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Gray matter myelination of 1555 human brains using partial volume corrected MRI images

Rebecca Shafee [a,f,g,1], Randy L. Buckner [a,b,c,e,2], Bruce Fischl [d,e,*]

[a] Center for Brain Science, Harvard University, Cambridge, MA 02138, USA
[b] Department of Psychology, Harvard University, Cambridge, MA 02138, USA
[c] Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[d] Computer Science and Artificial Intelligence Laboratory, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[e] Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA
[f] Department of Genetics, Harvard Medical School, 77 Ave Louis Pasteur, Boston, MA 02115, USA
[g] Broad Institute of Harvard and MIT, Cambridge, MA 02142, USA

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ABSTRACT

The myelin content of the cortex changes over the human lifetime and aberrant cortical myelination is associated with diseases such as schizophrenia and multiple sclerosis. Recently magnetic resonance imaging (MRI) techniques have shown potential in differentiating between myeloarchitectonically distinct cortical regions in vivo. Here we introduce a new algorithm for correcting partial volume effects present in mm-scale MRI images which was used to investigate the myelination pattern of the cerebral cortex in 1555 clinically normal subjects using the ratio of T1-weighted (T1w) and T2-weighted (T2w) MRI images. A significant linear cross-sectional age increase in T1w/T2w estimated myelin was detected across an 18 to 35 year age span (highest value of ~ 1%/year compared to mean T1w/T2w myelin value at 18 years). The cortex was divided at mid-thickness and the value of T1w/T2w myelin calculated for the inner and outer layers separately. The increase in T1w/T2w estimated myelin occurs predominantly in the inner layer for most cortical regions. The ratio of the inner and outer layer T1w/T2w myelin was further validated using high-resolution in vivo MRI scans and also a high-resolution MRI scan of a postmortem brain. Additionally, the relationships between cortical thickness, curvature and T1w/T2w estimated myelin were found to be significant, although the relationships varied across the cortex. We discuss these observations as well as limitations of using the T1w/T2w ratio as an estimate of cortical myelin.

Introduction

Myelin expedites the conduction of electrical signals along axons and is essential for normal, healthy function of the nervous system. While most abundant in the cerebral and cerebellar white matter, significant amounts of myelinated fibers are present in the cortical gray matter. Classic histological studies of postmortem brains by Vogt, Campbell, and Elliot Smith (Nieuwenhuys, 2013) depict how the distribution of myelinated fibers can vary significantly between cortical regions. Recently, advances of MRI techniques enabled the investigation of the estimated myelin content of the human brain in vivo. Studies have shown that the T1, T2 and T2* relaxation times of the brain tissue depend on the myelin content of the tissue (Bock et al., 2009, 2011, 2013; Geyer et al., 2011; Clark et al., 1992; Barbier et al., 2002; Walters et al., 2003, 2007; Clare and Bridge, 2005; Eickhoff et al., 2005; Bridge et al., 2005; Sigalovsky et al., 2006; Dick et al., 2012; Cohen-Adad et al., 2012; Lutti et al., 2013; Stüber et al., 2014). Using the ratio of T1- and T2-weighted (T1w and T2w) image intensities, Glasser and Van Essen (2011) detected the boundaries of myeloarchitectonically distinct cortical regions. Their method has subsequently been applied to link estimated cortical myelin content to cognitive performance and also to investigate the lifelong effect of age on cortical myelination (Grydeland et al., 2013). The myelin density map calculated from the ratio of T1w and T2w images has also been found to show significant correlation with the retinotopic map of the occipital cortex (Abdollahi et al., 2014).

The present paper builds on this prior work and explores a partial volume correction as applied to a large uniformly collected dataset. MR images common in biomedical research are subject to partial volume effect in which the intensity of the cortical gray matter (GM) can be contaminated by intensities of local white matter (WM) and cerebrospinal fluid (CSF). Here we introduce a partial volume correction

* Corresponding author at: 149 Thirteenth Street, Rm 2301, Charlestown, MA 02129, USA.
E-mail addresses: shafee@genetics.med.harvard.edu (R. Shafee), randy_buckner@harvard.edu (R.L. Buckner), Fischl@nmr.mgh.harvard.edu (B. Fischl).
[1] Mail: Room 9008B, Broad Institute of MIT and Harvard, 75 Ames Street, Cambridge, MA 02142, USA. Tel.: +1 617 755 1416.
[2] Mail: Northwest Building, Centre for Brain Science, Harvard University, 52 Oxford Street, Cambridge, USA. Tel.: +1 617 384 8230.

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algorithm to correct for this effect, and apply our technique to quantify the T1w/T2w intensity ratio as an estimate of myelin map (T1w/T2w myelin) of 1555 clinically normal 18 to 35 year old subjects using 1.2 mm isotropic voxel MRI.

It is important to note that T1w/T2w estimated myelin is not a pure measure of myelin but nonetheless an MR-accessible proxy. The ratio of the T1w and T2w images of a subject provides a unitless quantity that correlates with cortical myelination (Glasser and Van Essen, 2011; Glasser et al., 2013; Grydeland et al., 2013) but does not provide an absolute measure of myelin density. Also, iron, in addition to myelin, has been found to contribute to cortical MR image contrast. However, it has been shown that iron and myelin are often colocalized in the cortex (Fukunaga et al., 2010). Therefore, while we do not expect myelin to be the only factor contributing to the T1w/T2w image intensity ratio, a large fraction of the variation in T1w/T2w is likely due to variation in myelin density (more details in the MRI, myelin and comparison between subjects section).

With these caveats in mind, we (1) quantified partial volume effect on T1w/T2w myelin measurement, (2) used our technique to investigate the vertical distribution of myelin in the cortex, (3) quantified the effect of age on T1w/T2w myelin, and (4) investigated the relationship between cortical thickness, curvature and T1w/T2w myelin. We compared our results with high resolution in vivo MRI scans of five subjects and also a postmortem ex vivo brain scan to ensure that the difference in inner and outer layer myelination detected in the main dataset was not an artifact of mm-scale voxel size.

Materials and methods

Main dataset

1555 clinically normal, English-speaking subjects with normal or corrected-to-normal vision aged 18–35 years (mean age = 21.2 years, standard deviation = 3.0 years, 43.3% male) were included. Participants were recruited from universities around Boston, the Massachusetts General Hospital, and the surrounding communities. The subjects were acquired as part of the Brain Genomics Superstruct Project (http://neuroinformatics.harvard.edu/gsp) and subsets of the data have been published previously (e.g., Yeo et al., 2011; Holmes et al., 2012). Initially 1800 subjects were divided into two age and gender matched groups of 900 to check replicability of results. Subjects were excluded if fMRI signal-to-noise ratio (SNR) was below 100 (Yeo et al., 2011; Van Dijk et al., 2012), or if manual inspection of the MR images showed artifacts (the fMRI quality assessment was not specific to the structural images but allowed a general means to exclude participants with high motion). Quality control steps reduced the number of subjects in the two groups to 773 and 782 and results are reported only for these 1555 subjects. For 99 of these subjects, two separate scanning sessions were processed independently to check test–retest reliability of the results. Participants provided written informed consent in accordance with the guidelines of the Harvard University and Partners Health Care institutional review boards.

All images for the main dataset were collected on matched Siemens 3 T Tim Trio scanners at Harvard University and Massachusetts General Hospital using the vendor-supplied 12-channel phased-array head coil. Data included bandwidth-matched T1w and T2w images for each session of each subject. T1w images were acquired using a high-resolution multi-echo MPRAGE protocol (TR = 2200 ms, FA = 7°, 1.2 × 1.2 × 1.2-mm voxels, and FOV = 192 × 192). In this method (van der Kouwe et al., 2008) four structural scans are obtained (with TE values of 1.54, 3.36, 5.18 and 7.00 ms) over the same timespan as a conventional scan. This was achieved by using a much higher bandwidth than is usual in MPRAGE. Each subject's T2w image was acquired with 3D T2-weighted high resolution turbo-spin-echo (TSE) with high sampling efficiency (SPACE, Lichy et al., 2005) in the same scanner during the same session as the T1w image with TR = 2800 ms, TE = 327 ms, 1.2 × 1.2 × 1.2-mm voxels, and FOV = 192 × 192. Multi-echo MPRAGE T1w image acquisition allowed bandwidth matching of the T1w and T2w images (both acquired with 651 Hz/pixel). The matched bandwidth, spatial resolution and FOV of the T1w and T2w images of each subject imply that there is no differential distortion between the image types, allowing direct superposition and comparison of the two images. In conventionally acquired T1w images different brain regions would suffer different levels of distortion for T1w and T2w images and the images would not register properly everywhere.

High resolution data

In addition to the main dataset, high-resolution T1w in vivo scans (Siemens Magnetom 3 T scanner, MPRAGE sequence, 500 μm isotropic voxels, TR = 2530 ms, TE = 4.85 ms, flip angle 7°) of five subjects (mean age = 26.6 years, standard deviation = 4.8 years, 80% female) and a T2w ex vivo scan (Siemens Magnetom 7 T scanner, FLASH sequence, TE = 9.39 ms, TR = 22 ms) of a postmortem brain (male, 60 year old at time of death) with 200 μm isotropic voxels were used to investigate two-layer myelination.

MRI data preprocessing

Each subject's T1w image was processed using the FreeSurfer version 4.5.0 software package (RRID:nif-0000-00304) pipeline, which is freely available online (http://surfer.nmr.mgh.harvard.edu). The software package reconstructs an individual's cortical surface from the subject's T1w structural scan. Processing included the following steps: correction of intensity variations due to MR inhomogeneities (Dale et al., 1999), skull stripping (Ségonne et al., 2004), segmentation of cortical gray and white matter (Dale et al., 1999), separation of the two hemispheres and subcortical structures (Dale et al., 1999; Fischl et al., 2002, 2004) and eventually construction of smooth representations of the gray/white interface and the pial surface (Dale et al., 1999). After reconstruction of the individual's cortical surfaces, correspondence between the individual's gyral and sulcal patterns and that of an average brain was calculated (Fischl et al., 1999a,b). This information was later used to bring the individual myelin maps to a common surface for comparison.

Partial volume correction (PVC) and T1w/T2w myelin map estimation

We define the T1w/T2w estimated myelination of a region as the ratio of the PVC GM intensities of the T1w and T2w images in that region. First, the 1.2-mm voxel resolution raw T1w and T2w data was resampled to 1-mm isotropic voxels. Next, the T2w image of each subject was aligned to the T1w image using boundary-based registration (Greve and Fischl, 2009). For the two-layer analysis, an intermediate surface was generated at mid-thickness of the cortex using a novel surface deformation algorithm (Polimeni et al., 2010). Only the T1w image was used for surface construction and the generated surfaces were used with both the T1w image and the T2w image aligned to the T1w image. Next, PVC GM intensities were calculated as follows.

The intensity of a voxel of a T1w or a T2w image is due to signals from various tissue classes that might occupy the voxel. Voxels that intersect the pial surface contain both GM and CSF whereas those that intersect the white surface contain GM and WM. To calculate the partial volume corrected intensity of GM we assumed a linear forward model in which the observed image intensity $I(x)$ at location x, is a combination of true, unobservable intensities I_c for tissue class c, for each of C tissue classes (typically, GM, WM and CSF but also inner and outer GM for the two-layer analysis): where $f_c(x) \in [0, 1]$, $\sum_{c=1}^{C} f_c = 1$ is the fraction of the voxel at location x that is occupied by tissue class c. We estimated