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The development of corpus callosum microstructure and associations with bimanual task performance in healthy adolescents

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Abstract

Cross-sectional and longitudinal volumetric studies suggest that the corpus callosum (CC) continues to mature structurally from infancy to adulthood. Diffusion tensor imaging (DTI) provides in vivo information about the directional organization of white matter microstructure and shows potential for elucidating even more subtle brain changes during adolescent development. We used DTI to examine CC microstructure in healthy right-handed adolescents ($n = 92$, ages 9–23 years) and correlated the imaging data with motor task performance. The primary DTI variable was fractional anisotropy (FA), which reflects the degree of white matter's directional organization. Participants completed an alternating finger tapping test to assess interhemispheric transfer and motor speed. Task performance was significantly correlated with age. Analyses of variance indicated that 9–11 year-olds generally performed worse than each of the older groups. Males outperformed females. Significant positive correlations between age and FA were observed in the splenium of the CC, which interconnects posterior cortical regions. Analyses of variance indicated that individuals older than 18 years had significantly higher FA than 9–11 year-olds. FA levels in the genu and splenium correlated significantly with task performance. Regression analyses indicated that bimanual coordination was significantly predicted by age, gender, and splenium FA. Decreases in alternating finger tapping time and increases in FA likely reflect increased myelination in the CC and more efficient neuronal signal transmission. These findings expand upon existing neuroimaging reports of CC development by showing associations between bimanual coordination and white matter microstructural organization in an adolescent sample.

Introduction

The corpus callosum (CC) is the primary connection between cerebral hemispheres, allowing for the interhemispheric integration of sensory, motor, and cognitive processes. The CC is composed of densely packed, myelinated axons and is commonly partitioned into regions based on anatomical and functional connectivity with cortical regions. It contains interhemispheric projections that terminate in cortical layer IV (Schmahmann & Pandya, 2006). The structure and function of the CC has been studied extensively in callosotomy patients, through post-mortem studies, and through the use of in vivo brain imaging. Despite the vast literature

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regarding its structure and function, little has been reported on the development of the CC during childhood and adolescence. Although available reports are somewhat inconsistent, both cross-sectional and longitudinal studies (described below) suggest that the CC continues to mature structurally from infancy to adulthood. Whether these structural changes support behavioral changes has not been extensively studied.

Conventional magnetic resonance imaging (MRI) methods have yielded morphological information about the CC in relation to age, gender and pathology. In a large study of children ages 2–15 and adults ages 16–79 years, Allen et al. (1991) showed through midsagittal tracings of the CC that its area increased with age, reached a plateau in the group of children then decreased steadily with advancing age in the adults. The study also revealed gender differences in the morphology of the CC, with females exhibiting a bulbous shaped splenium compared to what was described as a more tubular shaped splenium in males. Pujol et al. (1993) conducted a longitudinal study of individuals 11–61 years old and found increases in CC area up to roughly the third decade of life. Males and females did not differ in total CC area, however males did show an increased rate of CC development compared to females. Regional distinctions in CC development have also been reported. In a large longitudinal study of 139 individuals ages 4–18, Giedd et al. (1999) examined CC size and found evidence of CC development through adolescence, even after correcting for total cerebral volume. The study showed a significant age-related increase in area of the posterior portion of the CC, especially in the splenium. The authors interpreted this pattern as possibly being indicative of an anterior-to-posterior gradient in CC development, where anterior regions were presumed to have reached adult sizes earlier in development. Similarly, Thompson et al. (2000) showed sharp increases in area of the posterior portion of the CC (isthmus and splenium) with age in normally developing children and adolescents from ages 6–15 years. This group also reported that children ages 3–6 years showed marked increases in anterior CC area, which, in part, corroborates the findings and hypotheses of Giedd et al. (1999). In contrast, Paus et al. (1999) studied individuals ages 4–17 using modified segmentation output from structural MRI scans and did not report any age-related differences in CC white matter density.

Conventional imaging methods can assess developmental trends in brain tissue macrostructure during childhood and adolescence, but they cannot provide specific information about microstructure, such as axonal organization and orientation. Diffusion tensor imaging (DTI) is an in vivo approach to examining white matter microstructure that has demonstrated sensitivity to both developmental and degenerative age-related changes in tissue integrity (Barnea-Goraly et al., 2005; Bonekamp et al., 2007; Sullivan & Pfefferbaum, 2006; Wozniak & Lim, 2006). DTI provides information about the magnitude and direction of water diffusion within tissue (Basser & Pierpaoli, 1996). Myelin, a lipid and protein rich axonal covering, restricts water diffusion in white matter. Intracellular water within myelinated axons diffuses in a more directional manner compared to diffusion in unmyelinated axons. Mean diffusivity (MD) and fractional anisotropy (FA) are two commonly derived scalar measures of DTI. MD describes the degree of diffusion in all directions, whereas FA describes the directional portion of diffusion. High MD corresponds to relatively unimpeded water diffusion and indicates regions of low tissue organization, while high FA corresponds to preferential diffusion along one direction, indicating a high level of tissue organization. Developmental studies utilizing DTI have shown age-related changes in microstructural development in the CC using both region of interest (ROI) and voxel-based analyses (Ashtari et al., 2007; Barnea-Goraly et al., 2005; Bonekamp et al., 2007; Li & Noseworthy, 2002; Snook et al., 2007). Li & Noseworthy (2002) revealed increases in FA and volume in the splenium with age in a sample of healthy 10–40 year-olds. Also, histograms that were generated suggested that development peaked at some point in the second decade of life and then declined with increasing age. In a study of forty individuals ages 5–19, Bonekamp et al. (2007) showed age-related decreases in the apparent diffusion coefficient of the splenium, but not the genu. Barnea-Goraly (2005) reported

age-related increases in FA and white matter density in the body of the CC using voxel based analyses. More recently, Ashtari et al. (2007) studied twenty-four healthy males, ages 10–20 and found that the older males had significantly higher FA in the splenium compared to younger males.

Although the imaging methods discussed thus far reveal a great deal about the CC's structural maturation, they lack direct information about how these structural refinements relate to the behavioral changes that accompany normal development. Numerous neuropsychological methods have been developed to assess the level of function in various brain regions, including the CC. A fundamental role of the CC, interhemispheric transfer of information, can be assessed in a number of different ways, from simple finger tapping exercises to complex visual hemifield stimulation. It has been suggested that there is both a clear increase in CC utilization throughout development and also increased utilization in children only, based on these behavioral measures (Banich et al., 2000; Marion et al., 2003). It has not been customary to examine the relationship between task performance and brain microstructure in normal development, however some studies have examined these associations in older individuals (Baird et al., 2005; Johansen-Berg et al., 2007; Roebuck et al., 2002; Sullivan et al., 2001). For example, Sullivan et al. (2001) reported correlations between FA and alternating finger tapping performance in a cross-sectional analysis of healthy adults. The group also reported regression analyses in which task performance was predicted by FA and age. In a study of ten healthy adults, Johansen-Berg et al. (2007) found relationships between bimanual coordination and FA of the CC midbody.

The current study uses DTI to investigate white matter changes with age using a cross sectional cohort of preadolescents, adolescents, and young adults. Regions of interest (ROI) were used to evaluate changes in CC white matter microstructure with age and whether these changes were associated with improved motor skills. Gender differences were examined in both task performance and DTI measures. Finally, regression analyses were performed to determine whether task performance could be predicted by age, gender and DTI values that showed age-related maturational changes. It was hypothesized that FA in multiple regions of the CC would correlate positively with age and that finger tapping performance would also improve with increased age. We also expected FA to correlate with bimanual finger tapping performance. We anticipated that MD would show similar, inverse relationships with age and task performance.

Materials and methods

Participants

Ninety-two right-handed adolescents and young adults (47 male and 45 female, aged 9–23 years) were recruited (see Table 1). Two methods for recruiting participants 17-years-old and under were utilized. The first method involved contacting potentially interested families through a participant database maintained by the University of Minnesota's Institute of Child Development (ICD). Participant lists from the ICD are created by sending postcards to families in the Twin Cities metro area after the birth of a child. These postcards ask families if they would be interested in having their child participate in future research studies at the University of Minnesota. Interested families return these postcards with necessary contact information. Their names and contact information are maintained in a database for use by researchers affiliated with the ICD. Our lab has recruited families to participate in previous studies of adolescent development (Hooper et al., 2004). The second method for recruiting minors involved sending postcards to University of Minnesota employees who may have had children in the desired age range. Interested families were directed to call our lab. Young adult participants, aged 18 years and above, were recruited through the use of flyers posted on the University of Minnesota campus.

After briefly explaining the study to potential participants, interested individuals completed a brief phone screening to ascertain eligibility. Exclusion criteria included major physical, neurological, or psychiatric illnesses, alcohol or drug abuse, head injuries resulting in loss of consciousness, mental retardation, learning disabilities, current or past use of psychoactive medications, non-native English speaking, vision and hearing that were not normal or corrected to normal, and MRI contraindications (e.g. metallic implants, severe claustrophobia, braces, etc). All procedures were approved by the University of Minnesota's Institutional Review Board.

Diagnostic Interview

After the successful completion of this phone interview, participants were invited to an in person screening session to verify information that was presented over the phone. The Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) was used to assess for any current or past history of DSM-IV axis I disorder (Kaufman et al., 1997). The presence or absence of DSM-IV disorders was determined later by consensus meetings among trained project staff members, including a clinical psychologist (P.F.C.). General intellectual functioning was assessed with the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). Additionally, handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). Participants who were strongly right-handed were selected for participation.

Behavioral testing

If participants were found eligible after the in person screening session, they were invited to complete an MRI scan and behavioral testing. Behavioral testing was conducted at the University of Minnesota's Center for Neurobehavioral Development and included an alternating finger tapping task (AFT). Other cognitive and personality measures were included in the battery but are not reported upon here.

The AFT was derived from a task previously used by other groups in studies of CC function (Pelletier et al., 1993; Sullivan et al., 2001). In the current study, the AFT was programmed in E-Prime (Psychology Software Tools, www.psnet.com). Three conditions were administered. In the first condition, participants were presented with a screen directing them to use their right index finger to press a response key 30 times as quickly as possible. After the completion of 30 responses, the elapsed time was shown on the computer screen. The second condition was identical, except participants were instructed to press the button with their left index finger. The third condition directed participants to alternate between pressing two different buttons, one with their right index finger and the other with their left index finger. Again, when 30 taps had passed, the elapsed time was presented on the computer screen. These three conditions were presented three times in this order, for a total of nine trials. E-Prime measured and recorded reaction times in milliseconds. Average completion times and standard deviations across the three trials in each condition were computed. A laterality index was calculated by subtracting the average elapsed time for the left hand condition from the average elapsed time for the right hand condition. Consequently, a high score would reflect a large difference in performance between the two hands, suggesting a more lateralized pattern of performance.

MRI data acquisition

Imaging data were acquired on a Siemens 3 Tesla Trio scanner (Erlangen, Germany) at the University of Minnesota's Center for Magnetic Resonance Research. DTI data were acquired axially using a dual spin echo, single shot, pulsed gradient, echo planar imaging (EPI) sequence (TR = 12.5s, TE = 98ms, 64 slices, voxel size = 2×2×2mm, 0mm skip, FOV = 256mm, 2 averages, b value = 1000s/mm²). Thirteen unique volumes were collected to compute the tensor: a b = 0 s/mm² image and 12 images with diffusion gradients applied in 12 non-collinear

directions: $(G_x, G_y, G_z) = [1.0, 0.0, 0.5], [0.0, 0.5, 1.0], [0.5, 1.0, 0.0], [1.0, 0.5, 0.0], [0.0, 1.0, 0.5], [0.5, 0.0, 1.0], [1.0, 0.0, -0.5], [0.0, -0.5, 1.0], [-0.5, 1.0, 0.0], [1.0, -0.5, 0.0], [0.0, 1.0, -0.5], [-0.5, 0.0, 1.0]$. Field maps were acquired and used to correct the DTI data for geometric distortion (TR = 700ms, TE = 4.62ms/7.08ms, flip angle = 90 degrees, voxel parameters identical to the DTI, magnitude and phase difference contrasts).

DTI data processing

The diffusion tensor was computed using the Diffusion Toolbox (FDT) from the FMRIB software library (Smith et al., 2004) (FSL, <http://www.fmrib.ox.ac.uk/>). Each diffusion weighted volume was aligned to the $b = 0$ image using an affine transformation to correct for the distortions caused by eddy currents (Haselgrove & Moore, 1996). The diffusion tensor was derived from the $b = 0$ image and the twelve aligned, eddy current corrected diffusion weighted images. Fractional anisotropy (FA) and mean diffusivity (MD) maps were created from the eigenvalue maps. The DTI $b = 0$ image and the MD and FA maps were corrected for the geometric distortion caused by magnetic field inhomogeneity using FUGUE (FMRIB).

Regions of Interest

The DTI $b = 0$ image was registered to standard space (Montreal Neurological Institute-152 brain) using a 6 parameter (rigid body) fit using FLIRT with trilinear interpolation. The FA and MD maps were subsequently registered to standard space using the same transformation obtained from the previously described step. Six circular regions of interest (13-mm² area) were manually defined on the mid-sagittal slice of the aligned $b = 0$ image; these ROIs included the genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium of the CC (Witelson, 1989). Figure 1 presents a schematic of these regions. ROIs were placed in the center of each callosal region to minimize partial volume effects. Mean FA and MD values were obtained from each ROI using a custom IDL-based program (IDL version 6.0, ITT Visual Information Solutions, Boulder, Colorado). Each ROI was defined by a single trained rater (R.L.M.). Twenty cases were defined twice, and intrarater reliability was found to be acceptable (genu, $r = 0.95$; rostral body, $r = 0.84$; anterior midbody, $r = 0.82$; posterior midbody $r = 0.67$; isthmus, $r = 0.73$; splenium, $r = 0.90$).

Statistical Approach

Data were analyzed using the Statistical Package for the Social Sciences, version 12.0 (SPSS for Windows, 2003). Relationships between age, task performance, and DTI measures in each callosal ROI were examined by calculating Pearson correlations. Because the literature is inconsistent regarding the relationship between gender and CC development, correlations were computed for the entire sample, as well as for males and females separately. In addition to examining age as a continuous variable, univariate analyses of variance (ANOVA) were used to assess performance differences between discrete age and gender groups (presented in Table 1) as well as gender differences in DTI measures in each callosal ROI. ROIs showing significant correlations with age were further evaluated between the age and gender groups described above with univariate ANOVAs. Finally, hierarchical regression analyses were also conducted to assess the contributions of age, gender and FA to task performance, using variables that were significantly correlated with age. An alpha level of .05 was used for all statistical tests.

Results

Sample Demographic characteristics

Table 1 presents the demographic characteristics of the sample. In addition to examining the whole sample, age groups were created that were approximately equivalent in size (ages 9–11, 12–14, 15–17, 18–20, and 21–23). These groups did not differ in gender distribution [χ^2 (4, N

$= 92) = 3.14, p > 0.05]$. Mean full scale IQ (FSIQ) was examined between age and gender groups, revealing a main effect of age group [$F(4,82) = 4.35, p < 0.01$] but not gender [$F(1, 82) = 0.21, ns$] and no interaction between age group and gender [$F(4,82) = 0.92, ns$]. Least significant difference (LSD) post hoc tests indicated that 9–11 year-olds obtained higher IQ scores than every other group. There were no other IQ differences between groups.

Alternated Finger Tapping (AFT)

As shown in Table 2, average elapsed times for the alternating condition and both of the unilateral conditions correlated significantly with age, with average elapsed times decreasing with age. These age-related changes in performance were significant for both males and females. In males, the laterality score also correlated with age, demonstrating that younger males have a greater difference between their right and left-hand completion times. In females, the laterality score was unrelated to age. Table 3 presents means and standard deviations for task performance in males versus females.

A univariate ANOVA to examine group differences in performance on the alternating condition revealed a main effect of age group [$F(4,82) = 4.07, p < 0.01$] and a main effect of gender [$F(1,82) = 11.04, p = 0.001$], but no interaction between age group and gender [$F(4,82) = 0.01, ns$]. LSD post hoc analyses showed differences were between the 9–11 year-olds and the 18–20 year-olds and 21–23 year-olds, with the youngest group performing slower. Similarly, on the right-hand condition, there was a main effect of age group [$F(4,82) = 5.72, p < 0.001$], a main effect of gender [$F(1,82) = 10.88, p = 0.001$], but no interaction between age group and gender [$F(4,82) = 0.11, ns$]. LSD post hoc tests indicated the 9–11 year-olds performed slower than every other group. For the left-hand condition, there was also a main effect of age group [$F(4,82) = 9.04, p < 0.001$], a main effect of gender [$F(1,82) = 10.92, p = 0.001$], but no interaction between the two [$F(4,82) = 0.56, ns$]. Again, LSD post hoc tests showed the 9–11 year-olds performed slower than every other group and that the 12–14 year-olds performed slower than the 18–20 and 21–23 year-olds. Males outperformed females with significantly faster completion times in each of the three conditions. No differences were observed between males and females for the laterality score (see Table 3), however there was a main effect of age group [$F(4,82) = 3.13, p < 0.05$]. LSD post hoc analyses showed the differences were between the 9–11 year-olds and the 18–20 and 21–23 year-olds, and also between the 12–14 year-olds and the 18–20 and 21–23 year-olds. Because there were age group differences in FSIQ, these analyses were re-done entering FSIQ as a covariate. The pattern of significant findings was unchanged when covarying for FSIQ.

DTI Findings

Correlation coefficients were computed to associate age with FA in each ROI. A significant positive correlation was observed between age and FA in the splenium, suggesting an age related increase in white matter development of the splenium in young children and adolescents (see Figure 2). A similar (but negative) relationship was observed between mean MD in the splenium and age. Correlational analyses with age did not change in terms of the overall pattern of significant findings when males and females were analyzed separately. Mean FA and MD in the other regions of the CC did not correlate significantly with age (see Table 4). Because age and splenium FA and MD were found to be significantly related, group differences were further examined. Univariate tests showed a main effect of age group for FA in the splenium [$F(4,82) = 3.656, p < 0.01$]. LSD post hoc tests showed the differences were between the 9–11 year-olds and the 18–20 and 21–23 year-olds, the 12–14 year-olds and the 18–20 year-olds, and the 15–17 year-olds and the 18–20 year-olds. There was no main effect of gender or interaction between age group and gender. Similar effects were observed with MD in the splenium. Patterns of overall significance did not change with FSIQ entered as a covariate. No differences in FA or MD were found between males and females in any region of interest.

DTI & Task Performance

Next, we considered whether age-related changes in CC FA and MD were associated with AFT performance. Mean FA in the splenium showed significant negative correlations with the left-hand and alternating elapsed time conditions of the AFT task. Higher FA was associated with faster left-handed and alternating performance (see Table 5). Similar correlations were observed with MD in the splenium. Neither right-hand performance nor the laterality score correlated significantly with DTI measures in any region of the CC. No other regions of the corpus callosum showed a significant relationship between FA or MD and performance on the AFT task, when examining both males and females together. Separate correlational analyses for males and females revealed significant relationships that were not present in the full sample. For example, correlations observed in the full sample were generally stronger in males only and were reduced or absent in females. Additionally, left-hand, right-hand, and alternating performance on the AFT correlated significantly with FA and MD in the genu of males, but showed no significant correlations in females.

Regressions—Because of the apparent impact of gender on task performance, multiple linear regression analyses were conducted to isolate the individual contributions of age, gender and FA to task performance. Hierarchical regressions were run with AFT task variables that were strongly correlated with CC FA. The AFT conditions were entered as the dependent variables. Predictors included age entered in the first step, gender added in the second step, and FA for each CC ROI in the final step. The right hand and left hand performance variables were not predicted by this model. However, the alternating condition of the AFT was predicted significantly by age, gender and splenium FA (see Table 6). This model accounted overall for 32% of the variance in performance.

Discussion

The current study examined white matter microstructural development of the corpus callosum in healthy children, adolescents and young adults using diffusion tensor imaging. Relationships between measures of white matter microstructure, age, gender and behavioral performance on a bimanual finger tapping task were investigated. These relationships were further evaluated with hierarchical regression analyses using age, gender and FA to predict bimanual task performance. Negative correlations between age and unilateral and bimanual finger tapping were observed, with younger participants performing significantly slower than older participants. Non-dominant (left-hand) performance exhibited stronger relationships with age, compared to both dominant-hand and alternating performance. The age-performance relationships found in this study have been attributed to maturation of the CC in previous behavioral studies (Marion et al., 2003). The stronger relationship between non-dominant-hand performance and age has been previously explained by increased non-dominant hemisphere involvement in generating motor responses. It has been proposed that left-hand innervations in right-handed individuals require additional motor signaling from the left hemisphere, thereby potentially increasing the amount of interhemispheric communication between the left and right motor cortices (Marion et al., 2003). In our dataset, these findings were also confirmed by univariate ANOVAs that indicated an asymptote in right-handed and alternating performance after age 11 but continued development of left-handed performance until at least age 15. This continued development also impacted the laterality score, which similarly showed evidence of development until age 15. These patterns were also found to be independent of FSIQ.

Age was correlated with white matter microstructure, with older individuals showing increased white matter integrity in the splenium. Our between-groups comparisons suggested that white matter integrity in the splenium continues to develop until 18 years of age. Similar age-related

changes in human splenium composition have been reported elsewhere, in terms of both area (Giedd et al., 1999; Thompson et al., 2000) and microstructural integrity (Bonekamp et al., 2007; Li & Noseworthy, 2002; Snook et al., 2007). Increases in midsagittal area of the CC seems to be related more to increased myelination rather than increased axonal density (Aboitiz et al., 1992; LaMantia & Rakic, 1990). Increased axonal myelin in the splenium is consistent with findings of increased splenium white matter volume in conventional MRI studies and increased splenium FA in DTI studies. Topographical studies of the CC have shown that the splenium is primarily responsible for the transmission of interhemispheric signals from the occipital lobes, and to a lesser extent the temporal and parietal lobes (Schmahmann & Pandya, 2006). The developmental relationship between age and FA of the splenium, but not other CC regions, is thus somewhat surprising, given that the occipital lobes have been reported to be nearly developed early in childhood (Huttenlocher, 1990; Lippe et al., 2007).

FA in the splenium in both males and females correlated significantly with alternating-hands performance, and also with left-hand performance in males only. Subsequent regression analyses indicated that when age and gender were controlled, alternating-hands performance was predicted significantly by splenium FA, indicating that individual differences in splenium white matter structure directly influenced the speed of bimanual motor coordination. The midbody of the CC has been shown to topographically interconnect cortical regions involved in motor innervation (Barnea-Goraly et al., 2005; Johansen-Berg et al., 2007), and the present study found moderate correlations between bimanual task performance and anterior midbody white matter microstructure, in males only. Males also showed a significant correlation between genu FA and performance in all three finger tapping conditions. Although no overall gender differences were observed in FA or MD of the CC, males and females differed significantly in task performance as well as in the strength of associations between task performance and FA. It is possible these differences are driven by gender differences in pubertal timing, with females (who tend to show earlier pubertal timing as compared to males) showing earlier development of the anterior CC.

Although it is possible to view excitatory and inhibitory actions at the neural level within the CC, these actions can also be viewed at the functional level (Bloom & Hynd, 2005). Increased interhemispheric signaling has been thought of as being either constructive (excitatory), when both hemispheres collaborate on specific goals or destructive (inhibitory), when hemispheric dominance is apparent. Inhibitory regulation mediated by transcallosal fibers can benefit from increased callosal size (Muller-Oehring et al., 2007) and it may also be the case that increased microstructural integrity in the CC enhances these inhibitory effects. Meaningful inhibitory controls likely require competent cortical systems to initiate the signal as well as an intact CC to propagate the signal to the contralateral hemisphere. A structurally defective or immature CC may create a bottleneck for interhemispheric information transfer, leading to dysregulated patterns of communication with the contralateral hemisphere. Callosal inhibitory control in the developing brain may be of particular interest when evaluating performance on various behavioral measures in relation to CC integrity. Although the task used in the current study was not designed to interpret inhibitory functions of the CC, our age-related findings demonstrate that care must be exercised when interpreting developmental behavioral and brain changes in the context of CC inhibitory control.

This study adds to the current literature in two distinct ways: 1) it examined a large sample with ages 9–23 all being well represented and 2) it examined relationships between task performance and white matter microstructure. With the large sample in this study, it was possible to examine age relationships in a continuous fashion with FA and MD of the CC. Previous literature has provided detailed developmental analyses of white matter microstructure and performance on fine motor tasks within separate neuroimaging and behavioral studies, whereas the current study demonstrated direct relationships between CC

white matter microstructure development and fine motor skills in childhood and adolescence. To our knowledge, this is the largest DTI study in this age range that shows developmental trends in CC microstructure, and the first to show bimanual task performance correlates of CC microstructure in children and adolescents. The ability to demonstrate relationships between task performance and underlying white matter microstructure has expanded the utility of diffusion tensor imaging however this utility has been taken one step further, with the incorporation of task, DTI and fMRI all in the same session. Baird et al. (2005) used both DTI and fMRI to assess cortical connectivity in fifteen adults. Regions of interest in left and right parietal and frontal cortices were defined and the group was able to show that both a decrease in blood oxygenated level dependent (BOLD) response within the cortical ROIs and faster reaction times on a picture recognition task were associated with higher FA in the splenium of the CC. Moreover, higher BOLD response in the same ROIs and longer reaction times were associated with increased FA in the genu of the CC. These results suggest longer compute time is associated with higher activation in frontal cortices, as well as stronger connectivity between these frontal cortices. Similarly, shorter compute time and decreased cortical activation is linked to stronger connectivity between the association areas. This concomitant use of DTI and fMRI will undoubtedly provide additional insight into the underlying changes associated with adolescent brain development.

The developmental findings reported here are limited by the use of a cross-sectional dataset for age analyses. Additionally, other reports have suggested that the CC continues to develop into the third decade of life (Pujol et al., 1993), indicating the need for a more comprehensive age sampling than we have accomplished to date. However, we are retesting all participants in this study two years after their initial enrollment, and by combining longitudinal and cross-sectional designs we will achieve a more comprehensive understanding of white matter development and its effects on behavior.

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Figure 1. The corpus callosum divided into six subregions

A T1 image is used for illustration only. Actual ROIs were defined on the $b = 0$ image. 1. genu; 2. rostral body; 3. anterior midbody; 4. posterior midbody; 5. isthmus; 6. splenium.

Figure 2. Scatter plots showing the relationships between age and mean FA and MD as measured in the splenium.

Table 1

Sample Characteristics: Age and Gender Frequencies

Age (years)	9–11	12–14	15–17	18–20	21–23
Total (n = 92)	18	14	20	27	13
Females (n = 45)	10	5	9	16	5
Males (n = 47)	8	9	11	11	8
Mean (SD) Task and DTI Values*					
Full Scale IQ	124.06 (10.87)	110.57 (7.86)	113.30 (11.22)	115.96 (9.07)	115.15 (6.68)
AFT Right-Hand	5813.30 (801.06)	5180.07 (749.90)	4799.37 (782.85)	4925.09 (785.07)	4672.46 (721.81)
AFT Left-Hand	6666.68 (940.92)	6014.62 (1395.95)	5519.63 (864.26)	5344.91 (789.14)	4956.85 (610.82)
AFT Alternating	4458.26 (1017.36)	3933.00 (763.41)	4019.83 (1199.09)	3521.07 (759.12)	3444.41 (539.70)
Laterality Score	853.39 (759.72)	834.55 (966.89)	720.27 (585.99)	419.82 (386.99)	284.39 (418.78)
Splenium FA ($\times 10^{-3}$)	775.73 (59.73)	793.05 (59.97)	794.30 (80.37)	841.39 (55.17)	831.94 (47.50)
Splenium MD ($\times 10^{-6}$ mm ² /s)	808.92 (93.66)	759.26 (96.22)	776.16 (128.83)	713.41 (86.14)	723.02 (82.36)

* AFT values in milliseconds (ms)

Table 2

Pearson correlations between age and alternating finger tapping task performance.

	Total Sample (n = 92)		Males (n = 47)		Females (n = 45)	
	r	p	r	p	r	p
Right-Hand	−0.423	<0.0001	−0.433	0.002	−0.448	0.002
Left-Hand	−0.523	<0.0001	−0.597	<0.0001	−0.496	0.001
Alternating	−0.382	0.0001	−0.441	0.002	−0.396	0.01
Laterality Score *	0.306	0.003	0.391	0.007	0.233	0.12

* The laterality score is the left hand-right hand difference, as described in the text.

Table 3

Gender differences in AFT task performance.

	Males (n = 47)		Females (n = 45)		Group Effects	
	Mean (ms)	SD	Mean (ms)	SD	F(df)	p
Right-Hand	4800.84	703.6	5360.60	909.1	10.881(1.82)	0.001
Left-Hand	5392.65	910.9	5997.66	1149.0	10.934(1.82)	0.001
Alternating	3559.86	764.5	4183.12	1039.3	11.038(1.82)	0.001
Laterality Score	591.81	611.3	637.05	701.0	0.635(1.82)	0.428

Table 4

Pearson correlations between age and DTI measures of Corpus Callosum ROI's.

Region of Interest	All (n = 92)		Males (n = 47)		Females (n = 45)	
	r	p	r	p	r	p
<i>Fractional Anisotropy</i>						
Genu	0.097	0.36	0.005	0.97	0.207	0.17
Rostral Body	0.002	0.99	-0.008	0.96	0.004	0.98
Anterior Midbody	0.001	0.99	0.030	0.84	-0.043	0.78
Posterior Midbody	0.050	0.64	0.019	0.90	0.084	0.58
Isthmus	-0.072	0.49	-0.109	0.47	-0.024	0.88
Splenium	0.348	0.001	0.362	0.013	0.345	0.02
<i>Mean Diffusivity</i>						
Genu	-0.068	0.52	-0.004	0.98	-0.137	0.37
Rostral Body	-0.049	0.64	0.035	0.82	-0.121	0.43
Anterior Midbody	-0.007	0.95	0.007	0.96	-0.014	0.93
Posterior Midbody	-0.015	0.89	0.012	0.93	-0.040	0.80
Isthmus	0.042	0.69	0.056	0.71	0.023	0.88
Splenium	-0.305	0.003	-0.36	0.013	-0.253	0.094

Table 5

Pearson correlations between task performance and FA of Corpus Callosum ROI's.

	Total (n = 92)		Males (n = 47)		Females (n = 45)	
	r	p	r	p	r	p
<i>Right-Hand</i>						
Genu	-0.156	0.14	-0.377	0.009	0.095	0.536
Rostral Body	-0.137	0.19	-0.248	0.092	0.045	0.771
A. Midbody	-0.188	0.07	-0.303	0.039	0.004	0.980
P. Midbody	-0.009	0.93	-0.044	0.767	0.068	0.658
Isthmus	0.046	0.66	0.061	0.684	-0.078	0.612
Splenium	-0.154	0.14	-0.281	0.056	-0.131	0.390
<i>Left-Hand</i>						
Genu	-0.150	0.15	-0.428	0.003	0.164	0.281
Rostral Body	-0.113	0.28	-0.346	0.017	0.168	0.269
A. Midbody	-0.189	0.072	-0.315	0.031	0.008	0.958
P. Midbody	-0.008	0.94	-0.085	0.570	0.105	0.491
Isthmus	0.007	0.94	0.036	0.809	-0.122	0.425
Splenium	-0.211	0.043	-0.385	0.008	-0.134	0.380
<i>Alternating</i>						
Genu	-0.231	0.027	-0.436	0.002	-0.024	0.877
Rostral Body	-0.234	0.025	-0.189	0.203	-0.203	0.181
A. Midbody	-0.264	0.011	-0.295	0.044	-0.181	0.233
P. Midbody	-0.075	0.479	-0.145	0.329	0.020	0.894
Isthmus	-0.076	0.473	-0.163	0.275	-0.126	0.411
Splenium	-0.336	0.001	-0.409	0.004	-0.391	0.008

Table 6
Summary of Hierarchical Regression Analysis for Variables Predicting the Alternating condition of the AFT (n = 92)

Step and Variable	B	Std. Error	β	p
Step 1				
Age	-89.32	22.792	-0.382	<0.001
Step 2				
Age	-87.56	21.523	-0.374	<0.001
Gender	606.45	175.16	0.319	0.001
Step 3				
Age	-65.17	22.109	-0.279	0.004
Gender	662.13	169.52	0.348	<0.001
Splenium FA	-3.95	1.37	-0.273	0.005

Note: $R^2 = 0.146$ for step 1 ($p < 0.001$), $\Delta R^2 = 0.101$ for step 2 ($p = 0.001$), and $\Delta R^2 = 0.065$ ($p = 0.005$) for step 3. The total R^2 was 0.312.