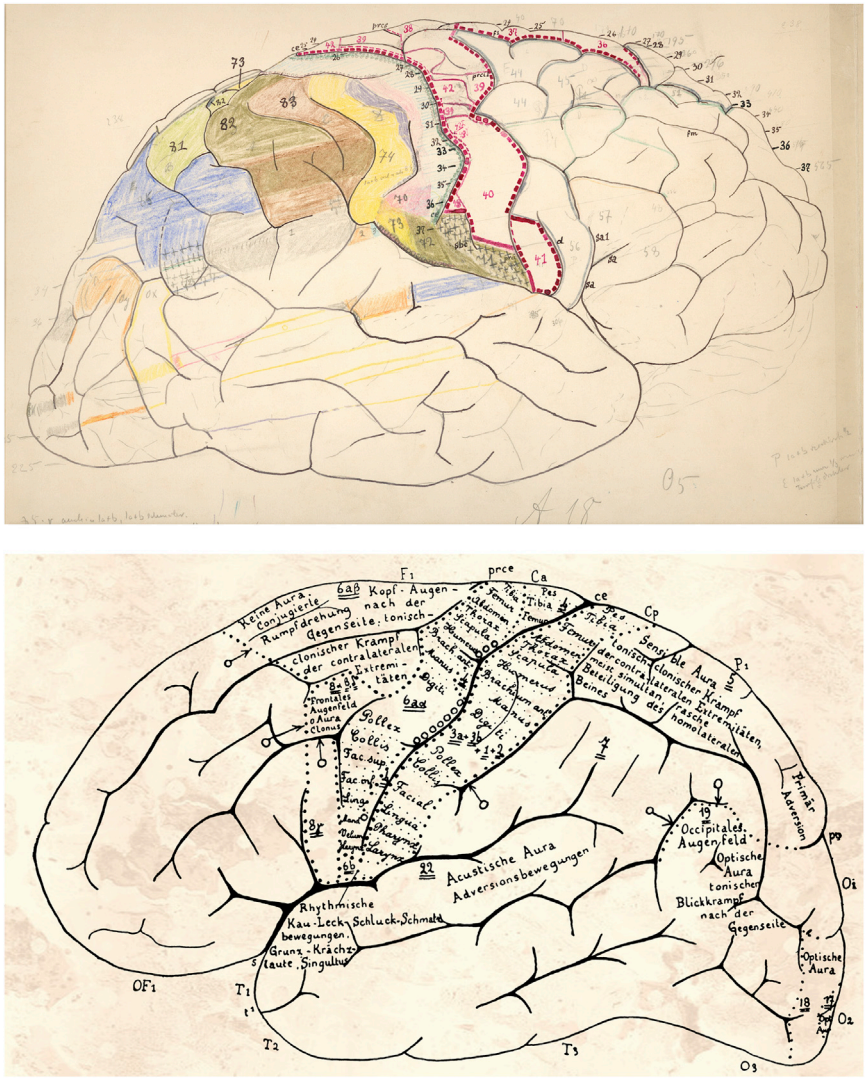

Figure 1. Early Maps of Cortical Segregation

Hand-drawn, myeloarchitectonic map by Oskar Vogt (provided by the C. and O. Vogt Archive, Heinrich Heine University Düsseldorf) and electrophysiological stimulation in patients under neurosurgery provided by Otfried Förster (from Vogt and Vogt, 1926). One of the research aims of the Vogts was to understand the physiology of brain areas, identified in myelo- and cytoarchitectonic studies, and to relate anatomical aspects of brain organization to their function in terms of neurobiological processes, but also mental processes.

differences in cyto- and/or myeloarchitecture enable the parcellation of the cerebral cortex into microscopically definable areas.

To take advantage of in vivo neuroimaging methods, maps were proposed that rely on macroscopical landmarks, and take gyral and sulcal patterns as criteria for parcellating the cortex (Lancaster et al., 2000; Tzourio-Mazoyer et al., 2002). Brodmann (1914) and Vogt and Vogt (1919) denied any precise correlation between macroscopically visible landmarks and borders of architectonic areas. Only the border between the primary motor and primary somatosensory areas is regularly found in the fundus of the central sulcus. The border between motor and premotor cortex, however, is not defined by a macroscopic landmark like the precentral or any other sulcus (Geyer and Zilles, 2005). For other areas, some borders seem to be associated with sulci, whereas others are not. A lack of co-localization of architectonic borders with macroscopical landmarks is found in the Broca region (Amunts et al., 1999; Amunts et al., 2004), extrastriate visual areas (Rottschy et al., 2007), areas within the superior (Scheperjans et al., 2005; Scheperjans et al., 2008b) and inferior parietal lobule (Caspers et al., 2006), and various other areas (e.g., Choi et al., 2006; Eickhoff et al., 2006b; Grefkes et al., 2001; Kurth et al., 2010; Malikovic et al., 2007; Malikovic et al., 2015). Areas of the fusiform gyrus, some visual areas, and the entorhinal cortex seem to be more closely related to sulci (Fischl et al., 2009; Hinds et al., 2009; Lorenz et al., 2015; Weiner et al., 2014). Thus, the inference from macroscopical landmarks to cytoarchitectonic borders may be useful for an approximate anatomical orientation, but the relationships of such landmark-based maps to the architecture must be proven for each brain region.

Can "tedious anatomy" required for architectonic studies at the level of layers and sublayers (Devlin and Poldrack, 2007) be overcome by using high-resolution structural MRI in the living brain? This would require a spatial resolution of less than ~40 μm because some cortical layers are only 30–40 μm wide (Von Economo and Koskinas, 1925). High-resolution post mortem (T2 weighted images using a 4.7 T scanner; in-plane resolution 59 × 68 μm^2; slice thickness 0.6 mm) and in vivo (T1 weighted images using a 1.5 T scanner; in-plane resolution 0.28 × 0.28 mm^2; slice thickness 0.25/0.35 mm; gray-scale normalized surface coil images) MRI (Eickhoff et al., 2005b) compared with microscopic cyto- and myeloarchitectonic observations in histological sections from the same tissue block demonstrate that the MRI signal mainly reflects the variation of the myelin density throughout the different cortical layers. Up to 84% of the signal variation is caused by the heterogeneous distributed myelin, while only 9%–16% is explained by the laminar variation of the packing density of cell bodies.

The Vogts identified 185 areas based on differences in the pattern of myelinated axons between cortical areas; for recent reviews and new maps based on the data of the Vogts and their collaborators, see (Nieuwenhuys, 2013; Nieuwenhuys et al., 2015). The Vogts stated that Brodmann, who described 43 areas, had probably missed numerous borders. By comparing cyto- and myeloarchitectonic maps, they were convinced that