



Inter-parietal white matter development predicts numerical performance in young children

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ABSTRACT

In an effort to understand the role of interhemispheric transfer in numerical development, we investigated the relationship between children's developing knowledge of numbers and the integrity of their white matter connections between the cerebral hemispheres (the corpus callosum). We used diffusion tensor imaging (DTI) tractography analyses to test the link between the development of the corpus callosum and performance on symbolic and non-symbolic numerical judgment tasks. We were especially interested in the interhemispheric connections of parietal cortex in 6-year-old children, because regions of parietal cortex have been implicated in the development of numerical skills by several prior studies. Our results revealed significant structural differences between children and adults in the fibers of the corpus callosum connecting the left and right parietal lobes. Importantly, these structural differences were predictive of individual differences among children in performance on numerical judgment tasks: children with poor numerical performance relative to their peers exhibited reduced white matter coherence in the fibers passing through the isthmus of the corpus callosum, which connects the parietal hemispheres.

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1. Introduction

The corpus callosum is the largest white matter structure in the brain and functions to coordinate information between the cerebral hemispheres (see Gazzaniga, 2000 for review). It is a critical structure for sensory and motor integration (e.g., Eliassen, Baynes, & Gazzaniga, 1999) and it is also an important component of the neural networks recruited during higher-order cognitive processes including comparison (e.g., Brown, Jeeves, Dietrich, & Burnison, 1999), executive function (Bookstein, Streissguth, Sampson, Connor, & Barr, 2002), attention (Dorion et al., 2002), and language (Dougherty et al., 2007; McDonald, Crosson, Valenstein, & Bowers, 2001). Here, we examine the role of the corpus callosum in predicting performance on numerical judgment tasks. In particular, we ask whether the development of interhemispheric transfer in parietal cortex (via the fibers traversing the isthmus of the corpus callosum) is related to mastery of numerical skills in children, since parietal cortex is known to play a critical role in adult numerical cognition (see Dehaene, Piazza, Pinel, & Cohen, 2003 for review).

Abnormalities in the structure of the corpus callosum have been linked to a broad set of developmental disorders. Morphological

abnormalities in the shape and size of the corpus callosum have been found in children with autism, schizophrenia, ADHD, and dyslexia (e.g., Egaas, Courchesne, & Saitoh, 1995; Hynd et al., 1995; see Bloom & Hynd, 2005 for review). Recent evidence has further established the link between the structural development of the corpus callosum and the development of cognitive functioning. For example, 18- to 40-month-old children with mental retardation due to generalized developmental delay exhibit reduced white matter volume in the corpus callosum relative to typically developing children (Cascio, Gerig, & Piven, 2007). A recent study with typically developing older children has also identified a link between the corpus callosum and general intelligence: children with higher IQ have significantly thicker callosal tracts than children with low IQ, independently of overall brain size (Luders et al., 2007). These data suggest that the corpus callosum may be a key substrate driving individual differences in cognitive development. Another recent study has found that the size of the corpus callosum correlates with lateralization of language development in children (Josse, Seghier, Kherif, & Price, 2008), indicating that asymmetries in brain function vary over development and correlate with corpus callosum development.

Coordination between hemispheres is likely an important feature of numerical processing. Brain imaging studies of adults engaged in numerical comparison tasks typically show bilateral intraparietal sulcus (IPS) activation (see Dehaene et al., 2003). Bilateral IPS activation is not critical, however, because neuropsychological studies of corpus

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callosotomy patients demonstrate that adults are able to make numerical comparisons of Arabic numerals, number words, and dot arrays within either hemisphere (Colvin, Funnell, & Gazzaniga, 2005). And, although basic numerical computations in adulthood appear to recruit both hemispheres in fMRI studies, studies of numerical cognition in children suggest that hemispheric asymmetries in parietal cortex may be quite pronounced early in development (Ansari & Dhital, 2006; Ansari, Garcia, Lucas, Hamon, & Dhital, 2005; Cantlon, Brannon, Carter, & Pelphrey, 2006; Rivera, Reiss, Eckert, & Menon, 2005). For example, 4-year-old children exhibit more strongly right lateralized BOLD activity in the IPS than adults during non-symbolic numerical comparisons of arrays of dots (Cantlon et al., 2006). Older children (7- to 9-year-olds) also display right-lateralized IPS activity when comparing small Arabic numerals (i.e., digits 1 to 9; Holloway & Ansari, 2009). However, when comparing large Arabic numerals that are not highly familiar, the same-age children exhibit greater activity in the left parietal hemisphere (Cantlon, Libertus, et al., 2009) and a similar left-hemisphere bias has been reported for adult corpus callosotomy patients who are asked to complete difficult numerical computations with large numbers (Funnell, Colvin, & Gazzaniga, 2007).

Children are equipped with the ability to represent number non-verbally from an early age however, their ability to understand, compare and manipulate numerical symbols such as written number words and digits is gradually acquired between 4 years of age and mid- to late-childhood.

For example, adults perform symbolic numerical comparisons more accurately than and almost twice as quickly as 6- to 7-year-old children (e.g., Girelli, Lucangeli, & Butterworth, 2000; Temple & Posner, 1998). Additionally, for children, digits do not automatically call up their meanings. Unlike adults, children only begin to show Stroop interference and automatic representation of Arabic numerals and number words at 8 or 9 years of age (e.g., Girelli et al., 2000). Thus, there are a number of important cognitive changes that occur between early childhood and adulthood in numerical processing. The functional and structural changes that support numerical development at the neural level are less clear.

Structural analyses of human white matter development *in vivo* have revealed that development of white matter typically increases steadily throughout the brain between 4 and 20 years of age following a trajectory from a rostral–lateral–ventral pole to a dorsal–medial–caudal pole (Giedd et al., 1996; Giedd et al., 1999; see Toga, Thompson, & Sowell, 2006 for review). These changes can occur in a number of different microstructural features: the number and size of axons, the common orientation of axons, brain water content, membrane density, glial population, and the myelination of axons (see Neil, Miller, Mukherjee, & Huppi, 2002 for review). All of these features are important for the integrity of information transmission throughout the brain.

Diffusion tensor imaging (DTI) measures both the direction and degree of water diffusion along an axis (see LeBihan, 2003 for review). Due to the coherent organization of neural fibers in the fatty white matter, water diffuses in a highly directional or, *anisotropic*, manner along the axis of a white matter tract. Consequently, brain regions that reflect high degrees of anisotropic water diffusion signify the location of a robust white matter tract. *Fractional anisotropy* (FA) is a scalar quantity that represents the degree to which water diffuses in a common direction at a particular location (see Mori & Zhang, 2006). On the basis of the FA index, several recent studies with children have demonstrated that white matter coherence in specific brain regions can yield important predictions about cognitive and brain functioning (Beaulieu et al., 2005; Dougherty et al., 2007; Nagy, Westerberg, & Klingberg, 2004; Olesen, Nagy, Westerberg, & Klingberg, 2003; Schmithorst et al., 2005).

However, in contrast to the more common scalar, volumetric techniques, fiber-based tractography analyses use information from the tensor field to infer both the degree of anisotropic water diffusion (e.g., FA) and the specific direction of diffusion. Tractography analyses

compute diffusion trajectories through a 3-dimensional image following the path with the greatest common diffusion (i.e., longest eigenvector) between pre-defined source and target regions (Mori & van Zijl, 2002). Since this method provides information about both the intensity and direction of diffusion, it presents an opportunity to track specific white matter pathways through the brain.

In the current study, we used fiber-based tractography to examine the integrity of the corpus callosum in adults and young children (6- to 7-year-olds) as a correlate of behavioral performance on a basic cognitive task: numerical comparison. We used correlation analyses to test the relationship between measures of corpus callosum development and performance on the numerical tasks.

We examined the white matter integrity of the corpus callosum in three regions of interest: the genu (prefrontal), isthmus (superior parietal), and splenium (occipito-temporal). The superior parietal fibers were selected to test our hypotheses that inter-parietal connectivity influences numerical performance. Callosal tracts of the prefrontal hemispheres were selected because frontal regions also exhibit age-related changes in the degree to which they are engaged during numerical tasks (e.g., Ansari et al., 2005; Cantlon, Libertus, et al., 2009; Rivera et al., 2005). The fibers traversing the splenium were selected as a control tract.

2. Methods

2.1. Subjects

Eighteen children (6.89 ± 0.62 years, 9 male) and 14 adults (23.2 ± 3.06 years, 9 male) with normal or corrected vision participated in the experiment. None of our participants had any history of psychiatric disorder. The study met criteria for approval from the Duke University Institutional Review Board. Written informed consent was obtained from each adult participant and from the parent or guardian of each child. Children and adults were recruited from the Durham, North Carolina community.

2.2. Task

All participants completed the same numerical judgment task inside the MRI scanner, prior to the DTI scan (Fig. 1). On each trial, participants were required to identify the larger of two numerical values on a computer screen. Participants responded by pressing a joystick button corresponding to the side of the selected numerical value (left or right). The response window in which subjects could make their choice was two seconds. An image of a sun followed correct responses while a black screen followed incorrect responses and failures to respond within the two-second response window. Each run lasted six minutes (72 trials), and participants completed four runs. Two of the runs required participants to judge Arabic numerals (Symbolic condition) and the remaining two runs tested numerical judgments of dot arrays (Non-symbolic condition). The numerical values were identical in the two conditions and the values ranged from 2 to 56. The specific numerical pairs tested were identical in the symbolic and non-symbolic conditions and included all pairs that formed either a 0.5 ratio or a 0.8 ratio when dividing the smaller by the larger value (rounded to the nearest tenth). Participants' accuracy and reaction time were recorded for each trial. During data analysis, subjects' accuracies were averaged for each ratio and then those accuracies were averaged to create an overall average of accuracy for the symbolic and non-symbolic conditions for each subject.

2.3. DTI acquisition and preprocessing

Scanning was completed on a GE Signa EXCITE HD with 40-mT/m gradients at 150 T/m/s slew rate at the Duke University Medical Center. The DT-MRI dataset was based on a single-shot EPI sequence

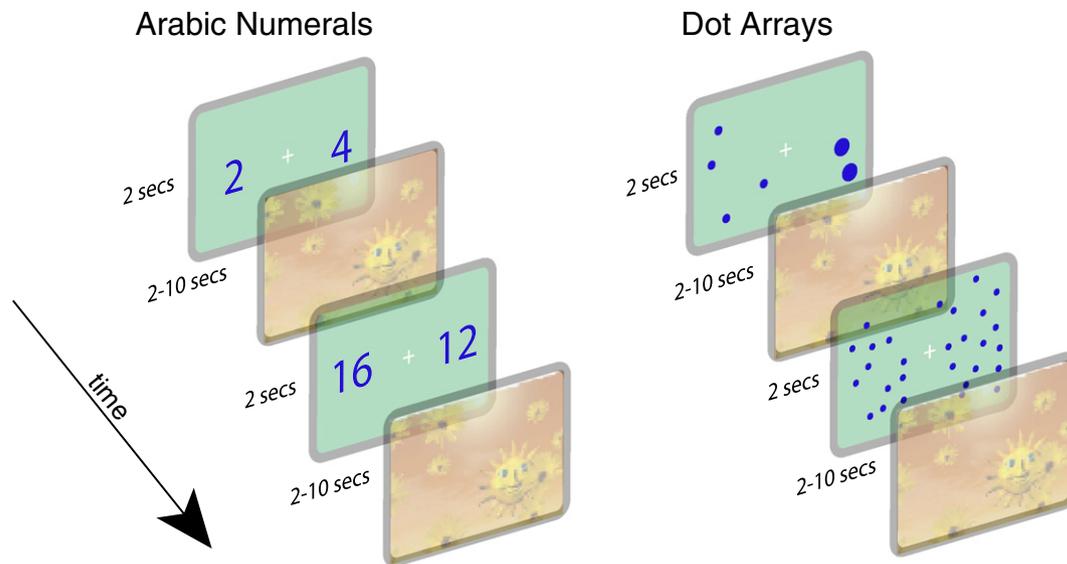


Fig. 1. The experimental task was to press a joystick button corresponding to the side of the screen with the larger numerical value. Subjects completed a Symbolic version of this task with Arabic numeral stimuli and a Non-symbolic version with arrays of dots as stimuli. Correct responses resulted in a reward screen: a picture of a bright sun and incorrect responses resulted in a black screen. Each trial was a maximum of 2 s after which the program would advance to the next trial.

(TE = 86 ms, TR = 17,000 ms, 50 contiguous slices of 2.0 mm thickness, FoV = 256×256 mm², matrix size 128×128 , voxel size $2 \times 2 \times 2$ mm, 1 non-diffusion weighted scan (b -value = 1000 s/mm²), 15 diffusion-sensitizing directions, 960 total images, total scan time approx. 5 min). Non-brain and ambient noise were removed from the diffusion weighted images using the Brain Extraction Tool (BET; Smith, 2002). An internally developed Matlab script condensed the 960 Dicom images into sixteen diffusion weighted images (DWIs). These DWIs were eddy-corrected and used to determine diffusion tensors in the computer program DTI Track 2005 (Pierre Fillard). Tensor construction was based on the fit of the tensor model to the diffusion data. Three eigenvectors, or diffusivities, ($\lambda_1 > \lambda_2 > \lambda_3$) were generated by diagonalization of the tensor. These voxel-specific eigenvectors represent the diffusivities throughout the three directions of the tensor and were the foundation of the diffusion properties investigated in our study.

2.4. Identification of seed and target regions

Seed and target brain regions were traced on subjects' anatomical images in order to narrow the scope of the fiber tracking algorithms to specific regions of interest (ROIs). The computer program ITK/SNAP (Yushkevich et al., 2006) was used to trace the corpus callosum (seed region) and the target ROIs for each subject. We defined our seed region as the midsagittal plane of the corpus callosum (white matter) and the target tracts were defined as those crossing the two sagittal slices adjacent to the midsagittal plane into cortex. Thus, to be included in our analysis, a tract had to cross the midsagittal plane of the corpus callosum and radiate out of the corpus callosum into cortex. We identified the subsections of the corpus callosum using an atlas. The Witelson method (1989) was used for the subdivision of the corpus callosum. The target region for the splenium-parietal fibers was the isthmus of the corpus callosum, and was located on 3–5 sagittal slices, using the presence of the body of the corpus callosum in the axial view as a superior boundary, and the top of the lateral ventricle as an inferior boundary. Anatomical borders for source regions were two parasagittal planes, 6–8 sagittal slices from the axial midline, including the parietal lobe posterior to the postcentral gyrus and anterior to the occipital-parietal sulcus. To isolate fibers connecting the splenium and parietal lobe, tract estimation was constrained to exclude any fibers terminating outside these borders. The central sulcus was used as a reference point for the placement of segmentation regions, and a diffusion atlas (Scarabino

et al., 2006) provided further anatomical guidelines for locating the tracts of interest and corresponding gray matter target ROIs.

2.5. Fiber tracking

The construction of fiber tracts was completed using FiberTracking software (UNC Chapel Hill). A fractional anisotropy (FA) map was computed for each subject using his or her tensor data and the traced seed and target regions. The three-dimensional fiber tracts were then constructed for each ROI using an edge-step algorithm that generated each tract on a voxel-by-voxel basis by continuously following the direction of greatest diffusivity in each voxel between the seed and the target ROIs (see above). An FA threshold was set at 0.2, and a curvature threshold (angle between the first eigenvector and the eigenvector in the next voxel) was set to 40°. The three fiber tracts (traversing the genu, splenium, and isthmus) were then evaluated according to a priori knowledge of adult tract organization (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004), and edited in FiberViewer 1.2.3 (Gerig, Gouttard, & Courouge (2004)) to remove outlier fibers that are a common artifact of the tracking algorithms used in tractography. Grouping algorithms were applied to refine tracts into fiber bundles that maintained directional coherence and common length. Thresholds cutting off the lower and upper bounds of fiber length were determined using a histogram of fiber lengths for each tract. The lower and upper threshold values were set at 50 and 150, respectively. This analysis technique yielded fiber tracts representing callosal pathways through the genu, isthmus, and splenium that closely paralleled the representations of Scarabino et al., (2006) and a validated DTI tractography atlas (Wakana et al., 2007). The average number of fibers in the entire cortex was 920 for adults and 715 for children (adult SD = 250 fibers, child SD = 400 fibers). The average number of fibers crossing the isthmus was similar for both children and adults (adults: mean = 243, SD = 106, child: mean = 232 SD = 85). Mean fiber length in the isthmus tract was about 90 mm for both adults and children.

Diffusion properties, including FA, axial (λ_1) and radial diffusivity ($(\lambda_2 + \lambda_3)/2$) were computed and evaluated at points along the cross section of each bundle of fiber tracts. Axial diffusivity occurs parallel to the primary direction of diffusivity, while radial diffusivity occurs perpendicular to the maximum (or, primary) diffusivity direction.

2.6. DTI and behavioral analyses

Structural DTI analyses measured FA, axial diffusivity, and radial diffusivity for the three ROIs (prefrontal/genu, parietal/isthmus, and occipitotemporal/splenium) in each participant. These analyses were conducted over the middle 50 mm of each tract as well as for smaller 5 mm subsections of each tract, including the midpoint, as described in the Results. Each tract was aligned at the mid-sagittal plane across subjects for group comparisons. Statistical contrasts were computed to quantitatively compare these structural measures between adults and 6-year-old children. These analyses are described in Results. Behavioral analyses were completed using regression analyses relating the diffusivity measurements in each ROI to the behavioral data for each participant. Reaction time and accuracy, both overall and separated by numerical notation (Arabic numerals or Dot Arrays), were the behavioral measures of interest.

3. Results

Our analyses revealed structural differences between children and adults in the interhemispheric white matter tracts connecting parietal and occipito-temporal cortices (i.e., through the isthmus and splenium). In addition, we found a relationship between behavioral performance on the numerical judgment tasks and white matter coherence in the superior parietal tract of the corpus callosum (isthmus) but not in the prefrontal (genu) or occipito-temporal tracts (posterior splenium). We describe these results in detail below.

3.1. Age-related structural differences

We compared the FA values along occipito-temporal (splenium), superior parietal (isthmus), and prefrontal (genu) callosal tracts to determine whether adults exhibited significantly greater white matter content than children in these regions. Fig. 2 shows the locus of each tract in a sample 6-year-old child. A repeated measures ANOVA comparing Group (Adults, Children) \times Tract (Genu, Isthmus, Splenium) \times Hemisphere (Left, Right) revealed a main effect of Group ($F(1,90) = 47.9, p < 0.001$), a main effect of Tract ($F(2,90) = 19.8, p < 0.001$), and a marginally significant main effect of Hemisphere ($F(1,90) = 3.36, p = 0.07$). None of the interactions were significant. The majority of the differences between children and adults were in tracts traversing the isthmus and splenium and there were greater differences in the left hemisphere than the right (Fig. 3). To validate this observation, we compared FA values at a regional level for each tract, averaging across lengths of 5 mm (FDR corrected $\alpha = 0.05$). Children exhibited significantly lower FA than adults at a small 5 mm length of the fibers traversing the left lateral genu and much larger extents (10–15 mm) of the left, right, and mid isthmus and splenium. Significant differences

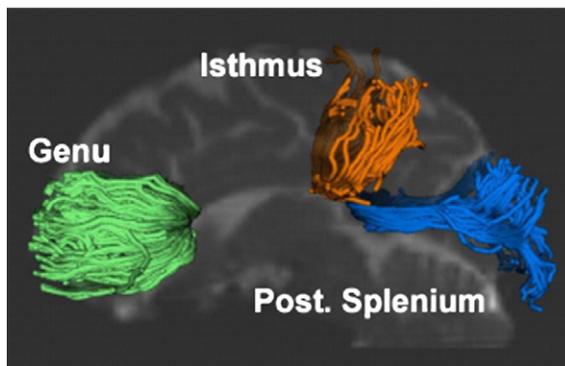


Fig. 2. The three tracts of the corpus callosum that were analyzed in the current study: fibers that crossed the genu (prefrontal cortex), the isthmus (superior parietal cortex), and the splenium (occipital cortex). Tracts are shown for a representative child subject.

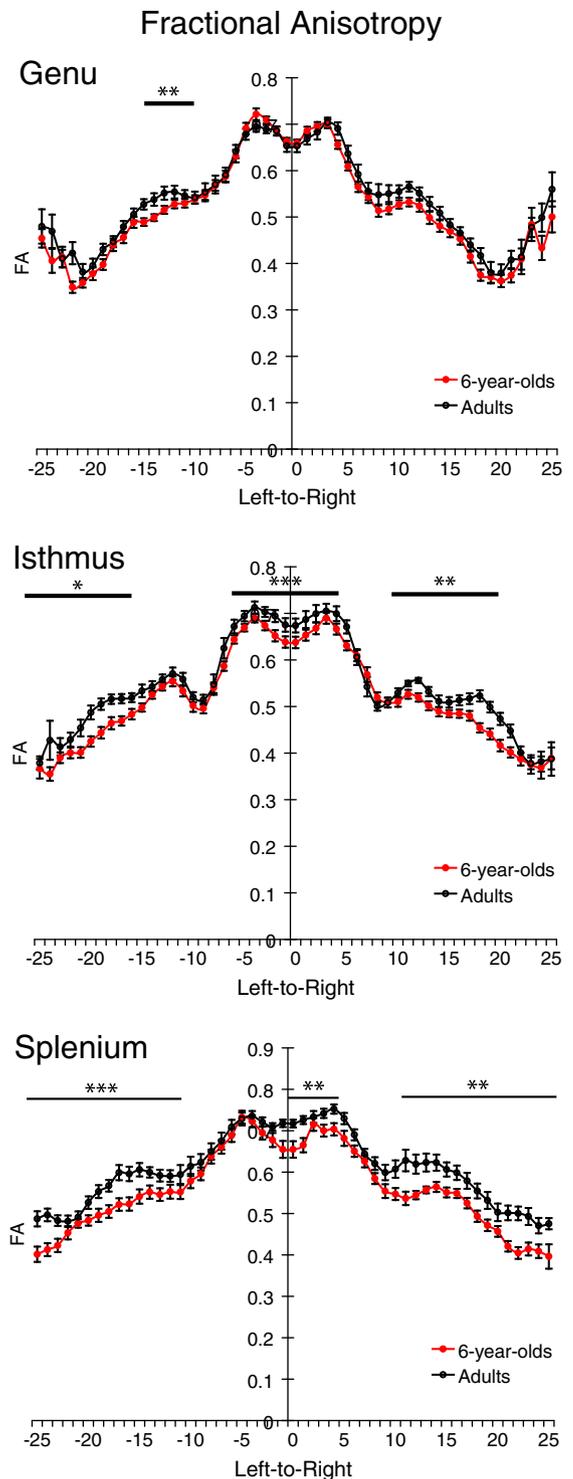


Fig. 3. Fractional anisotropy (FA) values for the fibers that traversed the genu (top), isthmus (middle), and splenium (bottom). The x-axis is left-to-right position in millimeters and the y-axis is the FA value. Children are shown in red and adults in black. Difference between children and adults are highlighted with black bars at the top of each panel (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; FDR corrected $\alpha = 0.05$). SEM is shown by error bars.

between children and adults along those tracts are highlighted in Fig. 3. These results are consistent with prior studies showing that corpus callosum growth continues throughout the tract during early and late childhood but exhibits the greatest growth in more posterior sections (Rajapakse et al., 1996). One possible explanation of the more

prolonged and dramatic growth in the more posterior callosal fibers is that these axons ultimately become more myelinated than those in anterior regions (Aboitiz, Lopez, & Montiel, 2003).

As described earlier, the FA value is a summary statistic of diffusivity in all three spatial dimensions. Therefore, increases in the FA value could represent more coherent diffusivity along the primary axis or, alternatively, it could represent reduced diffusivity along perpendicular axes. To explore the source of the differences in FA between children and adults, we examined the diffusivity components of the FA value: axial diffusivity (AD) and radial diffusivity (RD). An ANOVA comparing Group \times Tract on the dependent measure of AD revealed a main effect of Group ($F(1,90) = 5.99, p < 0.01$) and a main effect of Tract ($F(2,90) = 26.22, p < 0.001$) with no interaction ($p = 0.99$). The effect of Group is due to higher AD in children compared to adults (1.43 vs. 1.39, respectively) and the effect of Tract is due to greater AD in the genu compared to the other two tracts (both p 's < 0.001). The same ANOVA was tested with RD as the dependent measure and it yielded the same main effects of Group and Tract with no interaction ($F(1,90) = 38.3, p < 0.001$; $F(2,90) = 18.9, p < 0.001$; $p = 0.46$). These effects reflect the higher RD values of children compared to adults (5.9 vs. 5.3, respectively) and significant, step-like decreases in the magnitude of RD from the fibers traversing the genu to the isthmus to the splenium (all p 's < 0.02).

Figs. 4 and 5 show the differences between children and adults in AD and RD along each tract, measured in 5 mm increments (FDR corrected $\alpha = 0.05$). As can be seen in the figures, differences in RD between children and adults were more pronounced and extensive than differences in AD. However, the only whole tract that showed an overall difference between adults and children in RD versus AD was the splenium, in which RD was significantly more different between adults and children than AD ($t(60) = 8.3, p < 0.001$). AD is a white matter metric more attuned to the number and intrinsic characteristics of axons or changes in extra-axonal/extracellular space. RD, on the other hand, has been associated with changes in myelination or glial cell morphology (Song et al., 2003, 2005). Therefore, one possibility is that children exhibit more extensive differences from adults in RD than AD due to immature myelination. In particular, the strong dissociation between RD and AD in the more posterior segments of the corpus callosum fits with the argument, described earlier, that more posterior fibers ultimately become more myelinated than anterior fibers.

3.2. Brain-behavior correlations

Since there were clear differences in white matter coherence between children and adults, our next question was whether these structural measures were related to children's behavioral performance. FA values for each tract were tested against participants' performance on our two numerical judgment tasks: Symbolic (Arabic numerals) and Non-symbolic (arrays of dots).

The behavioral results from these two tasks are shown in Fig. 6. A ANOVA testing Age Group (Adults, Children) \times Condition (Symbolic, Non-symbolic) on accuracy revealed main effects of Age Group ($F(1,30) = 23.9, p < 0.001$) and Condition ($F(1,30) = 21.0, p < 0.001$) with no interaction. Adults were more accurate than children (93% vs 79%, $p < 0.001$) and both groups performed better with Arabic numerals than Dot Arrays (88% vs. 82%, $p < 0.001$). A parallel ANOVA on RTs revealed a significant interaction between Age Group and Condition ($F(1,30) = 53.8, p < 0.001$) wherein adults had faster RTs to Arabic numerals than Dot arrays but children showed no difference in RT between the two conditions (Fig. 6b). Adults were also significantly faster than children overall (738 vs. 1056 ms, respectively, $p < 0.001$). Thus, there are both speed and accuracy differences between children and adults in numerical comparison. Our goal was to understand whether structural differences in the corpus callosum could explain some of the variability in performance between groups.

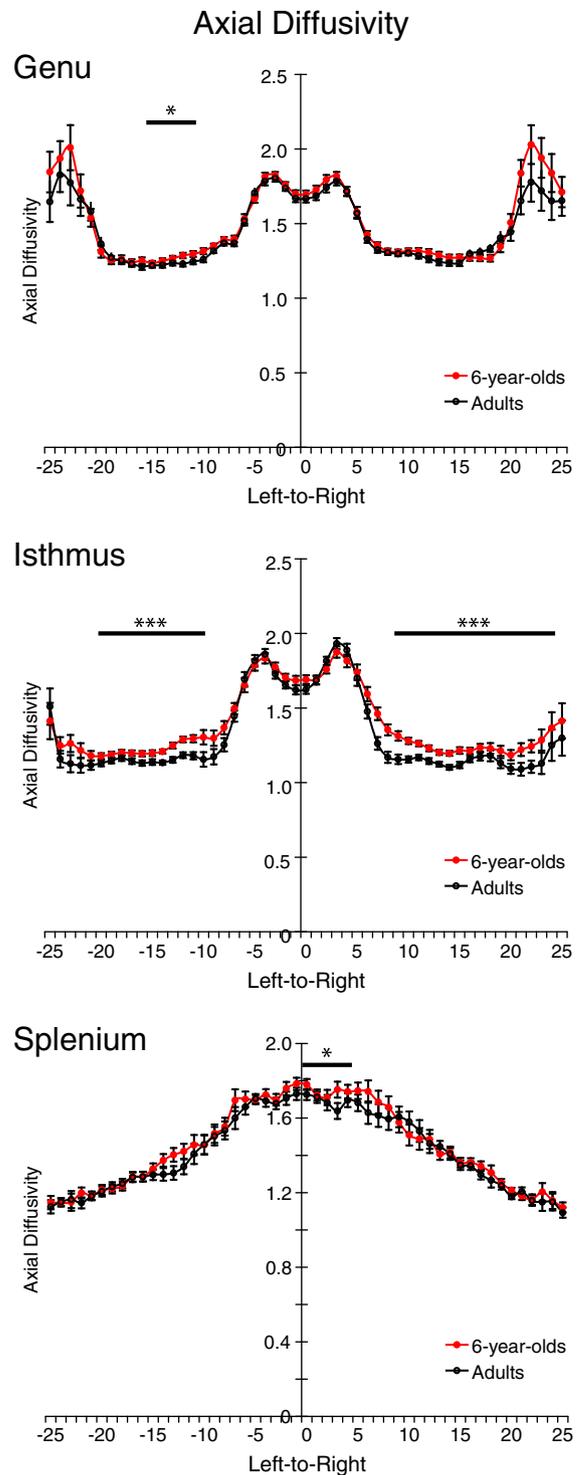


Fig. 4. Axial diffusivity (AD) values for fibers that crossed the genu (top), isthmus (middle), and splenium (bottom). The x-axis is left-to-right position in millimeters and the y-axis is the AD value presented in units of $10^{-3} \text{ mm}^2/\text{s}$. Children are shown in red and adults in black. Difference between children and adults are highlighted with black bars at the top of each panel (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; FDR corrected $\alpha = 0.05$). SEM is shown by error bars.

A multiple regression model with accuracy as the dependent measure and FA values for the left and right genu, isthmus, and splenium as predictors was significant as a whole ($R^2 = 0.50$, Adj. $R^2 = 0.38$, $F(6,25) = 4.1, p < 0.005$) and the only significant Beta coefficient in the model was from the fibers crossing the left isthmus (Beta = 0.61,

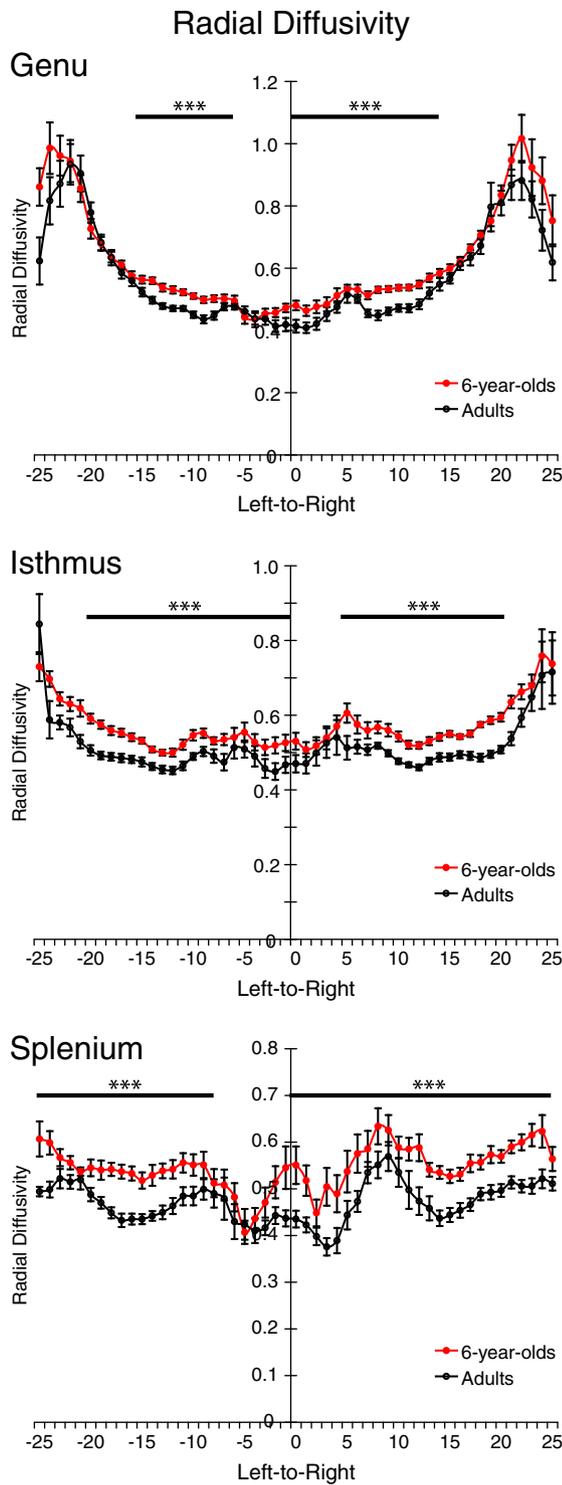


Fig. 5. Radial diffusivity (RD) values for the fibers traversing the genu (top), isthmus (middle), and splenium (bottom). The x-axis is left-to-right position in millimeters and the y-axis is the RD value presented in units of $10^{-3} \text{ mm}^2/\text{s}$. Children are shown in red and adults in black. Difference between children and adults are highlighted with black bars at the top of each panel (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; FDR corrected $\alpha = 0.05$). SEM is shown by error bars.

$t(25) = 2.74, p < 0.01$). All other Beta coefficients were less than 0.2. Similarly, the coefficient for the fibers that crossed the left isthmus was also marginally significant when the categorical factor of Age Group was included in the model (Beta = 0.44, $t(24) = 1.85, p = 0.06$). This expanded model was significant as a whole ($R^2 = 0.57, \text{Adj.}$

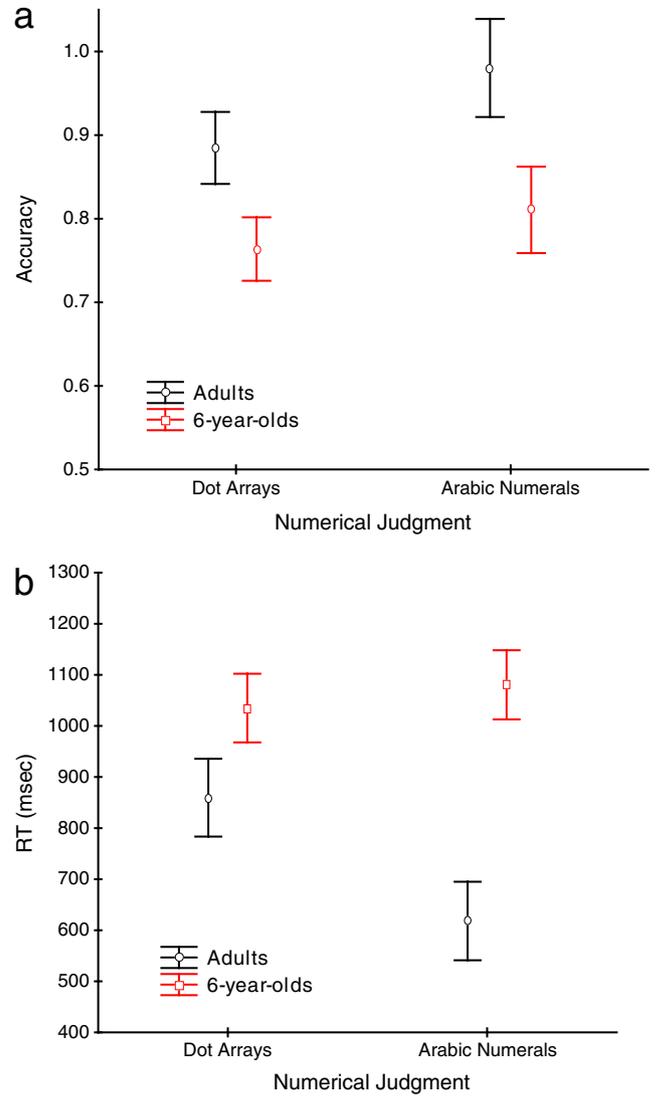


Fig. 6. Behavioral performance on the two numerical tasks. Accuracy (a) and RT (b) are shown for adults (black) and children (red) with 95% confidence intervals denoted by the vertical bars.

$R^2 = 0.45, F(7,24) = 4.6, p < 0.005$) and the main effect of Age Group was marginally significant ($F(1,24) = 4.23, p = 0.05$). However, the expanded model did not account for substantially more variance than the original model without the factor of Group (Mallow's $C_p = 8$ vs. 7 for the models with and without the Age Group factor, respectively). Thus, the relationship between accuracy on numerical tasks and white matter coherence (FA) is not entirely explained by group differences.

A similar pattern emerged from regression analyses with RT as the dependent variable. A model with the left and right genu, isthmus, and splenium as predictors was significant as a whole ($R^2 = 0.54, \text{Adj. } R^2 = 0.43, F(6,25) = 4.9, p < 0.005$) and the only significant Beta coefficient in the model was from the tract that traversed the left isthmus (Beta = $-0.52, t(25) = -2.5, p < 0.05$). When Age Group was entered as an additional predictor, the whole model was significant ($R^2 = 0.69, \text{Adj. } R^2 = 0.61, F(7,24) = 7.9, p < 0.001$) and the factor of Age Group was significant ($F(1,24) = 12.5, p < 0.01$). The highly significant factor of Age Group in predicting RT suggests that group differences might have played a greater role in the relationship between FA and RT than FA and accuracy.

To further investigate the relationship between FA and behavior, we conducted separate regression analyses for each numerical judgment type (Symbolic, Non-symbolic) and each age group. Fig. 7

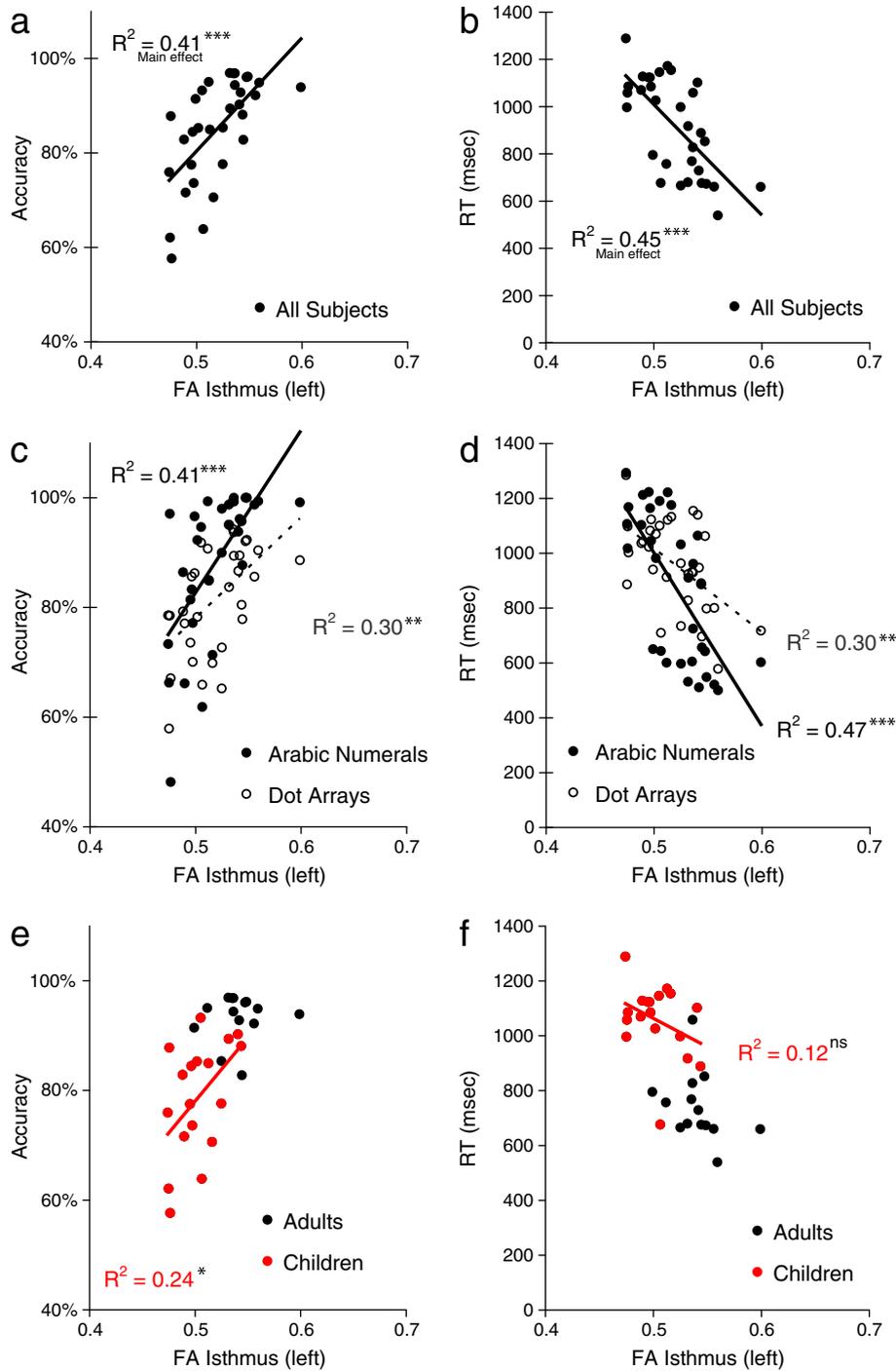


Fig. 7. Brain-behavior correlations. There was an overall correlation between accuracy (a), RT (b), and FA of the fibers crossing the left isthmus. The overall correlation was significant for each of the two numerical judgment types (Arabic numeral and Dot Arrays) in accuracy (a) and RT (b). The overall correlations for children only (red) are shown in panels e and f for accuracy and RT, respectively. Only the correlation between FA of the left isthmus tract and accuracy was significant within the child-only sample ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$).

shows the raw correlation coefficients for the dependent variables of accuracy and RT and the FA values of the tract that crossed the left isthmus (the parietal corpus callosum). These analyses demonstrate that there is an overall relationship between the robustness of the left parietal corpus callosum and performance (Fig. 7a and b: Accuracy $R^2 = 0.41$, $p < 0.001$; RT $R^2 = 0.45$, $p < 0.001$). That relationship persists across both the Symbolic and Non-symbolic numerical judgments (Fig. 7c and d): performance on both the Arabic numerals and Dot Arrays judgments were each significantly correlated with FA of the left parietal corpus callosum for both accuracy (Symbolic $R^2 = 0.41$,

$p < 0.001$; Non-symbolic $R^2 = 0.30$, $p < 0.01$) and RT (Symbolic $R^2 = 0.47$, $p < 0.001$; Non-symbolic $R^2 = 0.30$, $p < 0.01$). When children's data were analyzed separately (Fig. 7e and f), FA in the left parietal tract was found to correlate with accuracy ($R^2 = 0.24$, $p < 0.05$) but the relationship did not hold for adults. Thus, group differences between children and adults account for a significant amount of variance in the correlation between performance and FA in the left parietal tract however, the relationship between FA and performance in the left parietal tract also explains within-group variability for 6-year-old children.

4. Discussion

Our results provide novel evidence of a link between the maturity of the corpus callosum and the development of numerical skills in 6-year-old children. Specifically, the development of the region of the corpus callosum connecting the superior parietal hemispheres (marked by the isthmus at the mid-sagittal plane) was related to performance differences between adults and children as well as to performance differences among children. These data provide the impetus for further exploration of the neuro-cognitive link between the development of the corpus callosum and numerical skill acquisition, particularly in parietal cortex.

We did not find a relation between the development of the region of the corpus callosum connecting the prefrontal hemispheres and numerical performance. It might be the case that interhemispheric connections between prefrontal regions are not as important as the connections between prefrontal cortex and other cortical regions such as the temporal and parietal cortices. In fact, recent studies with older children and adults have shown that the integrity of the superior and inferior longitudinal fasciculi correlates with symbolic calculation performance (Tsang, Dougherty, Deutsch, Wandell, & Ben-Shachar (2009); van Eimeren, Niogi, McCandliss, Holloway, & Ansari, 2008). Prefrontal connections could be more important for higher level calculation than basic numerical knowledge. The role of prefrontal cortex in numerical development is hypothesized to be a domain-general function such as semantic association learning, relational reasoning, or working memory (e.g., Cantlon, Libertus, et al., 2009; Tsang et al., 2009). In contrast, the role of parietal cortex in numerical development is hypothesized to be domain-specific (see Dehaene et al., 2003 for review).

White matter volume in parietal cortex has been linked to performance in children with mathematics-specific impairments due to Velocardiofacial syndrome. A prior voxel-based morphometry study tested white matter volume in individuals with numerical- and mathematics-related developmental disorders. In that study, 8- to 18-year-old children and adults with Velocardiofacial syndrome exhibited reduced white matter volume along the length of the intraparietal sulcus, the angular gyrus, and the supramarginal gyrus, contingent on the degree of their impairment in mathematics (Barnea-Goraly, Eliez, Menon, Bammer, & Reiss, 2005). Furthermore, a recent DTI study with 7- to 9-year-old children reported correlations between the left inferior longitudinal fasciculus (which connects occipital and temporal cortices) and the left superior corona radiata (which inputs to temporo-parietal cortex) with performance on a paper-and-pencil calculation test (van Eimeren et al., 2008, 2010). Importantly, this correlation was specific to mathematics performance because measures of overall IQ were controlled in the model. Our results complement the conclusions of these two prior studies by providing evidence from typically developing, younger children indicating that the strength of the white matter connections between parietal hemispheres is linked to basic numerical performance.

Neuropsychological and functional neuroimaging studies in adults also implicate a specific role for intraparietal and superior parietal cortices in numerical judgments (see Dehaene et al., 2003 for review). In adults, bilateral regions of the intraparietal sulcus respond more strongly during numerical tasks than control tasks involving shape, color, letters, sentences, and a host of other stimuli. And, as described earlier, adults can compute numerical judgments within either hemisphere, as evidenced by studies of split-brain patients (Colvin et al., 2005; Funnell et al., 2007). Taken together, these studies provide evidence of bilateral, number-specific processing in regions of parietal cortex.

Developmental fMRI studies have shown that regions of parietal cortex become increasingly engaged by numerical tasks between the ages of 4 and 17 years, ultimately resulting in the adult pattern of bilateral parietal activation (e.g., Ansari & Dhital, 2006; Ansari et

al., 2005; Cantlon, Libertus, et al., 2009, Cantlon, Platt, et al., 2009, Cantlon et al., 2006; Rivera et al., 2005). Early in development, children often show hemispheric asymmetries in parietal activation that are linked to immature numerical performance. For example, Rivera et al. (2005) reported that older children and adults engaged bilateral parietal and prefrontal regions during a basic arithmetic task, but younger children (who performed worse than older children) primarily engaged right hemispheric loci. Other studies testing numerical judgments have also reported right-lateralized parietal activity in young children (Cantlon et al., 2006; Holloway & Ansari, 2009). The hemispheric asymmetry in BOLD activity in children could be caused by the lack of mature white matter connections between hemispheres. The fact that children tend to exhibit right-lateralized parietal activation during numerical tasks whereas adults more often exhibit bilateral parietal activation might be related to the weak white matter composition of the left parietal tract in children compared to adults and in poor-performing children compared to other children (reported in the current study). Interhemispheric connections in parietal cortex may thus be an important catalyst for mature numerical representation. It is important to note, however, that our data do not rule out the possibility that the relationship between white matter coherence in the parietal corpus callosum and numerical performance is related to cognitive performance in general (rather than numerical performance in particular).

A current debate regarding the specific role of the corpus callosum in integrating the cerebral hemispheres is centered on the issue of the excitatory versus inhibitory influence of the corpus callosum on the contralateral hemisphere (Bloom & Hynd, 2005). The basic question is whether the corpus callosum inhibits the contralateral hemisphere to generate hemispheric specialization and dominance or whether it excites the contralateral hemisphere to coordinate information in a joint information-processing effort. The answer to this question will be important for understanding developmental changes in the patterns of number-related activation between parietal hemispheres. At the moment, it is unclear whether the development of the left parietal corpus callosum is related to increased or decreased activation in the left parietal hemisphere or, increased or decreased activation in the right parietal hemisphere. Combined fMRI and DTI studies of numerical development will help to resolve this issue.

Our data also prompt some conclusions about the structural development of the corpus callosum. The structural data demonstrate that differences between adults and children in FA and diffusivity indices varied among callosal tracts. This finding is consistent with prior reports that immature commissural pathways are not spatially homogeneous (Berman et al., 2005). In particular, we observed greater differences between children and adults in parietal and occipital callosal projections than frontal projections. The observed differences in RD in these tracts suggest that the age-related differences reported here are driven largely by myelin formation, consistent with other DTI studies of children in this age range (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Paus, 2010). Myelination of the corpus callosum can thus occur at different rates for different cortical regions during early childhood.

In summary, our study provides evidence that structural differences in the white matter fibers of the corpus callosum that project between the parietal hemispheres are related to developmental progress in numerical performance in early childhood. Although prior fMRI studies implicate a specific role for intraparietal regions in numerical performance, the data from the current study do not afford any claims about the functional specificity of white matter development in superior parietal cortex. As mentioned earlier, studies of children with broad cognitive impairments have identified a link between the structure of the corpus callosum and general intelligence. Our results implicate a connection between white matter development and numerical performance that may either be specific to the numerical domain or, may be related to the development of general faculties such as attention and working memory. Parietal activation has previously been linked to those domain-general functions in adults and children (Casey,

Galvan, & Hare, 2005; Göbel, Johansen-Berg, Behrens, & Rushworth, 2004; Marshuetz, Reuter-Lorenz, Smith, Jonides, & Noll, 2006), but domain-general activity also has been shown to dissociate from number-related activation in the intraparietal sulcus (e.g., Cantlon, Libertus, et al., 2009, Cantlon, Platt, et al., 2009; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002; see Dehaene et al., 2003 for review). Given the importance of parietal cortex for a wide range of cognitive functions, there is a strong possibility that the development of the parietal corpus callosum plays a specific role in the development of numerical cognition but also contributes to more general aspects of cognitive development.

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