



Full Length Article

Anatomically motivated modeling of cortical laminae

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ABSTRACT

Improvements in the spatial resolution of structural and functional MRI are beginning to enable analysis of intracortical structures such as heavily myelinated layers in 3D, a prerequisite for in-vivo parcellation of individual human brains. This parcellation can only be performed precisely if the profiles used in cortical analysis are anatomically meaningful. Profiles are often constructed as traverses that are perpendicular to computed laminae. In this case they are fully determined by these laminae. The aim of this study is to evaluate models for cortical laminae used so far and to establish a new model. Methods to model the laminae used so far include constructing laminae that keep a constant distance to the cortical boundaries, so-called equidistant laminae. Another way is to compute equipotentials between the cortical boundary surfaces with the Laplace equation. The Laplace profiles resulting from the gradients to the equipotentials were often-used because of their nice mathematical properties. However, the equipotentials these Laplacian profiles are constructed from and the equidistant laminae do not follow the anatomical layers observed using high resolution MRI of cadaver brain. To remedy this problem, we introduce a novel equi-volume model that derives from work by Bok (1929). He argued that cortical segments preserve their volume, while layer thickness changes to compensate cortical folding. We incorporate this preservation of volume in our new equi-volume model to generate a three-dimensional well-adapted undistorted coordinate system of the cortex. When defined by this well-adapted coordinate system, cortical depth is anatomically meaningful. We compare isocontours from these cortical depth values to locations of myelinated bands on high-resolution ex-vivo and in-vivo three-dimensional MR images. A similar comparison was performed with equipotentials computed with the Laplace equation and with equidistant isocontours. A quantitative evaluation of the equi-volume model using measured image intensities confirms that it provides a much better fit to observed cortical layering.

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Introduction

The cerebral cortex contains neuronal cell bodies which are usually organized into six distinguishable layers. The layer structure varies spatially in regard to cell organization (cytoarchitecture) and myelination (myeloarchitecture), defining distinct cortical areas which are likely to perform different functions. Mapping these areas was pioneered at the beginning of the last century using cyto- and myeloarchitectonic staining techniques on post-mortem sections (Brodmann, 1909; Vogt and Vogt, 1919). In the last decade, computers and digitized images have enabled the use of observer-independent methods (Schleicher et al., 1999). With recent developments in high-resolution magnetic resonance imaging (MRI) which provide isotropic resolution below 500 μm , several researchers are starting to map myeloarchitectonic patterns in-vivo e.g. Geyer et al. (2011), Glasser and Van Essen (2011), and Cohen-Adad et al. (2012). In parallel, functional MRI (fMRI) resolution in human brain is now better than 1 mm enabling study of laminar specificity

in the BOLD signal (Koopmans et al., 2011; Trampel et al., 2012; Sanchez-Panchuelo et al., 2012), which was previously only feasible in animal models (Goense and Logothetis, 2006; Kim and Kim, 2010).

In order to analyze layer architecture or function, it is desirable to define a conformal coordinate system. In this coordinate system, cortical depth values within a given cortical area remain constant, independent of cortical curvature. Building this so-called well-adapted coordinate system is the topic of the present study. From depth isocontours, cortical profiles can be constructed that traverse the cortex. Anatomically consistent profiles allow correct assessment of cortical thickness and should enable accurate observer-independent mapping of structural brain areas, in three dimensions, using ex-vivo and in-vivo data.

Cortical profiles can be generated with computational techniques either by surface-based or voxel-based methods. Surface-based methods reconstruct cortical surfaces in order to generate the profiles, whereas voxel-based methods can generate the profiles directly from the segmentation. In both methodologies the Laplace equation has been widely used as a means of creating profiles.

In the following, we will refer to a computed cortical layer as a lamina. The term layer will only refer to layers as observed in cyto- and

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myeloarchitecture. The cortical surface that separates gray from white matter will be called the inner surface, the cortical surface separating gray matter from the pia mater will be referred to as pial surface.

The Laplace method solves the Laplace equation between the inner and the pial surfaces of the cortex, setting each of these as an equipotential. Cortical profiles may then be constructed along the gradient of this stratification (Jones et al., 2000). Compared with straight profiles corresponding to nearest distance (from a point on one boundary surface to the closest on the opposite boundary surface) or orthogonal projection methods, Laplace profiles have been claimed to provide more accurate and stable cortical thickness estimates (Haider and Soul, 2006). The main reasons for employing Laplace profiles in sampling intensity values in the cortex are that they provide a one-to-one correspondence between the cortical boundary surfaces, that they terminate perpendicularly at each boundary surface and that they do not intersect.

Cortical thickness measurements based on Laplace profiles using the voxel-based approach have been made by Yezzi and Prince (2003), Hutton et al. (2008), Geuze et al. (2008), Nagy et al. (2011), Strenziok et al. (2011) and van Swam et al. (2012). This voxel-based approach is computationally more efficient than surface-based methods, sidestepping the need to reconstruct cortical boundary surfaces, and is especially important for large data sets of population studies. The main drawback of this is the lack of accuracy, which has been partly addressed by Acosta et al. (2009) and Querbes et al. (2009) by incorporating partial volume information.

Surface-based methods employ the solution to the Laplace equation to generate one-to-one correspondences between the cortical boundary surfaces (Im et al., 2006) and even measure cortical thickness along the length of the links created by the Laplace profiles (Foster and Zatorre, 2010). The Laplace equation has also been used to model cortical layers for high-resolution fMRI (Zimmermann et al., 2011).

Voxel-based Laplace profiles have been worked with extensively for cortical parcellation on two-dimensional histological sections. Schleicher et al. (2005) used Laplace profiles on cytoarchitectonic stained sections, quantifying the differences between mean profiles of a sliding window to provide observer-independent detection of areal borders. This approach has been employed not only to study striate and extrastriate areas (de Sousa et al., 2010), but also to analyze neurotransmitter receptor distribution patterns (Eickhoff et al., 2007). Annese et al. (2004) applied Laplace profiles for myeloarchitectonic parcellation.

Laplace profiles have good mathematical properties, for instance they do not cross and are always perpendicular to the equipotentials they derive from. Because of this last property, the trajectory of the Laplacian profiles depends directly on the morphometry of the Laplacian equipotentials. The anatomy of the cortex also appears to have such a relationship: the cell columns running perpendicular to the cortical layers. Hence it is important to know whether observable cortical layers actually conform to the Laplace equation, or if a less mathematically constrained model is more appropriate to describe cortical anatomy. Schleicher et al. (2005) observed that some Laplace profiles follow cortical blood vessels on two-dimensional sections stained for cytoarchitectonics, and assumed that such profiles thus lie parallel to the cortical columns. Annese et al. (2004) asserted that the Laplace equipotentials lie parallel to myeloarchitectonic layers on their two-dimensional stained sections. De Vos et al. (2004) studied the relationship between local curvature and areal boundaries in parcellations of two-dimensional sections stained for cytoarchitectonics. The areal boundaries were deduced from samplings along Laplace profiles. They noted that the folding of the cortex can introduce artificial boundaries in observer-independent mapping. The challenge in these studies on two-dimensional stained sections is that the cutting angle of the section must be normal to the cortical boundaries to provide an interpretable relationship between two-dimensional sections and the actual three-dimensional structure. It is clear that to address the stratification question thoroughly, it is vital to have access to a three dimensional image of the cortex, together with a spatial resolution sufficient to

capture intracortical microstructure. In order to investigate this question we acquired high-resolution MR images of post-mortem samples, and compared in 3D the isocontours of the voxel-based Laplace solution with the bands of more intense myelination visible in the images (Waehnert et al., 2012). The outcome of this analysis on ex-vivo samples is described in the [Post-mortem samples](#) section and new, similar results on in-vivo data are described in the [In-vivo data section](#).

A real alternative to the Laplace equation for modeling cortical layers has to take into account the folding of the cortex, in the same way the neurons have to maintain their function although the cortex is being folded. The deep folding of the cerebral cortex in higher mammals enables to maximize surface area for given skull volume. The folding pattern was explained using the idea of white matter axonal tension (Van Essen, 1997), an idea supported by modeling cortico-cortical connections (Hilgetag and Barbas, 2006). However, Xu et al. (2010) argue that the folding pattern does not arise from axonal tension, but from different growth rates of the cortical layers. Smart and McSherry (1986) studied the development of the ferret brain. They found that the gyri form by longitudinal and radial expansion of the initially lissencephalic cortex between relatively fixed sulcal fundi.

Bok (1929) studied cyto- and myeloarchitectonic layers in the fully developed adult human brain. He was interested in the relationship between cortical folds and layer geometry. He pictured an artificial system of layer segments resembling a checkerboard pattern. This can be compared to a Cartesian coordinate system with Euclidean distances. The geometry of the checkerboard pattern changes when the layering is bent. One way the coordinate system behaves when it is bent, is to keep the volume and the arrangement of the segments constant, while the thickness and width of the compartments change to compensate for the bending. Bok found that this thought experiment matched his observations of the fully folded cortex (Fig. 1). Going along a cortical boundary surface, the layers appear to be squeezed in locations with high curvature and are relatively thick. Layer sections at places of small curvature appear to be stretched and are relatively thin.

Bok divided each cortical layer into segments that are bounded by the principal dendrites. He found by measurements on post-mortem histological sections that the volume of a segment *within* a given layer is kept constant with respect to curvature. As a result, neighboring segments in one layer have the same volume, whether they are located on a gyrus crown or the fundus of a sulcus. This comes about because the thickness of the cortical segment adjusts to adapt to the curvature, thus compensating for the folding. Bok found that not only the layer thickness compensates for folding, but also the form of the neurons changes with local curvature. He argued that these compensations enable the neurons to preserve their spatial arrangement and their segment volume, enabling the cortex to maintain its function although it is severely folded.

As stated, the aim of the present study is to model the well-adapted coordinate system from the folded cortical boundaries, guided by Bok's findings.

There have been several attempts to make computational cortical profiles and laminae anatomically more meaningful. One strategy consists of stretching and compressing the distance between sample points on profiles according to certain microanatomical landmarks. Koopmans et al. (2011) studied the fMRI signal in laminae of the primary visual cortex. They used the imaged stria of Gennari and the pial surface as landmarks. Eickhoff et al. (2007) used averaged cytoarchitectonic layers as microanatomical landmarks.

Another way to improve the profiles is to explicitly include the local curvature of the cortex. Sereno et al. (2012) studied the relationship between the MR longitudinal relaxation rate (T_1) and local curvature as a function of cortical depth. Polimeni et al. (2010a) calculated the curvature of the primary visual cortex from an image of a post-mortem sample, and related the curvature values to the distance between the stria of

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