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Cortical mapping by magnetic resonance imaging (MRI) and quantitative cytological analysis in the human brain: A feasibility study in the fusiform gyrus

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HIGHLIGHTS

- We tested a combined MRI-microscopy protocol applied to the same subject.
- We used MRI-based automated segmentation to define the region of interest.
- We used a large-scale stereological approach on whole-brain histological slices.
- The results show it is possible to link histological data directly to MRI mapping.
- Method may help clarify structure–function relationships in human cerebral cortex.

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ABSTRACT

The cerebral cortex is a layered cellular structure that is tangentially organized into a mosaic of anatomically and functionally distinct fields. In spite of centuries of investigation, the precise localization and classification of many areas in the cerebral cortex remain problematic because the relationship between functional specificity and intra-cortical structure has not been firmly established. Furthermore, it is not yet clear how surface landmarks, visible through gross examination and, more recently, using non-invasive magnetic resonance imaging (MRI), relate to underlying microstructural borders and to the topography of functional activation.

We have designed a multi-modal neuroimaging protocol that combines MRI and quantitative microscopic analysis in the same individual to clarify the topography of cytoarchitecture underlying gross anatomical landmarks in the cerebral cortex. We tested our approach in the region of the fusiform gyrus (FG) because, in spite of its seemingly smooth appearance on the ventral aspect of both hemispheres, this structure houses many functionally defined areas whose histological borders remain unclear. In practice, we used MRI-based automated segmentation to define the region of interest from which we could then collect quantitative histological data (specifically, neuronal size and density). A modified stereological approach was used to sample the cortex within the FG without a priori assumptions on the location of architectonic boundaries. The results of these analyses illustrate architectonic variations along the FG and demonstrate that it is possible to correlate quantitative histological data to measures that are obtained in the context of large-scale, non-invasive MRI-based population studies.

1. Introduction

Cortical areas (Barbas et al., 2002; Annese et al., 2005) can be functionally and anatomically defined according to several established criteria (van Essen and Maunsell, 1980; Kaas, 2010). In most circumstances, direct physiological recording of the human cerebral cortex is precluded by obvious practical and ethical concerns; nevertheless, functional subdivisions can be localized non-invasively through the use of functional magnetic resonance imaging (fMRI; Devlin et al., 2006) or positron emission tomography (PET; Haxby et al., 1994). Traditionally, the anatomical boundaries between functionally defined cortical areas could only be verified through studies of architectonics and connectivity patterns (Kaas, 2010) that were conducted on postmortem tissue and in experimental animals. The need to link MRI localization of functional landmarks to maps based on underlying microstructural anatomy has been previously raised multiple times (Crick and Jones, 1993; Passingham et al., 2002; Devlin and Poldrack, 2007). Toward this end, advances in the use of high-resolution MR to identify cortical boundaries have enabled researchers to localize regions with prominent features such as the stria of Gennari (Clark et al.,

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1992; Bridge et al., 2005) and the boundary between motor and somatosensory cortex (Glasser and van Essen, 2011). As evidenced by direct comparisons with histology, these borders are likely visible in MRI scans because of variations in the density of myelinated fibers (Geyer et al., 2011a, 2011b). However, histological studies and brain mapping using MRI are rarely conducted on the same subjects (Annese, 2012); thus, the relationship between MRI data and microanatomical structure as seen in histological examination remains unclear.

For example, the fusiform gyrus (FG) is an anatomical structure on the ventral surface of the cerebrum that is long and uninterrupted in appearance except for very shallow secondary sulci. While there are no gross anatomical landmarks that could be used to subdivide the FG into separate compartments, the gyrus houses several distinct regions involved in diverse cognitive functions, such as face recognition (Natu and O'Toole, 2011; Meng et al., 2012), orthography and reading (Devlin et al., 2006; Tsapkini and Rapp, 2010), semantic word retrieval (Perani et al., 1999; Sharp et al., 2010), processing of color information (Martin et al., 1995; Simmons et al., 2007), synesthesia (Jäncke et al., 2009) and other functions related to object identification (Wierenga et al., 2009). Linking the function of the FG to underlying micro-anatomical parcels is problematic because there are too few published histological reports and images that can be related to the variety of functions observed in vivo. Classical maps of the cerebral cortex, constructed on meticulous, but subjective, observations on the size and distribution of neuronal cell bodies (Brodmann, 1909; von Economo, 1929) or the density and arrangement of myelinated fibers (Vogt and Vogt, 1919; Hopf, 1951), subdivide the FG into only two or three subregions (Fig. 1). The lack of clear quantitative criteria and documentation makes it difficult to reference these studies when mapping the cortex of any individual subject.

In an effort to address these limitations in the field, we propose a novel method that can help establish a more direct correlation between quantitative cyto-architectonic data and MRI-based maps in the human brain. The proposed method leverages the combination of non-invasive MRI and postmortem imaging of the brain in the same individual at different levels of resolution. MRI is used to determine, via established segmentation algorithms, a region of interest (ROI) that is unique and reproducible across larger, population-based neuroimaging studies. In this study, we applied the FreeSurfer image processing pipeline (http://surfer.nmr.mgh.harvard.edu/; Fischl et al., 2004; Desikan et al., 2006) to label voxels that belong to the FG. These voxels are represented by corresponding vertices in the triangulated model of the surface of the cerebral cortex. Once the ROI was selected, we applied stereological tools to acquire quantitative data from whole-brain histological sections that cross the ROI. This approach allows for the analysis of stereological quantitative data, created without the bias of a priori assumptions regarding the location of architectonic boundaries within the FG; crucially, information describing microarchitecture can be related to other maps obtained with MRI and fMRI via the standard FreeSurfer segmentation. By combining these two robust approaches (automated segmentation and stereology), we demonstrate the potential to bridge the gap between two levels of mapping at macro- and microscopic levels and produce quantitative data in a way that directly relates to MRI features that are relevant to clinical and morphological population-based studies.

2. Materials and methods

2.1. The brain

This feasibility study was conducted using a single brain specimen, donated by a 50-year-old Hispanic male. The subject was a smoker (for 30 years) and had received cataract surgery in both eyes 6 months prior to his death. The donor worked as a private investigator.

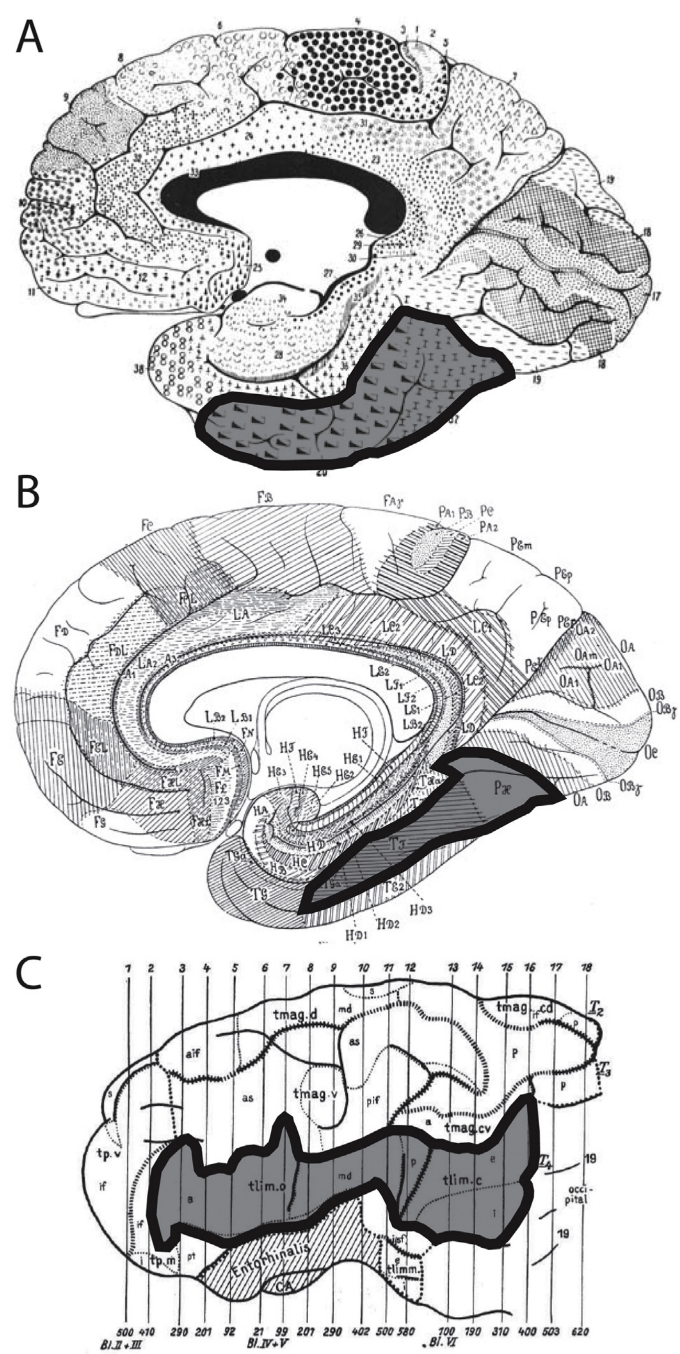

Fig. 1. Classical cortical architectonic maps based on (A) density and thickness of cellular layers (Brodmann, 1909); (B) density and thickness of cellular layers, as well as estimates of cell size and density (von Economo, 1929); and (C) the arrangement and orientation of intracortical fibers (Hopf, 1951). The region corresponding to the FG is highlighted on each map.

2.2. Magnetic resonance imaging (MRI)

MRI scans of the brain were acquired in situ on a General Electric "HDX" Twinspeed EXCITE 1.5 T scanner (Milwaukee, WI.) using an eight-channel, transmit-receive, phased-array head coil. Scan parameters (3D acquisition, T1-weighted, fast gradient echo; pixel spacing: 0.9375 mm × 0.9375 mm; slice thickness: 1.2 mm;