HHS Public Access

Author manuscript

Brain Struct Funct. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

Brain Struct Funct. 2019 March ; 224(2): 949–960. doi:10.1007/s00429-018-1804-0.

High-resolution Imaging of Distinct Human Corpus Callosum Microstructure and Topography of Structural Connectivity to Cortices at High Field

Byeong-Yeul Lee[*], **Xiao-Hong Zhu**, **Xiufeng Li**, and **Wei Chen**[*]

Center for Magnetic Resonance Research, Department of Radiology, University of Minnesota Medical School, Minneapolis, MN 55455

Abstract

Characterization of the microstructural properties and topography of the human corpus callosum (CC) is key to understanding interhemispheric neural communication and brain function. In this work, we tested the hypothesis that high-resolution T_1 relaxometry at high field has adequate sensitivity and specificity for characterizing microstructural properties of the human CC, and elucidating the structural connectivity of the callosal fibers to the cortices of origin. The high-resolution parametric T_1 images acquired from healthy subjects (N=16) at 7 Tesla clearly showed a consistent T_1 distribution among individuals with substantial variation along the human CC axis, which is highly similar with the spatial patterns of myelin density and myelinated axon size based on the histology study. Compared to the anterior part of the CC, the posterior mid-body and splenium had significantly higher T_1 values. In conjunction with T_1-based classification method, the splenial T_1 values were decoded more reliably compared to a conventional partitioning method, showing a much higher T_1 value in the inferior splenium than in the middle/superior splenium. Moreover, the T_1 profile of the callosal subdivision represented the topology of the fiber connectivity to the projected cortical regions: the fibers in the posterior midbody and inferior splenium with a higher T_1 (inferring a larger axon size) were mainly connected to motor-sensory and visual cortical areas, respectively; in contrast, the fibers in the anterior/posterior CC with a lower T_1 (inferring a smaller axon size) were primarily connected to the frontal/parietal-temporal areas. These findings indicate that high-resolution T_1 relaxometry imaging could provide a complementary and robust neuroimaging tool,useful for exploring the complex tissue properties and topographic organization of the human corpus callosum.

[*]**Corresponding authors:** Byeong-Yeul Lee, PhD, bylee@umn.edu, Wei Chen, PhD, wei@cmrr.umn.edu. Center for Magnetic Resonance Research, University of Minnesota, 2021 Sixth Street SE, Minneapolis, MN 55455, USA, Tel: 612-626-2001.

Compliance with ethical standards

Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of Interest

The authors declare no conflict of interest.

Keywords

Parametric T_1 MRI; corpus callosum; myelin density; axon size; structural connectivity; Topography

Introduction

The corpus callosum (CC) has the largest abundance of white matter fiber tracks connecting human homologous cortical regions across two hemispheres. It contains more than two hundred million fibers and numerous axonal projections essential to interhemispheric communication that is facilitated by the unique structure of myelinated axonal fibers enabling rapid and effective neural signaling and computation (Budd and Kisvarday 2012). Thus, noninvasive imaging and characterization of microstructural architectures and topographical organizations of the callosal subdivisions in human brains is of the utmost importance for providing new insights about interhemispheric structural connectivity and brain function (Myers 1959; Payne 1990; Wahl et al. 2007; Kontis et al. 2009; Sisti et al. 2012).

Quantitative analysis of the CC microstructures has relied on the transmission electron microscopy (TEM) as a gold standard method owing to its superior sensitivity and spatial resolution that make delineating the complex properties of myelinated callosal fibers with great precision and details possible. A number of microscopic studies have shown large variations in myelin density and myelinated axon size between the callosal subdivisions in the post-mortem human brain (Aboitiz et al. 1992a, b; Aboitiz and Montiel 2003) and non-human brain (Stikov et al. 2015b; Lamantia and Rakic 1990; Caminiti et al. 2013; Caminiti et al. 2009; Innocenti et al. 2010). However, TEM is not applicable for intact brain or longitudinal *in vivo* studies.

The advent of non-invasive MRI techniques has opened up opportunities for exploring the organization and microstructural properties of the cerebral white matter tissue *in vivo* (Le Bihan et al. 1986; Chenevert et al. 1990). Diffusion-based imaging methods have been used to explore callosal microstructural properties such as axon diameter and myelin thickness or contents (Assaf et al. 2008; Caminiti et al. 2013; Zhang et al. 2011; Assaf et al. 2013; Alexander et al. 2010; Tuch et al. 2002; Fabri et al. 2014; Hofer and Frahm 2006; Stikov et al. 2015a; Stikov et al. 2011; Jensen et al. 2005; Callaghan et al. 1988). The topographic information regarding the structural connectivity of callosal fibers to cortical origins has also been documented using the direct injection of axonal tracers in primate brains (Tomasi et al. 2012; Innocenti et al. 2010).

As for non-invasive approaches, there are already several geometric partitioning methods such as Witelson's classification that have been introduced to subdivide the CC structure in the human (Witelson 1989; de Lacoste et al. 1985). Recently, diffusion tensor tractography (DTT)-based approaches have been developed to study the callosal topography (Hofer and Frahm 2006; Huang et al. 2005; Park et al. 2008; Saenz and Fine 2010). However, there have been the lack of high-resolution MRI data linking the unique spatial distribution of callosal microarchitecture to the structural connectivity with a fine spatial scale.

As one of the non-invasive and measurable magnetic resonance (MR) parameters, the longitudinal relaxation time (T_1) or rate ($R_1 = 1/T_1$) has been commonly employed for brain research and clinical diagnosis due to the enhanced MRI tissue contrast and sensitivity to tissue environments such as myeloarchitectonics (Sereno et al. 2013; Sigalovsky et al. 2006). Although there is some evidence showing T_1 variations of the human CC in some extent (Hofer et al. 2015; Harkins et al. 2016; Wang et al. 2016), the relatively lower spatial resolution is a limiting factor for precise assessment of the fiber microstructural properties and its relevance to the topography of human CC.

In line with our previous report (Lee et al. 2014), in this work, we aimed to test the following hypotheses: 1) high-resolution T_1 relaxometry at high field could offer reliable assessment about microstructural properties of the CC and their variations in individual healthy human subjects; 2) the callosal T_1 variations would be a sensitive measure to link the key features of the myelin density and myelinated axon diameter; and 3) T_1 variations among the callosal subdivisions would be indicative of topography of the callosal fibers in relevance to cortical regions of origin. To test these hypotheses, high-resolution (0.5×1 mm^3 voxel size) parametric T_1 images of the human corpus callosum were acquired at a high magnetic field of 7 Tesla (T) to assess microstructure properties of the human CC with a minimal partial volume effect. Furthermore, we examined the relation between the T_1 variation of the CC subdivisions and its structural connectivity to the projected cortical regions using diffusion tensor tractography. For the validation of the correlate of the *in vivo* T_1 results with underlying microstructural properties, callosal T_1 imaging results were compared to the previous histology results of the postmortem human CC specimen (Aboitiz et al. 1992a; Aboitiz and Montiel 2003).

Materials and Methods

Subjects

Sixteen healthy subjects (mean age ± SD = 29.9 ± 12.0 years, 11 male / 5 female) participated in this study, which was approved by the institutional review board committee of the University of Minnesota. The informed consent was obtained from all participants.

MR imaging protocols

All MRI studies were conducted using an actively-shielded 7.0T/90cm whole-body human MRI scanner (MAGNETOM/Siemens, Erlangen, Germany) with a 32-channel ^1H receive array head coil (Nova Medical, Inc., MA, USA).

A mid-sagittal MRI slice across the central corpus callosum was selected under guidance of three-dimensional high-resolution T_1-weighted (T_1w) images as demonstrated in Fig. 1, which were acquired with a magnetization prepared rapid gradient echo imaging sequence (TR/TE/TI = 3000 ms / 2.4 ms / 1200 ms, radiofrequency (RF) pulse flip angle (FA) = 7°, field of view (FOV) = 256×256 mm^2, isotropic resolution = 0.8 mm, and GRAPPA parallel imaging acceleration factor = 2).

High-resolution diffusion-weighted images were acquired according to the protocol optimized by the Human Connectome Project (HCP) at 7T (Vu et al. 2015; Ugurbil et al.

2013) with the following acquisition parameters: TR/TE = 5700 ms / 66 ms, FA = 90 °, b = 2100 mm^2/s, number of diffusion direction = 114, in-plane resolution = 1.25 × 1.25 mm^2, slice thickness = 1.25 mm, GRAPPA acceleration factor = 3, and multiband factor = 2 (Moeller et al. 2010). Two diffusion image datasets with reversed phase-encode blips were collected for correcting the susceptibility-induced distortions and then combined into a single corrected one (Andersson et al. 2003), thus, a total of 228 image volumes were acquired.

A magnetization-prepared single-shot fast spin echo imaging sequence was used for the parametric T_1 measurement (Li et al. 2015) with the following parameters (TR/TE = 6000 ms / 16 ms, FOV = 192 × 192 mm^2, in-plane resolution = 0.5 × 0.5 mm^2, slice thickness = 1 mm, GRAPPA acceleration factor = 3 with 24 reference lines, receiver bandwidth (BW) = 814 Hz/pixel, a single mid-sagittal slice image covering the entire CC structure with a perpendicular fiber orientation). Based on the reported T_1 value (~1.2 s) of the human white matter at 7T (Rooney et al. 2007; Wright et al. 2008), all T_1 images were acquired under a full relaxation condition (TR = 6s) with various inversion recovery times (TIs) (0.1, 0.15, 0.3, 0.5, 0.8, 1.2, and 1.6 s). The uniform RF pulse flip angles for inversion (FA = 180°) and excitation (FA = 90°) across the selected mid-sagittal CC slice were achieved by applying a slice-selective adiabatic hyperbolic secant pulse (pulse length = 20 ms, BW = 1 kHz) (Garwood and DelaBarre 2001) and variable-rate selective excitation RF pulse (Hargreaves et al. 2004), respectively. The RF transmission power was calibrated using a 2D actual flip-angle imaging (Yarnykh 2007) (TR_1 / TR_2 = 70 ms / 120 ms, TE = 2.5 ms, FOV = 196 196 mm^2, in-plane resolution = 4 4 mm^2, and average = 5). All T_1 images were collected within 24 minutes under the FDA specific absorption rate limit.

T_1 mapping

T_1 relaxation maps were generated using the nonlinear least-square fitting algorithm using Matlab software (13.0v, Mathwork) according to the following equation (Li et al. 2015):

$$S(TI) = \sqrt{[So(1 - 2e^{(\frac{-TI}{T_1})} + e^{(\frac{-T_r}{T_1})})]^2 + C_{noise}^2} \quad [1]$$

where S(TI) is the measured imaging signal intensity at a given TI, S_o is the proton density, T_r is the recovery time after the inversion pulse, and C_{noise} is the noise-related constant.

T_1 distributions of callosal subdivisions

For the regional callosal T_1 analysis across subjects, a callosal T_1 image of each subject was first registered to a representative subject using a linear affine transformation (Good et al. 2001; Narr et al. 2000).

Using the registered T_1 maps, histogram analysis for the T_1 distribution of the callosal subdivision was performed; in conjunction with Witelson's classification scheme (Witelson 1989), the CC was parcellated into five vertical partitions based on arithmetic fractions of the maximum anterior-posterior extent: anterior third (rostrum (G1), genu (G2), and rostral

body (G3)), anterior midbody (B1), posterior midbody (B2), isthmus (I), and splenium (S). In particular, two partitioning methods were used for further classification of splenial subdivisions - superior (S1), middle (S2), and inferior (S3): an equidistant partitioning method (Aboitiz et al. 1992a; Björnholm et al. 2017; Thapaliya et al. 2017) and T_1-based partitioning with a k-means method.

Myelin density and axon diameter

The relation between the callosal T_1 variation and the myelinated axon size was examined based on an assumption of a linear relationship between the myelin density (or MWF: myelin water fraction) and R_1 (=1/T_1).

The *in vivo* axon diameter map was constructed from the use of g-ratio and MWF as a function of axonal diameter (d_a). Given the inverse relation between T_1 and MWF, the T_1 value can be expressed as a function of MWF (or d_a) according the following equations:

$$\text{g-ratio} = \frac{d_a}{d_a + 2t_m} \quad [2]$$

$$\text{MWF} = \frac{\pi}{4}\left(1 - \text{g-ratio}^2\right) \quad [3]$$

$$T_1 \approx \beta/\text{MWF} + \alpha \quad [4]$$

where t_m is the myelin thickness, and α and β are constants. Based on the reported mean value of human axon diameter (0.69 m) (Liewald et al. 2014) and mean callosal T_1 value (1.04 s) as measured in the current study, α and β were determined from the regression of Eqn. [4]. Finally, using the established relation between T_1 and MWF in Eqn. [4], the axon diameter of each voxel was determined by the corresponding clustered T_1 values according Eqns. [2] to [4], and then classified by the k-means method.

For a comparison purpose, another axon diameter map was scaled and constructed using a linear relation between T_1 values and axon diameter (Harkins Kevin et al. 2016). The predicted axon diameter for each voxel was determined according to the corresponding clustered T_1 values. This map was for visualization and comparison with the schematic draw of axon distribution of human CC based on the histology results as reported in the literature.

Structural Connectivity

The relation of T_1 variations among CC subdivisions with structural connectivity to the projected cortical regions was investigated using the DTT imaging method. All diffusion data were processed according to the HCP diffusion pipeline (Sotiropoulos et al. 2013) and a probabilistic fiber tractography was applied in subject-specific native space using FSL's

FMRIB's Diffusion Toolbox with the following parameters (number of diffusion direction = 3 / voxel, number of samples = 5000/voxel, curvature threshold = 0.2, and maximum number of step = 2000, and step length = 0.5 mm). The procedure of the probabilistic tractography is described in detail in the literature (Behrens et al. 2007). Representative regions of interest (ROIs) were first delineated on the callosal T_1 map. Using Bayesian estimation, fiber directions for each ROI were inferred and then the probability of a streamline connection was calculated as the proportion of the total number of streamlines. Seeded fibers were then classified according to their proportional streamline connection probabilities to the target cortical areas. Finally, voxels with a streamline connection probability of *p*-value > 0.01 (50 out of 5000 streamlines) were only used for fiber tracking to reduce statistical errors due to noise.

Statistical analysis

A statistical comparison for T_1 differences between discrete callosal areas was performed using a two-tailed paired t-test. The relation between *in vivo* $1/T_1$ (= R_1) profile and histology analysis of fiber density was examined using Pearson correlation analysis. A *P* value < 0.05 was considered statistically significant after accounting for multiple comparisons using Bonferroni correction if necessary. All statistical analyses were done using the IBM SPSS software version 21.0 (IBM Corp., Armonk, NY, USA). The mean and standard deviation are shown in the form of: (mean ± SD).

Results

Callosal T_1 Distribution

The mean of the T_1 relaxation time of the entire human CC was 1.04 ± 0.04 s, which was in an agreement with the reported T_1 values of the human white matter at 7T (Wright et al. 2008; Rooney et al. 2007). The T_1 relaxometry map showed a clear spatial trend and widespread variation from the anterior to posterior along the CC, which was consistently observed in all subjects (Fig. 2). Histogram analysis shown in Fig. 3 reveals a significant difference in the T_1 values between the anterior and posterior CC parts ($P < 0.001$). Higher T_1 values were found in the posterior CC areas including the posterior midbody (1.12 ± 0.04 s, Fig. 3B2) and splenium (1.15 ± 0.08 s, Fig. 3S). In contrast, relatively lower T_1 values were shown in the anterior CC areas (0.97 ± 0.01 s, Figs. 3G1-G3) and anterior midbody (1.04 ± 0.03 s, Fig. 3B1).

The Whitelson's partitioning scheme (Fig. 3D) showed large variations of T_1 values (i.e., SD) between three sub-sections of the splenial areas: the superior (T_1 = 1.08 ± 0.08 s, Fig. 3E-S1), the middle (T_1 = 1.14 ± 0.08 s, Fig. 3E-S2), and the inferior area (T_1 = 1.19 ± 0.08 s, Fig. 3E-S3). In contrast, the T_1-based clustering method (Fig. 3F) showed large mean T_1 differences with a much smaller SD: the superior (T_1 = 1.08 ± 0.01 s, Fig. 3G-S1), the middle (T_1 = 1.10 ± 0.02 s, Fig. 3G-S2), and the inferior area (T_1 = 1.25 ± 0.04 s, Fig. 3G-S3). This method resulted in a better separation of these areas (T_1 = 0.17 s, Fig. 3G) compared to the Whitelson's partitioning method (T_1 = 0.11 s, Fig. 3E).

Callosal Fiber Composition

There was a strong correlation between the R_1 values from MRI measurement (Figs. 4A and 4B) and the normalized fiber density from histology measurement (Fig. 4E) along the equidistant 10 sectors (Fig. 4D; regression coefficient $R = 0.81$, $P = 0.004$); the lowest R_1 value in the posterior midbody (B3) corresponded to the lowest fiber density, whereas the highest R_1 in the anterior parts of the CC (G1~G3) corresponded to the highest fiber density. As shown in Fig. 3, R_1 in the inferior splenium (S4) was significantly lower than in the middle (S3) / superior (S5) and even lower than in B3, implying the lowest fiber density among the CC subdivisions. Note that compared to the *in vivo* T_1 (Fig. 3A) or R_1 (Fig. 4A) imaging analysis, the histology analysis in the literature did not provide full spatial distribution of the fiber density across the entire CC structure since only a very small portion of callosal sub-sections could be analyzed for each CC subdivision (Aboitiz et al. 1992a). Interestingly, a recent diffusion study showed the similar distribution of CC axon diameters along the human CC, showing the high density of larger axon size in the inferior splenium as well as the mid-body (Genc et al. 2018). Taken together, our results suggest that the high-resolution callosal R_1 index or relaxometry map measured at high field highly correlates to the myelinated fiber density across the entire human CC (Hypothesis 1).

Figure 5B displays the estimated myelinated axon diameter map of the human CC (in a relative scale) based on the *in vivo* T_1 imaging measurement, showing a heterogeneous distribution along the human CC axis. The re-scaled axon diameter map (Fig. 5C) shows a similar pattern with the schematic drawing of axon diameter from the histology study (Fig. 5D taken from the literature (Aboitiz and Montiel 2003)). The similarity suggests that the callosal T_1 variation reflects different sizes of the myelinated axon in the human CC (Hypothesis 2).

Callosal Fiber Connectivity

Six representative ROIs were defined (i.e., ROI G-S3 as shown in Fig. 6 from a representative subject) for DTT Fiber tractography based on callosal regional T_1 profiles. DTT Fiber tractography analysis showed that the callosal fiber bundles located in the genu with the smallest T_1 value (ROI G, $T_1 = 0.98 \pm 0.02$ s) were primarily connected to the prefrontal cortex (Fig. 6A). The fiber bundles from two ROIs located in the posterior midbody of B2 (ROI B2, $T_1 = 1.09 \pm 0.02$ s; ROI B3, $T_1 = 1.13 \pm 0.03$ s) were connected to the primary motor cortex (Fig. 6B) and the somatosensory cortex (Fig. 6C), respectively. The fiber bundles in the superior (ROI S1, $T_1 = 1.07 \pm 0.03$ s) and middle part of the splenium (ROI S2, $T_1 = 1.14 \pm 0.05$ s) were mainly connected to the parietal lobe (Fig. 6D) and temporal lobe (Fig. 6E), respectively. In contrast, the ROI located in the inferior part of splenium with the highest T_1 value (ROI S3, $T_1 = 1.31 \pm 0.06$ s) projected the callosal axons to the visual cortex (Fig. 6F). These results support the reasoning that the regional T_1 profile of CC could reflect the key topographic features of callosal subdivisions in the human brain (Hypothesis 3).

Discussion

In this study, we demonstrate that the high-resolution T_1 relaxometry at 7T showed greater sensitivity and specificity for detecting the large degree of T_1 heterogeneity of the human CC in a fine spatial scale. In addition, such regional T_1 variation was relevant to the topographical organization of the fiber connectivity of origin, which was not shown in the previous MR relaxometry studies. Based on a tight correlation of T_1 (or R_1) to the myelinated axon size and myelin density, the callosal T_1 variation may reflect the biological variation, diversity, and structural/functional specialization of the callosal microstructure. Thus, our *in vivo* results support a key scientific notion: interhemispheric communication for sensorimotor/auditory/visual processing through the CC could be facilitated by the larger-diameter myelinated axons with a faster conduction velocity (Aboitiz et al. 1992a; Caminiti et al. 2013), which was associated with a higher T_1 value or lower myelin density in the connected CC subdivisions. In contrast, the relatively slower communication between higher-order neural processing cortical areas encompassing the frontal and parietal lobes could be facilitated by relatively higher fiber density and smaller-diameter axons with a low conduction velocity (Berlucchi 1972; Aboitiz and Montiel 2003). Therefore, the high-resolution T_1 relaxometry could provide a valuable and robust surrogate reflecting the callosal fiber and axon microarchitecture and neural communication functionality.

To date, several new classification methods for the CC partitions have been proposed to revise the classic viewpoint of human CC topology. For instance, DTT-based parcellation methods have indicated that most fibers in the primary motor cortex were projected toward the posterior midbody of the human CC (Hofer and Frahm 2006). Moreover, fibers from the primary visual cortex were projected toward the inferior part of the splenium (Huang et al. 2005; Putnam et al. 2010; Saenz and Fine 2010). Notably, these findings are strikingly consistent with our observation of regional callosal T_1 distributions (Fig. 3) and the concomitant fiber connectivity to the cortex (Fig. 6). Thus, the high-resolution T_1 map could be useful as a hallmark underlying topographic organization of the callosal subdivisions. Furthermore, it could provide a feature of the fiber connectivity of individual subjects and account for the inter-subject variability of callosal topography (Aboitiz et al. 1992b; Dougherty et al. 2005a).

Changes in T_1 or R_1 values in the CC are largely attributed to the degree of the myelinated fiber density or myelin-bound water fraction. R_1 relaxivity in the brain tissue can be described as the following (Rooney et al. 2007; Stuber et al. 2014):

$$R_1 \propto R_{1S} + R_{1M} \cdot d_M + R_{1Fe} \cdot [\mathrm{Fe}] \quad [5]$$

Where R_{1S} is the relaxivity of a pure saline solution (at physiological temperature) that can be treated as a constant; R_{1M} and R_{1Fe} are the T_1 relaxivities of macromolecule and iron, respectively. d_M is the macromolecular density and [Fe] is the iron concentration in the tissue. Since macromolecular composition is rich in the myelin sheath in the human CC tissue, R_{1M} and d_M could represent the relaxivity of myelin and myelin density, respectively,

in Eqn. [5]. The R_1 variation (R_1) within the CC structure can be approximated by the following equation:

$$\Delta R_1 \propto \Delta\left(R_{1M} \cdot d_M\right) + \Delta\left(R_{1Fe} \cdot [\mathrm{Fe}]\right). \quad [6]$$

Interestingly, the contribution from the second term $\left(\Delta\left(R_{1Fe} \cdot [\mathrm{Fe}]\right)\right.$ in the CC is negligible in considering several factors; i) very low [Fe] in the white matter (WM) compared to the sub-cortical grey matter tissues (Haacke et al. 2005; Langkammer et al. 2010; Hallgren and Sourander 1958); ii) less R_1 dependence on [Fe] compared to the R_2 dependence in WM (Haacke et al. 2005); and iii) a weak correlation between WM R_1 and [Fe] across the brain compared to the relation of R_2 or R * with [Fe] (Gelman et al. 2001; Gelman et al. 1999). Thus, the contribution of the second term in Eqn. [6] becomes negligible and the first term dominates the spatial R_1 variation in the human CC tissue and the equation can be simplified to:

$$\Delta R_1(x, y, z) \propto R_{1M} \cdot \Delta d_M(x, y, z), \quad [7]$$

Therefore, the parametric R_1 change mainly results from the underlying microstructural properties of myelinated CC tissue and is directly proportional to the myelin density (d_M).

The tissue properties of myelinated axons and distribution have been documented with great details by the histology studies. The majority of human CC axons (> 75%) have a diameter range of 0.3 – 1.0 m (mean = 0.69 m) (Liewald et al. 2014). Very few myelinated axons in the human brain CC have a small diameter (≤ 0.3 m) (Waxman and Bennett 1972) and less than 1% of axons have a large diameter (3 m) (Aboitiz et al. 1992a). In addition, the thickness of myelin sheath (t_m ~ 0.09 m) is relatively uniform for the axon population with a diameter range of < 1.0 m (Aboitiz et al. 1992a; Liewald et al. 2014). Given these factors and parameters reported in the literature, we proposed a simplified model to estimate the relation between axon diameter (d_a) and the MWF (Fig. 7C) or the T_1 parameter (Fig. 7D) for the human CC. The predicted T_1 dependence on the axon diameter is consistent with the reports of histological studies for a similar range of axon diameter (Waxman and Bennett 1972; Ford et al. 2015; Wang et al. 2016). As shown in Fig. 7C, an increase in the axon diameter decreases the MWF (or myelin density) in the human CC, resulting in a lower R_1 (or a longer T_1) value according to Eqn. [7] (Harkins et al. 2016; Wang et al. 2016). Recent *in vivo* MRI study showed that the MWF in the brain tends to increase in the anterior part of callosum and decrease in the mid-body and splenium (Stikov et al. 2015a). In line with our observation of the high correlate of the callosal R_1 with the fiber density (Fig. 4D) and T_1 dependence on axon diameter (Fig. 7D), it is likely that the high population of small-size axons in the anterior callosum links high myelin contents and/or increase myelin-water interface, consequentially leading to a short T_1 relaxation time. In contrast, the higher population of the large axons located in the posterior midbody and inferior splenium have relatively lower myelin contents and/or reduced myelin-water interfaces, resulting in a long T_1 value (Saenz and Fine 2010; Hofer and Frahm 2006; Dougherty et al. 2005b).

We postulate that the mean of callosal T_1 value (~1.04 s) over the entire mid-sagittal CC slice should correspond to the mean value of the human CC axon diameter (~ 0.69 m (Liewald et al. 2014)). Given the T_1-based model for axon diameter as depicted in Fig. 7D, the estimated diameter of the superior splenium (S1 in Fig. 3, T_1 = 1.08 s) and the inferior splenium (S3 in Fig. 3, T_1 = 1.25 s) were 0.72 m and 0.89 m, respectively, resulting in up to 19% difference within the splenium. On the other hand, the genu (Segment G in Fig. 3, T_1 = 0.97 s) has the smallest mean axon diameter of 0.61 m, resulting in 31% difference compared to the inferior splenium.

Despite the similar pattern of *in vivo* T_1 relaxometry data with the human CC fiber composition of post-mortem histology analysis, there are still limited factors to be considered for potential application and interpretation of the T_1 relaxometry data for human brain. First, the current image resolution of T_1 relaxometry is not sufficient to discriminate the populations of various fiber size down to a much fine spatial scale. Instead, we assumed that the T_1 value measured from a single MRI voxel represents an averaged quantity from all types of fiber or myelinated axon size. Under this assumption, we aimed to understand the key characteristics of CC subdivisions as investigated in this study. Further improved resolution of callosal T_1 image is needed to provide a more precise estimation of the fine fiber composition and distinct features of the human CC in healthy subjects. Secondly, the proposed model for axon diameter was used to visualize the key feature of callosal fiber diameter under the assumption of major contribution of MWF to the T_1 relaxation changes. Considering the complexity of fiber structure of the CC, this simplified model might underestimate the other mechanisms responsible for T_1 changes *via* the interactions with intracellular and extracellular water contents.

Conclusions

In summary, this study suggests that the CC characterization using the high-resolution T_1 relaxometry mapping method has the potential to robustly assess and quantify the microstructural properties, which links its functional connectivity in the human brain. Therefore, this T_1 imaging approach could be a highly useful neuroimaging tool for studying basic brain function and development, neural plasticity and aging process in healthy population.

Funding acknowledgement

This work was supported by NIH Grants RO1 NS070839 and MH111413; R24 MH106049, S10 RR026783, U01 EB026978, P41 EB015894, and P30NS076408 and the W.M. Keck Foundation.

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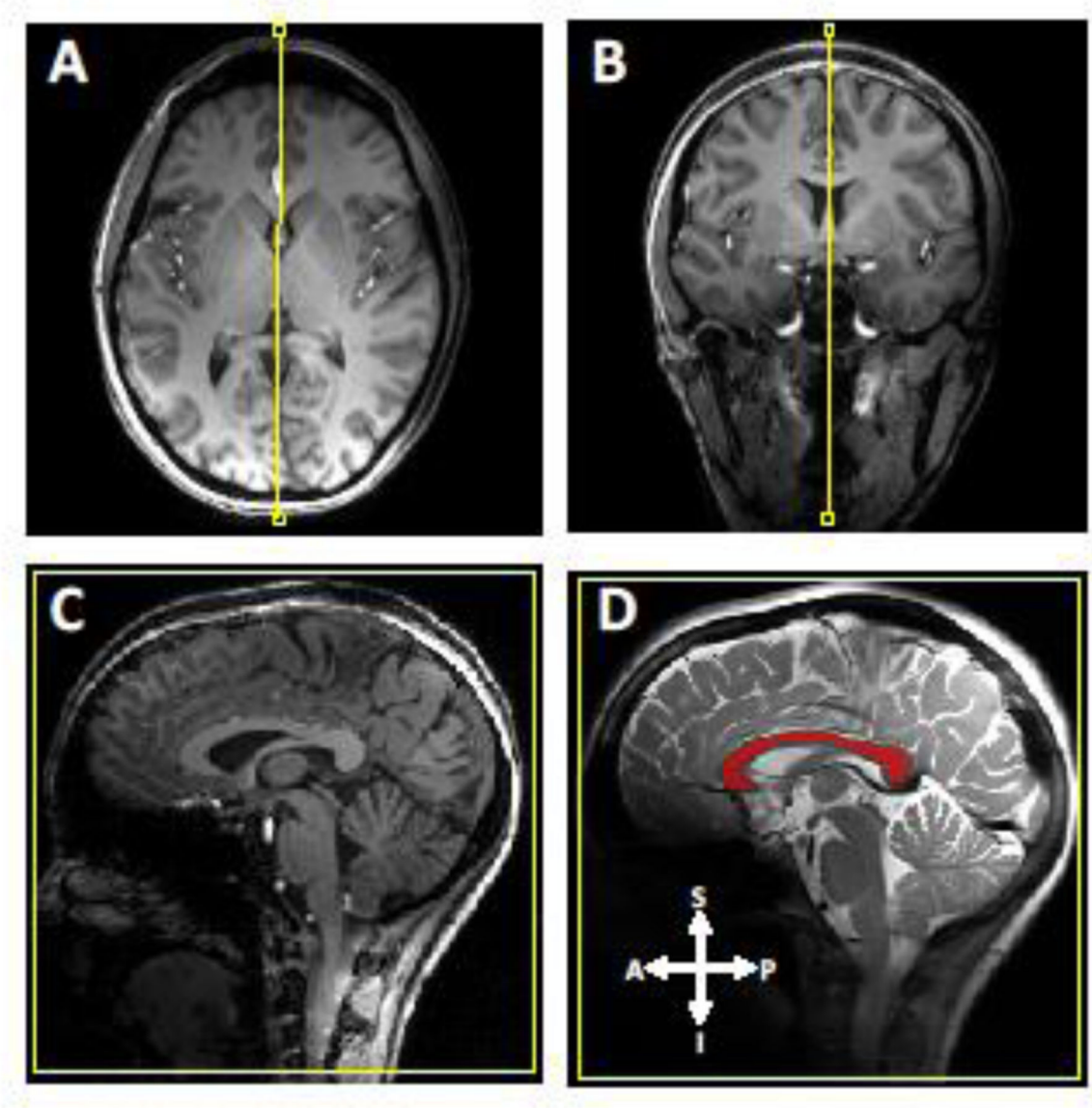

Fig 1.

A mid-sagittal slice selection of the human corpus callosum using high-resolution three-dimensional T_1-weighted images. Each panel of A, B, and C represents an axial, coronal, and sagittal view, respectively. Panel D shows the masked CC (red) displayed on the T_2-weighted sagittal image. The arrows shown in D represent different anatomical direction; A for anterior, P for posterior, I for inferior, and S for superior.

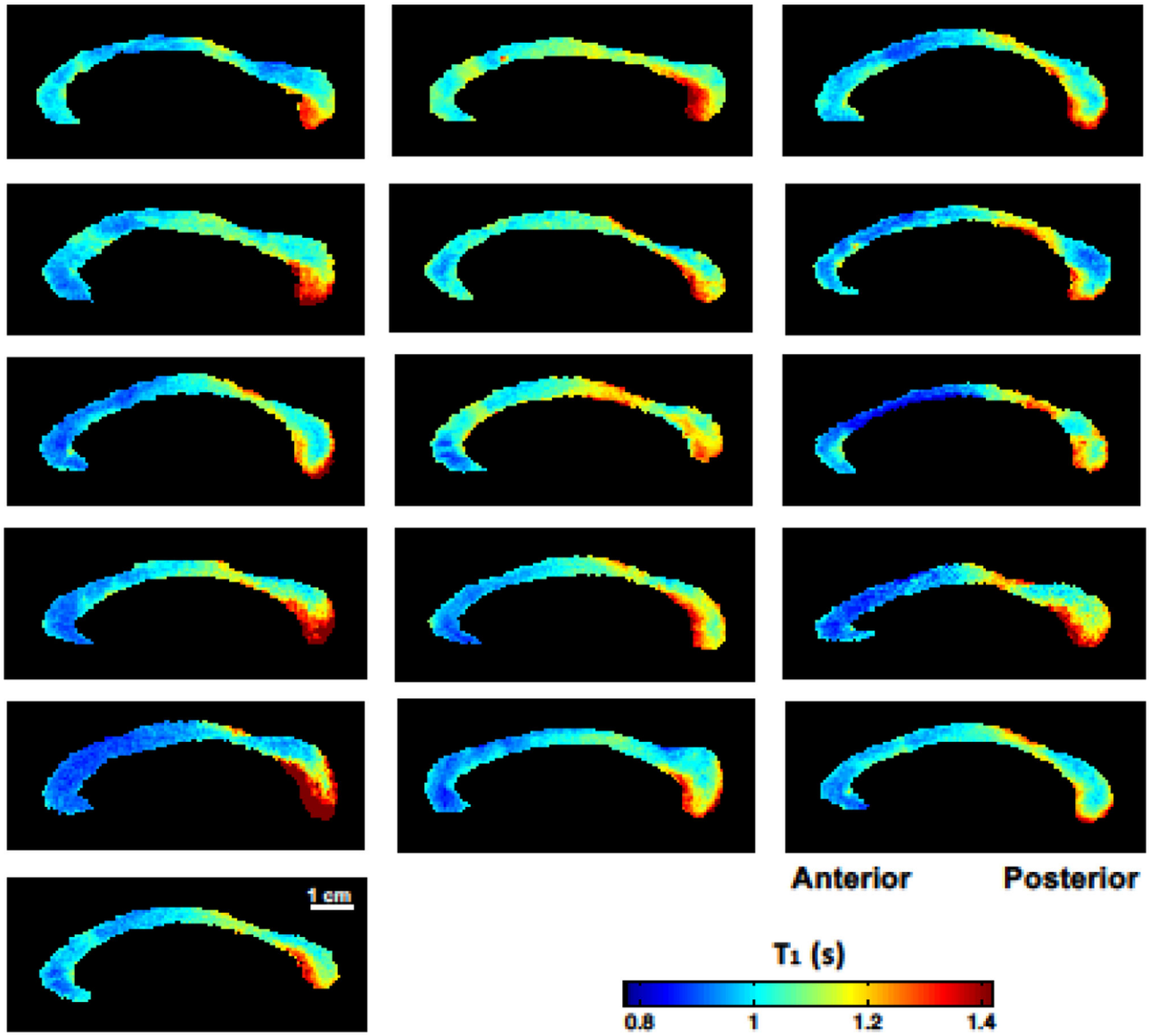

Fig 2.

High-resolution T_1 relaxometry maps of the mid-sagittal corpus callosum from 16 healthy human subjects. All T_1 maps were displayed in the same scale in the color bar. There was a common pattern of T_1 distributions along the CC; the smaller T_1 values in the anterior and higher T_1 values toward the posterior areas.

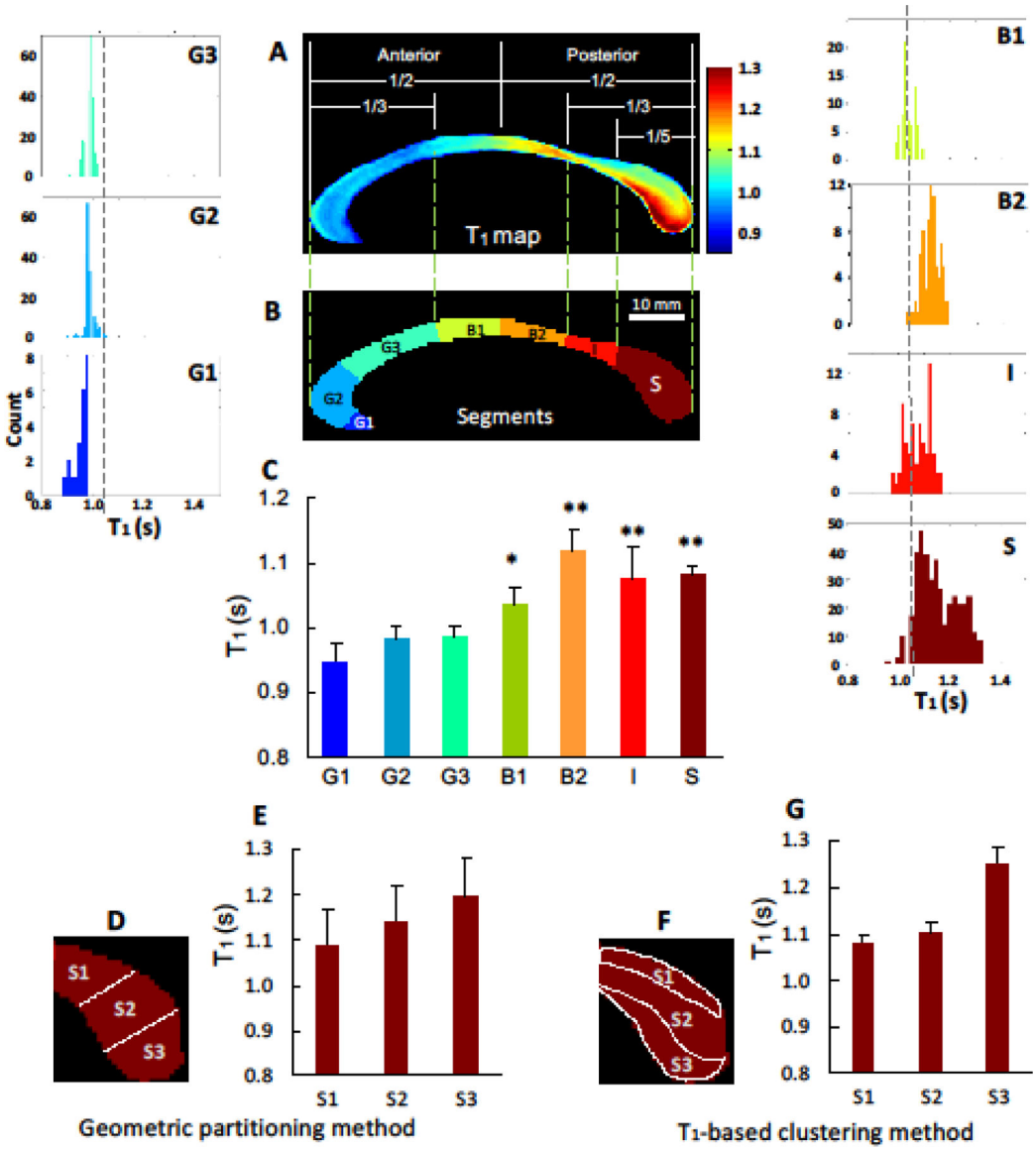

Fig 3.

Histogram analysis of regional T_1 distributions of the callosal subdivisions in conjunction with two partitioning methods. According to the geometric partitioning method, the mid-sagittal corpus callosum was segmented into 7 subdivisions: the anterior third including rostrum (G1), genu (G2), rostral-body (G3); midbody including anterior midbody (B1) and posterior midbody (B2); posterior-third including the isthmus (I) and splenium (S). The further segmentation for the splenial subdivisions – superior (S1), middle (S2), and inferior (S3) - were performed using the Witelson's partitioning (D and E) and T_1-based classification method (F and G). Overall, T_1 map shows a heterogeneous pattern of T_1 distribution from the anterior to the posterior part of the CC. Moreover, T_1-based classification method provides the better separation of splenial subdivisions compared to the Witelson's method. The vertical dashed lines in the histogram panels indicate the mean T_1 value (= 1.04 s) of the entire CC structure. All brackets show statistical comparisons for

regional callosal T_1 compared to mean of the anterior areas (G1~G3) using 2-tailed paired *t*-test. *$P < 0.001$, ** $P < 0.0001$

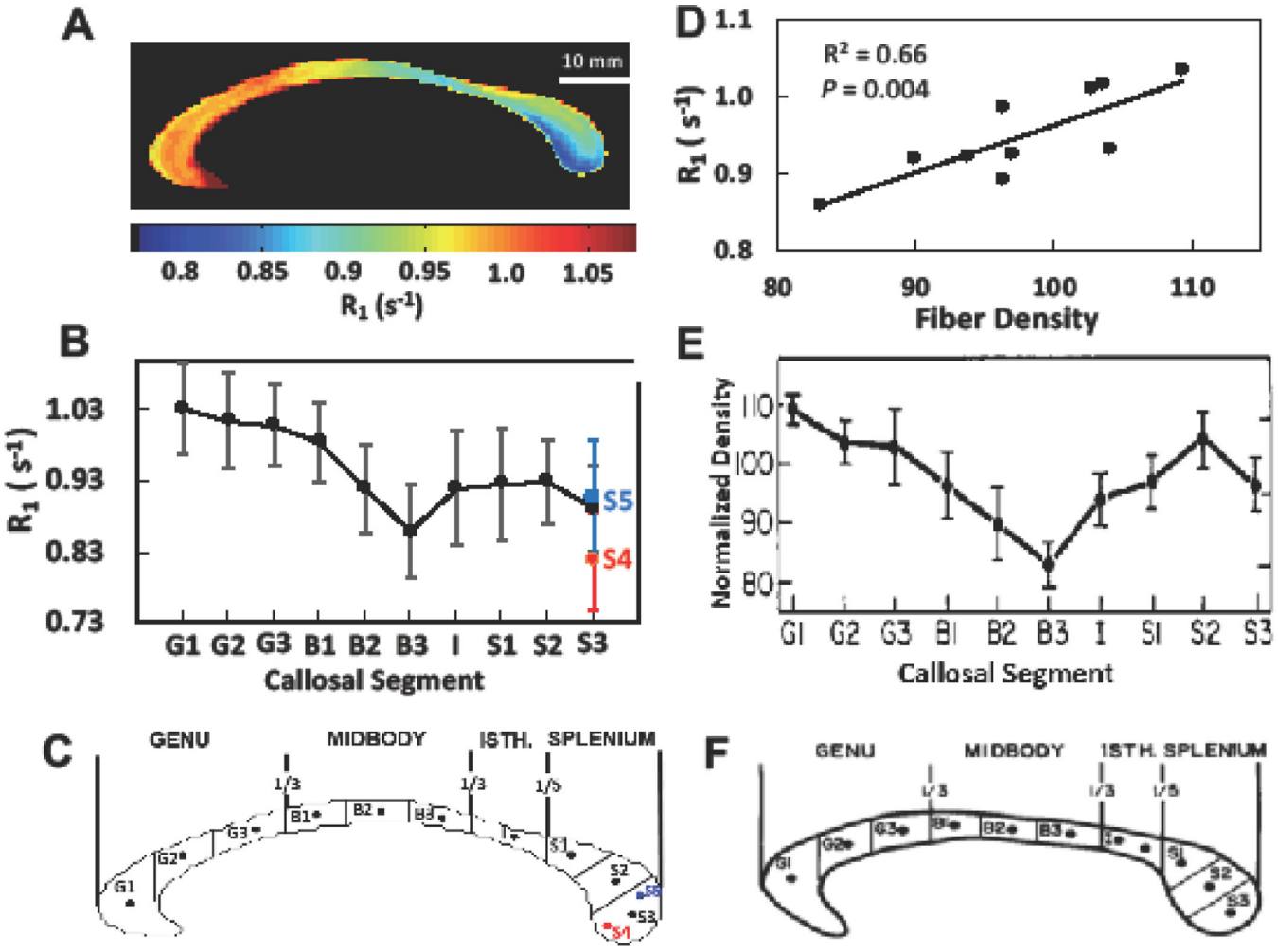

Fig 4.

Correlation study between *in vivo* callosal R_1 (=1/T_1) distribution and myelinated fiber density in the postmortem data. (A) The averaged *in vivo* R_1 relaxometry map of the human CC from all subjects (n = 16). (B) The *in vivo* R_1 profile along ten equidistant callosal segments: anterior third (G1~G3), midbody (B1~B3), Isthmus (I), and splenium (S1~S3) as shown in (C). (E) The normalized myelinated fiber density profile. (D) The fiber density shown in Panel E and *in vivo* R_1 shown in Panel B show a high correlation along the 10 segments. Error bar represents a standard deviation. The panels (E and F) were reprinted with the permission from the reference (Aboitiz et al. 1992a).

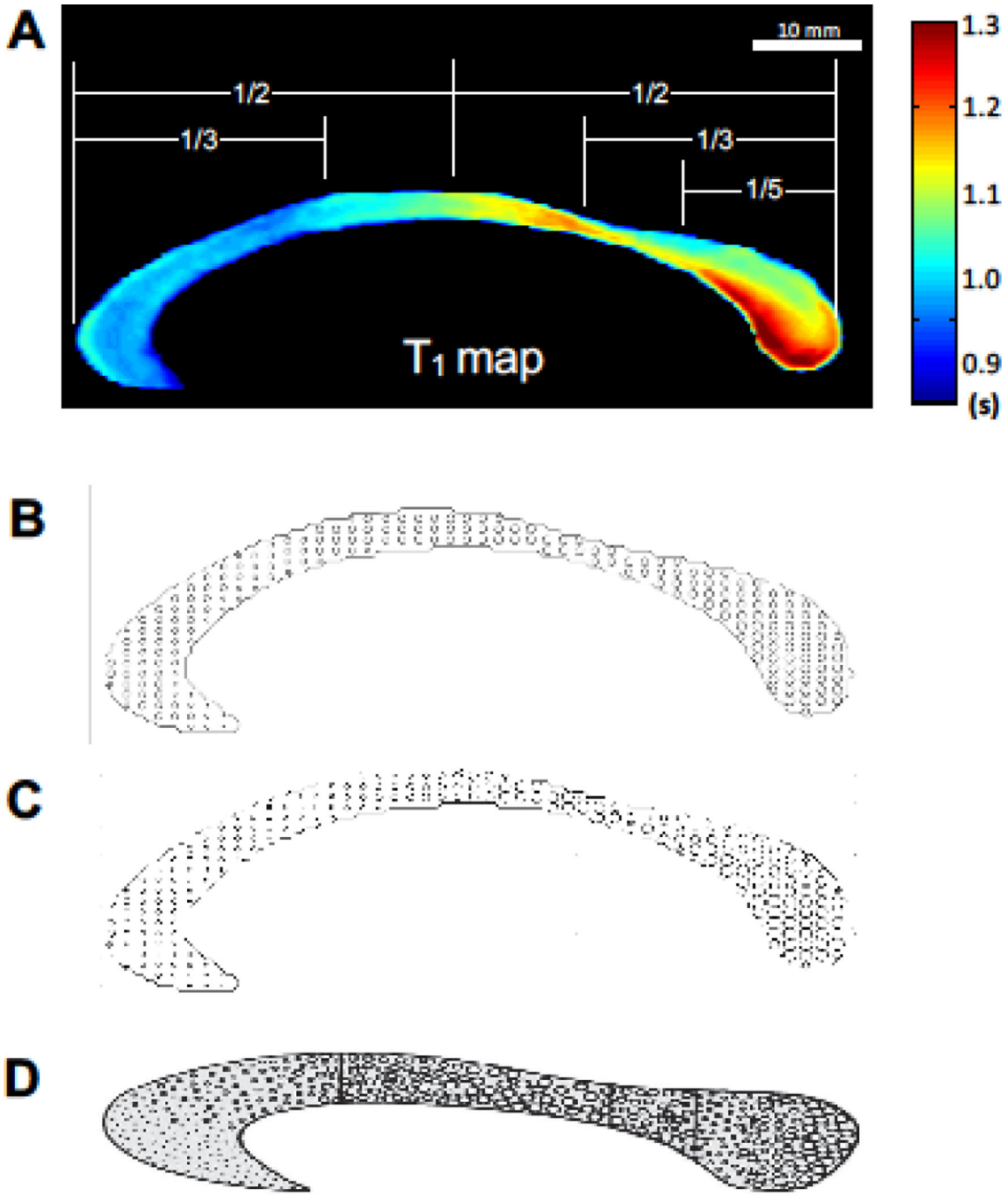

Fig 5.

In vivo axon diameter maps of the human corpus callosum (A–C). Each panel represents the subject-averaged T_1 relaxometry map (A), estimated *in vivo* axon diameter maps (B and C), and manual drawing of axon diameter map reported in the literature (Fig. 1. from the reference (Aboitiz and Montiel 2003)) (D). Panel C was drawn after rescaling the axon size distribution for matching the map shown in (D). There was a qualitatively similar distribution of axon diameter between the *in vivo* and *postmortem* estimations: large-size fibers are shown towards the posterior midbody and splenium, while small-size fibers are

found in the anterior callosum. Note that all axonal diameter maps provide schematic illustrations by scaling the non-uniform fiber size across the CC, thus, they do not represent the exact ratio of diameters between fibers with varied diameter. The panel in D was reprinted with the permission from the reference (Aboitiz and Montiel 2003).

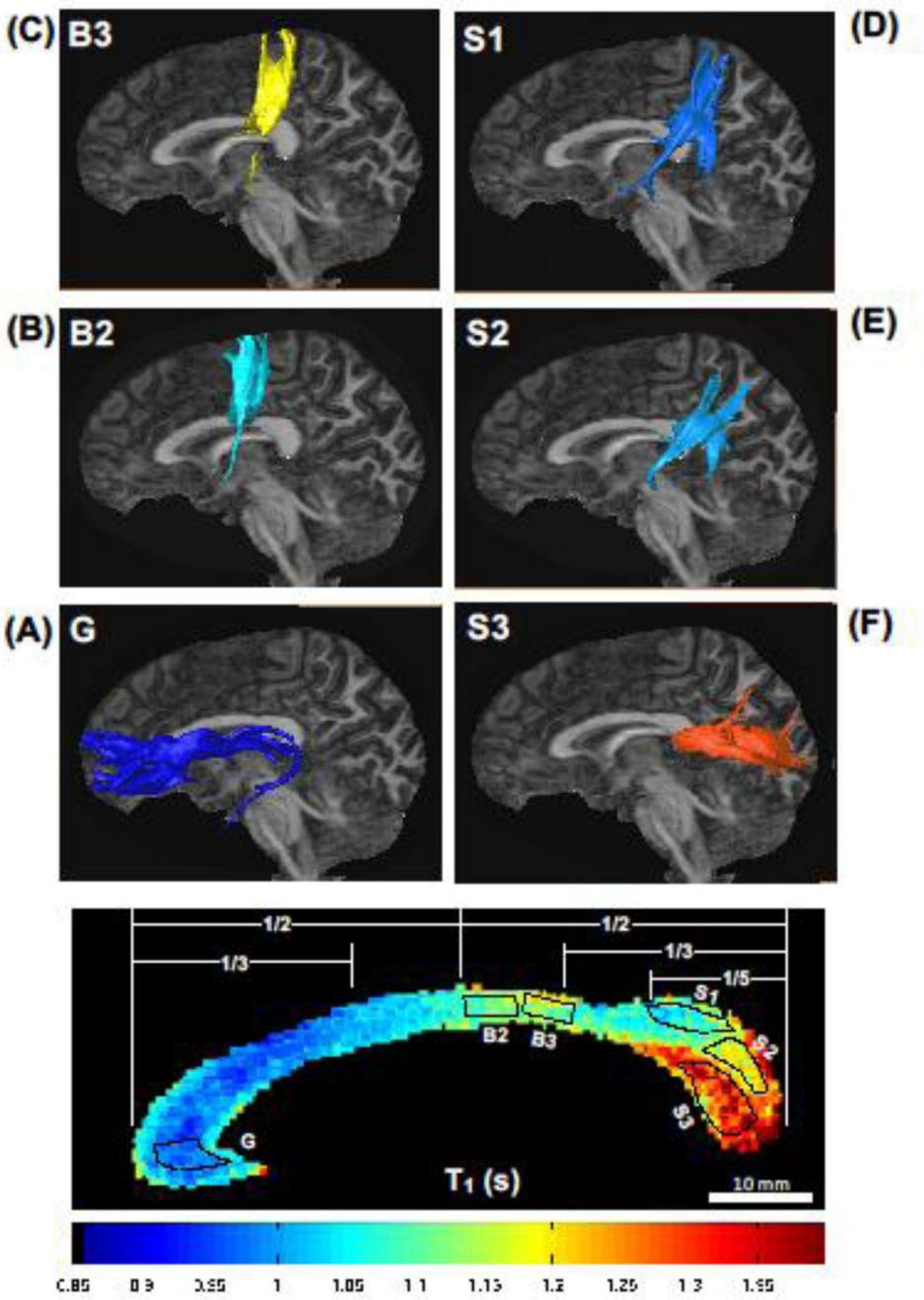

Fig 6.

Diffusion tractography for the human callosal fibers. The callosal fibers from each seeding region of interest (ROI, the dotted areas), which was delineated from the callosal T_1 relaxometry map (panel at the bottom), were connected to the structurally projected cortical areas: (A) ROI G to prefrontal lobe; (B) ROI B2 to motor cortex; (C) ROI B3 to sensory cortex; (D-E) ROIs S1 and S2 to parietal-temporal lobes; and (F) ROI S3 to occipital lobe.

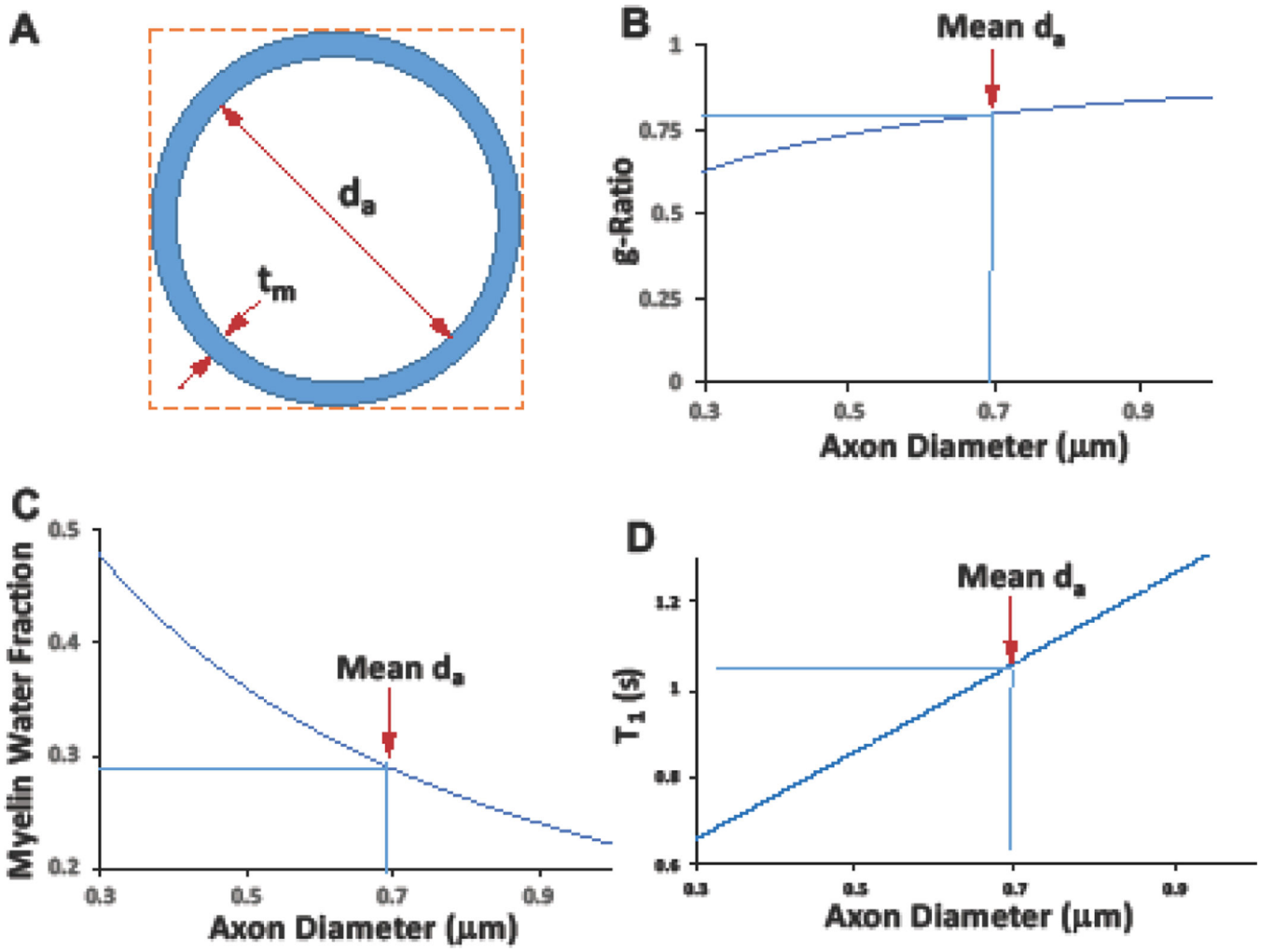

Fig 7.

In vivo model for myelinated axonal diameter. (A) A simplified model of myelinated axon diameter under assumption of an approximation of constant myelin sheath thickness (t_m ~ 0.09 m). (B) The estimated microstructure g-ratio $\left(= d_a/\left(d_a + 2\,t_m\right)\right)$, where d_a is the axon diameter, and its mean value is 0.69 m (pointed by the red arrow) in the human CC (Aboitiz et al. 1992b; Liewald et al. 2014)). (C) The estimated myelin water fraction (MWF = $\frac{\pi}{4}\left(1 - \text{g-ratio}^2\right)$ or $\frac{\pi}{4}\left(1 - \left(d_a/\left(d_a + 2\,t_m\right)^2\right)\right)$ as a function of axon diameter. (D) The estimated relation between T_1 and MWF (T_1 = 0.291/MWF +0.05).