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3D model-based approach to identification of laminar structures of the cerebral cortex: Application to Brodmann areas 17 and 18

C. Adamson[a,b,c,*], L. Johnston[a,c,e], I. Mareels[a,e], A. Toga[a,f], X. Huang[a,f], G. Egan[a,c,d]

[a] Howard Florey Institute, University of Melbourne, Australia
[b] Developmental Imaging, Murdoch Childrens Research Institute, Parkville, Australia
[c] Florey Neuroscience Institutes, Parkville, Australia
[d] Centre for Neuroscience, University of Melbourne, Australia
[e] Department of Electrical and Electronic Engineering, University of Melbourne, Australia
[f] Laboratory of Neuro Imaging, University of California, Los Angeles, United States

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ABSTRACT

The human cerebral cortex may be subdivided into architectonic fields according to variations within its laminar structure. Studies have shown correspondences between the locations of functional activation foci and architectonic regions. In order to perform accurate localization of functional activation foci to architectonic regions, a parcellation algorithm capable of segmenting architectonic regions on *in vivo* imaging datasets is required. This paper presents a novel 3D model-based approach to directly detect cortical layers and classify architectonic fields. The column-like structure of the cortex is modeled using a Laplace equation method which generates a collection of intensity profiles that span the cortical mantle. Bayesian evidence for intensity profile elements belonging to hyper- or hypo-intense bands, which represent cell or myelin poor or rich layers in imaging data, is gathered. A non-isotropic Markov Random Field model is used to encourage contiguous bands as well as a penalty term that completes bands across highly curved cortical regions where neighbouring evidence for banding is strong. This algorithm is validated on a 3D histological dataset of a macaque brain with visible layering at intermediate resolution between high-resolution MRI and histology. The algorithm detects the myelin-rich Stria of Gennari and uses this as the basis for finding the Brodmann Area 17/18 boundary.

1. Introduction

Classical histological studies have revealed that the human cerebral cortex can be subdivided or parcellated into distinct regions, called architectonic fields, according to their laminar structures. As many brain functions may be localised to subsets of architectonic fields, a major challenge of functional neuroimaging research involves the correlation of functional task-based activation foci to anatomical landmarks [1]. Functional neuroimaging studies typically report group results with respect to structural atlases. The most popular microstructural atlas used by neuroimaging studies is that of Brodmann [2], whose architectonic fields are referred to as Brodmann Areas (BA).

Brodmann's atlas, and other atlases produced in the early to mid 20th century (for example von Economo [3], Sarkissov [4], Flechsig [5], Vogt [6] and Mauss [7]) were produced by visual inspection of 2D histological sections. These atlases were based on one of the two principled criteria of cytoarchitecture (referring to size, arrangement, density and shape of neuronal cell bodies) or myeloarchitecture (referring to the orientation, density and thickness of myelin sheaths that surround axons). The subjective nature of the methods applied in classical histological analysis led to differences between their layering schemes and disagreements in the size and number of architectonic fields between atlases [8]. Furthermore, inter-subject variability that may be caused by genetic or environmental factors lead to unknown degrees of uncertainty when interpreting localisation results using these atlases on novel brain images.

In order to overcome the inherent uncertainties present of structural atlases, it is essential to apply objective, reproducible parcellation algorithms. Since the cortex is a 3D object with complicated geometry, such automated algorithms should operate in 3D. Desirably, architectonic field parcellation should be achievable *in vivo*. There is a growing body of evidence that high-resolution

* Corresponding author at: Murdoch Childrens Research Institute, Royal Children's Hospital, 50 Flemington Road, Parkville, VIC 3052, Australia.
Tel.: +61 3 99366780.
E-mail address: chris.adamson@mcri.edu.au (C. Adamson).

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MRI may be used to identify the laminar features of the cortex and thus potentially facilitate cortical parcellation of living subjects [9–17] (see [18] for a review).

Automated and objective microanatomical cortical parcellation algorithms have been proposed and applied to 2D stained histological tissue [19–21] and 3D MR images of postmortem specimens [22]. Schleicher et al. [19] proposed a sliding window technique in order to estimate the location of borders between architectonic fields in 2D. Schmitt et al. [21] proposed a method that examines changes in the distribution of statistical modes, peaks, to identify architectonic boundaries in 2D. Annese et al. [20] employed a hierarchical clustering technique in order to parcellate predefined numbers of architectonic fields that is 3D-capable. This method is limited since it requires knowledge of how many architectonic fields are to be identified. Bose et al. [22] presented a level-set method to isolate BA 17 by evolving an open surface tangentially to the cortical surface until the surface covered all intensity profiles whose patterns were in agreement with training data previously sampled from the same dataset. Such texture-based methods attempt to parcellate regions based on discriminating intensity patterns that are potentially different between architectonic fields. However, the algorithms do not attempt to explicitly detect the layers themselves and may be affected by changes to intensity profiles unrelated to layering.

This work addresses two limitations of current cortical parcellation literature: (i) parcellation algorithms based on detection of cortical layering in 3D, and (ii) application to a dataset whose resolution and intensity contrast is potentially achievable by *in vivo* MR imaging techniques and whose cortical laminar structures, and hence ground truth boundaries between architectonic fields, are visible. Such a dataset is important for quantitative algorithm evaluation.

This paper proposes a model-based algorithm that detects cell- or myelin-dense (or -poor) layers that appear as hypo- or hyper-intense surfaces, which we call "bands"[1] within the cortical mantle. This cortical parcellation technique involves the following steps: (1) segmentation of the image voxels into white matter (WM), grey matter (GM) and background (BG) tissue types, (2) representation of the columnar structure of the cortex by a collection of intensity profiles, which are vectors of sampled image intensities taken along trajectories that span the cortical mantle, (3) classification of intensity profile elements into bands and (4) identification of architectonic fields. The K-means algorithm [23] is employed as a generic intensity-based classifier for labelling voxels as WM, GM or BG tissue types. The Laplace equation method of Jones et al. [24] is used to construct cross-sectional streamlines for sampling intensity profiles from the cortical mantle; this produces equivalent results to the method of Schmitt et al. [25]. The Laplace equation method only guarantees orthogonal traversals of layers close to the inner and outer boundaries. The method of [26] proposed a modification that used image intensity gradients as a cue to the directionality of lamination, which was used to modify the direction of the streamlines to ensure orthogonal traversals of all layers in 2D. This method is effective in correcting the worst geometric distortions to laminae, which occur mostly in 2D imaging where the angle of cutting plane may vary from orthogonal to parallel to laminae within the image. Here, 3D images are used and the streamline trajectories are more likely to remain orthogonal to the layer orientations and correction using image data is less essential. The architectonic field classification algorithm is based on our previous work [27], which gathers Bayesian evidence that intensity profile elements belong to or do not belong to bright or dark bands. The cortical layers are expected to be contiguous, occupy a large number of intensity profiles and have limited local variation in depth. This belief is modelled using a Markov Random Field that encourages neighbouring elements to be like-classified. The algorithm Iterated Conditional Modes [28] is used to construct a locally optimal classification of intensity profile elements.

Cortical layer detection using MR imaging is difficult due to the typical voxel resolution being orders of magnitude coarser compared to the typical thickness of a layer. High-resolution MR imaging is able to achieve voxel sizes of the order of $(100\,\mu m)^3$ while layer thickness is of the order of 10 μm. Table 1 summarises the current cortical parcellation literature in terms of image resolution, modality and subject state. This data shows that resolution and image quality are key factors in machine identification of architectonic regions, which has only been successful using histology imaging or high resolution MR imaging on postmortem specimens.

To date, there has been no 3D dataset of resolution intermediate between typical layer thickness (10 μm) and MR $(100\,\mu m)^3$ that provides ground truth for architectonic field boundaries. To address this issue is the second aim of this work: application of a 3D cortical parcellation algorithm to a dataset whose resolution is potentially achievable by *in vivo* MR imaging techniques, whose cortical laminar structures are visible and whose intensity contrast in the cortex is similar to MR. The 3D histological macaque brain dataset of [29], with a resolution of 55 μm × 55 μm × 50 μm, is analysed in this work. The grey matter intensities of this dataset mimic myelin density and hence reflect myeloarchitecture, a feature of structural MR images [15,16].

Visually evident cues to cortical layering in the data are used as ground truth for evaluating the performance of the proposed algorithm. The focus of applying the algorithm in this paper is identifying Brodmann Area (BA) 17 which is occupied by the heavily myelinated Stria of Gennari (cytoarchitectonic Layer IVb of Brodmann [2], myeloarchitectonic Layer 4 of Mauss [7], outer stripe of Baillarger) and hence find the boundary between BA 17 and its neighbouring region BA 18, which contains no striking evidence of banding. The fields BA 17 and BA 18 are homologous between the Macaque and the human, and the Stria of Gennari has been a focus of cortical parcellation work using *in vivo* MR images. The algorithm is demonstrated to be able to identify a band corresponding to Layer IVb and hence find BA 17.

Cortical layer detection using MR image data is particularly difficult in highly curved regions of the cortical surface, where the cortical layers undergo significant depth and thickness variations [30], since the coarse voxel resolution leads to weak evidence of banding. Clare and Bridge [14] demonstrated that detection rates of Layer IVb in functional V1, putatively BA 17, ranged between 33 and 81% with most errors occurring in highly curved regions of the calcarine sulcus. This limitation is addressed by introducing a cortical surface curvature penalty term that encourages bands to be completed over regions of highly curved cortical surface. Thus, in regions of low data confidence we increase the weight of our prior belief of contiguous bands. For comparison, we demonstrate the results of the algorithm with and without this curvature penalty term. The curvature penalty term reduces the classification error rates in BA 17 whilst retaining the estimated BA 17/BA 18 border.

2. Materials and methods

2.1. Dataset

The 3D macaque dataset was acquired and preprocessed at the Laboratory of Neuroimaging, University of California, Los Angeles,

[1] As opposed to the term "Layer" which refer to a histologically defined entity whose characterisation requires specific criteria be satisfied. Since these criteria may not be satisfiable by the acquired image data, we do not claim that we are identifying Layers.