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Age and Sex Effects on Corpus Callosum Morphology Across the Lifespan

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Abstract

The corpus callosum (CC) is the largest inter-hemispheric white matter tract in the human brain, and is characterized by pronounced differences in morphology among individuals. There are limited data, however, regarding typical development, sex differences, and the neuropsychological correlates of individual differences within CC subregions. Magnetic resonance (MR) imaging exams were collected in a large cohort (N = 305) of healthy individuals (ages 8 to 68). We used a highly reliable program to automatically identify the mid-sagittal plane and obtain CC subregion measures according to approaches described by Witelson (1989) and Hampel (1998) and a measure of whole CC shape (i.e., circularity). CC measurement parameters, including area, perimeter, length, circularity and CC subregion area values were generally characterized by inverted U-shaped curves across the observed age range. Peak values for CC subregions were observed between ages 32 and 45, and descriptive linear correlations were consistent with sharper area changes in development. We also observed differing age-associated changes across the lifespan between males and females in the CC subregion corresponding to the genu (Witelson's subregion 2), as well as CC circularity. Mediation analysis using path modeling indicated that genu area mediated the relationship between age and processing speed for females, and the relationship between age and visual learning and executive functioning for males. Taken together, our findings implicate sex differences in CC morphology across the lifespan that are localized to the genu, which appear to mediate neuropsychological functions.

Keywords

corpus callosum; sex differences; lifespan; neuropsychological functioning

Introduction

The corpus callosum (CC) is the largest white matter (WM) tract and interhemispheric commissure in the human brain (Huang, 2005). The midsagittal segment of the CC is topographically organized such that its connective fibers run perpendicular to the cerebral falx and generally correspond to homologous regions of contralateral cortex (Hasan et al., 2009; Lebel et al., 2010; Chao, 2009; Hofer et al., 2006). In the typically developing human brain roughly 250–300 million axons traverse the midsagittal CC (Aboitiz, 1992) with the number of fibers comprising the CC believed to be largely fixed at birth (Luders, Thompson & Toga, 2010). The CC is structurally and functionally heterogeneous, and across different subregions cell axons vary substantially in number, density, diameter (Aboitiz et al., 1992; van der Knaap & van der Ham, 2011) and diffusion properties (Lebel et al., 2010). Moreover, midsagittal CC demonstrates substantial inter-individual variability in local morphology including area, perimeter, length, thickness and shape among healthy individuals (Bruner et al., 2012; Suganthy et al., 2003). Despite variability in whole, subregion and shape CC parameters, neuroimaging studies investigating these properties in large cohorts of healthy individuals across a wide age range are lacking.

There remains considerable controversy regarding the effects of age and sex on CC morphology (Ardekani et al., 2012; Bruner et al., 2012; Luders, et al., 2010), following early post-mortem work reporting a more bulbous splenium in females compared to males, as well as larger mid-sagittal CC area in males (De Lacoste-Utamsing & Holloway, 1982; Holloway & De-Lacoste). Following over a decade of research, an early meta-analysis reported absolute CC area is larger in males and sex differences in splenium area are not reliably present (Bishop & Wahlsten, 1997). More recently CC morphology has been investigated using a variety of neuroimaging methods and measurement parameters, yielding mixed results. For instance, while some investigations comparing adult CC area and the CC/ICV ratio between sexes indicate absolute CC area is greater in males, and CC/intracranial volume is greater in females (Westerhausen et al., 2011; Smith, 2005), other work including individuals ranging from 6.7 years old to middle age failed to find sex differences in the CC/ICV ratio (Hasan et al., 2009). More recently, results of one investigation indicate such differences may be attributed to brain size and not sex differences per se (Bruner et al., 2012), while a subsequent study controlling for age and sex reported larger whole CC area for female subjects (Ardekani et al., 2012).

Questions regarding sex and allometry exist in context of strikingly limited data regarding whole CC morphology and subregion area parameters across a wide age range of the human lifespan. In a cross-sectional sample spanning childhood to late middle age ($N = 99$), subregions projecting to frontal cortical areas reached peak volume at earlier ages than CC subregions that project to the posterior cortex (Hasan et al., 2009). Pronounced isthmus growth has been reported beginning at age 9 in girls and 11 in boys, suggesting some

variation in growth trajectories between sexes in early adolescence (Luders et al., 2010). It is generally agreed structural CC changes are probably most pronounced in the first 2 to 3 decades of life, with relatively less structural change through old age (e.g., Mclaughlin et al., 2007; Hasan et al., 2009), and only small effects of aging on corpus callosum volume were observed over an approximate 1–8 year interval in a cohort of 55 men and 67 women, age 20 to 85 (Pfefferbaum et al., 2013).

While there have been few comprehensive MRI-based investigations of age-related changes in CC measurement parameters, there have been almost no investigations of CC shape that would permit group comparisons unaffected by size differences. Recently, circularity, the mathematical resemblance of a shape to a circle, has been used to investigate CC morphology (Ardekani et al., 2013). Circularity is a transformation of area and perimeter sensitive to CC shape change due to myelination, pruning, local or global white matter degeneration, or deformation of the CC associated with increasing ventricular volume, among other factors. Because circularity is a composite measure that integrates information relevant to multiple brain-based changes associated with development and aging, it shows promise as a marker of global and local neurological status. In the only prior study to investigate circularity (196 subjects aged 60 or older), values were significantly higher in healthy controls compared to participants with very mild Alzheimer's dementia, and higher in participants with slight versus mild Alzheimer's (Ardekani et al., 2013). These results were presumably due to CC perimeter deformations and area decreases associated with global brain atrophy and white matter degeneration. There are presently no studies to our knowledge investigating changes in CC circularity from childhood through mid adulthood.

An emphasis on functional correlates of CC morphology has emerged relatively recently (e.g., Schulte & Müller-Oehring, 2010; Martín-Loeches et al., 2012; Fling et al., 2010). These studies, however, have neither included large numbers of healthy individuals across the lifespan nor employed formal mediation analysis to determine whether functional differences are associated with CC development or aging and thus, interpretation of findings has been difficult. It is presently unknown whether the CC allows for more efficient processing due to interhemispheric integration, inhibition of contralateral areas allowing for more efficient lateralized processing, or a combination of both processes in different corpus callosum subregions (Schulte & Müller-Oehring, 2010). Some work suggests that decreasing CC parameters are associated with better neurocognitive performance in children (Westerhausen et al., 2011; Ganjavi et al., 2011; Luders et al., 2011), while positive associations between CC parameters and performance have been reported based on the contrast of older adult and college student samples (Fling et al., 2011).

Because the white matter comprising the midsagittal area of the CC offers no morphologically distinct structures to permit reliable segmentation we used the approach described by Witelson (1989), which is based on non-human primate models and divides the CC into seven subregions, as well as the method proposed by Hampel and colleagues (1998), which divides the CC into five subregions. Because whole CC and subregion measurement requires reliable identification of the midsagittal plane its identification is critical for precise segmentation of the CC to ensure consistency of measurement across individuals. Thus, in this study we used a highly reliable and previously published

segmentation protocol that features automatic identification of the midsagittal plane (MSP; Ardekani et al., 1997) followed by automated standardization of the magnetic resonance (MR) images along the anterior and posterior commissures (Ardekani et al., 2009), thus minimizing 2 sources of operator bias. Subsequently, a recently published automated protocol (Ardekani et al., 2012; Ardekani et al., 2013) was used to segment the CC based on correspondence to multiple brain atlases, and to generate associated measurement parameters. In this last step we thus removed a third source of variance associated with CC measurement among individuals.

At present, little is known regarding age-associated changes in MR imaging-based whole CC parameters or CC subregion parameters over the course of the healthy human lifespan. While some prior research has examined sex differences in whole CC area (e.g., Bruner et al., 2012; Ardekani et al., 2012), analyses specific to subregions are limited. Furthermore, the functional importance of any potential sex differences across CC parameters remains unclear. The primary goal of this study was to (1) characterize age associated changes in CC measurement parameters and associated subregions across a wide age range (8–68 years) in a large (N = 305) cohort of healthy volunteers while controlling for intracranial volume, (2) assess age x sex interactions in these CC parameters, and (3) determine the extent to which sex differences mediate neuropsychological functioning.

Method

Participants

Three hundred five healthy individuals (52% male) between the ages of 8 and 68 years (mean = 29.50 ± 14.7 years) were recruited through local advertisements and by word of mouth in the community. None of the individuals in the current study participated in our prior study (Ardekani et al., 2012). Written informed consent was obtained from participants or from a parent or guardian if the participant was a minor; all minors provided written assent. Exclusion criteria included any history of a DSM-IV axis I major mood or psychotic disorder as assessed by structured diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (Kaufman et al., 1997) or Structured Clinical Interview for DSM-IV disorders Non-Patient Edition (First et al., 2002). Other exclusion criteria included intellectual or learning disability, MR imaging contraindications, pregnancy, or significant medical illness that could affect the brain. Handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971) and mean laterality quotient was 0.74 (SD = 0.48) and ranged between -1.0 (completely nondextral) to +1.0 (completely dextral).

Image Acquisition

MR imaging exams were conducted at the North Shore University Medical Center on a General Electric 3 Tesla HDx scanner. All scans were reviewed by a radiologist for gross anatomic pathology, which would preclude participation in this study. Scans were also reviewed by a member of the research team and scans with significant artifacts were repeated. Head movement was stabilized with cushions prior to scanning. SPGR images

with a 1mm slice thickness were acquired in the coronal plane (TR = 7.5 ms, TE = 3 ms, matrix = 256 × 256, FOV = 240 mm, 216 contiguous images).

Image Processing

The mid-sagittal plane of the CC and regions-of-interest were obtained from raw 3D MR images using the Yuki module within the Automated Registration Toolbox (ART) for CC segmentation (Ardekani, 2013). Briefly, identification of the mid-sagittal plane was performed for all subjects using a reliable algorithm (Ardekani et al., 1997), which was followed by automated identification of the anterior commissure (AC) and posterior commissure (PC) (Ardekani & Bachman, 2009). Individual voxels belonging to the CC were identified through automated comparisons between each voxel of the mid-sagittal slice and 49 brain atlases that were registered to the image based on AC-PC alignment (Ardekani et al., 2012). All voxels identified as belonging to the CC were labeled as one contiguous structure, extracted and saved in NIFTI image format. The NIFTI image of each midsagittal CC area was visually inspected and manually edited when necessary by an investigator (DP) blind to participant characteristics using ITK-Snap (Yuskevich et al., 2006). The NIFTI images conformed to the CC borders of the original mid-sagittal magnetic resonance imaging cross section. Following editing, measurement parameters of the CC were extracted using ART (Ardekani, 2013). Output data were analyzed using IBM SPSS version 21.0, SAS version 9.2, and SPSS AMOS version 16.

Automated segmentation and measurement parameters

Automated outputs were generated using the Yuki module in ART (Ardekani, 2013), and included area of the mid-sagittal CC (mm²), CC perimeter (mm), length (mm), and circularity, as well as the area (mm²) of seven CC subregions defined by Witelson (1989; Figure 1), and 5 CC subregions defined by Hampel (1998; Figure 2). The resulting Witelson subregions (Witelson, 1989) included the rostrum (W1), genu (W2), rostral body (W3), anterior midbody (W4), posterior midbody (W5), isthmus (W6) and splenium (W7). Hampel subregions (Hampel et al., 1998) included the genu and rostrum (C1), three midbody sections (C2, C3, C4), and the splenium (C5). Circularity values were calculated as a function of area and perimeter, where circularity is equal to $(4\pi * \text{Area}) / \text{Perimeter}^2$, with the maximum value of 1 corresponding to a circle and the minimum value of 0 corresponding to a line segment. Intermediate values occur when a less than maximal area is constrained by an object's perimeter.

Intracranial Volume

Intracranial volume (ICV) measurements (mm³) were generated using the Brainwash module in ART (Ardekani, 2011). Brainwash is an automated skull-stripping program that identifies which elements of an MR image represent brain tissue (e.g., white matter, gray matter, cerebrospinal fluid) based on correspondence to many (>15) MRI atlases of the human brain. Elements of the 3D MRI image other than brain tissue are removed from the MRI image (i.e., skull tissue), and a measurement of the remaining structure yields the ICV.

Neuropsychological Assessments

Subjects were administered 12 neuropsychological tests designed to assess a wide range of functions. Tests were grouped into 6 domains (processing speed, attention, verbal working memory, spatial working memory, visual learning and executive functioning) by using z-score transformations such that higher scores were indicative of better performance. Domains (along with Chronbach's coefficient alpha and sample sizes in parentheses) included: (1) Speed of Processing (.68): Brief Assessment of Cognition in Schizophrenia - Symbol Coding (n = 240), Trail Making Test - Part A (n = 268); (2) Attention (.85): Continuous Performance Test - identical pairs, average of d' 2 (n = 233), 3 (n = 232) and 4 (n = 232); (3) Spatial Working Memory: Wechsler Memory Scale 3rd edition - spatial span (n = 240); (4) Verbal Functioning (.68): Controlled Oral Word Association Test – total words (n = 266), Animal Naming Test (n = 267), UMd Letter-Number Span Task (n = 240), Hopkins Verbal Learning Test revised – immediate recall, total correct words (n = 240); (5) Visual Learning: Brief Visuospatial Memory Test revised - total recall (n = 238); and (6) Executive Functioning (.69): Neuropsychological Assessment Battery - mazes subtest (n = 239), Wisconsin Card Sorting Test - categories completed & percent errors (n = 152 and n = 152), Trail Making Test - Part B (n = 268).

Statistical Analysis

To minimize Type-I error we examined 3-way (age x sex x region) interactions for the Witelson (1989) and Hampel (1998) approaches respectively prior to investigating lower order models. For these analyses we used a mixed models approach with sex as the between subjects factor and subregion as a within subjects factor with age and age² in the model, controlling for intracranial volume. In the Witelson (1989) approach seven subregions included rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus and splenium (W1–W7). In the Hampel et al. (1998) approach five subregions included genu/rostrum, 3 midbody sections and splenium (C1–C5). In four subsequent analyses we investigated area, perimeter, length, and circularity with sex as a between subjects factor and age and age² in the model, again controlling for intracranial volume. Circularity values were scaled by a factor of 100 to promote model convergence. When interaction terms were significant in quadratic models, linear correlations for each sex were examined before and after peak values as in prior work (Peters et al 2014). These analyses were conducted for purely descriptive purposes to characterize age-linked changes independently on each side of peak values, addressing one weakness of quadratic modeling. In all analyses alpha was set to 0.05 (two-tailed).

When age-by-sex interactions were identified in a given CC region or measurement parameter, path analysis (Kline, 2010) was employed to assess whether a given CC parameter mediated the relationship between age and any of the six neuropsychological domains separately for each sex. Path models, which included all six neuropsychological measures, the CC parameter, age and age², were considered separately for males and females. We included age² in the diagrams to model the nonlinear relationship between age and CC parameter. The relationship between age and neuropsychological measures were determined to be linear (using regression plots); hence no paths were included between age² and the neuropsychological measures in the models. An indirect effect was considered

significant based on the following two criteria mentioned by Kline (2010, p. 165). First, Cohen and Cohen's (1983) rule of thumb states that "If all its component unstandardized path coefficients are statistically significant at the same level α , then the whole indirect effect can be taken as statistically significant at the same level α , too." Second, where paths between age, parameter and a neuropsychological domain were all significant, a test recommended by Baron and Kenny (1986), based on the approximate standard error estimates for the indirect effects by Sobel (1986) was used to determine whether significant mediation was present (Kline, 2010; pp.165). If a and b are unstandardized coefficients for paths $X \rightarrow M$ and $M \rightarrow Y$ then the product estimates the unstandardized indirect effect of X on Y through M . If SE_a and SE_b are the corresponding standard errors, then Sobel's

estimated standard error of ab is $SE_{ab} = \sqrt{b^2 SE_a^2 + a^2 SE_b^2}$. In large samples, the ratio ab/SE_{ab} follows approximately a normal distribution and hence a z test (Sobel's test) can be utilized to reject or accept the null hypothesis that the unstandardized indirect effect is zero.

Results

Male subjects (mean age = 31.5, SD = 15.3) were significantly [$F(1, 303) = 6.37, p = 0.012$] older, on average, than female subjects (mean age = 27.3, SD = 13.7). Handedness was not significantly different between male (mean = 0.71, SD = 0.50) and female (mean = 0.78, SD = 0.45) subjects. In addition, there were no significant differences between males (mean = 12.9, SD = 4.0) and females (mean = 12.9, SD = 4.2) in years of education. Descriptive data for all CC measurement parameters is provided in Table 1, which includes correlations before and after peak quadratic values for descriptive purposes.

Subregion Analyses

There were significant 3-way interactions of age² x sex x region for the Witelson [$F(13, 1621) = 5.21, p < 0.0001$] and Hampel [$F(9, 1107) = 3.31, p = 0.0005$] segmentation approaches, indicating non-uniform differences in subregions between sexes across the age range. In addition, there were significant 3-way interactions of age x sex x region for the Witelson [$F(13, 1602) = 6.15, p < 0.0001$] and Hampel [$F(9, 1070) = 4.86, p < 0.0001$] segmentation approaches. Subsequently, age and age² by sex interactions were examined for each individual subregion in both segmentation approaches. Significant interactions of sex x age [$F(1, 299) = 4.11, p = 0.043$] and sex x age² [$F(1, 299) = 4.20, p = 0.041$] were identified in W2 (see Figure 3). Area values for this region peaked at an earlier age for males (32.2 years) than females (40.1 years), with genu area for women surpassing that of men by approximately the fifth decade. A steeper linear slope was observed for females when compared to males prior to the age of the quadratic peak ($r = 0.376, p < 0.001$ vs. $r = 0.193, p = 0.07$) and females showed a less pronounced linear slope after peak ages were achieved ($r = -0.172, p = 0.339$ vs. $r = -0.292, p = 0.013$). Non-significant interactions between age x sex and age² x sex were observed for other Witelson subregions and all Hampel subregions. Two-way interactions (age x sex and age² x sex) were not statistically significant using either the Witelson or Hampel approaches (p 's $> .05$). There were no significant main effects of sex using either approach (p 's $> .05$). The main effect of age² was significant for both the Witelson and Hampel approaches [$F(1, 299) = 22.83, p < 0.0001$].

Whole Corpus Callosum Parameter Analyses

We examined age x sex and age² x sex interactions for the 4 additional CC measurement parameters. Neither significant age x sex nor age² x sex interactions were identified for area, perimeter or length measurements (p 's > .05). However, significant age x sex [$F(1, 299) = 4.83, p = 0.029$] and age² x sex [$F(1, 299) = 4.20, p = 0.041$] interactions were observed for CC circularity. Peak circularity values were observed at the low end of the age range for males (8.13 years), while circularity values for females peaked in the third decade (29.8 years) as illustrated in Figure 4. A more pronounced negative linear slope was observed in males ($r = -0.318, p < 0.001$) compared to females ($r = -0.276, p = 0.069$) following quadratic age peaks. Male circularity values were lower than female values after the mid-30s. Main effects of age and age² were not significant predictors of circularity (p 's > 0.070), though main effects of sex were found when predicting CC circularity in models including linear [$F(1, 299) = 7.63, p = 0.006$] and quadratic [$F(1, 299) = 7.00, p = 0.009$] age terms. Significant main effects of age and age² for analyses investigating area, perimeter, and length (all $p < 0.001$) indicate that values for these three parameters increased with age, with peak values observed in the early to mid 40s. Using the age² term significant main effects were identified for sex when predicting perimeter [$F(1, 299) = 4.25, p = 0.040$] and length [$F(1, 299) = 4.15, p = 0.042$], indicating that these measures were larger in males even while controlling for intracranial volume.

Mediation Analysis

Four path diagrams (two per sex) were constructed to assess whether W2 or circularity mediated the relationship between age (including age and age² terms) and any of the six neuropsychological domains. W2 significantly mediated different neuropsychological domains for male and female subjects. Path diagrams including significant maximum likelihood estimates for male and female subjects can be found in Figure 5 and Figure 6. Specifically, for females W2 area significantly mediated the relationship between age and (relatively stable) performance on processing speed tasks across the observed age range ($z = 4.87, p < 0.001$). For male participants, W2 area significantly mediated the relationships between age and visual learning ($z = -1.99, p = 0.048$), and age and executive functioning ($z = -2.95, p = 0.015$). In contrast to processing speed, both visual learning and executive functioning were characterized by linear decreases across the age range. CC shape as indexed by circularity did not significantly mediate any domain of neuropsychological functioning for either sex (all p 's > 0.05).

Discussion

To our knowledge this is the largest MR imaging study to investigate the effects of age and sex on multiple indices of CC morphology in healthy individuals, and the first to feature contrasting segmentation approaches. Overall, our findings suggest CC area, perimeter, length and circularity are characterized by inverted U-shaped curves across the lifespan with evidence for sex differences in genu size and circularity. We also observed changes in genu morphology have differential functional significance in males and females. Important methodologic strengths of our study include the use of reliable and automated algorithms for identification of the midsagittal plane (Ardekani et al., 1997), anterior and posterior

commissures (Ardekani & Bachman, 2009) and atlas-based segmentation of the CC (Ardekani et al. 2012a, 2012b), thus minimizing 3 sources of operator bias. In this regard potentially important limitations of prior studies examining the CC is the lack of standardization of the brain along the anterior and posterior commissures in the midsagittal plane and/or manual tracing of the CC (e.g., Dubb et al., 2003; Suganthi et al., 2003; Lebel et al., 2010; Hasan et al., 2009; Westerhausen et al., 2011). In addition, prior studies investigating sex differences also focused on an age range restricted to children or adults (e.g., Bruner et al., 2012, Dubb et al., 2003; Giedd et al., 1997; Luders, et al., 2010) or a smaller number of participants (e.g., Hasan et al., 2009; McLaughlin et al., 2007; Pfefferbaum et al., 2013; Holloway & de Lacoste, 1986). Moreover, few MR imaging investigations have utilized nonlinear modeling (e.g., Pfefferbaum et al. 2013) across the lifespan while investigating these measures in relationship to neuropsychological functioning.

In the present study main effects for sex controlling for ICV were found when predicting CC length, perimeter and circularity, but neither whole CC area nor any of its subregions. In the current study male callosa were longer than females with greater perimeter while controlling for ICV. In a relatively large (N = 102) study featuring young adults aged 18–27, Bruner and others (2012) reported that differences in mid-sagittal CC size and shape between males and females were primarily associated with brain size and not sex *per se*. Luders and others (2014) reported similar findings in an investigation of callosal thickness using a small number of male and female participants matched for brain size. Previously, a meta-analysis including 41 studies from 1982 to 1994, 5 of which reported significant sex-related size differences, found that sex differences accounted for roughly 1% of variance in CC size between sexes (Bishop & Wahlstein, 1997). More recently several studies have failed to identify significant CC sex differences (e.g., Hasan et al., 2009; Fling et al., 2011; Westerhausen et al., 2011). In contrast, however, Ardekani and colleagues (2012), found whole CC area was significantly larger in female subjects when statistically controlling for age and intracranial volume in a linear model, and also when matching a sub-sample of male and female participants by total brain size. Differences between our study and Ardekani and colleagues (2012) may be related to our inclusion of 88 subjects between 8 and 17 years of age and their inclusion of 73 subjects ages 70 to 94.

Our findings indicate that across all subjects the genu and isthmus reached peak area values earliest, followed by the body, the splenium and finally the rostrum. Moreover, genu area segmented using the Witelson approach reached peak values earlier in males compared to females, with significant linear slopes observed prior to the peak age in females and after the peak age in males. The large difference in peak ages between the genu and rostrum lends support to Witelson's (1987) decision to separate these two regions and contrasts with the approach used by Hampel et al (1998) wherein these subregions are combined. It is noteworthy, however, that with both approaches males reached peak area values before females, most prominently in the genu. A similar pattern of pronounced growth in childhood, slight volume decline in adulthood and later peak area values (early 30's) was reported by Hasan et al. (2009), although this work featured CC volumes derived from DTI fiber tracking. To our knowledge no prior studies investigated linear slopes on either side of

quadratic peak ages. Peak whole CC area (40.8 years), indicated ongoing myelination until early middle age, with a significant positive linear relationship observed before the peak value. A non-significant negative slope observed after the peak is partially consistent with Pfefferbaum et al. (2013) who reported non-significant changes in CC volume after age 20 in both sexes. In contrast to Pfefferbaum et al. (2013), however, our results suggest that CC growth continues until early middle age.

We identified sex differences across the age range localized to W2 using the Witelson approach. Genu area segmented using the Witelson (1989) approach appears to reach peak values earlier in males (32.2 years) than in females (40.1 years), with significant linear slopes observed prior to peak age in females and after peak age in males. Greater absolute area values were observed in males until the fifth decade. This finding was not observed in C1 (comprising the genu and rostrum) in the Hampel approach. Significant sex differences across the lifespan in genu area in the present study may be due to differences in the number of interhemispheric fibers between males and females at different stages of life, as the density of myelinated and unmyelinated fibers in the CC does not appear to vary with sex or CC area (Aboitiz, 1992). When creating her segmentation scheme, Witelson (1989) judged the rostrum to be separate from the genu, based on primate models, human dissection studies, and radiographic tracer studies. This differentiation is supported by work featuring tractography, which reports that the main body of the genu projects primarily to the anterior frontal cortex, while the rostrum projects primarily to orbitofrontal cortex (Lebel et al., 2010). Compared to the body of the corpus callosum, the genu is composed predominantly of smaller (0.2–1.0 micrometers) fibers and substantially more unmyelinated fibers (Aboitiz, 1992).

The finding that age x sex and age² x sex interactions significantly predicted CC circularity indicates its shape changes differently between sexes across the lifespan. Previous reports of CC shape differences between sexes exist, although methods and measurement parameters have not been comparable among studies. For example some studies used template deformation morphometry or surface based mesh modeling to yield CC thickness or bending angle (e.g., Narr et al., 2000; Walterfang et al., 2009; Dubb et al., 2003). This study is the first to utilize the parameter of circularity across a wide age range of healthy volunteers that includes both children and adolescents. In males, circularity values peaked near the minimum of the observed age range and assumed a significant negative trajectory through old age. For female participants, a parabolic trajectory was observed with the peak value observed at age 29.8 and non-significant linear trends on both sides of the peak age. While significant interactions were not found for CC area, perimeter and length values between sexes across the observed age range, shape changes indexed by circularity were pronounced in men.

To our knowledge this is the largest study to examine circularity across the lifespan and thus, the inclusion of this parameter allows for a conceptually coherent description of significant sex differences in CC shape. As a shape measure, circularity is invariant to object size, demonstrated by the lack of significant correlations between circularity and ICV and no differences in the circularity x age x sex interaction while controlling vs. not controlling for ICV. Because circularity is a transformation of area and perimeter, it can be perfectly

predicted when these parameters are known, and it is reasonable to question whether measuring circularity adds substantial information to area and perimeter. In our data, circularity appears to offer a unique view of CC development between sexes, as age x sex and age² x sex interactions were present when predicting circularity, but not area, perimeter or length (controlling for ICV). Because circularity has conceptual meaning as a shape measure, it is far more comprehensible than other arbitrary transformations of area and perimeter that could potentially detect such interactions.

Numerous studies have investigated the functional correlates of CC morphology in healthy volunteers. Decreased area in the genu (W2 specifically) has been associated with poorer working memory and psychomotor performance in older (over 65), but not young adult samples (Fling et al., 2011). Diffusion properties in the genu have been associated with working memory, processing speed and executive functioning, but not episodic memory (Kennedy & Raz, 2009). Age-related decline in splenium diffusion properties predicted memory and executive functioning (Voineskos et al., 2012). The genu has been implicated in interhemispheric inhibition as opposed to interhemispheric integration, which was associated with the posterior CC (Schulte & Muller-Oehring, 2010). With respect to shape, one recent study in young adults (ages 18 to 27) reported better performance on attention and response inhibition tasks associated with thinner and more curved CC (Martín-Loeches et al., 2012).

Of the 2 CC parameters that demonstrated sex differences, only W2 emerged as a mediator of neuropsychological functioning. For males, the pattern of development and aging that characterized W2 mediated linear decreases with age for both executive and visual learning performance. In contrast, for females the age-linked trajectory of W2 area mediated the relationship between age and processing speed. In contrast to executive functioning and visual learning performance, processing speed values did not vary with age. To date no known investigation of cross-sectional CC measurement parameters has featured such a mediation analysis across this range of the lifespan in healthy controls. Fling and others (2011) reported a positive correlation between W2 and W4 and a cognitive composite composed of verbal working memory and processing speed that was present in an older (65–80), but not a younger group (18–30). Other work indicates that the CC is related to global intellectual functioning (IQ). For example, Luders and colleagues (2007) reported that posterior CC thickness is positively correlated with IQ in adults, while others report significant negative associations between callosal thickness and IQ in children, primarily driven by males (Ganjavi et al., 2011; Luders et al., 2011). In addition, in one sample of young adults increasing attentional control was associated with CC thinness and curvature using procrustes analysis (Bruner et al., 2012).

The present work has several limitations that should be acknowledged. With the increasing use of diffusion tensor imaging other CC segmentation approaches have been reported based on connectivity between midsagittal CC and cortical regions of interest (Hasan et al., 2009; Huang et al., 2005; Lebel, Caverhill-Godkewitch & Beaulieu, 2010), as well as Brodmann areas (Chao et al., 2009). Investigation of the effects of age and sex in relationship to CC morphology was restricted to gross anatomy and some work suggests that diffusion tensor imaging may be a more sensitive technique for assessing white matter properties (Fjell et al.,

2008). It should be acknowledged, however, that structural morphology and diffusion tensor imaging (Voineskos et al 2010) can provide complementary information and may not directly correlate with one another (Tamnes et al., 2011). For example, in the current study whole CC and subregion areas peaked later when compared to diffusion tensor imaging studies, which reported peak diffusion properties in the early 20's in anterior regions and peak values in posterior regions as late as the early 30's (Hasan et al., 2009, Lebel et al, 2010). Indicating 2D parcellation schemes remain informative and valuable, multiple authors suggest conducting 2D segmentation following fiber tracking, and have proposed novel parcellation schemes (e.g., Hofer & Frahm, 2006; Chao, 2009). It should be noted, however, that some DTI-based CC segmentation algorithms (e.g., Hofer and Frahm 2006) may not present a compelling alternative to Witelson's (1989) parcellation scheme, which is not surprising given that Witelson's work was developed based on dissection studies. At the present time there is no well-established DTI-based parcellation scheme for CC segmentation, but rather a common focus on large cortical ROIs that differ between studies. Because Witelson's parcellation scheme is well established, easily implemented in a large number of subjects, and tracks well with results from dissection and DTI work, it remains the most practical parcellation scheme for the present purposes.

An additional limitation stems from the reduction of data secondary to the limited number of subregions included in Witelson (1989) and Hampel (1998) parcellation schemes. To this point, it may also be argued that DTI-based segmentations that feature 5–7 large cortical ROIs still represent coarse parcellation. An exception is the study by Chao and colleagues (2009) who used 28 Brodmann areas to characterize connectivity between mid-sagittal CC and cortex. Other methods for characterizing the CC using MRI (e.g., Luders, Thompson & Toga, 2010) offer more measurement points (e.g., more thickness values), and consequently more detailed data sensitive to local change. In the present study fewer measurements facilitated mediation analysis. Lastly, although both segmentation schemes have been widely used in the literature, they may still represent somewhat arbitrary subdivisions regarding the underlying neuroanatomy; however, it should be noted that the reliability of these metrics is much higher compared to other imaging modalities, including diffusion tensor imaging, which can be noisier.

In sum, we demonstrate sex differences across the lifespan in the human CC that were localized to the genu, and associated with neuropsychological functioning. Negative findings observed in CC regions other than W2 while controlling for ICV suggest that previous reports of sex differences outside of the genu may be due to allometric factors. Taken together, the present study allows for a clearer understanding of various CC parameters across the lifespan in healthy humans, and may have implications for future investigations of atypical development in psychiatric disorders (e.g., Bearden et al. 2011). Moreover, CC structural alterations may be suitable for use as endophenotypes for genetic mapping of psychiatric disorders based on heritability studies (Fears et al. 2014).

Acknowledgments

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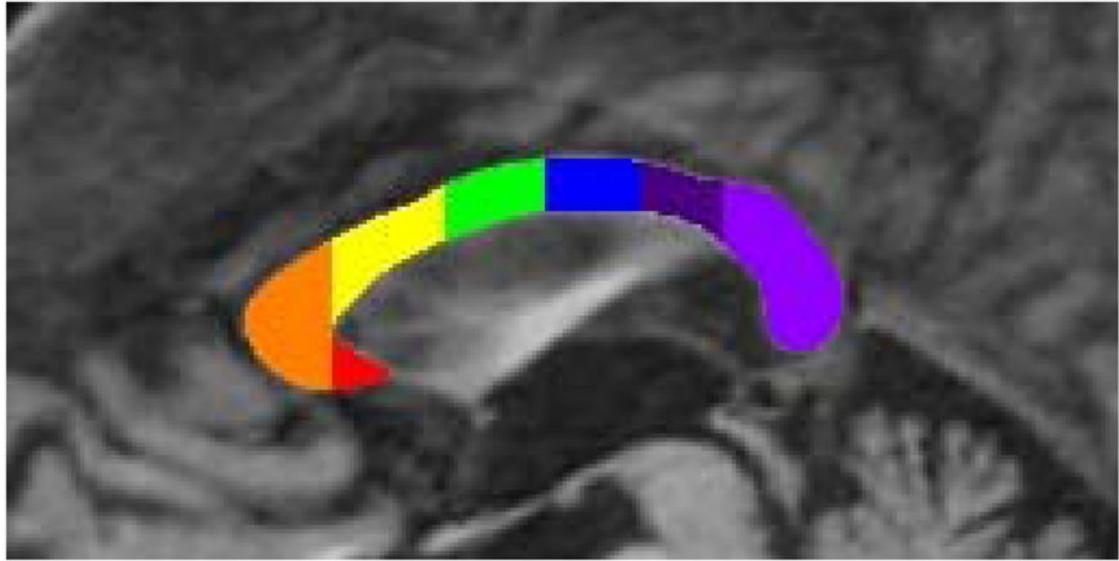
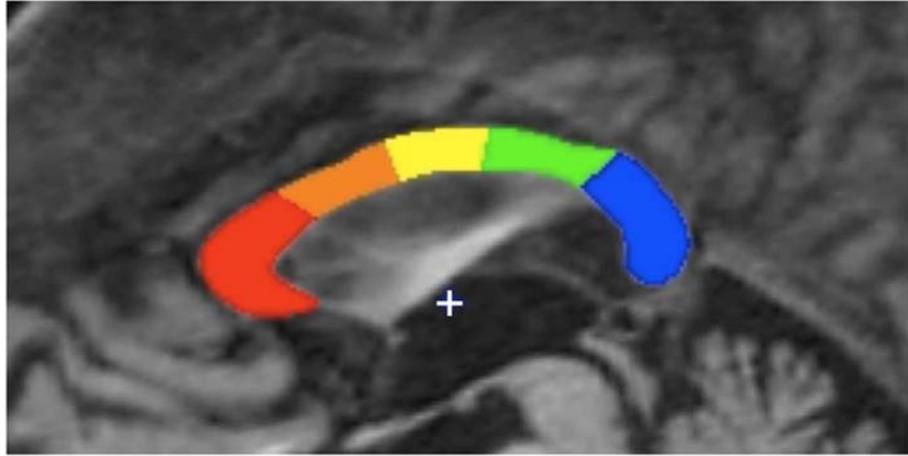


Figure 1. Witelson Subregion Segmentation

Notes. Segmentation using the Witelson (1989) approach was performed automatically by placing 5 perpendicular lines across the maximum length of the CC at $1/5$, $1/3$ and $1/2$ the distance from the outer limits of the genu and splenium. Subregion 1 (W1, red) corresponds to the rostrum, W2 (orange) corresponds to the genu, W3 (yellow) corresponds to the rostral body, W4 (green) corresponds to the anterior midbody, W5 (blue) corresponds to the posterior midbody, W6 (purple) corresponds to the isthmus, and W7 (lavender) corresponds to the splenium.

**Figure 2. Hampel Subregion Segmentation**

Notes. The segmentation scheme proposed by Hampel and colleagues (1998) was automatically performed by forming a rectangle bordering anterior, posterior, dorsal and ventral aspects of the CC and projecting 10 rays spaced 36-degrees apart around the center point (+) of the ventral line segment. Four rays within the rectangle constraining the CC divided it into five subregions including C1 (red, genu inclusive of the rostrum), C2 (orange, anterior midbody), C3 (yellow, posterior midbody) C4 (green, isthmus), and C5 (blue, splenium).

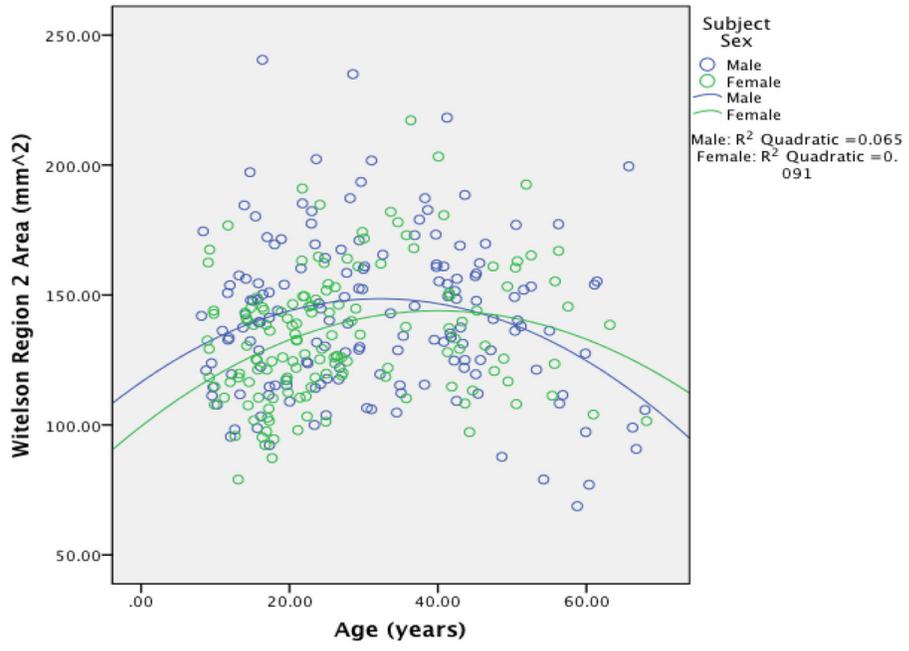


Figure 3.
Witelson Region 2 (W2) Values by Age and Sex

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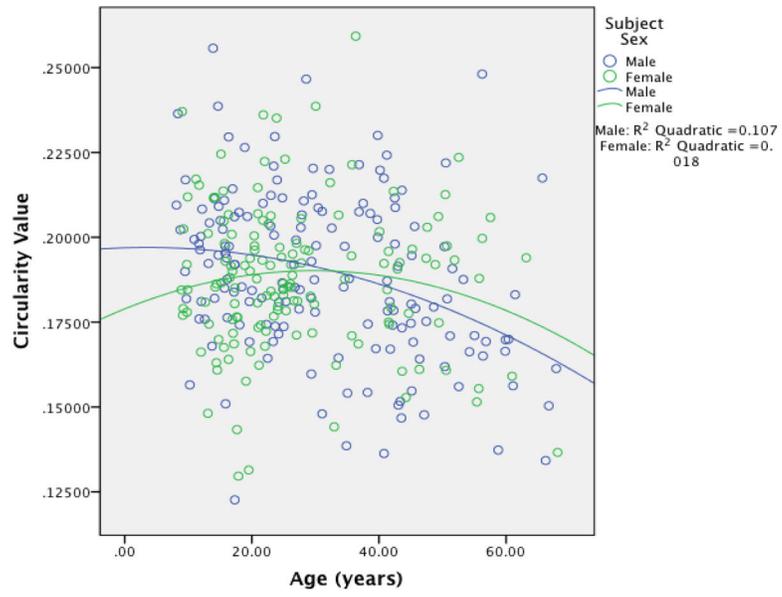


Figure 4.
Circularity Values by Age and Sex

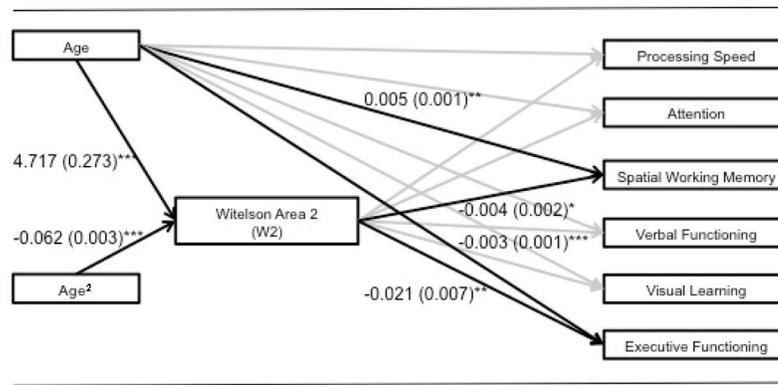


Figure 5.

Path diagram reflecting significant maximum likelihood estimates (standard errors) for male subjects. ^a

Significance level of maximum likelihood estimates: * 0.05, ** 0.01, *** 0.001

^aBlack lines reflect significant maximum likelihood estimates ($p \leq 0.05$), grey lines reflect non-significant findings ($p > 0.05$)

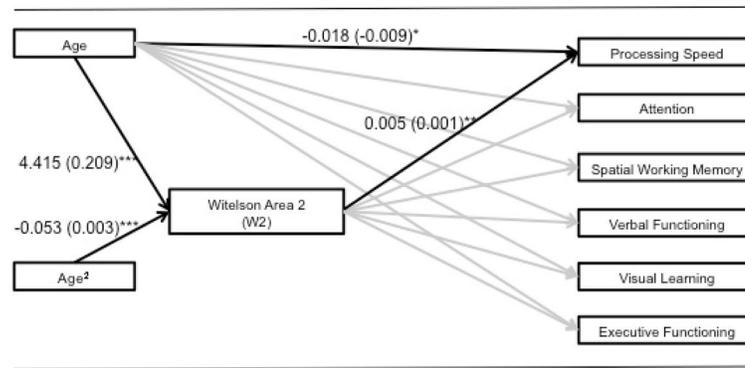


Figure 6.

Path diagram reflecting significant maximum likelihood estimates (standard errors) for female subjects.^a

Significance level of maximum likelihood estimates: * 0.05, ** 0.01, *** 0.001

^aBlack lines reflect significant maximum likelihood estimates ($p \leq 0.05$), grey lines reflect non-significant findings ($p > 0.05$)

Table 1

Corpus Callosum Measures

	Mean (SD) Values				Age at Peak Value			Linear Slope ^d	
	Sexes Combined (n = 305)	Men (n = 160)	Women (n = 145)	Sexes Combined (n = 305)	Men (n = 160)	Women (n = 145)	Before Age Peak	After Age Peak	
Area	621.5 (98.9)	637.4 (99.7)	603.9 (95.4)	40.80	38.63	42.31	0.450**	-0.091	
Perimeter	203.8 (16.9)	206.3 (17.9)	201.0 (15.3)	51.18	50.31	50.70	0.408**	0.089	
Circularity	0.188 (0.023)	0.189 (0.024)	0.187 (0.021)	19.50	8.13	29.82	N/A ^b (m) -0.001 (f)	-0.318** (m) -0.276 (f)	
Length	73.7 (5.2)	74.3 (5.4)	73.1 (4.9)	45.02	45.02	44.25	0.410**	0.029	
Subregions									
Witelson 1	21.6 (8.8)	22.9 (9.9)	20.3 (7.2)	49.43	48.61	47.59	0.337**	0.193	
Witelson 2	137.9 (27.9)	141.4 (30.0)	134.3 (24.8)	35.75	32.19	40.07	0.193 (m) 0.376** (f)	-0.295* (m) -0.172 (f)	
Witelson 3	88.5 (16.1)	90.7 (15.8)	86.0 (16.2)	41.88	40.78	43.26	0.324**	-0.017	
Witelson 4	72.7 (12.8)	74.7 (12.7)	70.5 (12.7)	40.78	38.63	41.88	0.465**	-0.120	
Witelson 5	62.2 (11.4)	63.8 (11.1)	60.5 (11.6)	40.16	38.63	41.62	0.423**	-0.141	
Witelson 6	52.7 (12.5)	54.5 (12.0)	50.7 (12.7)	38.63	35.33	40.07	0.257**	-0.110	
Witelson 7	185.8 (30.3)	189.5 (31.6)	181.7 (28.4)	45.23	45.02	45.23	0.359**	-0.074	
Hampel 1	194.2 (29.9)	198.2 (32.0)	189.7 (26.6)	38.26	36.87	40.07	0.392**	-0.337**	
Hampel 2	86.9 (19.3)	89.9 (18.9)	83.5 (19.2)	38.26	35.33	41.88	0.257**	-0.196	
Hampel 3	71.2 (16.9)	73.9 (15.6)	68.2 (17.7)	43.26	40.78	45.23	0.288**	-0.045	
Hampel 4	75.1 (20.3)	78.9 (18.9)	70.9 (21.0)	45.23	41.35	45.23	0.179**	-0.127	
Hampel 5	194.1 (30.4)	196.5 (31.7)	191.5 (28.7)	42.97	42.56	42.91	0.428**	0.007	
Intracranial Vol (mm ³)	1,528,168 (182,975)	1,619,129 (160,564)	1,427,796 (151,247)	-	-	-	-	-	

Note: Univariate statistics are reported for descriptive purposes only.

^a Slope reported separately for females (f) and males (m) where a significant age by sex interaction was found

^b Slope not reported due to an insufficient number of males younger than the peak age

* Correlation is significant at the 0.05 level (two-tailed);

** Correlation is significant at the 0.01 level (two-tailed)

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