Observer-Independent Analysis of High-Resolution MR Images of the Human Cerebral Cortex: In Vivo Delineation of Cortical Areas

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Abstract: Using high-resolution MRI, it is now possible to examine the living human cortex down to a resolution of less than 300 μm . Thus, in vivo imaging is now approaching the resolution that has been successfully used in histological analysis of the cerebral cortex for many years, e.g., low-magnification light microscopy. This allows unprecedented views of cortical microstructure that reflect defined histological features, specifically, individual cortical layers. As in histological brain mapping, it is possible to use the changes in the cortical lamination patterns to define individual cortical areas. This allows in vivo neuroanatomical maps to be generated for individual subjects and precise correlation of the results from functional imaging studies in these subjects with their own microanatomical information. To this end, we adapted the well-established observer-independent cytoarchitectonic mapping techniques for defining cortical borders based on changes in cortical lamination for in vivo parcellation of high-resolution structural MR images. *Hum Brain Mapp* 28:1–8, 2007. © 2006 Wiley-Liss, Inc.

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INTRODUCTION

The development of observer-independent methods for the definition of cortical areas has overcome many of the problems inherent in classical approaches to architectonic brain mapping. These techniques [Schleicher et al., 1999, 2000] have led to reliable and reproducible detection of cortical borders and the delineation and further subdivision of classical cortical areas, based on both neurotransmitter receptor mapping or cytoarchitecture [e.g., Amunts et al., 1999, 2000; Eickhoff et al., 2006a,b; Grefkes et al., 2001; Zilles et al., 2003]. By normalizing the defined cortical areas to the Montreal Neurological Institute (MNI) reference space [Holmes et al., 1998] and superimposing the results from multiple subjects, individual variability can be captured by generating probabilistic maps of the defined cortical areas [Eickhoff et al., 2005b; Mohlberg et al., 2003]. This allows the

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correspondence between structure and function within the human cerebral cortex to be examined on a group level by comparing the functional results from groups of living subjects with the group structure of (postmortem) subjects [Amunts et al., 2004; Eickhoff et al., 2005b].

By definition, however, probabilistic atlases cannot be used to examine an unambiguous relationship between the structure and function within a single individual. To gain precise information on the correspondence between macrostructure, microstructure, and function, the extent and location of cortical areas have to be defined within the same individual.

Recent developments in high-resolution MR imaging have allowed visualization of the microstructure of both living and postmortem cerebral cortex [Clark et al., 1992; Fatterpekar et al., 2002; Walters et al., 2003; Yoshiura et al., 2000]. In previous studies by our group, we showed distinctive lamination patterns for the visual cortical areas V1 and V5/MT+ in high-resolution MR images at a resolution of approximately 280 μm [Eickhoff et al., 2005a; Walters et al., 2003]. Intensity line profiles through the cortex were used to characterize these lamination patterns and were shown to differ qualitatively between these two cortical regions. The microanatomical basis for the lamination patterns observed in MR images has been found to correlate mostly with the degree of cortical myelination and to a minor extent with the cell density [Clark et al., 1992; Eickhoff et al., 2005a; Fatterpekar et al., 2002; Walters et al., 2003; Yoshiura et al., 2000].

These developments are an important step toward the generation of individual atlases of brain structure. In turn, these structural atlases will enable more precise interpretation of the results of functional brain imaging studies. However, before high-resolution structural MR imaging can be routinely used for structural *in vivo* brain mapping studies, a robust quantitative method of analyzing lamination patterns in MR images is required. Based on the previous findings that MR lamination patterns reflect cortical microarchitecture, a logical starting point for this development is to adapt existing and well-established methods of observer-independent mapping of histological specimens [Schleicher et al., 1999, 2000]. This method is based on the fact that each cortical area has its own characteristic laminar structure that differs from that of the neighboring areas. By quantifying the local differences in laminar structure along the cerebral cortex, those locations where there is a significant change in cortical architecture, (i.e., a border between different cortical areas) can be identified. This method is not restricted to the analysis of cytoarchitectonic sections, but can be equally applied to any imaging modality in which a laminar cortical structure is visible, for example, myeloarchitectonic sections and receptor autoradiography images [Schleicher et al., 2000].

In the present study, we adapt and apply this method to show its ability to automatically delineate cortical areas in high-resolution structural MR images of the *living* human brain based on statistical, quantitative criteria. Specifically, we apply this method to a region of cortex containing the motion-sensitive region V5/MT+ [Walters et al., 2003], and

compare the resulting parcellation with the location of functionally defined V5/MT+ activated in the same subjects in response to a visual motion stimulus.

SUBJECTS AND METHODS

This study focused on the structure and function of the motion-sensitive region V5/MT+ [Dumoulin et al., 2000; Watson et al., 1993; Zeki et al., 1991]. Acquisition and processing of the functional and structural MRI data have been described previously [Walters et al., 2003]. Two subjects were selected from this previous study and quantitatively analyzed using the observer-independent techniques. These subjects showed the greatest extent of cortex imaged perpendicular to the acquired coronal sections within the functionally defined V5/MT+ region. This minimized the number of tangential sections of cortex, which cannot at present be analyzed quantitatively. A brief description follows.

Functional and Structural MRI of V5/MT+

The functional study involved a two-condition subtraction design in which subjects were presented with an alternating stationary and moving black-and-white checkerboard stimulus. Echoplanar imaging (EPI) was performed using a 1.5 T MR scanner (Signa Echospeed, General Electric, Milwaukee, WI) with 32 whole brain volumes acquired per scanning session (TR/TE = 3000/60, FA = 30°; NEX = 1; matrix = $64 \times 64 \times 15$; FOV = 27 cm², slice thickness = 7 mm). Preliminary analysis using SPM99 was performed to locate the V5/MT+ region to enable optimal positioning of the surface coils for the structural study. The EPI images were realigned to correct for motion between scans using a linear registration tool [Jenkinson et al., 2001]. The EPI data were then aligned (using the same linear registration tool) to the subject's high-resolution average image from the structural MRI study [Walters et al., 2003]. The EPI data were then reanalyzed and the functional results were overlaid on each subject's structural MRI results.

In the structural study, 8 coronally oriented high-resolution surface coil T1-weighted 3-D volumes were acquired successively for each subject using twin surface coils (FOV 10 cm) positioned over the functionally defined V5/MT+ region (parameters for each volume: 3-D fast spoiled gradient echo sequence (FSPGR); number of slices 120, slice thickness 0.5 mm (subject NW) 0.7 mm (subject RC), FOV 16 cm², acquisition matrix 288×288 , in-plane resolution 0.556×0.556 mm², TE of 3.5 ms, TR of 15.9 ms, TI of 350 ms; NEX 1, FA of 25°). Images were manually segmented to remove nonbrain tissue and gray scale normalized to correct for signal attenuation due to the surface coils. The resulting images were aligned to one another, resampled, and averaged to create a single high-resolution structural average for each subject (in-plane resolution 0.28×0.28 mm; slice thickness 0.25/0.35 mm; subjects NW/RC) [Walters et al., 2003].

Regions of interest (ROIs) were subsequently defined in consecutive coronal slices of the high-resolution structural MR images for the quantitative architectonic analysis. These

Figure 1.

Analysis of an exemplary slice. **a:** Functional activation (red, $P < 0.05$ corrected) projected on the subject's structural MRI results. The laterally located activation focus corresponds to V5/MT+. **b:** Average high-resolution structural MR image ROI for left V5/MT+ (indicated by inset box in **a**). Note the lamination pattern in the sulcus covered by the functional activation. **c:** Location of the extracted line profiles projected onto the structural ROI. **d:** Mahalanobis distance function for block size ($b = 20$) plotted against the profile position of the border between the blocks. Significant maxima are marked by asterisks and drop lines. **e:** Summary of the location of the significant (main) maxima for block sizes from $12 \leq b \leq 24$. **f:** The positions of putative borders were overlaid on the ROI, defining four areas (1–4) within the cortical ribbon of interest. **g:** Visualization of the differences between the profiles of the defined sectors using a canonical analysis of the corresponding individual feature vectors. **h:** Mean intensity profiles (solid lines) and one standard deviation (dashed lines) for each of the four areas. The cortical sectors are arranged according to their position in **f**.

ROIs were defined separately for each hemisphere of both subjects as follows. All regions of interest were based on the results of the functional imaging experiment and cover the functionally identified V5/MT+ region in the depth of the lateral occipital sulcus as well as the neighboring cortex on both banks of this sulcus and the adjacent free surface. Slices where severe distortions or artifacts were present were excluded from further analysis. The thus-defined ROIs were copied from the 3-D volume and converted into 8-bit, 2D gray value images for further analysis. This is demonstrated in Figure 1a, where functional MRI (fMRI) results are shown in red, while the white box marks the extent of the ROI for the structural analysis. Figure 1b displays the cropped ROI from that structural MR image, corresponding to the inset region in Figure 1a.

Structural MRI Single-Slice Analysis

Contours were interactively drawn along the inner and outer gray matter borders. Equidistant intensity line profiles ($\sim 200 \mu\text{m}$ apart) were then extracted automatically perpendicular to the cortical ribbon of this region (Fig. 1c), and the

profiles in the vicinity of the V5/MT+ region were analyzed (i.e., the sulcus labeled 1–4 in Fig. 1f). These intensity line profiles characterized the cortical lamination (Fig. 1h; cf. Figs. 4, 5). The cortex outside this region was not analyzed, as no functional data were available for interpreting subparcellations of these regions. After standardizing the cortical depth from 0%–100%, the shape of each profile was quantified by extracting a 10-element feature vector based on central moments [Dixon et al., 1988]. These features were the mean MR intensity, the cortical depth of the center of gravity of the area beneath the profile curve, the standard deviation, the skewness, the kurtosis, and the analogous features from the absolute value of the first derivative of the profile [Schleicher et al., 2000].

Statistical comparisons between these feature vectors allowed the definition of borders between cortical areas: dissimilarities between the profile shapes were quantified by the Mahalanobis et al. [1949] distance between their feature vectors. The Mahalanobis distance was used as it is more sensitive to abrupt changes occurring at areal borders and less affected by gradual changes (e.g., induced by the cortical folding), compared to, for example, the Euclidean dis-

Figure 2.

Results for a series of consecutive slices in subject NW (right hemisphere shown in radiological convention). **a:** Functional activation (red, $P < 0.05$ corrected) projected on the subject's structural MR image (slice separation 1.0 mm). **b:** Average high-resolution structural MR image ROIs for right V5/MT+ (indicated by inset boxes in **a**). **c:** Location of the extracted line profiles indicated on the structural ROI shown above. **d:** Summary of the location of the significant (main) maxima for block sizes from $12 \leq b \leq 24$. **e:** Projection of the putative borders on the structural ROIs.

tance [Schleicher et al., 2000]. Maxima in this function (corresponding to pronounced changes in laminar structure) were tested for significance using Hotelling's T^2 test with Bonferroni correction for multiple comparisons [Schleicher et al., 1999, 2000]. This procedure was repeated for block sizes between 12 and 24 profiles. The positions of consistently occurring significant maxima (main maxima) were taken as putative architectonic borders (Fig. 1e). These putative borders were validated by comparing across a series of adjacent sections and the resulting borders were overlaid on the ROI for a comparison with the localization of the functional V5/MT+ data (Fig. 1f).

The dissimilarities between the cortical lamination patterns of the defined sectors were further examined by selecting 10–15 profiles from perpendicular regions of cortex within each sector and subjecting their feature vectors to a canonical variates analysis. The results were visualized in a 2D scatterplot based on the first and second canonical variables (Fig. 1g) [Krzanowski, 1988]. Mean intensity profiles were then calculated for each sector (Fig. 1h).

Structural MRI Multislice Analysis

The series of consecutive structural MRI slices covering the functionally defined V5/MT+ region were analyzed as above. Spatially correlated sectors across consecutive slices were grouped. Dissimilarities in cortical lamination within and between groups were also examined using canonical analysis of the mean feature vectors of the sectors within each group. Overall mean intensity profiles were calculated for the final groups.

RESULTS

The complete set of results for a series of example slices through the functionally defined V5/MT+ region of two hemispheres (one from each subject) are presented in Figures 2, 3, and 4. Figure 5 summarizes the results for a single structural area identified in all four hemispheres examined, which consistently correlates in location with the functionally defined V5/MT+.

Figure 3.

Results for a series of consecutive slices in subject RC (left hemisphere shown in radiological convention). **a:** Functional activation (red, $P < 0.05$ corrected) projected on the subject's structural MR image (slice separation 1.4 mm). **b:** Average high-resolution structural MR image structural MRI results (slice separation 1.4 mm) for left V5/MT+ (indicated by white boxes in **a**). **c:** Location of the extracted line profiles indicated on the structural ROI shown above. **d:** Summary of the location of the significant (main) maxima for block sizes from $12 \leq b \leq 24$. **e:** Projection of the putative borders on the structural ROIs.

Structural MRI Single-Slice Analysis

Border definition

The positions of the significant maxima of the Mahalanobis distance function identified those profiles where the most pronounced changes in the laminar pattern were found (Fig. 1d). Putative cortical borders were indicated when the locations of these significant (main) maxima reproducibly occurred at consistent profile positions across various block sizes (Fig. 1e; cf. Figs. 2d, 3d: red lines). Those borders that were not spatially correlated across slices were interpreted as artificial and removed [Schleicher et al., 1999, 2000]. The remaining borders were overlaid on the individual ROIs (Figs. 2e, 3e). In all hemispheres 3–4 cortical sectors were consistently identified across consecutive slices in the sulcus containing the functional V5/MT+ activation.

Profile analysis

Profiles from each sector formed discrete clusters in the canonical scatterplot (Fig. 1g). Two conclusions can be drawn from this observation: (1) profiles within each sector share a common laminar structure, and (2) this structure differed between sectors. In accordance with the latter conclusion, the mean profiles generated from these sectors clearly differed (Fig. 1h). In particular, note the marked

difference between the mean profiles from the two adjacent sectors labeled 2 and 3 within the analyzed sulcus (Fig. 1f).

Structural MRI Multislice Analysis

Mean feature vectors from spatially correlated sectors across the series of slices were grouped and subjected to canonical analysis. Groups 1 and 2 (for location see Fig. 4a) formed two distinct and separate clusters in the scatterplots of both subjects (Fig. 4b). The clusters formed by groups 3 and 4 overlapped in both subjects, suggesting they may either be part of the same area or two architecturally very similar regions. However, groups 3 and 4 together formed a distinct cluster that was well separated from both groups 1 and 2 (Fig. 4b). Thus, the spatially correlated sectors within each group also shared a highly similar lamination pattern, allowing us to interpret each of these groups as separate cortical areas.

An overall average profile for each of these cortical areas (1–4) was generated (Fig. 4c). The profile from one area in particular (Fig. 4a: area labeled 2) was distinctly different from the immediately adjacent cortical areas, showing two pronounced intensity peaks at cortical depths of ~20% and 60%. The profile from cortical area 1 appeared more similar to the profile from area 2 in both subjects compared to the profile from area 3. It also showed an intensity peak at about

Figure 4.

a: Schematic drawing of the location of the sectors corresponding to groups 1–4. **b:** Visualization of the differences between the mean feature vectors from spatially correlated sectors using scatterplots of the first and second canonical variables. All four groups form tight clusters, indicating that the sectors within a group share a common lamination pattern. The cluster formed by group 2 is clearly separated from the other groups, as is area 1, indicating these areas have a discrete cortical lamination pattern. The clusters of groups 3 and 4, however, overlap completely in (i) subject NW and to some extent in (ii) subject RC, indicating that they have a much more similar lamination pattern and may be from the same or highly related subregions. **c:** Mean profiles for the four defined areas across all slices. The cortical sectors are arranged according to their position in **a**. Note the similarity of the profiles from area 2 of both subjects.

20% cortical depth, but lacked the intensity peak at 60% cortical depth. Consistent with the overlapping clusters formed by groups 3 and 4 in the canonical scatterplots, their mean profiles were highly similar, although clearly different from the mean profile of cortical area 2.

An area displaying the distinctive laminar pattern of area 2 in Figure 4 could be identified in all examined hemispheres

Figure 5.

Mean profiles for area labeled 2 across all slices in the four hemispheres examined. This area showed a consistent spatial correlation with the functional activation corresponding to V5/MT+.

(Figs. 4, 5). This area showed a strong spatial correlation with the corresponding functional activation of V5/MT+ (e.g., Figs. 2, 3).

DISCUSSION

The well-established observer-independent mapping approach developed for postmortem studies of cerebral architecture [Schleicher et al., 1999, 2000] has for the first time been used on high-resolution MR images obtained from living human subjects. Specifically, this method was applied to the cortex corresponding to the functional location of the motion-sensitive region V5/MT+. Within this region of interest, 3–4 discrete cortical sectors were robustly identified across a series of consecutive slices. These sectors could be spatially correlated across different slices into four groups. The sectors within each group shared a similar cortical lamination structure based on the fact that each formed a discrete cluster in the canonical scatterplots. The four defined groups could thus be interpreted as contiguous, architectonically distinct areas. One of the defined areas (area labeled 2) had a particularly distinct cortical lamination structure, as quantified by its mean intensity profile, which was clearly different from that of the adjoining cortical areas (Fig. 4: cf. profile 2 to 1 and 3). The cortical areas immediately adjacent to area 2 (i.e., areas 1 and 3) also possessed distinct laminar structures that differed from each other. However,

the remaining cortical area (area 4) displayed a similar laminar structure to its neighbor, area 3 (Fig. 4: cf. profiles 3 and 4). These two areas (3 and 4) also formed overlapping clusters in the canonical scatterplot. These observations suggested that areas 3 and 4 might be highly related subregions.

Importantly, the lamination patterns of the different cortical areas (1–4) were consistent across the subjects analyzed (Fig. 4c), particularly the distinctive laminar structure of the area labeled 2 (Fig. 5). Of particular relevance, the location and borders of the area labeled 2 coincided very well with the spatial extent of the functionally defined V5/MT+ region in all hemispheres examined (e.g., Figs. 2, 3). More precisely, the observer-independent algorithm reliably identified a distinct cortical area on the deeper part of the lower bank of this sulcus. This area consistently showed a distinct bistratified laminar pattern, which was highly reproducible across all examined hemispheres (Fig. 5). Moreover, as evident from the comparison with the functional activation of the V5/MT+ complex in these hemispheres (Figs. 1, 2), there was a good match with the location of this structurally distinct area.

While the borders of this area were consistently observed in very close correspondence to the edges of the functional activation, a direct quantitative comparison between the extent of the functional activation and that of the anatomically defined area is problematic for two main reasons. First, the size of a functional activation depends not only on the preprocessing of the data and the statistical model, but most important on the threshold used to label a voxel as significant. Thus, a functional activation may be as small as a single voxel, when stringent thresholds and corrections for multiple comparisons are used, but comprise several dozen voxels at more liberal thresholds.

Second, the signal detected by fMRI (i.e., the blood oxygenation level-dependent (BOLD) effect) is vascular in nature. Due to the physiological regulatory mechanisms coupling the neuronal activity and the vascular response, the hemodynamic response function effectively incorporates a low-pass filter in both the temporal and the spatial domain, thus limiting the effective resolution for localizing absolute effects, i.e., those tested against baseline [Logothetis, 2002; Logothetis and Wandell, 2004; Stephan et al., 2004; Villringer, 1997]. Nevertheless, the close correlation between the functional and structural areas suggest that this area may represent a structurally discrete subdivision within the V5/MT+ complex, in agreement with recent functional imaging studies showing several subdivisions within the human V5/MT complex [Dukelow et al., 2001; Huk et al., 2002].

The successful application of quantitative analytical methods, originally developed to examine cortical cytoarchitecture, to in vivo MR images demonstrates several important points. First, intensity profiles are useful in characterizing the cortical lamination structure visible in high-resolution MR images [Eickhoff et al., 2005a; Fatterpekar et al., 2002; Walters et al., 2003]. Second, the MR intensity profiles vary across the cortex, reflecting the microarchitectonic differ-

ences between cortical areas. Third, statistical comparison of shape describing features extracted from MR intensity profiles can consistently detect changes in the laminar structure corresponding to the borders of cortical areas, as is well established for cytoarchitectonic mapping of postmortem brains, in spite of the lower resolution achievable in in vivo MR imaging. Moreover, these results are highly reproducible across individual MR slices and consistent between subjects, allowing corresponding cortical areas to be identified by their lamination structure in vivo.

The quantitative mapping of cortical areas on high-resolution structural MR images will have important applications in understanding the relationship between structure and function in the normal (and abnormal) brain. One application, for example, is overcoming the problem of inter-individual variability when examining the function of multiple (and possibly functionally related) adjoining areas in highly variable regions of cortex (e.g., in the parietal lobe). Identifying in vivo structural correlates for these areas in any individual may allow function to be localized precisely to each individual's exact neuroanatomy, affording new opportunities to examine the relationship between structure and function of the human cerebral cortex.

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