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Diffusion Tensor Quantification of the Human Midsagittal Corpus Callosum Subdivisions across the Lifespan

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Abstract

The midsagittal corpus callosum (CC) cross-sectional area subdivisions have been used as early and sensitive markers of human brain white matter connectivity, development, natural aging and disease. Despite the simplicity and conspicuity of the appearance of the CC on anatomical magnetic resonance imaging (MRI), the published quantitative MRI literature on its regional sex and age trajectories are contradictory. The availability of noninvasive quantitative methods to assess the CC regions across the human lifespan would help clarify its contribution to behavior and cognition. In this report, we extended the utility of a recently described semi-automated diffusion tensor imaging (DTI) tissue segmentation method to utilize the high orientation contrast of the CC on DTI. Using optimized DTI methods on a cohort of 121 right-handed children and adults aged 6–68 years, we examined the CC areas and corresponding DTI metrics of the different functionally specialized sectors of the CC. Both the area and fractional anisotropy metrics followed inverted U-shaped curves, while the mean and radial diffusivities followed U-curve reflecting white matter progressive and regressive myelination dynamics that continue into young adulthood.

Keywords

Diffusion tensor imaging; corpus callosum; child; adult; brain development; aging; lifespan; Witelson Corpus Callosum Subdivisions

1. Introduction

The corpus callosum (CC) is the largest interhemispheric fiber network in the human brain (De Lacoste et al., 1985; Cook, 1986; Clarke et al., 1989; Gazzaniga, 2000). The corpus callosum is composed of region-dependent fiber density and myelination levels that reflect its functional specialization (Aboitiz et al., 1992; Highley et al., 1999; Tomasch, 1954; Zaidel and Iacoboni, 2003). The CC has been used as an early and sensitive marker of brain development

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(Clarke et al., 1989; Georgy et al., 1993; Pandya et al., 1971; Rakic and Yakovlev, 1968), hemispheric lateralization (Witelson and Goldsmith, 1991; Westerhausen et al., 2004; Putnam et al., 2008), function (Bengtsson et al., 2005; Bonzano et al., 2008; Fryer et al., 2008; Klass et al., 1999; Luders et al., 2007; Muetzel et al., 2008; Ringo et al., 1994; Schulte et al., 2005), development (Durstion et al., 2001; Rajapakse et al., 1996; Keshavan et al., 2002) and natural aging (Allen et al., 1991; Biegion et al., 1994; Cowell et al., 1992; Johnson et al., 1994; Lebel et al., 2008; McLaughlin et al., 2007; Rauch and Jinkins, 1994; Stadlbauer et al., 2008). The CC has also been implicated as a surrogate marker of a host of developmental (Alexander et al., 2007; Cascio et al., 2006; Giedd et al., 1994; Highley et al., 1999; Machado et al., 2007; Overmeyer et al., 2000; Plessen et al., 2006; Rotarska-Jagiela et al., 2008; von Plessen et al., 2002), neurodegenerative (Biegion et al., 1994; Cader et al., 2007; Evangelou et al., 2000; Georgy et al., 1993; Hampel et al., 1998; Hasan et al., 2005; Head et al., 2004) and acquired pathologies (Ewing-Cobbs et al., 2006; Estruch et al., 1997; Gupta et al., 2006; Jackowski et al., 2008; Moeller et al., 2005; Pfefferbaum et al., 2007; Wilde et al., 2006; Yu et al., 2008).

Involved in integrating cortico-cortical communication (Cook, 1986; De Lacoste et al., 1985; Lamantia and Rakic 1990; Ringo et al., 1994; Zaidel and Iacoboni, 2003; Wahl et al., 2007), the CC has been subdivided based on its microstructural and functional specialization using different approaches (Alexander et al., 2007; Aboitiz et al., 1992; Cascio et al., 2006; Head et al., 2004; Highley et al., 1999; Hofer and Frahm, 2006; Huang et al., 2005; Rotarska-Jagiela et al., 2008; Shin et al., 2005; Sullivan et al., 2002; Westerhausen et al., 2004; Witelson, 1989; Xu et al., 2006). The seven midsagittal callosal subdivision convention (CC1-CC7) seems to be the most common approach in quantitative magnetic resonance imaging (MRI) studies (Levin et al., 2000; Rajapakse et al., 1996; Overmeyer et al., 2000; von Plessen et al., 2002; Witelson and Goldsmith, 1991). The rostrum (CC1), genu (CC2), and rostral body (CC3) are associated with the units comprising prefrontal and frontal lobe structures. The anterior midbody (CC4), posterior midbody (CC5), isthmus (CC6) and splenium (CC7) are associated with sensorimotor, midtemporal, and occipital parcellation units, respectively (Aboitiz et al., 1992; Witelson, 1989).

The human CC has been the subject of hundreds of articles and reviews regarding its heterogeneous structure and function as well as differences related to sex, development and aging (Bishop and Wahlston 1997; Cook, 1986; Dubb et al., 2003; Zaidel and Iacoboni, 2003). Aside from some discrepancies, the majority of independent MRI publications on children (Alexander et al., 2007; Rajapakse et al., 1996; De Bellis et al., 2001; Lenroot et al., 2007), adults (Davatzikos and Resnick, 1998; Doraiswamy et al., 1991; Johnson et al., 1994; Keshavan et al., 2002; Mitchell et al., 2003; Salat et al., 1997; Sullivan et al., 2001) and lifespan (Allen et al., 1991; Cowell et al., 1992; Hasan et al., 2008; Hayakawa et al., 1989; Pujol et al., 1993; Rauch and Jinkins, 1994; McLaughlin et al., 2007) would predict that the entire CC (eCC) cross-sectional area growth curve follows an inverted U-curve across the human lifespan.

Specific lifespan studies based on quantification of MRI measures of CC development are scant. Major conclusions regarding the CC aging trajectories and gender relations require validation from large populations that include both children and adults. In particular, simultaneous estimation of the corpus callosum regional areas and the corresponding microstructural diffusion tensor metrics across the lifespan would help provide an important baseline for the interpretation of data collected from patients (Hasan et al., 2008).

There have been several quantitative diffusion tensor imaging (DTI) studies of the human corpus callosum using region-of-interest (Chepuri et al., 2002; Pierpaoli et al., 1996; Hasan et al., 2005), fiber tracking (Huang et al., 2005; Xu et al., 2002;), and voxel based morphometric methods (Bengtsson et al., 2005). These studies include samples ranging from in utero (Bui et

al., 2006) to preterm (Partridge et al., 2004) and term infants (Dubois et al., 2006), children and adolescents (Hermoye et al., 2006; Mukherjee et al., 2001; Snook et al., 2005;), and adults (Abe et al., 2002; Chepuri et al., 2002; Hasan et al., 2005; Salat et al., 2005; Ota et al., 2006; Sullivan et al., 2006; Westerhausen et al., 2004). To the best of our knowledge, there are three DTI reports on the quantification of the CC across the human lifespan from 5–70 years. These studies showed nonlinear regional age-trajectories of the tensor anisotropy (Hasan et al., 2004; Hasan et al., 2008; McLaughlin et al., 2007).

The main goal of this work is to extend the utility of a DTI-based tissue segmentation methodology described recently (Hasan et al., 2007a; Hasan et al., 2008) to the midsagittal corpus callosum subregions. In addition, we applied the validated methods on a cohort of children and adults to demonstrate spatiotemporal development and gender relations of the CC areas along with the corresponding DTI metrics such as fractional anisotropy and radial diffusivity. We hypothesized that the midsagittal corpus callosum regional development and aging trajectories are best characterized by nonlinear curves across the human lifespan that would consolidate results of prior studies examining the impact of development and aging on the CC area based on conventional MRI and quantitative DTI measurements.

2. Results

2.1 DTI based regional CC Comparisons

Group Mean Values and Nonlinear Trends of Regional CCA, FA, Radial and Mean Diffusivity—Table 1 summarizes the group mean values of the CC2-CC7& eCC midsagittal areas and corresponding FA, radial and mean diffusivities on both children and adults. Note that comparisons of the mean values between children and adults may provide misleading results due to the fact that simple averaging does not account for nonlinear development and aging trends. To illustrate, Table 2–Table 4 summarize the quadratic curve best fits of the CCA, FA, radial and mean diffusivities. The best fit parameters were used to generate Figure 1 which shows clearly for (a) CCA (b) FA (c) radial and (d) mean diffusivities that across the lifespan, simple averaging and comparisons of data collected on children and adults need to be replaced with statistical models that incorporate the linear and quadratic age effects.

Table 2–Table 5 and Figure 2–Figure 5 summarize our main quantitative results in regards to the callosal subregional areas (CC2-CC7& eCC) and the corresponding DTI metrics' (FA, radial and mean diffusivities) heterogeneity and their dependence on age and sex using the quadratic models described in the Methods. Note that our measurements are best fit with quadratic curves as function of age (Figure 1; Table 2–Table 4; Figure 2–Figure 4). The fit parameters and age at peak (mean, standard deviation, and significance) statistics for males, females, males vs. females and the pooled sample (males and females) are provided in the Table 2–Table 4 for the segments CC2-CC7 and the entire CC. The entire CC refers to the sum of all CC midsagittal areas and their corresponding area weighted-average DTI metrics.

2.2 Regional Callosal Area Heterogeneity, Age, and Sex Effects

Table 2 summarizes the main results of our work on the fitted callosal midsagittal areas (in mm²) and the entire CC. As a representative graphical illustration, Fig. 2 (a, b, c, and d) show the genu (CC2 = gCC), anterior midbody (CC4 = bCC), splenium (CC7 = sCC) and the entire corpus callosum (eCC) age trajectories for both males and females, respectively.

2.3 Regional Callosal Fractional Anisotropy Heterogeneity, Age and Sex Effects

Table 3 details the age trajectory and age at peak for the callosal FA of the midsagittal areas and the entire CC. Figure 3 (a, b, c, and d) show the FA of the genu (CC2 = gCC), anterior midbody (CC4 = bCC), splenium (CC7 = sCC) and entire CC (eCC) age trajectories,

respectively. The FA callosal trajectories followed an inverted U curve for both males and females. Note the diffusion tensor anisotropy heterogeneity trend $FA(CC7) > FA(CC2) > FA(CC4)$ (see Figure 3). For example, a statistical comparison of $FA(CC5)$ and $FA(CC7)$ of the intercept, linear and quadratic parameters in Table 5 provides $p=0.0000$, 0.01 and 0.03 , respectively. A detailed quantitative listing of all possible paired comparisons on all variables in this study is not provided in the current manuscript (see Figure 1 for a graphical summary)

2.4 Regional Callosal Radial and Mean Diffusivities Heterogeneity, Age and Sex Effects

Callosal radial and mean diffusivities of the midsagittal areas and the entire CC are depicted in Table 4–Table 5. Figure 4–Figure 5 (a, b, c, and d) show the radial and mean diffusivities of the gCC, bCC, sCC and eCC age trajectories, respectively. The average radial and mean diffusivity callosal trajectories followed a U curve for both males and females.

3. Discussion

The corpus callosum offers one of the largest and most studied compact white matter systems to model using noninvasive MRI methods (Bartzokis et al., 2004; Caviness et al., 1996; Hasan et al., 2008; Peters and Sethares, 2002). The MRI literature on the CC is extremely discordant in regards to age-related growth rates, sex and lateralization effects (Bishop and Wahlsten, 1997; Durston et al., 2001; Clarke et al., 1989). In this study, we focused on right-handed healthy controls to avoid possible confounding effects of handedness (Westerhausen et al., 2004; Witelson and Goldsmith, 1991).

This is the first report using an entirely DTI-based semiautomated and validated approach to segment the CC using DTI-derived and co-registered scalar and vector metrics on a cohort of healthy controls aged 6–68 years. The CC segmentation approach implemented in this work extends our previous DTI-based tissue segmentation approach in which scalar and rotation-invariant DTI-derived metrics have been used to partition the brain into white matter, gray matter and cerebrospinal fluid (Hasan et al., 2007a; Hasan et al., 2008).

In this work, the diffusion anisotropy combined with the excellent orientation contrast of the CC has been used to isolate the CC upon careful identification of the midsagittal section (Hasan et al., 2005; Hasan et al., 2008; Kanabar et al., 2005). Our DTI data were acquired using high signal-to-noise ratios and high spatial resolution that minimized diffusion tensor estimation biases (Hasan, 2007; Pierpaoli et al., 1996) and partial volume averaging (Alexander et al., 2001; Pfefferbaum et al., 2003). Due to its potential relation with regional functional specificity (Aboitiz et al., 1992; Highley et al., 1999; Witelson, 1985), the callosal subdivision paradigm implemented in this work has been adopted by several conventional MRI (Rajapakse et al., 1996; Levin et al., 2000) and DTI studies (Cascio et al., 2007; Moeller et al., 2005; Hasan et al., 2005).

3.1 Regional Midsagittal Corpus Callosum Anisotropy Heterogeneity

Our DTI results reproduce commonly reported significant findings, including that the human corpus callosum diffusion anisotropy is higher in the posterior CC than in other brain regions, and that anisotropy is greater in posterior than anterior CC regions in both males and females at all ages (see Figure 3). These trends have been reported by several previous DTI reports on healthy children (Alexander et al., 2007; Snook et al., 2005) and adults (Abe et al., 2002; Chepuri et al., 2002; Hasan et al., 2005; Head et al., 2004; Madden et al., 2004; Ota et al., 2006; Peled et al., 1998; Pfefferbaum et al., 2000; Salat et al., 2005; Sullivan et al., 2006). It is noteworthy that some studies did not report this trend on healthy controls (Foong et al., 2000; Plessen et al., 2006; Schulte et al., 2005). The explanation of the diffusion anisotropy heterogeneity trend $FA(CC7) > FA(CC2)$ in terms of axonal packing, axonal microstructure, geometry and

myelination is an important, but unresolved challenging problem in MRI that enquires more modeling and histological correlations (Aboitiz et al., 1992; Beaulieu, 2002; Hasan et al., 2005; Hasan et al., 2008; Highley et al., 1999; Pierpaoli et al., 1996; Vorisek and Sykova, 1997).

3.2 Age Effects

Our results (see summary in Figure 1; Table 2–Table 5; Figure 2–Figure 5) show that the growth trajectories of CC subdivisions are nonlinear and vary with region at the macrostructural (CC_A) and microstructural (FA, radial diffusivity) levels. The nonlinear growth rates of CC_A confirm earlier reports predicting nonlinear growth curves of the CC (Allen et al., 1991; Cowell et al., 1992; Hayakawa et al., 1989; Pujol et al., 1993; Rauch and Jinkins, 1994). The quadratic trajectories obtained across the lifespan provide more complete information than linear curves obtained in samples with restricted age ranges that predict constant growth rates of the corpus callosum areas as has been described on studies using children (De Bellis et al., 2001; Lenroot et al., 2007; Rajapakse et al., 1996), young adults (Keshavan et al., 2002) and older adults (Salat et al., 1997; Sullivan et al., 2001).

Our DTI results on both children and adults agree well with recent DTI publications that show increasing CC anisotropy starting in utero (Bui et al., 2006), and extending to preterm neonates (Partridge et al. 2004), infants (Dubois et al., 2006), and children (Mukherjee et al., 2001; Snook et al., 2005; Alexander et al., 2007) and decreasing trends in adults (Abe et al., 2002; McLaughlin et al., 2007; Ota et al., 2006; Pfefferbaum and Sullivan, 2003; Salat et al., 2005; Sullivan et al., 2006). Some contradictions in published MRI reports on the rate of growth of the CC regions, in particular the splenium (Abe et al., 2002; Bonekamp et al., 2007; Pfefferbaum et al., 2000; compare Pfefferbaum et al., 2000; 2003; 2007) may be attributed to the use of different acquisition paradigms, the size and composition of samples, and the adoption of different CC quantification methods that did not account for the CC regional heterogeneity.

The correspondence between the CC_A and its corresponding anisotropy for both males and females at all ages (compare Fig. 2 with Fig. 3) may offer an important surrogate marker for tissue maturation, development and natural aging (Hasan et al., 2008). Such strong positive correlations between callosal anisotropy and its volume attributes have been reported on healthy controls (Alexander et al., 2007; Hasan et al., 2008; Rotarska-Jagiela et al., 2008). The regional and entire CC trajectories (areas and FA) resemble those published on whole brain white matter (Courchesne et al., 2000; Hasan et al., 2007b; Sowell et al., 2003). The DTI-related metrics (FA, eigenvalues) provide complementary information about the microstructural substrates of the contributors to callosal regional maturation rates (Caviness et al., 1996; Lamantia and Rakic, 1990; Mukherjee et al., 2001). In particular, the decrease in the transverse eigenvalues during childhood and increase during adulthood with advancing age may reflect the regional dynamics of myelination and demyelination (Bartzokis et al., 2004; Beaulieu, 2002; Drobyshevsky et al., 2005; Hasan and Narayana, 2006; Rakic and Yakovlev 1968; Song et al., 2005; Vorisek and Sykova, 1997).

3.3 Sex Effects

In addition to age dependence, the CC area and anisotropy have been reported to vary with other factors such as sex and handedness. In the current study, we did not find significant differences in the rates of growth characterizing the macro and microstructural attributes of the CC in our age-matched population of boys/girls, men/women, and males/females (see Table 1–Table 4 and Figure 1–Figure 4). The callosal area growth rates have been reported to be similar in age-matched developing boys and girls (Lenroot et al., 2007; Rajapakse et al., 1996), while other studies reported that the CC_A growth rates are larger in boys than girls (De

Bellis et al., 2001). In adults, Johnson et al. (1994) showed the CC_A rate decreases faster in men than women, while Salat et al. (1997) showed CC_A decreases faster in older women than age-matched men.

As noted above, our DTI results indicate a sex-independent statistically significant trend $FA(CC7) > FA(CC2)$ which has been also reported in both children (Snook et al. 2005) and adults (Abe et al., 2002; Hasan et al., 2005; Ota et al., 2006; Peled et al., 1998; Sullivan et al., 2001; Sullivan et al., 2006). The available DTI reports on sex-based anisotropy differences concluded that $FA(\text{males}) > FA(\text{females})$ (Shin et al., 2005; Westerhausen et al., 2004), while a study by Price et al. (2005) has reported that $FA(\text{women}) > FA(\text{men})$ in the genu of the CC and another study by Szesko et al. (2003) has reported $FA(\text{women}) > FA(\text{men})$ in frontal areas that cross the genu of the CC.

Studies examining effects of handedness on CC area and anisotropy are inconsistent. For example, Witelson (1985) reported that the CC_A is larger in consistent left-handers compared to consistent right-handers, while Westerhausen et al. (2004) data indicate that CC_A of consistent left-handers is significantly smaller than CC_A of right-handers. The CC anisotropy may vary with musical training (Bengtsson et al., 2005), age (Ota et al., 2006), pathology (Alexander et al., 2007) and other confounders. The hypothesis of sex-based axonal geometry has been discussed by Allen et al. (2001) who argued against sex-based differences in axonal microstructure. A comprehensive account of all possible contributors to these findings is beyond the scope of this work and may require a larger population.

3.4 Limitations and Concluding Remarks

Our normative database has been formed by pooling cross-sectional data collected on healthy children and adults using the same DTI protocol to help in the interpretation of data collected from patients. Due to advancing DTI technology longitudinal DTI studies are expected to be more challenging than cross-sectional studies. The primary goal of this work was to validate a DTI-based method for simultaneous measurement of both macro and microstructural attributes of the CC. We have validated the DTI method using a cross-sectional cohort and a lifespan experimental design that accounted for the confounding and nonlinear age effects.

In clinical applications (Bieganski et al., 1994; Schulte et al., 2004), the midsagittal corpus callosum area and corresponding MRI-derived measures are commonly used to provide noninvasive biomarkers of central white matter atrophy which may be caused by demyelination, impaired remyelination and axonal loss due to lesions, infarcts and Wallerian degeneration (Gupta et al., 2006; Evangelou et al., 2000; Hasan et al., 2005; Highley et al., 1999; Moeller et al. 2005; Wilde et al. 2006). The CC midsagittal area, by a commonly held conjecture in neuroscience and clinical psychology, may reflect the number of axons involved in interhemispheric communication (Aboitiz et al., 1992; Highley et al., 1999; Ringo et al., 1994). A measurable loss of callosal axons, coherence and myelination impairment may result in cognitive dysfunction affecting interhemispheric communication by visual, somesthetic, auditory, and motor systems as well as complex cognitive processes involving language, attention, and spatial processing (Alexander et al., 2007; Dougherty et al., 2007; Ewing-Cobbs et al., 2006; Hasan et al., 2005; Schulte et al., 2004; Wilde et al., 2006).

These preliminary results are being investigated further using larger cohorts to incorporate age, handedness, sex and psychometric-cognitive scores in addition to DTI simulations and modeling of the relations between the macro and microstructural attributes (Hasan et al., 2007a; Hasan et al., 2008). The application of the current validated methods for callosal quantification to longitudinal studies is warranted.

Future extensions of the current studies include (I) the inclusion of more participants per decade for both males and females, (II) the modeling of the regional relations between the micro and macro structural organization, (III) the comparison of the midsagittal CC results with different approaches for CC subdivision and fiber tracking, (IV) the investigation of covariates such as volume of white matter connected through the CC to the cortex (Janicke et al., 1999; Sullivan et al., 2001; Zarei et al., 2006), and (V) the study of the interplay between CCA regional trends, cortical gray and white matter integrity (Hasan et al., 2007b; Hasan et al., 2008; Sowell et al., 2003; Shaw et al., 2008).

4. Experimental Procedure

4.1 Participants

This study included 23 boys (age mean $\pm$ SD = 11.7 $\pm$ 3.1 years), 20 girls (age mean $\pm$ SD = 10.3 $\pm$ 2.9 years), 32 men (age mean $\pm$ SD = 36.7 $\pm$ 13.5 years) and 46 women (age mean $\pm$ SD = 37.8 $\pm$ 13.4 years). Table 6 summarizes the age distribution for both males and females. The children and adolescents (N = 43; age mean $\pm$ SD = 11.0 $\pm$ 3.0 years), adults (N = 78; age mean $\pm$ SD = 37.3 $\pm$ 13.4 years), and male (N = 55; age mean $\pm$ SD = 26.2 $\pm$ 16.2 years) and female (N = 66; age mean $\pm$ SD = 29.9 $\pm$ 16.7 years) groups did not differ in age ($p > 0.3$). All participants (N = 121; age mean $\pm$ SD = 28.0 $\pm$ 16.7 years; range = 6–68 years) were primarily English-speaking, identified as neurologically normal by review of medical history, and were healthy at the time of the assessments. All healthy subjects were screened for history of trauma, surgery, chronic illness, alcohol and/or drug abuse, neurological illness, and current pregnancy. Controls in this study were recruited through local advertisements and did not report any neurological conditions. The MRI scans were read as “normal” by a board certified radiologist (L.A.K.). Written informed consent from the adults, guardians and adolescents, and assent from the children participating in these studies was obtained per the University of Texas Health Science Center at Houston institutional review board regulations for the protection of human subjects.

4.2 MRI and DTI Data Acquisition and Processing

We acquired whole-brain data using a Philips 3.0 T Intera system with a SENSE parallel imaging receive head coil (Philips Medical Systems, Best, Netherlands). The MRI protocol included (a) conventional MRI (3D spoiled gradient-echo (SPGR), field-of-view=240 $\times$ 240 mm² (isotropic voxel size = 0.9375 mm), (b) 2D dual spin-echo images with echo/repetition times of $T_{E1}/T_{E2}/T_R=10/90/5000$ ms, in the axial plane (44 axial slices, 3mm thickness, 0 gap covering the entire brain from foramen magnum to vertex) (c) and a phase-sensitive MRI in the sagittal and axial planes, in addition to a matching volume of diffusion-encoded data as described below.

The diffusion-weighted data were acquired using a single-shot spin echo diffusion sensitized echo-planar imaging (EPI) sequence with the balanced *Icosa21* encoding scheme (Hasan and Narayana, 2003), a diffusion sensitization or b-factor of 1000 sec.mm⁻², a repetition and echo times of $T_R=6100$ ms, $T_E=84$ ms, respectively. EPI distortion artifacts were reduced by using a SENSE acceleration factor or k-space undersampling R=2 (Hasan et al., 2008). Spatial coverage matched the conventional MRI sequences described above (e.g., 44 axial sections, 3mm slice thickness and 0 mm gap with identical field-of-view). DTI acquisition time was approximately 7 minutes and resulted in SNR-independent DTI-metric estimation (Hasan, 2007).

In this work, the DTI-derived rotationally-invariant metrics included the fractional anisotropy (FA), radial and mean 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; Hasan and Narayana, 2006; Song et al., 2005). The mean diffusivity is the average of the three eigenvalues ($D_{av} = (\lambda_1 + \lambda_2 + \lambda_3)/3$). The details of the DTI image processing (Hasan et al., 2007a) and DTI quality control measures (Hasan, 2007) are found elsewhere (Hasan et al., 2005; Hasan et al., 2008).

4.3 DTI based Segmentation of the Corpus Callosum and Validation

The midsagittal CC identification procedure was assisted by an experienced neurosurgeon based on the appearance of the interthalamic mass and the fornix on the isotropically interpolated DTI maps as described elsewhere (Hasan et al., 2005). The CC was then segmented on the midsagittal slice using mean diffusivity (D_{av}), fractional anisotropy (Hasan et al., 2007a) and the principal eigenvector (Kanabar et al., 2005; Hasan et al., 2008). To standardize the orientation for all subjects, an orientation angle γ is calculated at which the line joining the maximum anterior–posterior points of the corpus callosum is oriented with the horizontal or long axis (Figure 6a). The midsagittal CC is then rotated by $-\gamma$ so that the midsagittal CC can be brought into a standard frame of reference for making the subdivisions (Hasan et al., 2008; Kanabar et al., 2005). We optimized the thresholds by comparing the segmented CC areas on a cohort of healthy control subjects (children and adults) with the respective areas obtained by manual boundary selection of the CC on corresponding mid-sagittal phase sensitive T₁-weighted images which were acquired in the same scan session (see Figure 6). The procedure outlined provides the CC seven segments: CC1-rostrum, CC2-genu (or gCC), CC3-rostral midbody, CC4-anterior midbody (or bCC), CC5-posterior midbody, CC6-isthmus and CC7-splenium (or sCC; see Fig. 6a) along with the mean, standard deviation (SD) of the $b=0$, and DTI metrics (FA, eigenvalues, coherence etc.). Because CC1 measures were less reliable due to significant anatomic variation, we report findings for CC2 through CC7 and the entire midsagittal corpus callosum (eCC) which is defined as the sum of all callosal midsagittal sections. The DTI metric mean value of the midsagittal eCC was taken as the CC subregional area-weighted average. A detailed description of the validation of the DTI-based CC segmentation using manually delineated high resolution anatomical MRI data (Figure 6b) is provided in Hasan et al. (2008).

4.4 Statistical analysis

All analyses of corpus callosum midsagittal cross-sectional areas and the corresponding DTI metrics variation were conducted using a generalized linear model with effects of both age and sex. Given previous reports (Allen et al., 1991; Bartzokis et al., 2004; Courchesne et al., 2000; Hasan et al., 2004; Hasan et al., 2007a,b; Hasan et al., 2008; McLaughlin et al., 2007; Pujol et al., 1993; Rauch and Jinkins, 1994), both linear and quadratic age terms were included. The DTI metrics (e.g., FA, $\lambda_{\perp}$) were modeled (fitted) for both males and females as $y = \beta_0 + \beta_1 * age + \beta_2 * age^2$, then the general least-squares methods were used to compute the coefficients, standard errors and their significance using analysis-of-variance (ANOVA) methods (Hasan et al., 2007b; Hasan et al., 2008). For comparison of two fit parameters between males and females, we used a two-tailed t-test of the difference $(\beta_{iM} - \beta_{iF})$ divided by the root of the pooled variance $\sigma(\beta_{iM})^2 + \sigma(\beta_{iF})^2$ at the corresponding degrees of freedom (Glantz, 2002). All statistical analyses were conducted using MATLAB R12.1 Statistical Toolbox v 3.0 (The Mathworks Inc, Natick, MA).

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Figure 1.

Graphical summary of the fitted curves of the CC2-CC7 (genu = gCC = CC2; bCC = CC4; isthmus = CC6; splenium = sCC = CC7) and entire CC (eCC) on the entire 121 males and females (a) midsagittal areas (b) fractional anisotropy (c) radial diffusivity and (d) mean diffusivity (see Table 1 for the average values on both children and adults).

Figure 2.

Scatter plot of the measured and fitted data of the midsagittal area (mm²) as function of age for the (a) gCC (b) bCC (c) sCC and (d) the entire CC (Note the quadratic dependence of CC_A vs. age; see also Table 2).

Figure 3.

Scatter plot of the measured and fitted data of the midsagittal callosal subdivisions fractional anisotropy ($1000 \times FA$) as function of age for the (a) gCC (b) bCC, (c) sCC and (d) the entire CC (Note the inverted-U quadratic dependence of FA vs. age; see also Table 3).

Figure 4.

Scatter plot of the measured and fitted data of the midsagittal callosal subdivisions radial diffusivity as function of age for the (a) gCC (b) bCC (c) sCC, and (d) the entire CC (see Table 4).

Figure 5.

Scatter plot of the measured and fitted data of the midsagittal callosal subdivisions mean diffusivity as function of age for the (a) gCC (b) bCC (c) sCC, and (d) the entire CC (see Table 5)

Figure 6.

Illustration of (a) the DTI-based segmentation of the 7 subregions of the human corpus callosum based on the Witelson (1989) seven segments geometric approach. (CC1-CC7: CC1 = rostrum; CC2 = genu = gCC; CC3 = rostral body; CC4 = anterior midbody = bCC; CC5 = posterior midbody; CC6 = isthmus = iCC; CC7 = splenium = sCC), and (b) the manual delineation of the entire midsagittal callosal area (eCC) on conventional MRI acquired in sagittal sections. The upper panel in (a) depicts a fusion of the mean diffusivity map with the principal eigenvector modulated by fractional anisotropy. Note that red color depicts compact fibers oriented in the right-left (e.g. corpus callosum), fibers oriented in the anterior-posterior are shown as green (e.g. fornix), while fibers oriented superior-inferior are shown in blue. The lower panel in (a) shows the magnified seven segments of the midsagittal CC based on the semiautomated DTI implementation of the Witelson (1989) geometric CC subdivisions.

The mean values and standard errors of the DTI-based midsagittal corpus callosum cross sectional (a) areas (mm^2) and corresponding (b) fractional anisotropy, (c) radial diffusivities, and (d) mean diffusivities of the CC2-CC7 segments and entire CC.

Table 1

		Average Regional Corpus Callosum Midsagittal			
		Area (mm^2)	FA ($\times 1000$)	Radial Diffusivity ($\mu\text{m}^2 \cdot \text{msec}^{-1}$)	Mean Diffusivity ($\mu\text{m}^2 \cdot \text{msec}^{-1}$)
CC2	Child	173.7 $\pm$ 33.8	535.2 $\pm$ 42.2	639.6 $\pm$ 59.9	975.1 $\pm$ 69.7
	Adult	184.8 $\pm$ 37.1	544.5 $\pm$ 38.6	612.4 $\pm$ 61.4	943.3 $\pm$ 64.3
	All	180.8 $\pm$ 36.2	541.2 $\pm$ 40.0	622.0 $\pm$ 62.0	954.6 $\pm$ 67.7
	C vs. A (p)	0.11	0.22	0.02	0.01
CC3	Child	90.6 $\pm$ 21.2	406.0 $\pm$ 42.8	778.0 $\pm$ 86.9	1034.4 $\pm$ 91.8
	Adult	97.3 $\pm$ 20.3	420.9 $\pm$ 29.3	772.7 $\pm$ 83.0	1041.7 $\pm$ 96.2
	All	94.9 $\pm$ 20.8	415.6 $\pm$ 35.3	774.6 $\pm$ 84.1	1039.1 $\pm$ 94.3
	C vs. A (p)	0.09	0.026	0.74	0.69
CC4	Child	79.3 $\pm$ 14.3	388.8 $\pm$ 48.7	794.7 $\pm$ 89.0	1040.5 $\pm$ 87.1
	Adult	86.7 $\pm$ 12.6	410.2 $\pm$ 35.8	773.6 $\pm$ 79.4	1032.9 $\pm$ 90.0
	All	84.1 $\pm$ 13.6	402.6 $\pm$ 41.9	781.1 $\pm$ 83.2	1035.6 $\pm$ 8.7
	C vs. A (p)	0.004	0.007	0.18	0.66
CC5	Child	77.2 $\pm$ 16.2	378.8 $\pm$ 58.3	805.8 $\pm$ 132.8	1043.7 $\pm$ 129.6
	Adult	90.6 $\pm$ 14.3	424.6 $\pm$ 36.0	761.7 $\pm$ 71.3	1031.3 $\pm$ 82.0
	All	85.8 $\pm$ 16.2	408.3 $\pm$ 50.1	777.4 $\pm$ 99.4	1035.7 $\pm$ 101.1
	C vs. A (p)	<0.0000001	4e-007	0.02	0.52
CC6	Child	74.6 $\pm$ 16.7	407.4 $\pm$ 67.0	848.5 $\pm$ 120.5	1129.5 $\pm$ 118.5
	Adult	82.9 $\pm$ 15.1	443.9 $\pm$ 46.6	808.2 $\pm$ 95.4	1114.4 $\pm$ 105.6
	All	79.9 $\pm$ 16.1	430.9 $\pm$ 57.2	822.5 $\pm$ 106.3	1119.8 $\pm$ 110.1
	C vs. A (p)	0.006	0.0006	0.046	0.47
CC7	Child	191.8 $\pm$ 32.7	573.7 $\pm$ 43.5	652.7 $\pm$ 65.6	1045.1 $\pm$ 71.8
	Adult	210.8 $\pm$ 28.8	96.6 $\pm$ 30.1	605.6 $\pm$ 54.3	1000.6 $\pm$ 72.9
	All	204.1 $\pm$ 31.5	588.5 $\pm$ 36.9	622.3 $\pm$ 62.5	1016.4 $\pm$ 75.3
	C vs. A (p)	0.001	0.0009	0.00004	0.002
Midsagittal Whole CC	Child	697.0 $\pm$ 99.9	478.6 $\pm$ 33.8	721.5 $\pm$ 57.1	1033.7 $\pm$ 59.4
	Adult	764.5 $\pm$ 83.51	499.7 $\pm$ 21.7	691.0 $\pm$ 49.6	1011.7 $\pm$ 56.9
	All	740.5 $\pm$ 95.0	492.1 $\pm$ 28.3	701.8 $\pm$ 54.2	1019.5 $\pm$ 58.5
	C vs. A (p)	0.0001	0.00001	0.003	0.048

A = Adult; C = Child.

DTL-based callosal areas (mm²) (CC2-CC7 and weighted average across the entire midsagittal CC) fit statistics on males and females.

Table 2
Corpus Callosum Midsagittal Areas (mm²) Quadratic
Least Squares Fit: $y = \beta_0 + \beta_1 * \text{age} + \beta_2 * \text{age}^2 + \eta$

		R ²	$\beta_0 \pm \text{SD (p)}$	$\beta_1 \pm \text{SD (p)}$	$\beta_2 \pm \text{SD (p)}$
CC2	M	0.087	147.2±17.1 (p*)	2.80±1.26 (0.03)	-0.042±0.019 (0.03)
	F	0.065	151.0±15.0 (p*)	2.15±1.04 (0.04)	-0.029±0.015 (0.06)
	M&F	0.071	150.0±11.1 (p*)	2.39±0.79 (0.003)	-0.034±0.013 (0.004)
	M vs. F (p)		0.87	0.69	0.61
CC3	M	0.094	78.2±9.7 (p*)	1.63±0.72 (0.02)	-0.028±0.007 (0.0001)
	F	0.032	82.5±8.7 (p*)	0.60±0.60 (0.32)	-0.006±0.009 (0.48)
	M&F	0.037	81.9±6.5 (p*)	0.97±0.46 (0.04)	-0.013±0.007 (0.05)
	M vs. F		0.74	0.28	0.18
CC4	M	0.126	68.5±6.4 (p*)	1.282±0.47 (0.009)	-0.019±0.007 (0.01)
	F	0.202	64.1±5.2 (p*)	1.32±0.36 (0.0005)	-0.017±0.005 (0.002)
	M&F	0.152	66.5±4.0 (p*)	1.28±0.29 (0.0001)	-0.017±0.004 (0.0001)
	M vs. F		0.60	0.94	0.81
CC5	M	0.251	58.9±6.7 (p*)	2.05±0.50 (0.0001)	-0.028±0.007 (0.0001)
	F	0.302	59.1±6.0 (p*)	1.57±0.41 (0.0001)	-0.017±0.006 (0.007)
	M&F	0.250	59.8±4.5 (p*)	1.73±0.32 (0.0001)	-0.021±0.005 (0.0001)
	M vs. F		0.98	0.46	0.23
CC6	M	0.116	61.2±7.2 (p*)	1.37±0.53 (0.01)	-0.019±0.008 (0.02)
	F	0.197	57.3±6.4 (p*)	1.49±0.44 (0.001)	-0.017±0.006 (0.009)
	M&F	0.152	59.3±4.7 (p*)	1.41±0.34 (0.0001)	-0.018±0.005 (0.001)
	M vs. F		0.69	0.89	0.88
CC7	M	0.112	175.2±13.6 (p*)	2.49±1.01 (0.02)	-0.038±0.015 (0.01)
	F	0.276	153.7±12.2 (p*)	2.89±0.84 (0.001)	-0.030±0.012 (0.02)
	M&F	0.147	165.0±9.3 (p*)	2.62±0.66 (0.0001)	-0.032±0.010 (0.001)
	M vs. F		0.24	0.76	0.67
Midsagittal Whole CC	M	0.224	602.6±39.4 (p*)	11.30±2.92 (0.0003)	-0.166±0.044 (0.0004)
	F	0.289	574.2±35.7 (p*)	10.30±2.47 (0.0001)	-0.120±0.036 (0.001)
	M&F	0.225	591.7±26.6 (p*)	10.45±1.9 (0.00001)	-0.136±0.028 (0.00001)
	M vs. F		0.59	0.80	0.42

p* < 0.000001, M=Males, F=Females.

Fractional anisotropy of (CC2-CC7 and weighted average across the entire midsagittal CC) fit statistics on males and females.

Table 3

		Corpus Callosum Midsagittal			Fractional Anisotropy (x 1000)		
		Quadratic Least Squares Fit: $y = \beta_0 + \beta_1 * \text{age} + \beta_2 * \text{age}^2 + \eta$					
		R ²	$\beta_0 \pm \text{SD}$ (p)	$\beta_1 \pm \text{SD}$ (p)	$\beta_2 \pm \text{SD}$ (p)		
CC2	M	0.121	501.4±18.5 (p [*])	3.599±1.372 (0.01)	-0.055±0.020 (0.01)		
	F	0.072	525.6±16.4 (p [*])	1.625±1.138 (0.16)	-0.030±0.017 (0.08)		
	M&F	0.084	515.5±12.2 (p [*])	2.438±0.870 (0.006)	-0.040±0.013 (0.002)		
	M vs. F (p)		0.33	0.27	0.35		
CC3	M	0.123	373.1±17.1 (p [*])	3.260±1.263 (0.01)	-0.044±0.019 (0.03)		
	F	0.095	380.7±13.8 (p [*])	2.430±0.952 (0.01)	-0.033±0.014 (0.02)		
	M&F	0.105	377.9±10.6 (p [*])	2.760±0.759 (0.0001)	-0.037±0.011 (0.001)		
	M vs. F		0.73	0.60	0.65		
CC4	M	0.156	344.0±19.2 (p [*])	3.934±1.420 (0.008)	-0.050±0.021 (0.02)		
	F	0.105	361.2±16.8 (p [*])	2.966±1.164 (0.01)	-0.038±0.017 (0.03)		
	M&F	0.128	353.3±12.5 (p [*])	3.388±0.890 (0.0001)	-0.043±0.013 (0.001)		
	M vs. F		0.50	0.60	0.65		
CC5	M	0.303	323.7±20.7 (p [*])	5.768±1.531 (0.0001)	-0.068±0.023 (0.004)		
	F	0.333	316.5±17.5 (p [*])	5.598±1.211 (0.0001)	-0.065±0.018 (0.0001)		
	M&F	0.312	320.8±13.2 (p [*])	5.626±0.944 (0.0001)	-0.066±0.014 (0.0001)		
	M vs. F		0.79	0.93	0.93		
CC6	M	0.165	388.1±26.3 (p [*])	2.555±1.950 (0.20)	-0.017±0.029 (0.57)		
	F	0.220	344.1±20.9 (p [*])	4.936±1.447 (0.001)	-0.057±0.021 (0.009)		
	M&F	0.168	364.4±16.6 (p [*])	3.917±1.186 (0.001)	-0.041±0.017 (0.02)		
	M vs. F		0.19	0.33	0.27		
CC7	M	0.068	563.6±16.5 (p [*])	1.499±1.224 (0.23)	-0.015±0.018 (0.41)		
	F	0.192	537.0±15.0 (p [*])	3.097±1.035 (0.004)	-0.035±0.015 (0.03)		
	M&F	0.130	549.0±11.0 (p [*])	2.406±0.783 (0.003)	-0.026±0.012 (0.02)		
	M vs. F		0.24	0.32	0.41		
Weighted Average @ Midsagittal Whole CC	M	0.197	450.5±12.9 (p [*])	3.037±0.958 (0.003)	-0.038±0.014 (0.01)		
	F	0.253	446.1±10.2 (p [*])	2.992±0.705 (0.0001)	-0.038±0.010 (0.001)		
	M&F	0.220	448.6±8.0 (p [*])	2.988±0.569 (0.0001)	-0.038±0.008 (0.0001)		
	M vs. F		0.79	0.97	0.96		

p^{*}<0.000001, M=Males, F=Females.

Radial diffusivity ($\mu\text{m}^2 \text{msec}^{-1}$) of (CC2-CC7 and weighted average across the entire midsagittal CC) fit statistics on males and females.

Table 4

		Midsagittal Corpus Callosum			
		Radial Diffusivity ($\mu\text{m}^2 \text{msec}^{-1}$)			
		Least Squares Fit: $y = \beta_0 + \beta_1 \text{age} + \beta_2 \text{age}^2 + \eta$			
		R^2	$\beta_0 \pm \text{SD (p)}$	$\beta_1 \pm \text{SD (p)}$	$\beta_2 \pm \text{SD (p)}$
CC2	M	0.258	720.5 $\pm$ 25.9 (p*)	-8.096 $\pm$ 1.921 (0.0001)	0.121 $\pm$ 0.029 (0.0001)
	F	0.125	678.6 $\pm$ 25.2 (p*)	-4.908 $\pm$ 1.746 (0.0007)	0.076 $\pm$ 0.025 (0.004)
	M&F	0.174	696.4 $\pm$ 17.9 (p)	-6.220 $\pm$ 1.281 (0.0001)	0.094 $\pm$ 0.019 (0.0001)
	M vs. F (p)		0.25	0.22	0.24
CC3	M	0.214	873.6 $\pm$ 40.1 (p*)	-9.224 $\pm$ 2.971 (0.0003)	0.156 $\pm$ 0.044 (0.001)
	F	0.109	818.3 $\pm$ 31.0 (p)	-4.762 $\pm$ 2.148 (0.030)	0.080 $\pm$ 0.031 (0.01)
	M&F	0.149	841.4 $\pm$ 24.7 (p)	-6.55 $\pm$ 1.764 (0.0001)	0.110 $\pm$ 0.026 (0.000)
	M vs. F (p)		0.28	0.23	0.16
CC4	M	0.170	906.0 $\pm$ 41.4 (p*)	-9.768 $\pm$ 3.065 (0.0002)	0.149 $\pm$ 0.046 (0.002)
	F	0.047	820.6 $\pm$ 30.8 (p)	-3.751 $\pm$ 2.135 (0.08)	0.054 $\pm$ 0.031 (0.09)
	M&F	0.094	857.8 $\pm$ 25.2 (p*)	-6.230 $\pm$ 1.801 (0.0001)	0.092 $\pm$ 0.027 (0.001)
	M vs. F (p)		0.10	0.11	0.09
CC5	M	0.132	928.3 $\pm$ 54.6 (p*)	-11.271 $\pm$ 4.041 (0.0007)	0.158 $\pm$ 0.060 (0.011)
	F	0.166	877.7 $\pm$ 30.9 (p)	-7.303 $\pm$ 2.135 (0.001)	0.096 $\pm$ 0.031 (0.003)
	M&F	0.137	899.0 $\pm$ 29.4 (p)	-8.912 $\pm$ 2.100 (0.0001)	0.121 $\pm$ 0.031 (0.0001)
	M vs. F (p)		0.42	0.39	0.36
CC6	M	0.075	947.6 $\pm$ 60.8 (p*)	-8.636 $\pm$ 4.502 (0.06)	0.113 $\pm$ 0.067 (0.1)
	F	0.171	923.1 $\pm$ 32.3 (p*)	-6.506 $\pm$ 2.232 (0.0005)	0.075 $\pm$ 0.033 (0.025)
	M&F	0.105	933.1 $\pm$ 32.0 (p)	-7.345 $\pm$ 2.287 (0.0002)	0.090 $\pm$ 0.034 (0.009)
	M vs. F (p)		0.72	0.67	0.61
CC7	M	0.131	708.1 $\pm$ 29.7 (p*)	-5.613 $\pm$ 2.200 (0.01)	0.072 $\pm$ 0.033 (0.03)
	F	0.308	711.7 $\pm$ 21.4 (p*)	-5.429 $\pm$ 1.483 (0.001)	0.056 $\pm$ 0.022 (0.01)
	M&F	0.209	709.4 $\pm$ 17.7 (p)	-5.443 $\pm$ 1.264 (0.0001)	0.062 $\pm$ 0.019 (0.001)
	M vs. F (p)		0.92	0.94	0.68
Weighted Average @ Midsagittal Whole CC	M	0.250	804.9 $\pm$ 26.3 (p*)	-8.066 $\pm$ 1.948 (0.0001)	0.120 $\pm$ 0.029 (0.0001)
	F	0.244	772.5 $\pm$ 17.3 (p*)	-5.222 $\pm$ 1.199 (0.0001)	0.069 $\pm$ 0.017 (0.0001)
	M&F	0.227	785.7 $\pm$ 15.2 (p)	-6.343 $\pm$ 1.083 (0.0001)	0.088 $\pm$ 0.016 (0.0001)
	M vs. F (p)		0.31	0.22	0.13

p* < 0.000001, M=Males, F=Females.

Table 5

Mean diffusivity ($\mu\text{m}^2 \text{msec}^{-1}$) of (CC2-CC7 and weighted average across the entire midsagittal CC) fit statistics on males and females.

		Corpus Callosum Midsagittal			
		Mean Diffusivity ($\mu\text{m}^2 \text{msec}^{-1}$)			
		Least Squares Fit: $y = \beta_0 + \beta_1 \cdot \text{age} + \beta_2 \cdot \text{age}^2 + \eta$			
		R^2	$\beta_0 \pm \text{SD}$ (p)	$\beta_1 \pm \text{SD}$ (p)	$\beta_2 \pm \text{SD}$ (p)
CC2	M	0.230	1058.9 $\pm$ 28.2 (p*)	-8.183 $\pm$ 2.086 (0.0001)	0.121 $\pm$ 0.031 (0.0001)
	F	0.122	1024.9 $\pm$ 28.0 (p*)	-5.732 $\pm$ 1.940 (0.007)	0.082 $\pm$ 0.028 (0.004)
	M&F	0.163	1039.6 $\pm$ 19.7 (p*)	-6.738 $\pm$ 1.408 (0.0001)	0.098 $\pm$ 0.021 (0.0001)
CC3	M vs. F (p)		0.39	0.39	0.36
	M	0.237	1126.6 $\pm$ 43.5 (p*)	-8.889 $\pm$ 3.222 (0.008)	0.162 $\pm$ 0.048 (0.001)
	F	0.102	1066.0 $\pm$ 35.6 (p*)	-4.151 $\pm$ 2.467 (0.10)	0.077 $\pm$ 0.036 (0.04)
CC4	M&F	0.150	1091.6 $\pm$ 27.7 (p*)	-6.047 $\pm$ 1.977 (0.003)	0.110 $\pm$ 0.029 (0.0001)
	M vs. F		0.28	0.25	0.16
	M	0.164	1139.8 $\pm$ 42.5 (p*)	-8.815 $\pm$ 3.149 (0.007)	0.145 $\pm$ 0.047 (0.003)
CC5	F	0.020	1051.2 $\pm$ 35.1 (p*)	-2.282 $\pm$ 2.432 (0.35)	0.038 $\pm$ 0.035 (0.29)
	M&F	0.065	1089.2 $\pm$ 27.3 (p*)	-4.945 $\pm$ 1.950 (0.001)	0.080 $\pm$ 0.029 (0.006)
	M vs. F		0.11	0.10	0.07
CC6	M	0.092	1144.0 $\pm$ 54.9 (p*)	-8.837 $\pm$ 4.066 (0.03)	0.139 $\pm$ 0.061 (0.03)
	F	0.053	1084.8 $\pm$ 35.4 (p*)	-4.515 $\pm$ 2.449 (0.07)	0.067 $\pm$ 0.036 (0.06)
	M&F	0.067	1110.3 $\pm$ 31.1 (p*)	-6.278 $\pm$ 2.221 (0.006)	0.095 $\pm$ 0.033 (0.004)
CC7	M vs. F		0.37	0.36	0.36
	M	0.065	1239.7 $\pm$ 64.9 (p*)	-8.886 $\pm$ 4.803 (0.07)	0.136 $\pm$ 0.072 (0.06)
	F	0.063	1167.8 $\pm$ 32.8 (p*)	-3.786 $\pm$ 2.268 (0.10)	0.044 $\pm$ 0.033 (0.19)
Weighted Average @ Midsagittal Whole CC	M&F	0.048	1199.0 $\pm$ 34.2 (p*)	-5.853 $\pm$ 2.443 (0.02)	0.080 $\pm$ 0.036 (0.03)
	M vs. F		0.32	0.34	0.24
	M	0.109	1120.5 $\pm$ 38.4 (p*)	-7.043 $\pm$ 2.842 (0.02)	0.097 $\pm$ 0.042 (0.03)
Weighted Average @ Midsagittal Whole CC	F	0.212	1090.3 $\pm$ 25.5 (p*)	-4.511 $\pm$ 1.767 (0.01)	0.043 $\pm$ 0.026 (0.01)
	M&F	0.137	1102.7 $\pm$ 22.3 (p*)	-5.492 $\pm$ 1.591 (0.001)	0.064 $\pm$ 0.023 (0.01)
	M vs. F		0.51	0.45	0.28
Weighted Average @ Midsagittal Whole CC	M	0.243	1120.6 $\pm$ 28.4 (p*)	-8.134 $\pm$ 2.102 (0.0001)	0.128 $\pm$ 0.031 (0.0001)
	F	0.143	1073.4 $\pm$ 19.8 (p*)	-4.362 $\pm$ 1.371 (0.002)	0.058 $\pm$ 0.020 (0.005)
	M&F	0.166	1093.2 $\pm$ 17.0 (p*)	-5.863 $\pm$ 1.216 (0.0001)	0.085 $\pm$ 0.018 (0.0001)
Weighted Average @ Midsagittal Whole CC	M vs. F		0.18	0.14	0.07

Table 6

The distribution of males (N = 55) and females (N = 66) in the cohort of children and adults grouped by age.

Age Group (years)	Number of Males	Number of Females
6.7–12	14	17
13–19	11	3
20–29	9	17
30–39	9	9
40–49	3	11
50–59	8	6
60–68.3	1	3
Total		
6.7–68.3	55	66