

Delineating extrastriate visual area MT(V5) using cortical myeloarchitecture

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Abstract

Visual area MT is a model of choice in primate neurophysiological and human imaging research of visual perception, due to its considerable sensitivity to moving stimuli and the strong direction selectivity of its neurons. While the location of MT(V5) in the non-human primate is easily identifiable based on gross anatomy and appears consistent between animals, this is less the case in human subjects. Functional localization of human MT+ with moving stimuli can identify a group of motion-sensitive regions, but defining MT proper has proved more challenging. In this review we consider approaches to studying the cyto- and myeloarchitecture of this cortical area that may, in the future, allow identification of human MT *in vivo* based on anatomy.

The primate visual system has been divided into more than 30 distinct areas delineated by functional and cyto-architectonic criteria. This is based on a large body of literature ranging from histology and single unit recordings in non-human primates to the ever-increasing volume of functional magnetic resonance imaging studies acquired from human subjects. While the latter technique can deliver both functional and structural data in vivo, the resolution at which different regions can be visualized and thus differentiated is clearly limited. Recent MR studies also indicate large individual difference in size and location of extrastriate visual areas. Examining primary visual cortex (V1) and the visual motion area MT, this review considers possible ways in which these limitations can be addressed and how we may, in the future, be able to combine information from human and animal imaging work to gain a comprehensive understanding of the cerebral cortex.

1. Identification of visual areas in human brain imaging

The hierarchical nature of processing in the primate visual system means that the capacity to identify individual areas is a critical part of understanding the multitude of processing streams. To this end, research into the visual system has led the way in determining individual cortical areas on a subject by subject basis using a variety of methods. The two main functional characteristics that have been exploited for identification are the retinotopic representation, which is most evident in the early visual areas, and the distinct functional properties of

populations of neurons which, at least in extra-striate regions, tend to be similar within a given visual area. While the former feature is exploited in functional MRI techniques such as retinotopic mapping (DeYoe et al., 1996; Engel et al., 1997; Engel et al., 1994; Sereno et al., 1995) and population receptive field mapping (Dumoulin and Wandell, 2008; Harvey and Dumoulin, 2011), the latter is necessary for 'functional localisers' to identify areas such as the fusiform face area (Kanwisher et al., 1997) or the visual motion area MT (Huk et al., 2002) although this technique is not without its critics (Friston et al., 2006; Poldrack, 2007). One issue is the considerable inter-subject variability in location of visual areas delineated by functional responses. Based on retinotopic mapping alone, at least 16 areas can be identified in the occipital lobe (Wandell et al., 2007).

In addition to the identification of visual areas based on functional properties, over the past decade, the increase in field strength and coil arrays has allowed structural scanning at sub-millimeter resolution. It has been known for over a century that different cortical regions can be distinguished based on cyto- and myelo-architecture, and multiple different types of divisions have been made, which have been laid out in detail elsewhere (Geyer et al., 2011). Cyto-architecture refers to the unequal distribution of cells with different cell body morphology in different parts of the brain; myelo-architecture refers to the different degrees of myelination, a fatty tissue sheath, around axons serving different brain areas, and the patterns they form in the cortical gray matter. By far the most distinctive region of myeloarchitecture is in the striate cortex, named after the stria of Gennari present in layer 4. With a thickness estimated to be around 300 μm (Funkhouser, 1915), standard 1mm³ isotropic T1-weighted

imaging is not sufficient for visualization. Multiple attempts to image the stria at 3 Tesla produced visible intensity differences in layer 4, although scan times were often long and isotropic voxels were not possible (Barbier et al., 2002; Bridge et al., 2005; Clare and Bridge, 2005; Turner et al., 2008; Walters et al., 2003).

The availability of 7 Tesla scanners which sufficiently increase the signal:noise ratio in very high resolution structural scans, means that the stria of Gennari can now be readily identified using a number of different approaches. Figure 1A shows examples of T2*-weighted images at 7 Tesla, 0.4 mm³ isotropic resolution. The stria is indicated with the white arrows in each of the different views. T2*-weighted images are sensitive to the magnetic susceptibility of the tissues being imaged, or more specifically in the differences in magnetic susceptibility between neighbouring tissues. The contrast/noise ratio achieved for a given susceptibility difference is proportional to the square of the magnetic field, which means that at ultra high magnetic fields (7 Tesla and above) the cortical patterns are particularly clear. Duyn et al. (2007) found that the strong banding detected in T2*-weighted images of the stria of Gennari was dependent on the increased tissue iron in layer IV of the cortex. However, susceptibility contrast of this type is dependent on the angle of the tissue boundaries relative to the static magnetic field, and as such can change through the image without the underlying tissue iron varying. For this reason, T2-weighted images may be more useful in detecting these myelin patterns, since, whilst the contrast is not as high, there is less orientation dependence. T2-weighted imaging at ultra high field is particularly demanding due to the challenges of getting uniform RF transmission,

and not exceeding energy deposition limits (SAR) to the tissue being imaged, however our initial images are encouraging (Figure 1B).

Figure 1 about here

There have also been some attempts to delineate extrastriate areas like visual area MT based on myelination patterns (Desimone and Ungerleider, 1986; Sanchez-Panchuelo et al., 2012). However, to validate these measures for routine use in humans, the correlation between zone and pattern of myelination obtained with these methods *in vivo* and more conventionally used functional maps has to be established.

2. Why are we interested in MT?

Extrastriate visual area MT(V5) is an ideal candidate to test the validity and reliability of MR maps of myelination patterns obtained *in vivo*. It is one of the most intensively studied brain areas and has been well characterized physiologically and anatomically in humans and monkey. MT was one of the first extrastriate areas to be characterized functionally in the non-human primate. Parallel work in the owl monkey (middle temporal area MT) and in the macaque (visual area V5 in the superior temporal sulcus) described a distinct visual area where neuronal responses were selective for direction of motion (Allman and Kaas, 1971; Dubner and Zeki, 1971; Zeki, 1974). A human homologue was identified later by comparing moving and static visual stimuli (Zeki et al.,

1991b): the MT+ complex however comprises more than one visual area, likely including area MST and possibly FST (Huk et al., 2002; Sereno et al., 2012).

The importance of area MT in the macaque lies in our detailed understanding of response properties and intrinsic organisation from electrophysiological studies in non-human primates. MT neurons are retinotopically organised and are strongly selective for direction of motion (Zeki, 1974). Many neurons are also selective for binocular disparity (Maunsell and Van Essen, 1983) including absolute and relative disparity (DeAngelis and Uka, 2003; Krug and Parker, 2011). Neurons are organised in columns of similar selectivity for direction of motion and binocular depth (Albright et al., 1984; DeAngelis et al., 1998; DeAngelis and Newsome, 1999). Histologically, the pattern of intrinsic connections has been shown to be highly patterned and regular (Ahmed et al., 2012).

Research on extrastriate visual area MT is central to the quest of linking brain signals to cognitive processes like perception and attention. As early as the 1980s, area MT had been linked to the perception of motion through lesions in humans and monkeys (Newsome and Pare, 1988; Zihl et al., 1983). Fluctuations in neuronal firing in neurons of area MT were linked to the perception of motion, binocular depth and structure-from-motion (Bradley et al., 1998; Britten et al., 1996; Dodd et al., 2001; Krug et al., 2004; Uka and DeAngelis, 2004). Electrical microstimulation of MT neurons causally alters the reported percept in direction of motion and binocular depth tasks (DeAngelis et al., 1998; Salzman et al., 1992)

3. Post mortem and in vivo identification of myeloarchitecture in the non-human primate: histology and imaging

In the macaque monkey, area MT can reliably be identified histologically by its dense pattern of myelination, visualized with the silver stain Gallyas as seen in Figure 2 (Gallyas, 1979; Van Essen et al., 1981). Dorsal pathways in extrastriate visual cortex of the macaque process information about moving stimuli and are thought to be strongly myelinated to allow faster signal transmission for fast behavioural responses. MT is consistently located as a dense region of dark myelin on the posterior bank of the Superior Temporal Sulcus (STS), which is particularly discernible on parasagittal and horizontal sections. This location has been confirmed through electrophysiological mapping. On the anterior bank, an equally dense band of myelin can be found, which is part of visual area MST. In parasagittal sections the bottom of the sulcus is usually less densely stained and is thought to contain area FST.

Figure 2 about here

Van Essen et al. (2012a) compared the size and location of MT in the macaque across several different studies using Surface-Based- Registration. They found that while area MT differed in size and exact location between studies, it was always located on the posterior bank of the STS. When defined with cyto- and myelo-architectural methods, parcellations generally showed a substantial degree of overlap. This was also the case with a probabilistic MT map based on

functional imaging obtained by Kolster et al 2009, but there was more variability in how putative subdivisions of MT+ were aligned with myelo-architectural MT when individual retinotopic maps were registered. Of course, the registrations were made between data obtained from different animals. Comparing the alignment of these functional maps to detailed electrophysiological recordings might also be interesting to examine.

The Marmoset, a New World monkey, has a flat, smooth cortical surface and while MT can still be identified by staining for myelin, MT lies here on the cortical surface. Using quantitative T_1 mapping at 7T *in vivo*, Bock and colleagues (Bock et al., 2011; 2009) showed that areas of high myelin content can be distinguished from neighbouring areas of low myelin content. MT identified in this way through MR imaging corresponds qualitatively to MT determined by histology in the same animal. Furthermore, estimates of size of cortical areas obtained with MR in this way are consistent between individual animals.

Using T_2^* -weighted imaging in the macaque *in vivo*, Chen and colleagues (2012) have recently been able to distinguish different laminae in V1 at 4.7T. The profile of the signal obtained at different cortical depth appears to reflect myelin content and cell body density and might be utilised to distinguish different cortical areas, such as area MT *in vivo*.

Because of the clear histological definition and the high level of consistency between animals, area MT in monkeys is an excellent model to test novel imaging techniques for identification of cortical areas by myelo-architecture. Working in

an animal model allows the comparison of *in vivo* imaging results with subsequently obtained histological results in the same individual.

4. Post-mortem visualization and anatomical localisation of human MT

Interestingly, there have been relatively few histological studies of the human brain, particularly those that have focussed on MT. Two studies specifically shed light on the type of patterns of cyto- and myelo-architecture found in this region of human cortex. Annese et al. (2005) employed histological processing and computational methods to identify MT based on myelination patterns in 12 human post mortem brains. Using Gallyas staining, the myelination patterns in area MT could be visualized in slices as thin as 25-30 μm , and a wavelet analysis determined regions with consistent myelination patterns. The main features described were a distinctive outer band of Baillarger and dense myelination in the lower layers of the cortex. The inner band of Baillarger was more or less obscured by this myelination, suggesting that the reduced resolution of *in vivo* imaging would make the second band or even the distinction between the two band undetectable. The wavelet analysis allowed delineation of cortical regions based on the myelination patterns measured from profiles normal to the surface. This objective measurement gave consistent definitions of a region adjacent to the lateral occipital and inferior occipital sulci across all brains. As in the primate brains described earlier, this region was surrounded by different myelination patterns, including very light myelination and clearly discernible double band of Baillarger.

While the study by Annese et al. concentrated on the distinctive myeloarchitecture, Malikovic et al. (2007) used cytoarchitectonic methods to identify a region that they refer to as hOc5. Again, automated methods for determining profiles normal to the cortical surface were employed, allowing classification of profiles into regions of consistent cellular architecture. Figure 3 shows the probabilistic maps generated from these post mortem brains, as implemented in the FSLview program from the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl). The inter-subject variability of this region is evident, as there are no regions in which the areal definition in all 10 brains overlap. It should, however, be noted that these brains were aligned using a volumetric registration (see Eickhoff et al. 2005 for details) which does not take sulcal pattern into account. Based on cyto-architecture, Malikovic et al. define hOc5 within the lateral occipital sulcus, whereas the myeloarchitecture study of Annese et al. found MT to lie on the convexity of the middle occipital gyrus.

In contrast to the apparent variability in the location of these areas defined using cyto- and myelo-architecture, Dumoulin et al. (2000) suggested that human area MT/V5 might potentially be identified based on sulcal patterning. Using a low contrast checkerboard pattern stimulus, they identified the peak of activation in 19 hemispheres and found that in 95% of cases it lay within a sulcus, although the specific sulcus varied across individuals, half being within the ascending limb of the inferior temporal sulcus (ITS), 11% within the ITS and a quarter within the posterior continuation of the ITS. At first sight, while a useful guide, this pattern appears more variable than the macroscopic localisation of MT in the macaque.

Figure 3 about here

Clearly it would be of interest to acquire post-mortem imaging of the myelo-architecture and structure at a whole brain level to compare directly the micro- and macroscopic methods. In order to resolve the discrepancy in MT localisation in humans when based on different histological methods, myelination and cytoarchitectural analyses should be performed on adjacent sections of the same brains. Ultimately, we need to be able to align functional and myelin based maps in the same brains in order to validate these methods of MT localization.

5. Functional characterization of the human MT complex

Since the human MT complex can be defined by the comparison of moving and stationary dots, it was one of the earliest regions to be identified using PET and then fMRI (Watson et al., 1993; Zeki et al., 1991a). Since that early study identifying the entire complex, a variety of approaches, based predominantly on knowledge of the macaque areas MT, MST and FST have been employed to subdivide this large region. The main distinctions exploit differences in neuronal preferences between these regions, including (i) the retinotopic organisation of MT, which is much less precise in MST and (ii) representation of the ipsilateral visual field in MST but not MT. Huk et al. (2002) were the first to attempt to subdivide the MT complex, determining two distinct areas, one of which exhibited a retinotopic map, suggested to be MT, and the other, MST, which showed responses to ipsilateral as well as contralateral stimulation suggesting large receptive field spanning the midline. However, subsequent studies

employing more detailed retinotopic mapping (notably a narrower wedge stimulus) have identified at least two retinotopic regions within the complex (Amano et al., 2009; Kolster et al., 2010; Sereno et al., 2012). Two retinotopically-mapped areas are defined by Amano et al. (TO-1 and TO-2), suggested to correspond to MT and MST respectively and Sereno et al. who refer to MT and FST. In both cases, the authors perform averaging across subjects to improve the border distinction. In contrast, driven by homology with the macaque, Kolster et al. subdivide the motion-sensitive MT complex into four areas: MT/V5 proper, putative MSTv, putative FST and putative V4t (transitional zone), based upon the retinotopic maps combined with responses to functional localizers. The latter authors suggest that Amano et al. may have been unable to define an additional reversal due to a shorter rotation period for the stimulus which could result in a suboptimal hemodynamic response. Given this discrepancy and the challenge of identifying high-level areas for individual subjects, complementary anatomical data may provide additional distinction, particularly when anatomical markers could be validated with similar measurements from the macaque.

6. Inter-subject identification of structure/function relationships in human

MT *in vivo*

While the identification of V1 based on myeloarchitecture and retinotopic mapping is now almost routine *in vivo* (at least at 7 Tesla), human extrastriate regions remain more challenging. Partly due to its importance in visual

processing and partly due to its distinctive myelination pattern described earlier, MT is a prime target for investigation. In fact, there was a very early attempt to combine fMRI using moving dots with high resolution structural MRI. Walters et al. (2003), in addition to showing slices with the stria of Gennari, showed slices from within a region of extra-striate cortex functionally activated by the moving dots which showed some evidence of a double stripe, similar to that shown in their histological data. However, although a valiant attempt to show the myelination patterns at 1.5 Tesla with surface coils over the occipital lobe, the myelination pattern in MT was not particularly distinct. This study did, however, provide reassurance that it was not unfeasible to expect to identify human MT in this manner.

Glasser and van Essen (2011) used an automated approach to delineate cortical areas based on myelin gradients computed from the ratio of T1- and T2-weighted images collected at 3 Tesla in vivo. They identified a larger area of strong myelination as the MT+ complex comprising a number of constituent areas including putative hOc5. Indeed, more recently van Essen et al. (2012b) compared the location of the retinotopically-defined areas from subjects scanned by Kolster et al. (2010) to the cytoarchitectonic definition of hOc5, defined probabilistically. In each case, the anatomically defined area appears to lie at the confluence of the 4 areas Kolster et al defined within the MT complex, and appears to be larger than the retinotopically defined MT, although as the authors point out, this could be due to the lack of peripheral functional activation. However, the anatomical definition was still derived from a probabilistic atlas, rather than obtained from the same individual.

In the past year, two papers have compared the structural and functional definitions of human MT *in vivo* employing patterns of myelination and retinotopic mapping techniques. Two complementary approaches have been used to identify this area based on myelination. Firstly, as can be seen in Figure 2, there is an increase in total myelin content within the cortical ribbon. The second approach is to consider the myelin patterns within the cortex rather than the quantity. In humans, Sereno et al. (2012) compared quantitative T1 mapping (at 3 Tesla) with retinotopic mapping (at 1.5 Tesla) in area MT and found that the region of dense myelination on the lateral occipital surface was considerably larger than retinotopically defined MT. The anatomical and functional definitions averaged across subjects are shown in Figure 4. Specifically, only the posterior portion of this region lay within the functional definition of MT, suggesting consistency with the macaque in which the anterior bank of the superior temporal sulcus (STS) contains area MST, which has similarly dense myelin (Figure 2).

In order to investigate human myeloarchitecture patterns *in vivo*, the image resolution has to be increased to allow multiple voxels within the cortical ribbon. Therefore, Sanchez-Panchuelo et al. (2012) acquired data at 7 Tesla to allow acquisition at 0.4 mm³ isotropic using T2*-weighted imaging and 0.4 x 0.4 x 0.6 mm³ using T1-weighted MPRAGE. While this approach was very successful at identifying the stria of Gennari, regions in the vicinity of human MT containing a hypointense band did not appear to correlate well with retinotopically defined MT. The example data shown in the paper suggest that the band is present on two banks of the sulcus, but not in the fundus, a pattern found in the early 3T work on the stria of Gennari, which could possibly be due to difficulty in

detection in areas of high curvature (Clare and Bridge, 2005). The myelin pattern outside of the retinotopic region may represent MST which has less retinotopy. Another explanation would be that this pattern could delineate two retinotopic regions within the large MT+ complex as identified by Sereno et al. which they refer to as FST And MT.

7. Challenges & future directions

In order to fully understand the relationship between the myelo- and cyto-architecture of MT, along with myelin quantity, it is necessary to perform both *in vivo* and post mortem imaging on the same brains. Post-mortem imaging of partial brain volumes can be performed to a resolution of $120\ \mu\text{m}^3$ (Augustinack et al., 2012), while resolution acquired *in vivo* in the macaque is around $0.5\ \text{mm}^3$ (Sallet et al., 2011). Comparison of these types of image should allow a direct comparison of myelination quantity and pattern. A further advantage of using *in vivo* imaging is the opportunity to perform retinotopic mapping, which can be carried out in humans and animals (Brewer et al., 2002), to determine the relationship between the myelin measures and functionally defined MT. While the combination of post mortem and *in vivo* imaging is possible in the macaque, it is of course less feasible in human subjects.

One of the biggest challenges in extrapolating from the macaque to the human is the vastly increased variability in location of the MT homologue in humans. This means that in humans, functional imaging is more critical in narrowing down the cortical region to be investigated for specific myeloarchitecture, which in turn

requires the limits of current imaging technology to be pushed further. One challenge will be to reconcile the varying functional definitions of MT and other areas of the MT+ complex in the human. Combining imaging in the monkey with the more fine-grain topographic and functional mapping that electrophysiology can afford might provide greater insight into functional boundaries and whether they can be anchored by specific patterns of myeloarchitecture. While the work by Kolster et al suggests clear functional homologies between the areas of the putative MT+ complex, another question poses the potential similarity of the specific pattern of myelin in homologous areas. While the results discussed above strongly suggest that human and monkey MT can both be defined by high levels of myelin in the cortical sheet, there is no clear answer as to whether the pattern of myelin normal to the surface is similar between the species and for example also between different subdivisions of the MT+ complex.

As discussed earlier, T2- and T2*-weighted images both present their own challenges. For T2-weighted images at ultra high field, methods that enable uniform RF transmission over the volume being imaged need to be developed. This can be achieved by using technologies such as dielectric pads (Webb, 2011) or parallel transmission (Katscher and Bornert, 2006). For T2*-weighted images, the challenge is to remove the orientation dependence of the signal, thus providing more quantitative measures of iron content. This could be achieved by inverse modeling (Liu et al., 2009); however such approaches need larger data sets and often require the subject to move their head significantly between scans. An alternative may be to use approaches that model the cortical

folding and determine the level of detection that might be achieved in any particular region, similar to that proposed in Clare and Bridge (2005).

By combining histology, post mortem and *in vivo* imaging from non-human primates with very high-resolution structural and functional imaging in human subjects, it may be possible to develop criteria to identify area MT based on cortical architecture. Until that point, however, it will be necessary to employ functional localization to reduce the number of possible locations. Beyond area MT, the challenge to identify regions based on cortical architecture will be increased due to a lack of functional localizer stimulus and/or the lack of homology with the non-human primate. However, it is precisely these properties that make it imperative to provide objective definitions on a subject-by-subject basis.

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Figure Legends

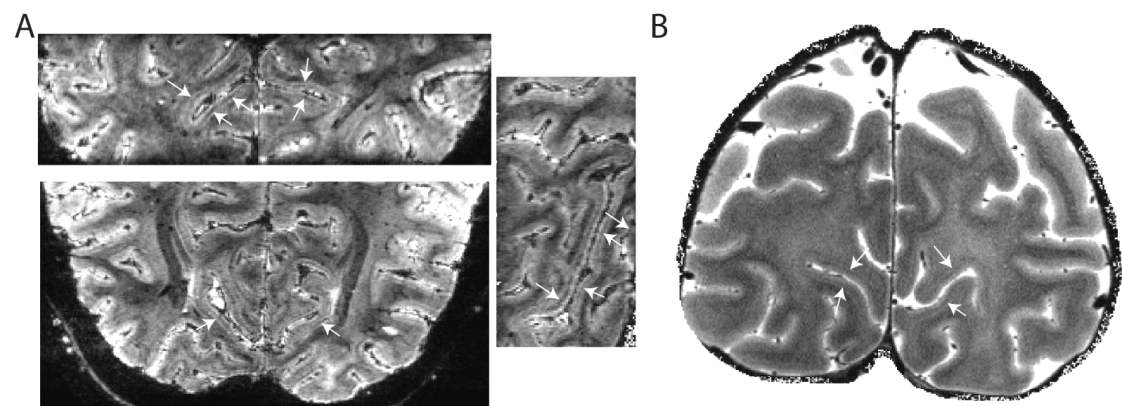


Figure 1. The stria of Gennari can be identified with a range of protocols, including T2*-weighted (A) and T2-weighted (B). White arrows indicate extended regions of the visible stria. The image in A was acquired at a resolution of 0.4 mm^3 while B is at $0.3 \times 0.3 \times 0.5 \text{ mm}^3$.

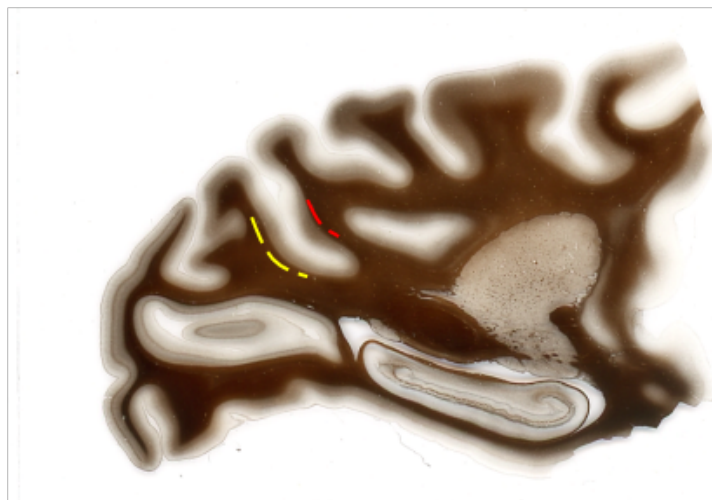


Figure 2. Myelination in MT of the macaque monkey. $30 \mu\text{m}$ parasagittal section through the macaque brain stained with a Gallyas silver stain. Darker area of staining on the posterior bank of the STS delineates MT (right to yellow dashed line), on the anterior bank area MST (left to red dashed line).

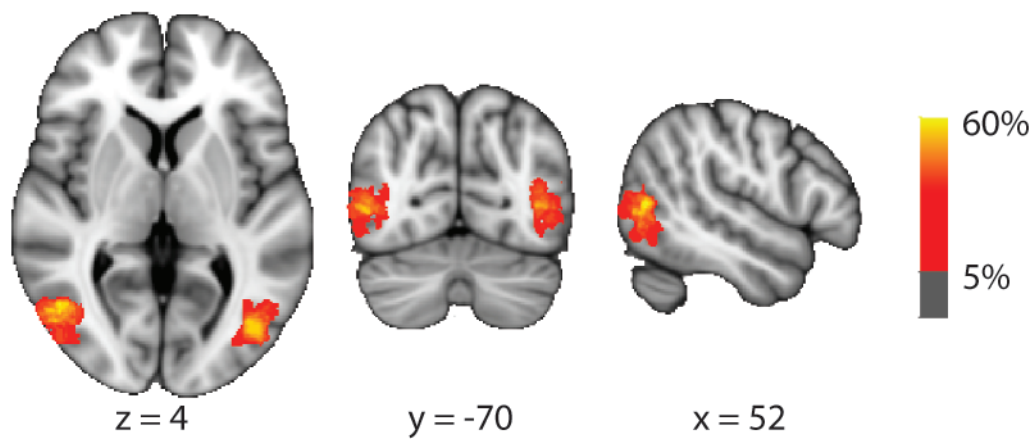


Figure 3. Probabilistic maps of human area MT (hOc5) from the Juelich Histological Atlas implemented in fslview. The definitions are taken from the post mortem identification of Malikovic et al. (2007).

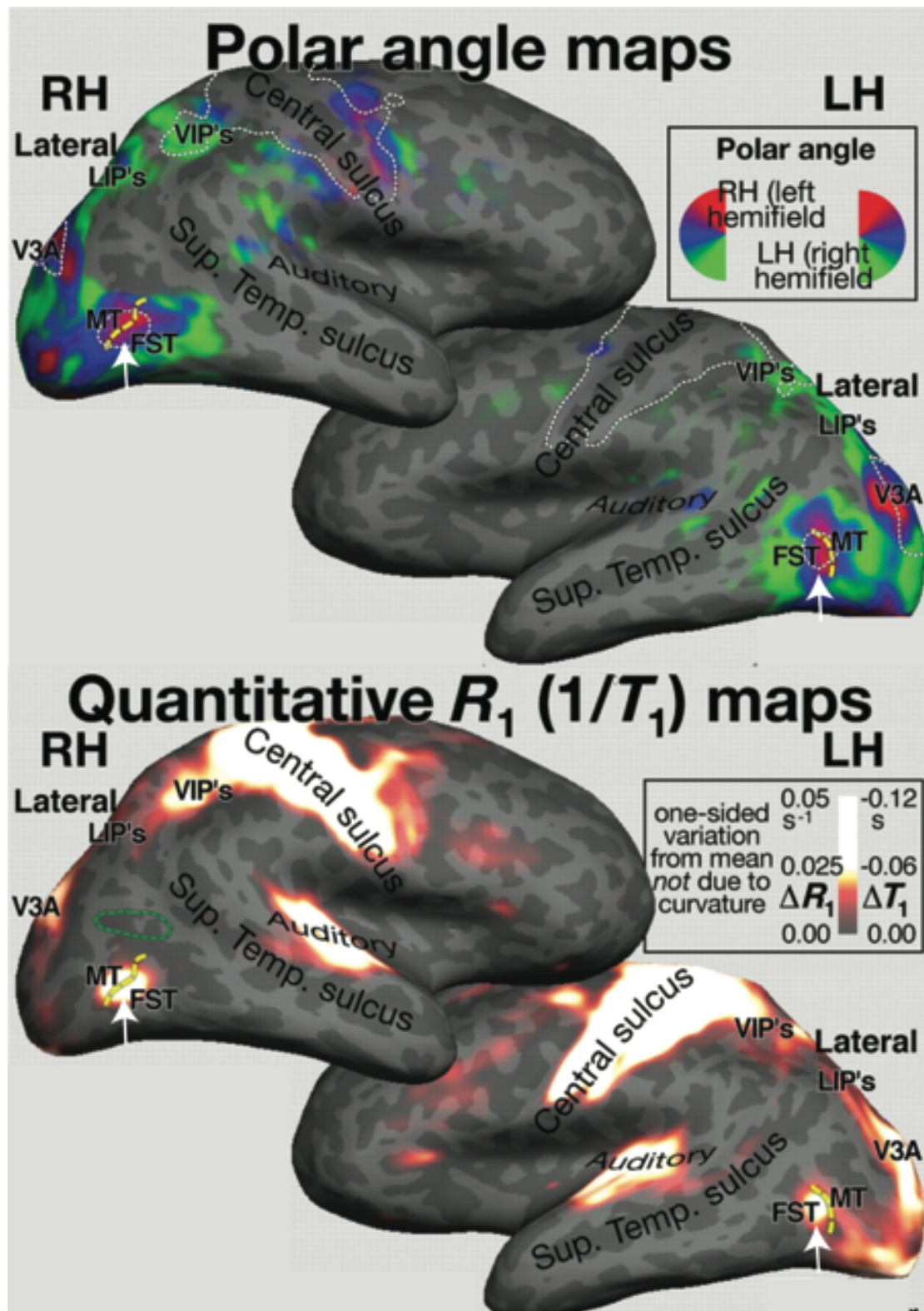


Figure 4. A comparison of the retinotopic map and regions of high myelination in the human MT complex. The white arrows indicate the retinotopically defined

MT and FST (upper panel) and the relationship with regions of high myelination (lower panel). Adapted from Sereno et al. (2012).