Localization of the Human Cortical Visual Area MT Based on Computer Aided Histological Analysis

We describe human area MT histologically based on the observer independent analysis of cortical myeloarchitecture, multiple complementary staining techniques and 3-D reconstruction. The topography of an architectonic field that presented constant structural characteristics across specimens was studied in relation to the sulcal geography of the occipito-temporal region. Objective and semi-automated analysis of local microstructure revealed a distinct cortical architecture and matched topographically the localization of MT derived from functional imaging. MT was localized by the histotopographic method in relation to definite macroscopic landmarks. This study demonstrates a new set of distinguishing architectonic features of human MT that permit localization on structural grounds and suggests that the characteristic laminar structure of this area may be related to its unique pattern of connections and to its role in visual perception.

Keywords: architectonics, histology, motion perception, MT, visual cortex

Introduction

The visual cortex of primates can be shown, by specific staining methods, to vary locally in the pattern of lamination (Garey, 1993; Zilles and Clarke, 1997), and architectonic boundaries are especially obvious when the tissue is stained to reveal myelinated fibers (Sanides, 1972; Annese et al., 2004). The definition of a visual cortical area is subordinate to the localization of architectonic boundaries in respect to the demonstration of a characteristic pattern of connectivity, a complete topographic representation of the visual field and mapping of specific neuronal response properties (Kaas, 1982; Kaas, 1997; Van Essen, 1985; Krubitzer and Kaas, 1990). The coincidence of these criteria was ascertained across different species of primates for area MT, localized within the superior temporal sulcus (STS; Zeki, 1969, 1974; Allman and Kaas, 1971; Dubner and Zeki, 1971; Van Essen et al., 1981; Desimone and Ungerleider, 1986). Anatomically, area MT in primates can be localized by direct and highly convergent projections from area V1 (the primary visual cortex; Cragg, 1969; Allman and Kaas, 1971; Zeki, 1971) and by a well-defined pattern of dense myelination, which resides on the ventral bank of the superior temporal sulcus (STS); physiologically, it is characterized by a significant concentration of neurons responsive to the direction and motion of visual stimuli (Orban, 1997).

In human subjects, a direct demonstration of a plausible area MT was provided on the basis of its selective activation in response to moving visual stimuli. Early positron emission tomography (PET) experiments (Lueck et al., 1989; Zeki et al., 1991; Watson et al., 1993) and subsequent functional magnetic resonance imaging (fMRI) studies (Tootell et al., 1995) demonstrated the existence of a cortical field that not only invariably responded to the presentation of moving visual stimuli but that was also substantially bilateral and topographically consistent among subjects. The faithfulness of the putative human area MT to a particular location on the lateral aspect of the brain’s hemispheres has been expressed in terms of stereotaxic coordinates (Talairach and Tournoux, 1988; Lueck et al., 1989; Zeki et al., 1991; Watson et al., 1993, Tootell et al., 1995) and in relation to the sulcal pattern of the cortical mantle (Watson et al., 1993; Dumoulin et al., 2000; Walters et al., 2003).

In contrast with the large amount of functional evidence for human MT, very few histological studies, foreshadowed by Flechsig’s myelogenetic survey of the cerebral cortex (Flechsig, 1901), have provided structural cues for its localization. Previous work related functional activation of human MT to an area of early (Flechsig, 1920; Watson et al., 1993) and dense (Clarke and Miklossy, 1990; Tootell and Taylor, 1995; Sereno and Allman, 1991) myelination described at the junction of occipital and temporal lobes. However, human MT is still essentially defined by its stimulus-specific metabolic behavior and an eloquent — and quantitative — description of its histological features is missing.

Seeking structural evidence for human MT, we re-examined the architectur of the occipito-temporal region of the mantle using an automated quantitative method designed to analyze cortical myeloarchitecture (Annese et al., 2004). The combination of this approach with the application of alternative tissue staining protocols and 3-D reconstruction was aimed at resolving a unique architectonic field as a candidate for human MT. The goal was to ascertain whether an architectonic singularity could be matched, across subjects, to the topography of activation of human MT. Given that a direct synopsis of functional and morbid exploration in the human subject is desirable but hardly practicable, our histotopographic survey post-mortem relied initially on largely consistent landmarks previously established in vivo (Watson et al., 1993; Dumoulin et al., 2000).

Materials and Methods

Morbid Preparation and Histological Processing

The retrosplenial region of 12 human brains were examined. Post-mortem T1 weighted scans of the fresh cerebra were acquired in a 1.5 T GE Signa LX (Dept. of Radiology, Dartmouth-Hitchcock Medical Center) immediately after autopsy (3-D fast SPGR sequence; 92 x 256 matrix; field of view = 26 cm; slice thickness = 1.5 mm; TR = 12; TE = minimum; flip angle = 60°). After the imaging procedure, specimens were cleaned of the pial membranes and fixed by immersion in frequent changes of 4% phosphate-buffered paraformaldehyde. By removing the membranes that enveloped the hemispheres we effectively exposed the entire surface of the cortex to the fixative solution; this procedure eliminates possible staining inhomogeneities that occur as deeper portions of the cortex fix later than superficial areas (this is a possible source of artifact in archival material that is fixed slowly by immersion in formalin; Annese

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and Toga, 2002). The post-mortem interval ranged from 4 to 10 h. Fixed tissue was embedded in 7% gelatin in order to minimize the distortion of the gyrri when sections were mounted on glass and cryoprotected by infiltration with solutions of increasing concentration of sucrose (10, 20 and 30 % sucrose by volume).

Semi-thin sections were cut frozen on a Jung Tetramer manual sliding microtome (Jung, Heidelberg) at an interval of 50-60 μm. The cutting plane was orthogonal to the main axis of the calcarine sulcus. Pairs of thinner sections (25–30 μm) were collected at regular intervals and designated to immunohistochemical protocols. All sections were stored free floating in phosphate-buffered solution at 4°C before being stained. Every sixth or twelfth section from the continuous series harvested at the microtome was mounted on glass and stained according to the silver impregnation technique of Gallyas (1979) complicated with a differentiation step (Hess and Merker, 1983) and further optimized for quality and consistency of staining (Annese et al., 2004). Sections immediately adjacent to those processed for myelin were colored with cresyl violet or thionine in acetate buffer in order to image cortical lamina by cellular distribution.

Selected sections were stained for acetylated lysine according to the method of Tago et al. (1986). Cytochrome oxidase (CO) histochemistry was applied to regular series of sections from three specimens following the protocol that is described in detail by Wong-Riley (1979) and Wong-Riley et al. (1993). Staining was assessed to be satisfactory by virtue of the clear modular pattern resolved in V1, where the cortex was sectioned more or less tangentially along layer III. Cat-301 monoclonal antibody and WFA (Wisteria floribunda) lectin (Vector Labs, Burlingame, CA) were used in this study in view of their demonstrated ability to recognize specific classes of neurons belonging to the primate cortical network that involves area MT (DeYoe et al., 1990; Hockfield et al., 1996). MAB Cat-301 recognizes a chondroitin sulfate proteoglycan on the extrasympatric surface of cortical neurons of several morphological species (Hendry et al., 1984; Zaremba et al., 1989). WFA labels specific residues of glycoproteins within the extracellular matrix of several types of cortical neurons and its distribution in the human visual cortex has been shown to be area- and lamina specific (Murakami et al., 1994, 1995; Seeger et al., 1996).

These molecular agents were engaged according to the same basic immuno-histochemical protocol. Following multiple rinses in 0.1 M Tris buffer (pH 7.4, 1% bovine serum; plus 0.3% Triton X-100 to permeabilize the tissue), the sections were immersed in a methanol-hydrogen peroxide mixture to exhaust any endogenous peroxidase activity. The tissue was incubated in the primary monoclonal antibody or the lectin for 12-18 h at 4°C with very gentle agitation (dilutions in 1% bovine serum and 0.1% sodium azide; Cat 301 at 1:20; SMI-32 at 1:5000; WFA, 1:500). WFA lectin was used in biotinylated form; the other material was processed with Vectastain Elite ABC amplification kit (secondary antibody at 1:400 to 1:1000 dilution). Sections were exposed to biotinylated secondary antibody for 1 h at room temperature (secondary antibody at 1:400 to 1:1000 dilution). Sections were processed with Vectastain Elite ABC amplification kit (Vector Labs) and developed with diaminobenzidine (DAB) as the chromagen (0.5 mg/ml; Sigma, St Louis, MO; with 0.1% H2O2 and 1 mM imidazole).

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Visualization, Architectonic Analysis and 3-D Reconstruction

Whole myelin stained sections were digitized on an Agfa Duoscan flat bed scanner (Agfa Corporation, Ridgfield Park, NJ) by means of a transparent attachment. Higher magnification images were captured with a Microfire digital camera (Optronics, USA), mounted on an Olympus AX70 research microscope (Olympus, USA). Digitized sections were aligned using an iterative scheme of linear (rigid) transformations based on a block matching algorithm (Ourselin et al., 2001). The last image of the series (at the level of the splenium of the corpus callosum) was chosen as the reference image for the registration. The resampled slices were stacked into a 3-D geometrically coherent volume at an inter-slice distance that corresponded to the interval (50-60 μm) of the physical sectioning procedure. Alignment relied on rigid transformations; local distortions that were created when histological sections were mounted on glass were accounted for applying the piecewise warping algorithm of Pitiot et al. (2003). This procedure identifies the regions in the sections (gyri and lobules) that depart from the main deformation field adopting a clustering rationale and registers these regions independently.

The MRI volumes of the specimens were registered to the stereotaxic space of Talairach and Tournoux (1988) and used to further align the histological reconstructions to the original geometry of the brains (Ourselin et al., 2001).

The limiting borders of the cortical ribbon were traced from myelin-stained sections creating two contours representing the pial surface and the border between the white matter and grey matter respectively. These contours were the basis for the computation of cross sectional traverses (pixel intensity profiles) and 3-D wireframe reconstruction of the retrosplenial region of the hemispheres as explained below (Fig. 1). 3-D reconstructions from traced contours, MRI and histological volumes were viewed and manipulated using the program Amira (Version 3.1.1; TGS Inc. San Diego, CA).

Quantitative myeloarchitectonic analysis of the occipito-temporal region was conducted with a semi-automated and observer independent method that was validated previously (Annese et al., 2004). The procedure begins with the manual delineation of the outer cortical surface (the perimeter of the histological section) and of the border between the white and gray matter. The density of staining in each layer of the cortex is recorded by an algorithm that measures pixel intensity values along cross-sectional lines (traverses) running from the pial surface to the white matter border. These profile lines are computed by the solution of a partial differential equation (the classic heat conduction equation) that generates a graded vector field between the reference contours of the cortex which are used as boundary conditions.

In the next step of the procedure cortical profiles in each section are classified based on the significant components that emerge from wavelet analysis (Daubechies, 1988). This method differs from a straightforward quantification of intensities by spatial-frequency analysis (Hopf, 1965, 1968; Zilles and Schleicher, 1993) in that wavelet decomposition recovers only a discrete number of significant descriptor parameters from the pattern of intensities. Cluster analysis (unsupervised learning) is then applied to profiles that share features in the compact representation produced by the wavelet analysis. The cluster algorithm that we employed conforms to the standard agglomerative hierarchical cluster method described in (Johnson, 1967) applied, in our case, with a single link.

Intensity profile arrays belonging to separate clusters are reparametrized and averaged to produce templates representing area-specific template of cortical myeloarchitecture. This reparameterization corrects for the variations in the thickness of the cortex that occurred within the same architectonic field realigning the position of the features of interest across the profile array belonging to the cluster.

Results

Topography of MT Myeloarchitecture

The myeloarchitectonic pattern underlying the posterior temporal, occipital and parietal regions was consistent across the specimens that were studied. The results of the observer-independent analysis were displayed on the outer contour of the sections (corresponding to the pial surface) so that the actual architectonic borders could be visualized in relation to the sulcal pattern of the hemisphere (Fig. 1). In every case, the classification localized a field with very distinct laminar architecture that was typically framed by the lateral occipital sulcus (lo) dorsally and inferior occipital sulcus (io) ventrally (Fig. 2). In coronal sections cut more or less orthogonal to the angle of the cuneus (this is highly variable in different individuals) MT was localized below the posterior lobe of the angular gyrus (lobule of Retzius). When the middle occipital gyrus was split into two parallel lobules posteriorly, MT-like architecture was found in the inferior portion, while the superior counterpart rostrally merged into the angular gyrus.
At a (magnified) glance, the most eminent structural feature of area MT is a dominant tangential band of myelination that corresponds to the outer stria of Baillarger and that occupies the lower tier of layer III and superficial part of layer IV (Figs 3A–C and 4). An inner band of horizontal fibers was detected in layer V, although it was obscured to a certain extent by the myelination of the deeper layers of the cortex. These contain large radial fibers that extend towards the pial surface to the border of layer II, becoming sparser as they reach the supragranular layers.

This myeloarchitecture differed clearly from the cortex located dorsally (the posterior lobule of the angular gyrus). Its ventral border was less evident posteriorly (Talairach coordinates: y = –75 to –70; Fig. 5) where the cortex was equally densely stained but a stronger double lamination was detected. More anteriorly (Talairach coordinates: y = –70 to –65) the lamination pattern changed more dramatically across the lateral sulcus onto the fusiform gyrus due to a general decrease of myelination and the withering of both stria of Baillarger. Our architectonic analysis did not suggest any obvious architectonic difference in opposite hemispheres of the same brain and across specimens.

The morphological variability that we observed on the surface of the hemispheres could be traced to a consistent general pattern that does not depart significantly from that sketched by Dumoulin et al. (2000). The inferior temporal sulcus and its posterior vertical branch [i.e. the ascending limb of the inferior temporal sulcus of Cunningham (1892, 1902)] could be identified clearly. The latter segment was the anterior limit of area MT while the lateral occipital and the inferior occipital sulci proved to be the most reliable dorsal and ventral boundaries respectively. These sulci run roughly parallel to each other (Duvernoy, 1990; Ono et al., 1990) and are charted in the classic maps by Flechsig (1901, 1905, 1920), Elliot Smith (1907) and Lungwitz (1937).

We found a clear correspondence between our maps and the myeloarchitectonic topography of Flechsig’s map (Flechsig, 1901), where the subangular gyrus is charted precisely. In this case, human MT as defined in our study matches Flechsig’s area 10 (Flechsig, 1901). A second interesting topographic correspond-
of the visual world. A certain residual variability, even after the registration of anatomical landmarks, would be expected given that in the macaque and owl monkey the location of MT varies within the STS (Gattass and Gross, 1981; Van Essen et al., 1981).

The results of our histological survey agree topographically with functional maps, the lateral occipital sulcus and the inferior occipital sulcus being the most constant landmarks for the localization of area MT. In our sample, area MT extended on the crown of the middle occipital gyrus (mog) and its predominant architectonic features withered more or less gradually towards the floor of its limiting sulci. Significant architectonic boundaries were found on the dorsal and medial banks of the mog at variable distance from the sulcus.

Our results need to be reconciled with those gathered from functional localization studies because MT-specific activation has been typically mapped within the depth of several possible sulci and not explicitly on the convexity of any gyrus. Dumoulin et al. (2000) report that in the great majority of their subjects ‘V5 (MT) was located within the depth of a sulcus’. However, ‘one activation peak that was not located within a sulcus was positioned on the gyrus directly posterior to the alits. This peak of activation resided on the middle occipital gyrus and thus matches the position of MT observed histologically. In a study that combined functional localization with high-resolution structural MRI, Walters et al., (2003) described human MT on the banks of the inferior temporal sulcus.

These functional results seem to leave much of MT-like myeloarchitecture unaccounted for; it is likely that this apparent discrepancy derives from limitations of both functional and histological methods for cortical localization.

The topographic resolution of functional imaging is reduced by methodological and biological effects. Blurring of functional data to increase signal to noise ratio lowers the resolution of functional maps. Another possible source of artifact in MRI images is the contribution that vasculature plays in generating T2-based blood oxygenation level-dependent signals, especially at lower field strengths (Ogawa et al., 1998; Menon et al., 1993; Disbrow et al., 2000; Ugurbil et al., 2003). Finally, fMRI images

Figure 2. Position of the human visual area MT on the lateral aspect of six representative hemispheres. alits: ascending limb of the inferior temporal sulcus; ios: inferior occipital sulcus; los: lateral occipital sulcus; ***: in this particular hemisphere the posterior border of area MT was not clearly classified.
are subject to several processing steps and estimated by statistical models. The distortion of functional images when these are coregistered with anatomical images may not be recovered completely, leading to mispositioning of functional responses. These effects lower the accuracy of functional maps and may account to a certain extent for the apparent discrepancy we have drawn attention to.

On the other hand it should be noted that histological methods also present (certain) limitations. The architectonic description of a cortical field is necessarily subordinate to the geometry of the cortex and to the location of the sample. A cortical cross section acquired within or close to the concave floor of a sulcus will appear to have higher densities of myelination in the lower layers because of the special tangential organization of the tissue. This phenomenon is especially serious in the convoluted human cortex (Bok, 1959; Smart and McSherry, 1986a,b; Welker, 1990; Annese et al., 2004). Our method of histological analysis reduced this concern by modeling the curvature of the cortex prior to the computation myeloarchitectonic profiles. Another limitation of histological localization ex vivo lies in the idiosyncrasies that are inherent in neurohistological techniques and in our case, the age variability of the specimens that were examined (50–80 years; Annese et al., 2004). Nevertheless, the architecture of area MT, as assessed quantitatively by the automated histological classification, was strikingly consistent (Fig. 3).

**Architectonic Characterization of area MT**

Our myeloarchitectonic characterization of human MT is remarkably consistent with descriptions of primate MT architecture and suggests strong homologies across species. Notwithstanding differences in staining methods, the major myeloarchitectonic feature of MT in the monkey is dense staining of layers III and V. This bilaminar feature is obscured in the infragranular layers by dense bundles of radial fibers that reach the lower border of layer II. Allman and Kaas (1971) textually described MT in the owl monkey with ‘densely stained
Figure 4. A section of the (visual) cortex is flattened computationally into a linear segment which results in parallel profiles through the array (below). This figure illustrates the wavelet analysis of intensity for one representative intensity profile in MT (the segment a–b through the cortex; the dorsal border of MT is marked by the red arrow which corresponds to the marker shown in Fig. 3). Original intensities (in red) are decorrelated by the wavelet transform into compact band-limited signal components (in green). These features are used to construct a wavelet ‘shrinkage’ scheme for processing the data in the wavelet domain (time domain reconstruction in blue). This smoothed version of the native data is later used to classify corresponding cortical profiles.

Figure 5. 3-D wireframe reconstruction of left and right MT from the same specimen. Talairach coordinates are shown for particular locations that determine the 3-D boundaries of the architectonic field. Wireframe reconstructions were generated from the histological volume.

Figure 6. (A) Staining of multipolar and pyramidal cortical neurons in layer 3 of area MT with the antibody Cat-301 (Hockfield et al., 1983; Hendry et al., 1984; DeYoe et al., 1990). A very similar tinctorial pattern (B) is expressed by Wisteria floribunda agglutinin, a plant lectin that labels residues of glycoproteins within the extracellular matrix. Scale bars: 20 μm.
myelin of the deeper layers of the cortex; however, their figure shows the strongest myelination in layer III and layers V–VI which are pervaded with radial fibers. This picture of MT architecture has been substantiated in the rhesus macaque by careful neuroanatomical studies (Van Essen et al., 1981; Lewis and Van Essen, 2000) and matches our description of human MT.

In the human visual cortex, Clarke and Miklossy (1990) describe human area MT (V5) as a field of dark myelin staining and marked double lamination. The outer and internal stria of Ballainger are described as being composed of coarse and fine tangential fibers. The authors also note the presence of numerous bundles of radial fibers. Zilles and Schleicher (1993) reported multiple horizontal stripes in an area that matched the topography of human MT. This pattern was derived from the measure of staining density along a manually selected profile. The pattern of intensities through the cortical depth was obscured by high-frequency noise. Images of cortical tissue stained for myelin by sensitive silver methods contain high-frequency intensity fluctuations that reduce the usefulness of straight forward analysis of staining density. The transposition into the wavelet domain that we computed smoothed the jagged course of intensity profiles into a synthetic pattern that approximates the myeloarchitecture of MT more clearly (Annese et al., 2004).

**Functional Considerations**

The myeloarchitectonic profile of human MT may reflect relevant aspects of its functional neuroanatomy. Area MT receives direct projections from the striate visual cortex. Distinctively, these projections originate from spiny stellate cells in layer IVB and giant Meynert cells in layer VI of V1 (Shipp and Zeki, 1989). This unique projection pattern was demonstrated in the marmoset (*Callithrix*; Spatz and Tigges, 1972), the squirrel monkey (*Saimiri*; Tigges et al., 1981), the rhesus monkey (*Macaca*; Maunsell and Van Essen, 1983), the owl monkey (*Galago;* Allman and Kaas, 1971; Montero, 1980; Weller et al., 1984) and the cebus monkey (*Cebus*; Rosa et al., 1993).

New high-resolution anterograde tracers (such as PHA-L and biocytin) further showed that axons from V1 have a bistratified distribution in MT (Rockland, 1989, 2002) with large and numerous collaterals in layers III–IV and with smaller terminations in layer VI (these axons typically have two arbors in layer IV and one in layer VI). The caliber of these afferent axons and the size of their terminations is uncommonly large: up to three times larger than the average cortico-cortical fiber (Rockland, 2002). This specialization is consistent with fast transmission of phasic geniculostriate input, associated with the magnocellular pathway (Ungerleider and Mishkin, 1979; Zeki and Shipp, 1988; Felleman and Van Essen, 1991). As noted above, the most conspicuous architectonic determinant of human MT was the tremendously dense outer band of Baillarger. We suggest that this feature reflects the cumulative architectonic expression of the connectional pattern that was resolved in primates at the single axon level (Rockland, 1989) between V1 and area MT.

The patterns of WFA and Cat-301 staining in V1 and MT also fit the connectional model discussed above (Fig. 7). Conspicuous staining of layers IVb and VI in V1 were mirrored by selective staining in layers III–IV and VI of MT. These results provide evidence for a visual pathway in human cortex involved in processing moving components of visual stimuli that is equivalent to the magnocellular pathway in the monkey.

The distinctive pattern of myelination we have described may not be exclusive of MT and it is possible for such architecture to reside elsewhere in the visual cortex and in other regions of the cortical mantle. If, as we propose above, the architectonic pattern of myelinated fibers reflects functional dynamics, then areas with analogous computational and connectional properties at similar levels of functional hierarchy may show similar...
myeloarchitectonic profiles. We refer to this principle as architectonic equivalence. This principle also suggests a distinction between ‘specialization’ and ‘localization’. In the case of area MT, the demonstration that functional activation is relatively coincident with an architectonic area does not necessarily demonstrate that the latter is ‘specialized’ structurally for the analysis of motion.

Contrary to conclusions of previous architectonic studies (Lungwitz, 1937; Clarke and Miklossy, 1990), we demonstrate that a careful architectonic analysis of myelination by means of objective quantitative criteria can provide useful insight in the function of the cortex. The relationship between functional and histological characterization of human cortical areas will eventually be established directly, as suggested by recent MR imaging studies of the brain at microscopic resolution both post-mortem (Beuls et al., 1993; Kruggel, 2001; Barbirer et al., 2002; Fatterpekar et al., 2002) and in vivo (Clark et al., 1992; Burgess et al., 1999; Walters et al., 2003). Myelin is the primary contrast element for MR images of cortical anatomy (Clark et al., 1992; Burgess et al., 1999); in view of the histological potential of MRI it is important to produce accurate and reproducible definitions for cortical areas which at this stage can only be compiled through post-mortem histological analysis and quantification (Annese and Toga, 2002; Annese et al., 2004). Accurate histological definitions are the prerequisite to establish a correct etiology for meaningful structure–function correlations. The architectonic characteristics of MT that we have defined in relation to surface landmarks is important for the validation of further detailed studies of cortical localization by MRI.

Notes
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