Published in final edited form as:

Brain Res. 2009 January 16; 1249: 91–100. doi:10.1016/j.brainres.2008.10.026.

Diffusion tensor tractography quantification of the human corpus callosum fiber pathways across the lifespan

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Abstract

Several anatomical attributes of the human corpus callosum (CC) including the midsagittal cross-sectional area, thickness, and volume, have been used to assess CC integrity. We extended our previous lifespan quantitative diffusion tensor imaging (DTI) study of the regional CC midsagittal areas to include the CC volumes obtained from DTI fiber tracking. In addition to the entire CC tracked subvolumes we normalized volume with respect to each subject's intracranial volume (ICV) and the corresponding DTI metrics of the different specialized fiber pathways of the CC on a cohort of 99 right-handed children and adults aged 7–59 years. Results indicated that the CC absolute volume, the normalized volume fraction, and the fractional anisotropy followed inverted U-shaped curves, while the radial diffusivities followed a U-shaped curve reflecting white matter progressive and regressive myelination dynamics that continue into young adulthood. Our study provides for the first time normative baseline macro- and microstructural age trajectories of the human CC subvolumes across the lifespan that can be helpful for normative behavioral and clinical studies.

Keywords

Diffusion tensor imaging; Fiber tracking; Corpus callosum; Child; Adult; Brain development; Aging; Lifespan; Witelson subdivisions

1. Introduction

The noninvasive quantification of the macrostructural (morphometry) and microstructural (morphology) aspects of the different pathways of the human corpus callosum (CC) across the lifespan has not been previously attempted. Previous magnetic resonance imaging (MRI) studies have used several anatomical attributes of the CC, including thickness (Luders et al., 2007), area (Johnson et al., 1994), and volume (Allen et al., 2008), to assess the CC in both health and disease (see Hasan et al., 2008 for an extensive review). While the midsagittal crosssectional areas appeal to regional histological evaluations of the CC (Aboitiz et al., 1992), the area measurements are limited as they lack information about the extent to which cortical regions are connected through the CC (Durstun et al., 2001). The CC sectors have unique three-dimensional pathway architecture (Cook, 1986; De Lacoste et al., 1985;

Pandya and Seltzer 1986; Aboitiz and Montiel, 2003) that is currently best mapped using noninvasive DTI fiber tracking methods (Abe et al., 2004; Xu et al., 2002; Dougherty et al., 2007).

The CC in this work (see Fig. 1 and Experimental procedures) is subdivided into eight subvolumes CC1–CC8 based on its connections to the (1) prefrontal, (2) anterior frontal, (3) superior frontal, (4) posterior frontal, (5) anterior parietal, (6) posterior parietal, (7) temporal, and (8) occipital cortices. Although the volume of the entire corpus callosum (eCC), from healthy controls has been reported recently, the use of different methods has resulted in contradictory values (Haut et al., 2006; Rotarska-Jagiela et al., 2008; Allen et al., 2008; see Table 1 for recent reports). Existing reports have not quantified functionally specialized volumes from distinct CC subregions. In addition, the intracranial volume (ICV), has not been incorporated in previous studies to account for CC volume variability between subjects due to differences in brain size (Jancke et al., 1999).

There have been several diffusion tensor tracking (DTT) methods to map the CC connections based on the CC anisotropy and orientation information. These methods can generally be grouped into deterministic (Xu et al., 2002) and probabilistic (Park et al., 2008) approaches. The deterministic approaches use midsagittal CC cross-sectional area geometric subdivision paradigms for initial seeding combined with general knowledge of the fiber tracking topology (Xu et al., 2002; Abe et al., 2004; Huang et al., 2005; Cascio et al., 2006; Sullivan et al., 2006; Hofer and Frahm, 2006; Ota et al., 2006; Dougherty et al., 2007; Wang et al., 2008). Probabilistic approaches use segmented cortical maps as seeds in combination with their callosal terminations (Park et al., 2008; Zarei et al., 2006).

The main goal of this work is to extend our recently described lifespan work on the midsagittal cross-sectional CC areas (Hasan et al., 2008) to include the CC subvolumes obtained from DTI fiber tracking methods. We applied DTI fiber tracking methods on a cohort of right-handed children and adults to quantify the spatiotemporal relations of the entire CC and its subvolumes along with the corresponding DTI metrics, such as fractional anisotropy (FA) and radial diffusivity. We hypothesized that the development and aging trajectories of the macro- and microstructural attributes of the entire CC and its subvolumes are best characterized by nonlinear curves across the human lifespan.

2. Results

2.1. Entire CC volume group mean value differences

Table 2 summarizes the group mean values and comparisons of the ICV and entire CC volume (eCCV) and corresponding FA, and radial diffusivities between boys/girls, men/women and males/females. The ICV and eCCV were larger in males compared to females ($p < 0.03$). The eCC volume-to-ICV ratio ($eCCV/ICV \times 100\%$), and corresponding FA and radial diffusivity were not significantly different between males and females ($p > 0.6$; see Table 2). Based on these comparisons, which indicate non-significant sex effects, we pooled all age-matched males and females (Hasan et al., 2008). In the remainder of the results, we reported on the entire population of children and adults.

In Fig. 2 plots of the scatter data and least-squares fit of the eCCV, eCCV/ICV, FA and radial diffusivity are presented. Note the difference in growth rates between children and adults, which necessitated quadratic models for their description (Hasan et al., 2008; see Experimental procedures).

2.2. Regional heterogeneity and age effects for callosal volume, FA and radial diffusivity

Tables 3–6 summarize the quadratic curve best fit parameters (mean, standard deviation, significance, and R^2) of the absolute and ICV-normalized CC subvolumes, corresponding FA and radial diffusivity. The best fit parameters in Tables 3–6 were used to generate Fig. 3 which shows (a) CCV (b) CCV/ICV (c) FA and (d) radial diffusivities.

Across the lifespan, the absolute CCV, ICV-normalized CCV and FA followed an inverted U-shaped curve, while the radial diffusivity was not inverted, but followed a U-shaped curve. Note the different diffusion tensor anisotropy values for different callosal regions, with FA (posterior CC) > FA (anterior CC) > FA (middle CC) (see Fig. 3 and Tables 3–6).

3. Discussion

The CC offers one of the largest and most studied compact white matter systems using noninvasive MRI methods (Johnson et al., 1994). As in our recent lifespan study on the CC midsagittal areas (Hasan et al., 2008), we focused on right-handed healthy controls to avoid possible confounding effects of handedness (Witelson and Goldsmith, 1991).

This is the first lifespan study on the development and aging of the entire CC and its subvolumes using noninvasive DTI fiber tracking methods. In this work, the diffusion anisotropy combined with the excellent orientation contrast of the CC have been used to track the CC cortico-cortical connections (Xu et al., 2002; Huang et al., 2005; Dougherty et al., 2007).

We have presented and compared both absolute CC subvolumes and ICV-normalized values (Jancke et al., 1999). The ICV values on our healthy cohort are comparable to those reported in other studies on controls (Buckner et al., 2004). The entire fiber-tracked CC volume (eCCV) on our healthy adults ($N=63$; eCCV= 79.7 ± 12.1 mL) is comparable to the values reported in a recent fiber tracking study (Wang et al., 2008; $N=12$; eCCV= 78.0 ± 11.4 mL; see Table 1).

Consistent with previous reports on the healthy CC (Ota et al., 2006; Hasan et al., 2008), we report statistically insignificant sex effects on the entire CC, its subvolumes, or corresponding DTI metrics. The age-dependent growth rates of CC subvolumes extend and confirm earlier reports predicting nonlinear growth curves of the CC cross-sectional area (Allen et al., 1991; Pujol et al., 1993; Rauch and Jenkins, 1994; Johnson et al., 1994; see Hasan et al., 2008).

3.1. Regional callosal anisotropy heterogeneity

Our DTI results reproduce a commonly reported trend using region-of-interest (Chepuri et al., 2002; Hasan et al., 2005), voxel-based and fiber tracking methods that diffusion anisotropy is greater in posterior CC than anterior CC regions at all ages (see Fig. 3). These trends have been reported by several previous DTI reports on healthy controls (see Hasan et al., 2008 and references therein).

3.2. Age effects

Our results (see summary in Fig. 3; Tables 2–6) show that the growth trajectories of CC subvolumes and corresponding DTI metrics are nonlinear across the lifespan (McLaughlin et al., 2007; Lebel et al., 2008) and vary with region (Ota et al., 2006). Based on the radial eigenvalue trends (Fig. 3 and Table 6), the anterior CC regions seem to attain a growth maximum earlier than middle and posterior regions. This trend may reflect the reported histological finding that middle CC areas are populated with large myelinated fibers and that

anterior regions are populated by thin and unmyelinated fibers (Aboitiz et al., 1992; Highley et al., 1999). The posterior CC regions (see Fig. 1 and Fig. 3) are traversed by three functionally specialized groups of myelinated fibers (Aboitiz and Montiel, 2003; Huang et al., 2005; Dougherty et al., 2007; Zarei et al., 2006) that connect parietal (CC6), temporal (CC7) and occipital lobes (CC8).

Our DTI results concur with recent DTI publications that show increasing CC anisotropy in children (Alexander et al. 2007; McLaughlin et al., 2007) and decreasing trends in adults (Ota et al., 2006; Sullivan et al., 2006; Stadlbauer et al., 2008; McLaughlin et al., 2007).

The CC subvolume and corresponding DTI age trajectories resemble those published on whole brain white matter volume (Hasan et al., 2007a; Sowell et al. 2003) and the CC cross-sectional areas (Hasan et al., 2008). The DTI-related metrics (FA, eigenvalues) provide complementary information about the microstructural substrates of the contributors to callosal regional maturation rates (Rakic and Yakovlev, 1968). In particular, the decrease in the radial eigenvalues during childhood and increase during adulthood with advancing age may offer early predictors of the regional dynamics of myelination and demyelination (Rakic and Yakovlev 1968; Song et al., 2005). The correspondence between the CC subvolumes and corresponding DTI metrics may offer important surrogate markers for healthy tissue development (Dubois et al., 2006; Ding et al., 2008), natural aging (Hasan et al., 2008) and its interplay with pathology mechanisms such as Wallerian degeneration (Hampel et al., 1998; Gupta et al., 2006; Wang et al., 2008; De Lacoste et al., 1985).

3.3. Limitations, future extensions and concluding remarks

Our normative database has been formed by pooling crosssectional data collected on healthy children and using the same DTI protocol (data collected ~Dec 2004–Dec 2007) to help in the interpretation of data collected from patients. The cross-sectional assembly of the cohort and the lifespan experimental design account for the confounding and nonlinear age effects and warrant future longitudinal studies. Future extensions of the current studies include the study of the interplay between CC subvolumes and corresponding cortical gray matter thickness and volume in both health (Sowell et al., 2003; Shaw et al., 2008) and disease (Evangelou et al., 2000; Haut et al., 2006; Gupta et al., 2006).

4. Experimental procedures

4.1. Participants

This study included a total of 99 healthy right-handed children and adults (age range 6.7–58.9 years; see Table 7a and Table 7b). The boys/girls, men/women and males/females groups were age-matched ($p>0.2$). All participants were primarily English-speaking, identified as neurologically normal by review of medical history, and were healthy at the time of the assessments. The MRI scans were read as “normal” by a board certified radiologist (LAK). Written informed consent from the adults, guardians and adolescents, and assent from the children participating in these studies was obtained per institutional review board regulations for the protection of human subjects. Due to gender, age range matching and fiber tracking methodology requirements (see below), we have included only 99 participants in the current study from a larger cohort ($N=121$) that was described in a recent study on the CC (Hasan et al., 2008).

4.2. MRI and DTI data acquisition and processing

These studies utilized a high signal-to-noise ratio whole-brain DTI protocol at 3.0 T that was kept under 7 min. The diffusion-weighted data were collected axially (field-of view=240×240; square matrix=256×256 pixels) using 44 contiguous 3.0 mm sections that

covered the entire brain (Hasan et al., 2007a,b; Hasan et al., 2008). The diffusion sensitization of b -factor=1000 s mm⁻² and the encoding scheme used 21 uniformly distributed directions (Hasan, 2007). In this protocol, the DTI-derived rotationally-invariant metrics included the fractional anisotropy (FA) and radial diffusivity. The radial diffusivity is defined as the average of the second and third eigenvalues ($\lambda_{\perp} = (\lambda_2 + \lambda_3)/2$) and has been shown by several researchers to be a marker of myelination (Beaulieu, 2002; Drobyshevsky et al., 2005; Song et al., 2005). The details of the computation of the intracranial volume (ICV), DTI image processing (Hasan et al., 2007b) and DTI quality control measures are found elsewhere (Hasan, 2007).

4.3. Fiber tracking of the corpus callosum

The commissural fibers traversing the CC were separated into eight segments (see Fig. 1) by a slight modification of the original seven subdivisions proposed by Witelson (1989) and the ten sector method of Aboitiz et al. (1992). The rostrum and genu segments in the Witelson method correspond closely to CC1 (prefrontal). The Witelson segments 3–6 correspond to CC2 (anterior frontal), CC3 (superior frontal), CC4 (posterior frontal) and CC5 (anterior parietal) based on the cortical origin/ termination of the fibers passing through these selected midsagittal areas. The splenium was further subdivided into three segments based on the fact that, unlike other segments, the splenium is occupied by three different populations of fibers (Fig. 1 and Figs. 4a, b) that connect the three different lobes of the brain (Aboitiz and Montiel, 2003; Huang et al., 2005). These include fibers connecting the right and left posterior parietal lobes (CC6=posterior parietal), temporal lobes (CC7) and occipital lobes (CC8).

Compact white matter fiber tracking was performed using DTI Studio software (Johns Hopkins University, Baltimore, MD; cmrm.med.jhmi.edu; Jiang et al., 2006) based on fiber assignment by continuous tracking (FACT) algorithm (Mori et al., 1999) with a fractional anisotropy threshold of 0.2 for initial seeding and stopping, and a principal eigenvector angle stopping threshold of 60°. The tracking thresholds (FA and angle) are similar to those used in previous fiber tracking studies of the CC (Wang et al., 2008; Huang et al., 2005; Ota et al., 2006). The CC parcellation followed careful adaptation of recently described paradigms (Xu et al., 2002; Huang et al., 2005; Ota et al., 2006; Dougherty et al., 2007) and started with the identification of the CC anterior-to-posterior dimensions on the midsagittal section (see Figs. 4a,b) using the DTI orientation-coded maps (Hasan et al., 2008). A seed region-of-interest (ROI) is drawn manually to include segments 1 and 2 of the Witelson method and was combined; all fibers that go through this region are followed anteriorly on the coronal slices till 10–12 slices anterior to the anterior end of the genu (Fig. 4c). Two separate target ROIs were drawn manually on this coronal slice to select all fibers that pass through both the original sagittal seed ROI and the two coronal target ROIs. Fibers passing through segments 2–5 were reconstructed as follows: seed ROI is drawn manually on the midsagittal slice to include the corresponding midsagittal area, and the fibers were then followed upwards till 3–4 slices above the axial slice corresponding to the superior most part of the midsagittal CC (Fig. 4c). Two separate target ROIs were drawn on each hemisphere and fibers reconstructed as described earlier. For segments 6–8 the seed ROI include the entire splenium, target ROIs for CC6 were selected on an axial slice (Fig. 4d) as for segments 2–5, whereas segments 7 and 8 were selected on coronal slices (Figs. 4e,f).

In this study, we have included a total of 99 subjects on whom all eight cortico-cortical callosal pathways were successfully completed using the same tracking procedure.

4.4. Statistical analysis

All analyses of callosal subvolumes and their corresponding DTI metrics variation were conducted using a generalized linear model with effects of both age and sex as described elsewhere (Hasan et al., 2008). Given previous reports (Allen et al., 1991; Hasan et al., 2008; McLaughlin et al., 2007; Pujol et al., 1993; Rauch and Jenkins, 1994), both linear and quadratic age terms were included. The DTI metrics (e.g., fractional anisotropy=FA; radial diffusivity= $\lambda_{\perp}$) were modeled for both males and females as $y = \beta_0 + \beta_1 * \text{age} + \beta_2 * \text{age}^2$, then the general least-squares methods were used to compute the coefficients, standard errors and their significance using analysis-of-variance methods (Hasan et al., 2008). All statistical analyses were conducted using MATLAB R12.1 Statistical Toolbox v 3.0 (The Mathworks Inc, Natick, MA).

Acknowledgments

This work was funded by NIH-NINDS R01 NS052505-03 awarded to KMH, NIH-NINDS R01 NS046308 awarded to LEC, P01 HD35946 awarded to JMF and 1 P01 NS46588 awarded to ACP. The authors wish to thank Vipul Kumar Patel for helping in data acquisition.

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Fig. 1. Illustration of the DTI-based fiber tracking of the 8 subvolumes of the human corpus callosum (CC1–CC8) and the their traversal of the axial, coronal and parasagittal planes on a fused anatomical MRI data set acquired from one healthy adult control.

Fig. 2. Scatter plot of the measured and fitted data (linear and quadratic regressions) as function of age for the entire CC (a) volume (b) normalized volume (c) fractional anisotropy and (d) radial diffusivity.

Fig. 3.

Graphical summary of the fitted curves of the CC1–CC8 and entire CC (eCC) on the entire 99 healthy controls' (a) tracked subvolumes (in mL) (b) tracked CC subvolumes normalized by the ICV from each subject ($\text{CCV}/\text{ICV} \times 100\%$) (c) fractional anisotropy and (d) radial diffusivity (see Tables 3–6 for the average values). Note that the age span (horizontal x-axis) on this fitted plot is 5–65 years.

Fig. 4. Illustration of the DTI-based fiber tracking and parcellation methodology of the eight subvolumes of the human corpus callosum (CC1–CC8; see also Fig. 1). (a) Identification of the midgittal section and CC seeding nbased on the Witelson subdivisions (b) the CC fiber tracks (c) selection of the coronal plane for the frontal CC fibers (d) identification of an axial section showing the CC fibers (e) identification of occipital CC pathways using a coronal plane and (f) identification of temporal CC pathways.

Table 1

A list of recent publications that reported the entire CC volume

Authors	Healthy control population <i>N</i>	Age (years)	Entire CC volume (mL)
Alexander et al., 2007	34	14.44±5.97 8–29 years	24.93 ±3.77
Allen et al., 2008	38	23–47	9.3–14.9
Ding et al., 2008	55	0.2–39 years 2–6 years 6–39	1–5 mL 5–10
Haut et al., 2006	31	52.4±5.5	7.4±1.1
McLaughlin et al., 2007	10	7–12 years	14.47 ± 2.42
	36	13–18	17.59±2.9
	35	25–40	18.53±3.54
	22	60–80	18.19±2.2
Rotarska-Jagiela et al., 2008	24	39.21 ±8.95	4.16 ±0.60
Wang et al., 2008	12	26.0±8.1 16–37 years	78.0±11.4

Table 2

The mean values and standard errors of the (a) intracranial volume (mL=cm³) and diffusion tensor tracking-based (b) absolute (c) ICV-normalized volume (CCV/ICV×100%) and corresponding (d) fractional anisotropy, (e) radial diffusivities of the entire CC

ICV and eCC macro- and microstructural metrics	ICV MN ± SD (mL)	eCCMN±SD (mL)	eCC/ICV (× 100%)	FA(eCC) (×1000)	Radial diffusivity (eCC) (μm ² /ms)
Boys	1548.0±98	81.4±12.4	5.26±0.73	573.17±24.72	505.24±41.67
Girls	1440.9±116.0	68.1 ±12.2	4.73±0.79	574.92 ±20.95	498.53±28.66
Children	1494.4±110.1	74.8±13.9	5.0 ±0.80	574.05 ±22.60	501.88±35.41
<i>P</i> (boys vs. girls)	0.005	0.0026	0.046	0.82	0.58
Men	1485.9±135.5	81.5 ±14.0	5.48 ±0.79	573.49 ±20.19	495.30±22.99
Women	1367.3±124.6	78.7±12.6	5.79 ±0.99	569.41 ±17.54	497.90 ±19.17
Adults	1410.6 ±140.0	79.7±12.1	5.68 ±0.93	569.40 ±16.00	494.95 ±20.47
<i>P</i> (men vs. women)	0.0008	0.4	0.20	0.10	0.92
Males	1513.2±123.2	81.5±13.2	5.38±0.76	573.50±20.19	499.66 ±32.46
Females	1390.1±125.7	75.4±13.3	5.46 ±1.05	569.41 ±17.54	495.92±22.35
All	1441.1 ±138.2	77.9±13.5	5.43 ±0.94	571.10±18.7	497.47 ±26.91
<i>P</i> (males vs. females)	0.000005	0.03	0.67	0.29	0.50

The values are provided and compared for boys vs. girls, men vs. women, and males vs. females.

Table 3

Diffusion tensor fiber tracking-based estimation of the CC subvolumes (mm³) (CC1–CC8 and weighted-average across the entire CC) fit statistics on all controls

Regional CC fiber tracts CC volume (mL)	Quadratic fit model: $y = \beta_0 + \beta_1 \text{ age} + \beta_2 \text{ age}^2$			
	R^2	$\beta_0 \pm \text{SD} (p)$	$\beta_1 \pm \text{SD} (p)$	$\beta_2 \pm \text{SD} (p)$
CC1 (prefrontal)	0.085	15.26 ± 1.10 (p^*)	0.128 ± 0.084 (0.13)	−0.003 ± 0.001 (0.04)
CC2 (anterior frontal)	0.110	7.52 ± 1.106 (p^*)	0.131 ± 0.078 (0.096)	−0.003 ± 0.001 (0.02)
CC3 (superior frontal)	0.148	4.52 ± 0.74 (p^*)	0.199 ± 0.056 (0.001)	−0.004 ± 0.001 (0.0001)
CC4 (posterior frontal)	0.131	4.81 ± 0.84 (p^*)	0.196 ± 0.064 (0.003)	−0.003 ± 0.001 (0.02)
CC5 (anterior parietal)	0.158	5.26 ± 1.03 (p^*)	0.324 ± 0.079 (p^*)	−0.005 ± 0.001 (p^*)
CC6 (posterior parietal)	0.081	4.62 ± 1.33 (p^*)	0.258 ± 0.102 (0.01)	−0.005 ± 0.002 (0.006)
CC7 (temporal)	0.073	5.10 ± 1.16 (p^*)	0.128 ± 0.089 (0.15)	−0.001 ± 0.001 (0.40)
CC8 (occipital)	0.037	12.12 ± 1.68 (p^*)	0.237 ± 0.128 (0.068)	−0.003 ± 0.002 (0.098)
Entire CC	0.175	59.22 ± 4.67 (p^*)	1.60 ± 0.36 (p^*)	−0.026 ± 0.006 (p^*)

*
 $p < 0.0001$.

Table 4

Diffusion tensor fiber tracking-based estimation of the CC subvolumes (mm³) normalized by ICV (CCV/ICV ×100%) (CC1–CC8 and weighted-average across the entire CC) fit statistics on all controls

Regional CC fiber tracts CC volume/ICV (×100%)	$y = \beta_0 + \beta_1^* \text{age} + \beta_2^* \text{age}^2$			
	R^2	$\beta_0 \pm \text{SD} (p)$	$\beta_1 \pm \text{SD} (p)$	$\beta_2 \pm \text{SD} (p)$
CC1 (prefrontal)	0.068	0.998 ± 0.068 (p^*)	0.012 ± 0.005 (0.026)	−0.0002 ± 0.0001 (0.013)
CC2 (anterior frontal)	0.097	0.486 ± 0.069 (p^*)	0.011 ± 0.0053 (0.04)	−0.0002 ± 0.0001 (0.01)
CC3 (superior frontal)	0.148	0.289 ± 0.051 (p^*)	0.0152 ± 0.0039 (p^*)	−0.0003 ± 0.0001 (p^*)
CC4 (posterior frontal)	0.169	0.319 ± 0.0587 (p^*)	0.0140 ± 0.0045 (0.002)	−0.00017 ± 0.00007 (0.02)
CC5 (anterior parietal)	0.198	0.336 ± 0.072 (p^*)	0.024 ± 0.0055 (p^*)	−0.0003 ± 0.0001 (p^*)
CC6 (posterior parietal)	0.086	0.292 ± 0.089 (0.001)	0.0192 ± 0.0068, (0.005)	−0.00033 ± 0.00011 (0.003)
CC7 (temporal)	0.107	0.320 ± 0.086 (p^*)	0.0011 ± 0.0066 (0.1)	−0.0001 ± 0.0001 (0.37)
CC8 (occipital)	0.064	0.793 ± 0.012 (p^*)	0.0018 ± 0.0089 (0.044)	−0.00023 ± 0.00014 (0.11)
Entire CC	0.227	3.826 ± 0.314 (p^*)	0.125 ± 0.024 (p^*)	−0.00184 ± 0.0004 (p^*)

*
 $p < 0.0001$.

Table 5

Diffusion tensor fiber tracking-based estimation of the fractional anisotropy corresponding to the CC subvolumes (mm³) (CC1–CC8 and weighted-average across the entire CC) fit statistics on all controls

Regional CC fiber tracts fractional anisotropy	$y = \beta_0 + \beta_1^* \text{age} + \beta_2^* \text{age}^2$			
	R^2	$\beta_0 \pm \text{SD} (p)$	$\beta_1 \pm \text{SD} (p)$	$\beta_2 \pm \text{SD} (p)$
CC1 (prefrontal)	0.304	573.44 ± 9.13 (p^*)	−0.346 ± 0.698 (0.62)	−0.012 ± 0.011 (0.30)
CC2 (anterior frontal)	0.134	522.97 ± 9.07 (p^*)	0.446 ± 0.693 (0.52)	−0.017 ± 0.011 (0.13)
CC3 (superior frontal)	0.047	539.23 ± 8.97 (p^*)	1.320 ± 0.686 (0.057)	−0.018 ± 0.011 (0.11)
CC4 (posterior frontal)	0.126	523.59 ± 11.77 (p^*)	3.122 ± 0.900 (0.001)	−0.044 ± 0.014 (0.003)
CC5 (anterior parietal)	0.025	528.77 ± 11.02 (p^*)	1.315 ± 0.843 (0.122)	−0.021 ± 0.014 (0.126)
CC6 (posterior parietal)	0.143	572.80 ± 9.90 (p^*)	−0.617 ± 0.827 (0.46)	−0.003 ± 0.013 (0.84)
CC7 (temporal)	0.009	573.80 ± 11.11 (p^*)	0.785 ± 0.849 (0.36)	−0.013 ± 0.014 (0.13)
CC8 (occipital)	0.040	632.59 ± 8.9 (p^*)	0.805 ± 0.681 (0.24)	−0.017 ± 0.011 (0.13)
eCC	0.067	569.25 ± 6.87 (p^*)	0.515 ± 0.525 (0.33)	−0.013 ± 0.008 (0.129)

*
 $p < 0.0001$.

Table 6

Diffusion tensor fiber tracking-based estimation of the radial diffusivities corresponding to the CC subvolumes (CC1–CC8 and weighted-average across the entire CC) fit statistics on all controls

Regional CC fiber tracts radial diffusivity ($\mu\text{m}^2/\text{ms}$)	$y = \beta_0 + \beta_1^* \text{age} + \beta_2^* \text{age}^2$			
	R^2	$\beta_0 \pm \text{SD}, p$	$\beta_1 \pm \text{SD}, (p)$	$\beta_2 \pm \text{SD}, (p)$
CC1 (prefrontal)	0.138	$490.87 \pm 10.79 (p^*)$	$-0.829 \pm 0.83 (0.32)$	$0.025 \pm 0.013 (0.064)$
CC2 (anterior frontal)	0.087	$553.71 \pm 11.14 (p^*)$	$-2.330 \pm 0.852 (0.007)$	$0.041 \pm 0.014 (0.004)$
CC3 (superior frontal)	0.184	$568.22 \pm 11.77 (p^*)$	$-3.804 \pm 0.900 (p^*)$	$0.059 \pm 0.012 (p^*)$
CC4 (posterior frontal)	0.226	$578.73 \pm 15.33 (p^*)$	$-5.139 \pm 1.172 (p^*)$	$0.067 \pm 0.019 (0.001)$
CC5 (anterior parietal)	0.121	$563.42 \pm 13.94 (p^*)$	$-3.267 \pm 1.066 (0.003)$	$0.043 \pm 0.017 (0.014)$
CC6 (posterior parietal)	0.048	$509.50 \pm 14.15 (p^*)$	$-1.574 \pm 1.082 (0.15)$	$0.031 \pm 0.017 (0.07)$
CC7 (temporal)	0.074	$551.62 \pm 14.69 (p^*)$	$-2.411 \pm 1.123 (0.034)$	$0.030 \pm 0.018 (0.098)$
CC8 (occipital)	0.058	$486.24 \pm 13.37 (p^*)$	$-2.489 \pm 1.022 (0.017)$	$0.039 \pm 0.016 (0.018)$
eCC	0.081	$523.95 \pm 9.82 (p^*)$	$-2.188 \pm 0.751 (0.004)$	$0.034 \pm 0.012 (0.006)$

* $p < 0.0001$.

Table 7

a Basic age demographics of the healthy control population				
Gender and age distribution and demographics	N	Age range (years)	Age ± SD (years)	
Boys	18	6.7–16.3	11.8±3.1	
Girls	18	6.9–18.7	10.4±2.9	
Children	36	11.1–3.1	6.7±18.7	
P(boys vs. girls)			0.20	
Men	23	20.8–58.9	34.5 ±11.5	
Women	40	20.3–58.8	34.9 ±11.6	
Adults	63	20.3–58.9	34.9 ±11.4	
P(men vs. women)			0.99	
Males	41	6.7–58.9	24.7 ±14.6	
Females	58	6.9–58.8	27.3±15.0	
All	99	6.7–58.9	26.2 ±14.8	
P(males vs. females)			0.40	

b The gender distribution for the different age groups						
	6–12 (years)	13–19 (years)	20–29 (years)	30–39 (years)	40–49 (years)	50–59 (years)
Males	10		8	8	3	41
Females	15		19	7	10	58
Total	25	11	27	15	13	99