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White matter growth as a mechanism of cognitive development in children

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We examined the functional role of white matter growth in cognitive development. Specifically, we used hierarchical regression analyses to test the unique contributions of age versus white matter integrity in accounting for the development of information processing speed. Diffusion tensor imaging was acquired for 17 children and adolescents (age range 6–17 years), with apparent diffusion coefficient (ADC) and fractional anisotropy (FA) calculated for 10 anatomically defined fiber pathways and 12 regions of hemispheric white matter. Measures of speeded visual–spatial searching, rapid picture naming, reaction time in a sustained attention task, and intelligence were administered. Age-related increases were evident across tasks, as well as for white matter integrity in hemispheric white matter. ADC was related to few measures. FA within multiple hemispheric compartments predicted rapid picture naming and standard error of reaction time in sustained attention, though it did not contribute significantly to the models after controlling for age. Independent of intelligence, visual–spatial searching was related to FA in a number of hemispheric regions. A novel finding was that only right frontal–parietal regions contributed uniquely beyond the effect of age in accounting for performance: age did not contribute to visual–spatial searching when FA within these regions was first included in the models. Considering we found that both FA in right frontal–parietal regions and speed of visual–spatial searching increased with age, our findings are consistent with the growth of regional white matter organization as playing an important role in increased speed of visual searching with age.

Introduction

Despite recent evidence that white matter plays a critical role in physiological mechanisms of brain maturation and neural signaling (Helmuth, 2001; Reed et al., 2004; Tsuda et al., 2003, 2005; Ullian et al., 2001) the evaluation of analogous brain/behavior relations in human cognitive development is limited. Information speed is the general rate at which a person can complete cognitive operations: age-related increases in information processing speed are robust and are recognized as a mechanism of cognitive development and intellectual outcome (Kail, 2000; Kail and Park, 1994; Luciano et al., 2004). To test the functional role of white matter growth in cognitive development we examined age-related changes in white matter integrity for children and adolescents using diffusion tensor imaging, and related these to information processing speed. Documenting the connection between structural brain growth and cognitive function is a necessary first step in integrating molecular and physiological mechanisms of brain maturation with behavior change. Such integration is important for understanding how brain maturation may mediate functional change, has wide-ranging applications for brain/behavior models in neuroscience, and may ultimately yield novel information for characterizing and treating developmental neurological disorders.

White matter growth is the main source of increased brain volume during child development and continues well into the second decade for some regions (Casey et al., 2000; Giedd et al., 1999; Paus et al., 2001). Diffusion tensor imaging (DTI) provides quantitative indices of the diffusion of water within tissue and is an excellent technique for measuring age-related changes in the biological properties of white matter in vivo (Beaulieu, 2002; Pfefferbaum et al., 2000; Schmithorst et al., 2002). Such information is necessary to quantify subtle changes in white matter organization with maturation and relate those changes to behavior. Both the magnitude

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of water diffusion, expressed as apparent diffusion coefficient, and the directionality, expressed as the degree of anisotropy provide indices of white matter organization (Beaulieu, 2002). Decreased magnitude and increased directionality of water diffusion across multiple white matter pathways are associated with increased age in children and adolescents (Barnea-Goraly et al., 2005; Ben Bashat et al., 2005; Li, 2002; McGraw et al., 2002; Mukherjee et al., 2001; Schmithorst et al., 2002; Schneider et al., 2004; Snook et al., 2005; Suzuki et al., 2003). White matter is likely important in the ontogeny of information processing speed as it facilitates the rate of transmission of electrical signals along axons (Aboitiz et al., 1992; Schmithorst et al., 2002) which is a primary means of neural communication. Further, damage to white matter yields slow processing speed (Kail, 1998). Finally, white matter integrity is related to information processing speed in adults (Madden et al., 2004; Tuch et al., 2005). Anisotropy within right parietal and occipital hemispheric white matter predicts reaction time in young healthy adults (Tuch et al., 2005). Changes are also observed with aging: anisotropy in the splenium of the corpus callosum is related to reaction time for young adults while anisotropy in the anterior internal capsule is most relevant for older adults (Madden et al., 2004).

Although DTI has been used widely to document compromised white matter in clinical pediatric populations (Ashtari et al., 2005; Barnea-Goraly et al., 2004; Filippi et al., 2003; Khong et al., 2003, 2005, 2006; Mabbott et al., 2006; Molko et al., 2004; Peng et al., 2004), the functional implications of white matter growth for normal development have received less attention. General intelligence has been related to white matter integrity within bilateral association areas involving frontal and occipital–parietal areas (Schmithorst et al., 2005). Intelligence measures are not sufficient for explaining the development of brain/behavior relations however, as they are composite measures of multiple cognitive processes (Kail, 2000; Neisser et al., 1996). In terms of specific functions, increased anisotropy within left temporal–parietal white regions is related to proficiency in reading ability in children and adults (Beaulieu et al., 2005; Deutsch et al., 2005; Klingberg et al., 2000; Niogi and McCandliss, 2006). To account for development in examining brain/behavior relations, researchers have controlled for age when calculating correlations between DTI indices and behavioral performance (Liston et al., 2006; Nagy et al., 2004; Olesen et al., 2003; Schmithorst et al., 2005). Independent of age (a) faster reaction time in cognitive control is associated with increased organization of white matter tracts from the caudate to frontal grey matter (Liston et al., 2006) and (b) visual–spatial working memory is related to white matter organization in the anterior corpus callosum, left frontal lobe, and left temporal–occipital regions (Nagy et al., 2004; Olesen et al., 2003). Though such findings support the role of white matter maturation in the development of cognitive function they are incomplete. White matter integrity and age are correlated: because of this multi-collinearity, the use of partial correlations to control for age only may not reflect the shared variance in the model. Age is simply a surrogate index of maturation and experience.

A more robust approach is to test the unique contribution of both age and white matter integrity in predicting cognitive performance. To do this we examined the relations between age, white matter organization, and individual differences in information processing speed using hierarchical regression. We acquired DTI indices of white matter integrity for 17 children and adolescents ranging in age from 6 to 17 years. Apparent diffusion coefficient (ADC) and fractional anisotropy (FA) were calculated bilaterally for (a) large commissural and projection fiber pathways including the corpus callosum, internal capsule, and external capsule (Fig. 1), and (b) hemispheric white matter compartments including inferior frontal, frontal, frontal–parietal, temporal, parietal–occipital, and occipital regions (Fig. 2). Information processing speed was measured using visual–spatial searching, rapid picture naming, and sustained attention reaction time. First, the presence of age-related changes in white matter integrity was assessed. If developmental changes are present in white matter integrity, then decreases in ADC and increases in FA will be associated with increasing age. Second, the specificity of relations between the regions of white matter and different measures of information speed were examined. If explicit white matter pathways are related to specific cognitive functions, then ADC and FA for different brain regions should differentially predict performance on the various tasks of information processing speed. Third, for white matter regions where age-related effects were observed, we employed multiple hierarchical regression analyses to predict information processing speed and compared the relative increase in the variance accounted for by the model when age versus DTI indices was entered first. If white matter growth accounts for development of information processing speed, then DTI indices should reduce the contributions of age in predicting information processing speed.

Methods

Subjects

Seventeen typically developing children (13 males) ranging from 6 to 17 years old (mean = 11.60, SD = 3.53) participated in the study. Relations between white matter integrity and cognition have been identified using similar age ranges and/or sample sizes (Deutsch et al., 2005; Liston et al., 2006; Nagy et al., 2004; Olesen et al., 2003; Tuch et al., 2005). Participants were recruited through community newspapers and parent networks and had no prior history of neurodevelopmental disability or injury. Informed consent was obtained from parent's prior participation, as was verbal assent from the participants.

Image acquisition and processing

Measurements were performed using a GE LX 1.5T MRI scanner (General Electric Healthcare, Milwaukee, WI) and a single channel quadrature head coil and consisted of a 3D T1 SPGR (TR/TE = 8.6/4.2 ms, 122 contiguous axial slices, 1.5 mm thick, 256 × 192 matrix) and a Proton Density/T2 interleaved (TR/TEPD/TET2 = 2800/30/90 ms, 54 axial slices with 2.5 mm spacing, 5 mm thick, 256 × 192 matrix) sequence used for region of interest analyses and to facilitate automatic registration, respectively. The diffusion tensor data were acquired using a single shot spin echo DTI sequence with an EPI readout (25 directions, TR/TE = 8300/79 ms, 32 contiguous axial slices, 3 mm thick, 128 × 128 matrix, $b = 1000 s/mm^2$, one $b = 0$ image). Eddy current correction was conducted on the diffusion weighted raw data: images were visually inspected and slices containing artifact were removed from the calculation of the tensor. Subsequently, ADC and FA maps were calculated (Bammer et al., 2003; Mori and van Zijl, 2002).

For each subject, regions of interest (ROI) were traced bilaterally on the AC/PC aligned T1 scan across multiple slices to cover all the anatomy of the region. Anatomically defined fiber pathways were chosen to provide comprehensive coverage and include the genu,

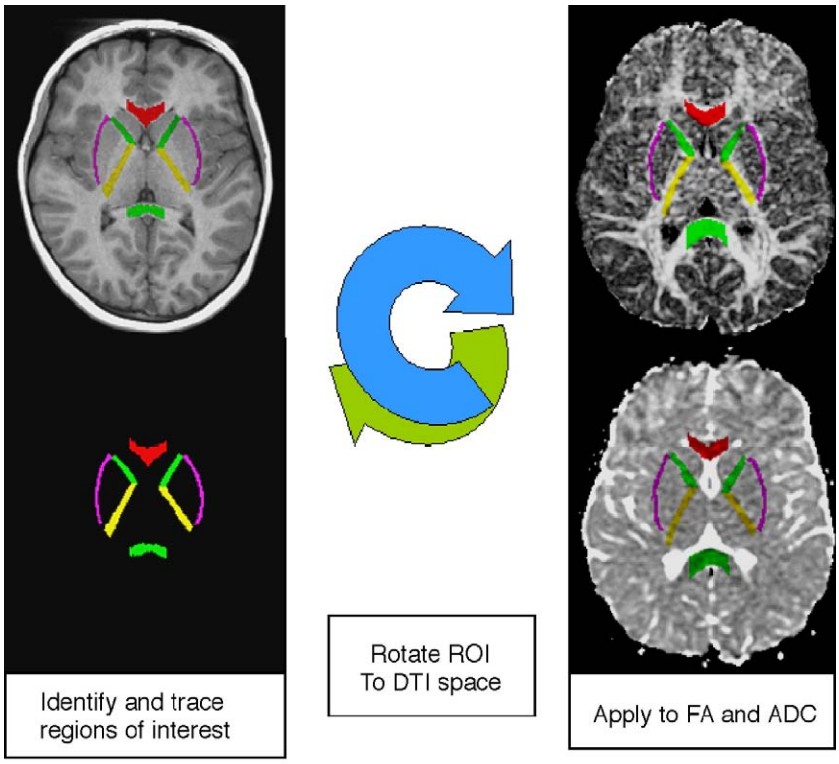

Fig. 1. Anatomically defined fiber pathways. The left-sided panel includes regions traced on the T1 (top) and the corresponding ROI mask (bottom). Regions include the genu, body, and splenium of the corpus callosum, the anterior and posterior limbs of the internal capsule, and the external capsule and are traced bilaterally across multiple slices for the complete structures on an AC/PC aligned T1 scan. The T1 scan is then linearly registered to DTI space with an automatic rotation algorithm (represented in the middle panel). Means for the DTI indices within these regions are calculated once the mask is applied to the FA (top right side panel) and ADC (bottom right side panel) maps.

anterior body, posterior body, and splenium of the corpus callosum, the anterior and posterior limbs of the internal capsule, and the external capsule (Fig. 1). ROI analysis was conducted using the T1 rather than the ADC or FA maps to avoid the problem of using the dependant variable (i.e., quantitative indices of ADC or FA) to define the anatomic regions (Pfefferbaum et al., 2000). To create hemispheric white matter compartments (Fig. 2) the T1 scan was classified into CSF, grey, and white matter using an automatic tissue segmentation algorithm (Zhang and Smith, 2001). The previously defined fiber pathways, as well as the basal ganglia and cerebellum were removed, so that only hemispheric white matter masks remained. A 12 compartment white matter template, subdivided into bilateral hemispheric regions (prefrontal, frontal, temporal, frontal–temporal–parietal, parietal–occipital, and occipital) was created on a single representative subject and applied via affine transformation to all subjects (Giedd et al., 1999; Woods et al., 1998). T1 scans were registered to DTI acquisition space with a combination of linear and non-linear automatic transformation algorithms (Woods et al., 1998). The non-linear transformation was applied to compensate for EPI distortion in the DTI images.

Mean ADC and FA were calculated for each region of interest and hemispheric white matter compartment. To determine the reliability in tracing the fiber pathways, all regions of the corpus callosum, internal capsule, and external capsule were traced on 5 subjects by two raters and interclass correlations coefficients were calculated for mean FA. Coefficients ranged from 0.78 to 0.99, indicating high reliability in the placement of regions. Hemispheric white matter is composed of multiple fiber pathways. In order to obtain measures of the most highly organized fiber pathways within these regions, median FA was first computed and then mean FA for the region was calculated for only those values above that median (Fig. 3): voxels with higher FA are considered the most robust measures of fiber tracks (Mori and van Zijl, 2002).

Behavioral measures

Simple motor speed was evaluated using a finger tapping task. The speed of finger tapping for the dominant hand was measured. Mean number of taps within 10 s over 10 trials was recorded. Three subtests from the Woodcock Johnson Tests of Cognitive Ability, Third Revision (Woodcock et al., 2001) were used to evaluate information processing speed for visual–spatial (Visual Matching and Pair Cancellation) and auditory–verbal (Rapid Picture Naming) material. These subtests are sensitive to age-related increases in information processing speed (Kail, 1998, 2000). Test–retest reliability for Visual Matching, Pair Cancellation, and Rapid Picture Naming for children from age 6–17 are $r=0.88$, 0.78 and 0.97, respectively (McGrew, 2001). For the Visual Matching subtest, children were asked to locate and circle two identical numbers in a row of six numbers for as many single- to triple-digit numbers series as possible within 3 min. The number of pairs correctly circled was recorded. For Pair Cancellation, the children's task was to locate and mark as many repeated patterns (e.g., a picture of a soccer ball followed by a picture of a dog) within a series of visual stimuli as possible within 3 min. The number of repeated patterns correctly marked was recorded. To increase reliability and reduce the number

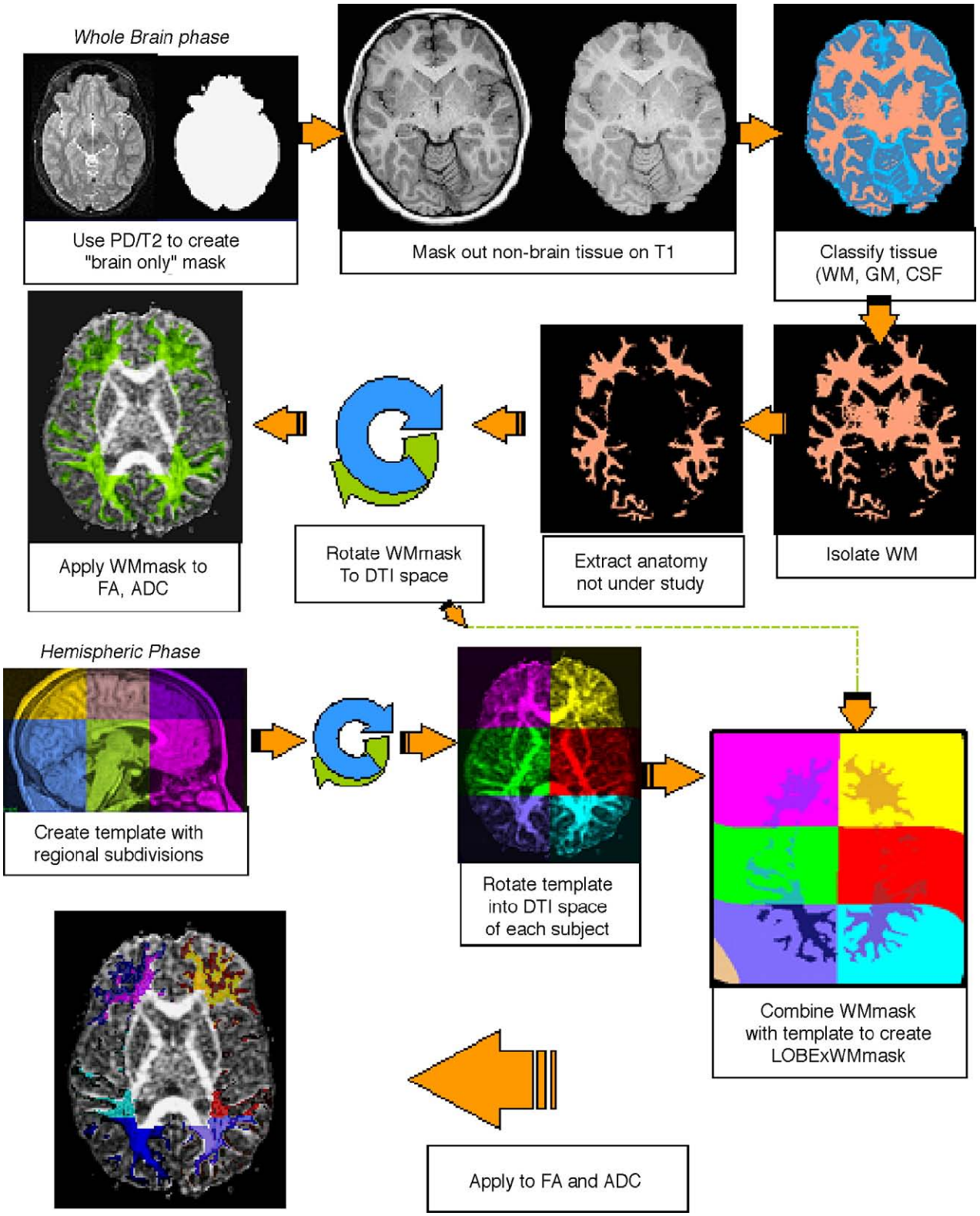

Fig. 2. Compartments of hemispheric white matter. The whole brain phase is depicted in the 7 panels of the top sequence and includes segmenting white matter (WM) grey matter (GM) matter, and CSF, and isolating anatomy not under study to create a WM mask (depicted in the first 5 panels of the top sequence) which is then rotated into DTI space (depicted in the last 2 panels of the top sequence). In the regional division phase (depicted in the 5 panels of the bottom sequence) a template brain was created including 12 regional subdivisions (prefrontal, frontal, temporal, frontal–temporal–parietal, parietal–occipital, and occipital bilaterally), combined with the previously created WM mask, and applied to the DTI maps, allowing for the calculation of DTI measures within the hemispheric regions, standardized across participants.

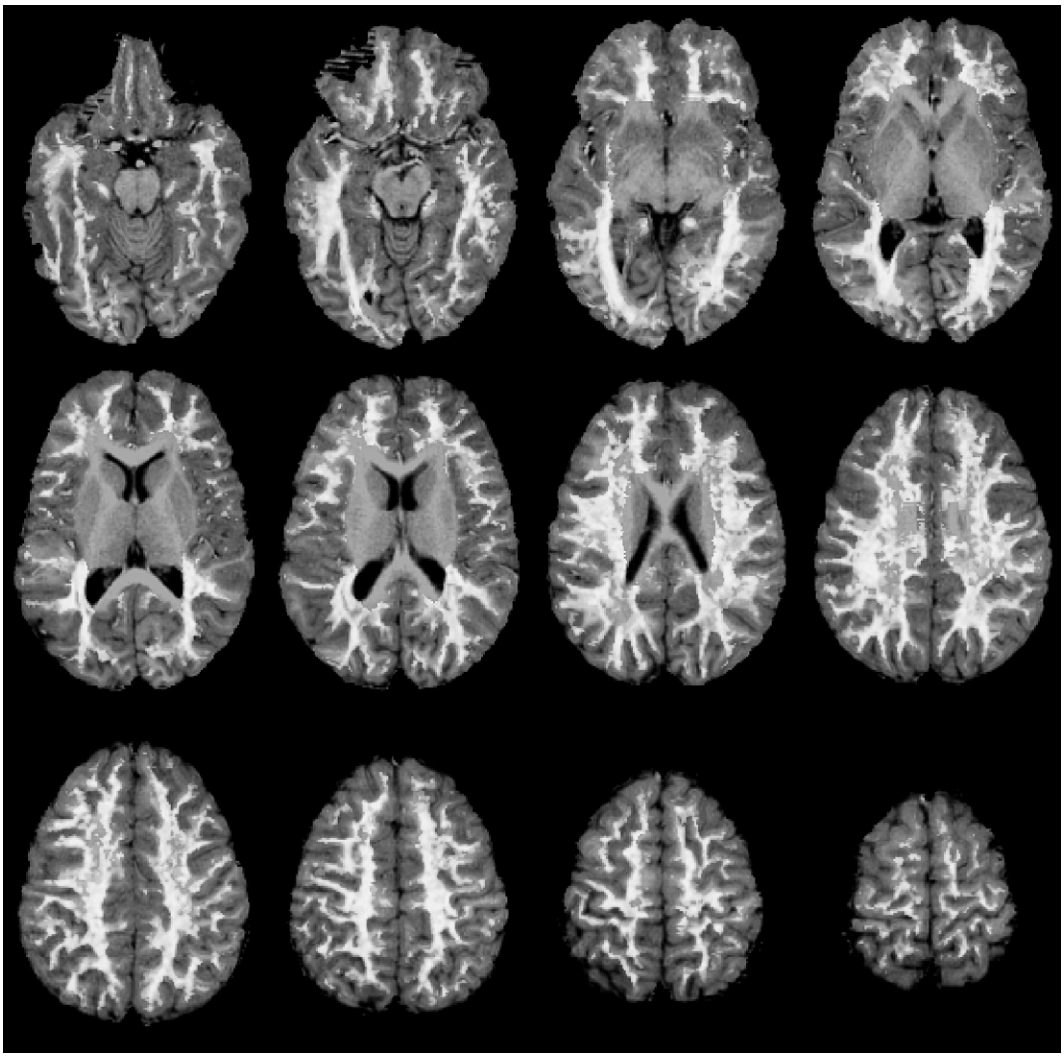

Fig. 3. Median-split FA map for normal appearing white matter. FA map for normal appearing white matter for a representative subject, including only voxels with values above the median, overlaid on the anatomical T1 scan for visualization purposes.

of statistical analyses required, a composite visual–spatial searching measure was calculated by combining the visual matching and pair cancellation raw scores. For the Rapid Picture Naming task, children were required to name as many pictures presented on a sheet of paper as possible within a 2-min time limit. The number of pictures correctly named was recorded. The Connors Continuous Performance Task II (CPT II) was used to evaluate sustained attention(Conners, 2000). Stimulus presentation and data acquisition were controlled by a computer. Children were required to press the "spacebar" on the keyboard in response to the presentation of individual letters of the alphabet on the screen and to refrain from responding when the letter "X" was presented and reaction time was recorded. Standard error of reaction time provides an index of the variability in reaction time for responding to stimuli in a continuous performance task. It is well established as a measure of sustained attention: increased standard error in reaction time (i.e., increased variability in the speed of responding) is associated with poor accuracy (Epstein et al., 2003). Depending on the age of the subject, intellectual testing was conducted using an abbreviated version of either the Wechsler Intelligence Scale for Children – Fourth Revision or the Wechsler Adult Intelligence Scale –Third Revision. A short-form estimate of Full Scale Intelligence Quotient (short-form IQ) was calculated for each subject based on 5 subtests, including Vocabulary, Information, Block Design, Digit Span, and Coding (Tellegen and Briggs, 1967).

Statistical analyses

First, correlation analyses (two-sided) were conducted for age, information processing speed, and regional FA/ADC. Because of the identified relations between intelligence and DTI indices of white matter (Schmithorst et al., 2005), partial correlations accounting for short-form IQ were conducted for information processing speed and FA/ADC. Second, hierarchical regression analyses (two sided) were employed to determine the unique contributions of age versus regional FA/ADC in accounting for individual differences in information processing speed. Only regions of interest where age-related effects were evident for FA/ADC were included in the regression analyses.

Because performance on Visual Matching and Pair Cancellation requires speeded motor responding (e.g., these are paper and pencil

tasks requiring the participant to quickly moving a pencil to circle or cross out items), speed of finger tapping for the dominant hand was controlled for in all analyses involving the composite visual–spatial information processing measure. Hemispheric white matter regions were not created for 1 participant due to motion artifact and hence analyses involving these regions were conducted using 16 participants. Two participants with English as a second language were not included in analyses of rapid picture naming. To correct for multiple comparisons, results were considered significant at the $p<0.01$ level only for all analyses.

Results

Age-related changes

Information processing speed

Means and correlations for the behavioral measures are found in Tables 1 and 2, respectively. Age-related increases were evident for rapid picture naming and visual–spatial searching, $ps<0.01$ (Table 2). For sustained attention, reaction time did not increase with age, though a significant decrease in standard error in reaction time was evident with age, $p=0.001$: only this measure is used in subsequent analyses. Simple motor speed was related to increased performance on visual–spatial searching, $ps<0.004$, as was rapid picture naming, $p=0.001$. Standard error in reaction time for sustained attention was also related to the visual–spatial searching and rapid picture naming, $ps=0.002$, but not simple motor speed, $ps>0.05$. The rapid picture naming task did not require an upper extremity motor response and was not related to simple motor speed, $p>0.05$.

DTI indices

Across the sample, greatest FA was evident for the genu, anterior body, posterior body and splenium of the corpus callosum (0.64, 0.68, 0.65 and 0.73, respectively) and right and left posterior internal capsule (0.68 and 0.65, respectively). Mean FA was next largest for the right and left anterior internal capsule (.52 and 0.53, respectively). Mean FA above the median within the hemispheric white matter ranged from 0.48 to 0.53 (Fig. 3). Finally, mean FA for the right and left external capsule were lowest (0.40 and 0.42 respectively). Significant age-related increases in FA were evident for the posterior body of the corpus callosum, right inferior frontal, left parietal–occipital, and bilateral frontal, frontal–parietal, temporal, and occipital regions, $ps<0.01$ (Table 3). Mean ADC ranged from 0.00067 to 0.00081 mm^2/s across deep white matter pathways and from 0.00071 to 0.0008 mm^2/s across hemispheric white matter. ADC decreased with age within the right frontal–parietal, left temporal, and bilateral occipital regions, $p<0.01$ (Table 3).

Table 1
Means and standard deviations across the sample for the behavioral tasks

	Mean	Standard deviation
Short form estimate of IQ	115.41	15.00
Finger tapping dominant hand	41.33 [a]	7.78
Visual searching/scanning	51.64 [b]	11.02
Rapid picture naming	100.29 [c]	17.84
Sustained attention	7.38 [d]	2.44

[a] Mean number of finger taps within 10-s time period.
[b] Composite mean number of items completed within 3 min for the Pair Cancellation and Visual Matching tasks.
[c] Mean number of pictures named within 2 min.
[d] Mean standard error of reaction time in seconds for the CCPT.

Table 2
Correlations among age, simple motor speed, and information processing speed

	Age	Finger tapping dominant hand	Visual–spatial searching	Rapid picture naming	Sustained attention
Age	–				
Finger tapping dominant hand	0.79 *	–			
Visual searching/scanning	0.81 *	0.66 *	–		
Rapid picture naming [a]	0.75 *	0.47	0.74 *	–	
Sustained attention	−0.71 *	−0.44	−0.72 *	−0.66 *	–

[a] Two subjects were removed from these analyses as English was their second language.
* $p<0.01$.

Relations between information processing speed and white matter

Visual–spatial searching

Partial correlations between visual–spatial searching and FA/ADC were calculated controlling for simple motor speed for the dominant hand and short-form IQ. Better performance on visual–spatial searching was associated with increased FA within left external capsule, right parietal–occipital and bilateral frontal, frontal–parietal, temporal, and occipital regions, $p<0.01$ (Table 3). Significant relations between the visual–spatial searching and ADC were not present, except for the splenium of the corpus callosum, $r=0.66$, $p<0.01$.

Regression analyses were conducted to examine the influence of age and FA for hemispheric white matter on visual–spatial searching. Separate analyses were conducted for each region, including right and left frontal, frontal–parietal, temporal, or occipital regions, yielding 8 sets of analyses. To control for simple motor speed, finger tapping for the dominant hand was entered first for these analyses. Across all regions of interest, both FA and age accounted for a significant portion of the variability in visual–spatial searching, $Fs<12.00$, $ps<0.01$. FA for most regions (e.g., left frontal, frontal–parietal, temporal, and bilateral occipital) and age shared a considerable amount of variance in accounting of visual–spatial processing speed, and neither FA values with these regions nor age accounted for unique variance when the other was included in the model, $F>6.89$, $p>0.01$. The fact that FA values and age together account for so much variability in information processing speed ($R^2s<0.75$) but so little unique variability implies that the impact of these two variables on information processing speed is difficult to separate statistically for these regions. In contrast, FA within the right frontal and frontal–parietal regions contributed uniquely in accounting for visual–spatial searching, after age had been considered (Fig. 4): age did not contribute significantly to the model when entered after FA for these regions (Table 4; Fig. 5). A similar trend was observed for right temporal white matter (Table 4).

Table 3
Correlations between the DTI indices for fiber pathways/hemispheric white matter, and age or information processing speed

Region of interest	Age		Visual–spatial searching		Rapid picture naming		Sustained attention	
	FA	ADC	FA	ADC	FA	ADC	FA	ADC
Corpus callosum								
Genu	0.37	0.34	0.33	0.45	0.34	0.23	−0.52	−0.37
Anterior body	0.29	−0.04	−0.14	0.45	0.07	−0.08	−0.18	−0.15
Posterior body	0.61**	−0.41	0.42	0.24	0.55	−0.36	−0.68**	0.18
Splenium	0.37	0.04	0.32	0.65**	0.37	0.01	−0.24	−0.37
Internal capsule								
Right anterior	0.23	−0.06	0.03	0.46	−0.03	0.15	−0.25	−0.24
Right posterior	0.06	−0.05	0.19	0.40	−0.04	0.08	0.01	−0.25
Left anterior	0.28	−0.31	0.14	−0.16	0.04	−0.36	−0.31	0.04
Left posterior	0.18	−0.18	0.31	0.44	−0.07	−0.04	−0.26	−0.09
External capsule								
Right	0.45	−0.18	0.30	0.34	0.08	0.07	−0.46	−0.20
Left	0.41	−0.52	0.64**	−0.03	0.32	−0.32	−0.60**	0.29
Frontal region						1		
Right	0.61**	−0.47	0.71**	0.16	0.52	−0.21	−0.63**	0.05
Left	0.74**	−0.44	0.69**	0.15	0.51	−0.18	−0.61**	0.04
Inferior frontal region								
Right	0.62**	−0.33	0.57	0.34	0.40	−0.05	−0.62**	−0.07
Left	0.59**	−0.45	0.61	0.18	0.38	−0.13	−0.61**	−0.07
Frontal–parietal region								
Right	0.61**	−0.70**	0.71**	−0.26	0.52	−0.42	−0.63**	0.37
Left	0.74**	−0.37	0.69**	0.14	0.51	−0.18	−0.61**	0.09
Temporal region								
Right	0.71**	−0.59	0.72**	0.04	0.52	−0.24	−0.66**	0.22
Left	0.66**	−0.64**	0.70**	−0.02	0.47	−0.27	−0.64**	0.22
Parietal–occipital region								
Right	0.53	−0.38	0.76**	−0.25	0.52	−0.24	−0.68**	0.13
Left	0.61**	−0.17	0.55	0.28	0.45	0.01	−0.64**	−0.06
Occipital region								
Right	0.66**	−0.70**	0.69**	−0.30	0.57	−0.42	−0.56	0.32
Left	0.69**	−0.65**	0.76**	−0.14	0.67**	−0.40	−0.68**	0.22

** $p<0.01$.

Rapid picture naming

Increased number of pictures named for the rapid picture naming task was related to increased FA within the left occipital region only, $p<0.01$ (Table 3): FA within this region did not predict rapid picture naming after accounting for age $F=1.69$, $p>0.10$. Neither did age account for unique variance in the model after considering FA within the left occipital region, $F=3.80$, $p=0.08$. That age and left occipital FA together account for so much variability ($R^2=0.63$, $p=0.004$) but so little unique variability implies that the impact of these two variables on picture naming speed is difficult to separate statistically. Significant relations between the rapid picture naming and ADC were not present.

Reaction time for sustained attention

Decreased standard error for reaction time was related to increased FA within the left external capsule, posterior body of the corpus callosum, and all hemispheric regions of white matter $p<0.01$, except the right occipital region (Table 3). FA for the left external capsule did not show age-related effects and was hence not included in subsequent hierarchical regressions. FA for the posterior body of the corpus callosum and across all hemispheric white matter regions did not predict sustained attention, after accounting for age, Fs>4.10, ps>0.05. Similarly, age did not account for unique variance in sustained attention, after accounting for FA across all regions, Fs>6.17, ps>0.02. Significant relations between the sustained attention measure and ADC were not present.

Discussion

There has been limited study of the relations between white matter maturation and cognitive development where the unique contributions of white matter integrity versus age have been tested. Our approach provides an innovative strategy to elucidate the role of brain maturation as a mechanism of cognitive development (Casey et al., 2005; Durston and Casey, 2006a) and a number of novel findings are noted.

Consistent with the existing literature, age-related increases in white matter organization were evident in our sample of school age children and adolescents: because we included comprehensive coverage of multiple white matter regions we were able to identify a pattern of stability and change across the brain. Increased FA was associated with increased age within the posterior body of the corpus callosum and all regions of hemispheric white matter. Decreased ADC was related to increased age for only right frontal–parietal, left temporal, and bilateral occipital regions. Changes in DTI measures of white matter with age have been attributed to reduction in brain water, myelination, increases in fiber diameter, greater cohesiveness and compactness of the fiber tracts, and

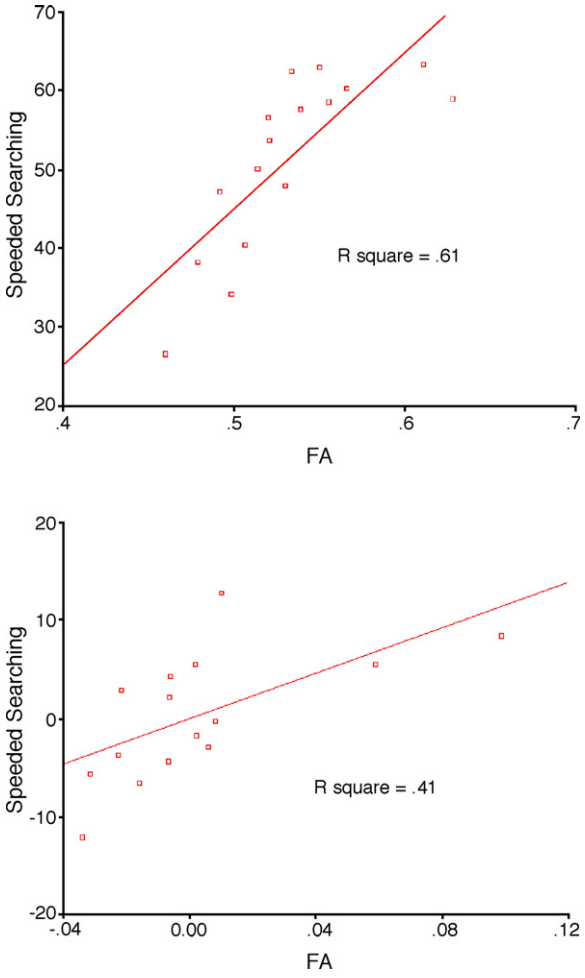

Fig. 4. Scatter plot of speeded visual–spatial searching as a function FA within the right frontal region (top panel), and of the residuals for speeded visual–spatial searching as a function of FA within the right frontal region, after accounting for simple motor speed and age (bottom panel). Plots were similar when considering FA within the right frontal–parietal region, hence these plots are not presented.

reduced extra-axonal spaces (i.e., greater packing) (Beaulieu, 2002; Schmithorst et al., 2002; Suzuki et al., 2003). Anisotropy in particular likely reflects the influence of axonal membranes on water diffusion, including axonal density (Beaulieu, 2002; Schmithorst et al., 2002). Age-related increases in white matter organization of large fiber pathways, including the corpus callosum and internal capsule are most evident in infants and young children, with a relative attenuation for older children and adolescents (Barnea-Goraly et al., 2005; Ben Bashat et al., 2005; Li, 2002; McGraw et al., 2002; Mukherjee et al., 2001; Schmithorst et al., 2002; Schneider et al., 2004; Snook et al., 2005). In contrast, increases in FA for hemispheric white matter are protracted and most evident in older children and adolescents (Barnea-Goraly et al., 2005; Ben Bashat et al., 2005; Schneider et al., 2004). The profile of stability and change we identified in our sample of older children and adolescents is consistent with this pattern: fewer age-related changes were observed for large commissarial and projection fiber pathways relative to hemispheric white matter. Such findings support the conclusion that white matter matures at different rates within different regions of the brain. Future work is necessary to examine differences in the rates of change across white matter in order to characterize regional growth patterns.

Independent of intelligence, speed of visual–spatial searching was related to FA in a number of hemispheric regions. A striking finding was that only right frontal–parietal–temporal regions contributed uniquely beyond the effect of age in accounting for performance, however. Further, age did not contribute significantly to visual–spatial searching when FA within these regions was first included in the models. Similar right-sided pathways are known to mediate visual–spatial information processing speed in adults (Tuch et al., 2005). Based on fMRI studies in adults, right frontal–parietal and temporal regions subserve visual attention and spatial awareness (Corbetta et al., 1993; Hopfinger et al., 2000; Karnath et al., 2001; Nobre et al., 1997): these are likely critical components of speeded visual searching. Considering that we found that both FA in right frontal–parietal–temporal regions and speed of visual–spatial searching increased with age, our findings are consistent with the role of white matter growth as mediating age-related changes in this critical cognitive function and delineate the role of regional brain growth as a mechanism of cognitive development.

Finally, relations with FA were observed for measures of rapid picture naming and sustained attention independent of intelligence: evidence that the maturation of white matter accounted for age-related changes in these processes was not present, however. We found that rapid picture naming, which involves both object recognition and lexical access, was related to FA within the left occipital

Table 4
Hierarchical regression models predicting visual–spatial searching with simple motor speed, age, and FA

	Model R^2	Model F ratio	Increment R^2	Increment F ratio
Right frontal				
Model 1:1 [a]				
1. Finger tapping and age	0.67	13.30 **	–	–
2. FA added	0.81	16.55 **	0.14	8.24 **
Model 1:2				
1. Finger tapping and FA	0.71	15.54 **	–	–
2. Age added	0.81	15.72 **	0.10	6.20
Right frontal–parietal				
Model 2:1				
1. Finger tapping and age	0.67	13.30 **	–	–
2. FA added	0.81	16.56 **	0.14	8.24 **
Model 2:2				
1. Finger tapping and FA	0.71	15.54 **	–	–
2. Age added	0.81	16.56 **	0.10	6.19
Right temporal				
Model 3:1				
1. Finger tapping and age	0.67	13.30 **	–	–
2. FA added	0.79	15.44 **	0.12	7.14 *
Model 3:2				
Finger tapping and FA	0.72	16.65 **	–	–
Age added	0.79	11.10 **	0.07	4.38

[a] Models were labeled separately for each relevant region of interest (i.e., Model 1 for the Right Frontal region, Model 2 for the Right Frontal–Parietal region, and Model 3 for the Right Temporal region). Within each region of interest, separate models were labeled with a second digit for those where either age was entered first (i.e., Model 1:1) or FA within the region was entered first (i.e., Model 1:2).

* $p<0.02$.

** $p<0.01$.

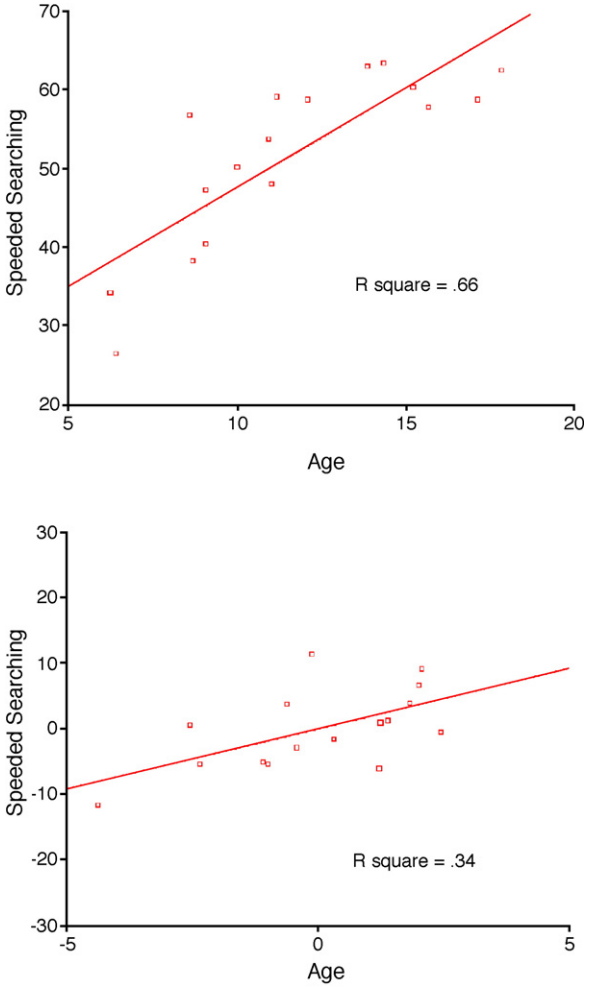

Fig. 5. Scatter plot of speeded visual–spatial searching as a function of age (top panel), and of the residuals for speeded visual–spatial searching as a function of age, after accounting for simple motor speed and FA within the right frontal region (bottom panel). Plots were similar when considering FA within the right frontal–parietal region, hence these plots are not presented.

lobe. Naming typically involves cortical networks within left frontal and temporal regions for adults (Gronholm et al., 2005; Hirsch et al., 2001). Increased organization of white matter within the left occipital lobe may facilitate faster access to relevant neural signals by these language processing networks. Decreased standard error in reaction time on a task of sustained attention was related to FA across multiple regions. Sustained attention is the ability to inhibit responding to detect rarely and unpredictably occurring signals over prolonged periods of time (Sarter et al., 2001). For children and adults it is mediated by primarily anterior neural networks (Coull et al., 1996; Lawrence et al., 2003; Sarter et al., 2001). That we did not detect unique contributions of white matter maturation for rapid picture naming or sustained attention suggests that either the time period we examined is not sensitive to change, or development of these functions are less related to white matter growth. It is notable that change in lexical processing have been related primarily to maturation of frontal and temporal neural activation (Brown et al., 2005, 2006; Schlaggar et al., 2002), and cognitive inhibition to frontal activation (Coull et al., 1996). Future work should focus on different trajectories relating brain maturation to behavior and the time course of changes across different regions and cognitive functions.

Our findings must be interpreted in light of the following limitations. First, we relied on cross-sectional methods to evaluate changes in structure–function relations. Such an approach may not be sensitive to cohort effects in brain structure or task performance (Brown et al., 2006; Durston and Casey, 2006b). Age was used as a continuous variable within our regression analyses however, which provides greater sensitivity in examining brain maturation (Brown et al., 2005). Second, some concerns exist regarding the representativeness of our sample, which limit generalizability. The distribution between males ($n=13$) and females ($n=4$) in the sample is not desirable for accounting for the effects of sex when considering developing brain behavior relations. As our sample included primarily males, our findings may reflect an underestimate of what might be seen for females when considering white matter growth, information processing speed and IQ. Further, mean IQ for our sample was almost one standard deviation above the normative mean. Third, variability in the tissue characteristics of white matter at the periphery of the brain with age must be considered when evaluating our findings within the hemispheric compartments. Finally, we did not account for the effects of experience on white matter integrity and performance in our design. Indeed, there is growing evidence that structural and functional reorganization in the brain can occur as a result of experience-related changes in cognition (Dick et al., 2006; Gaser and Schlaug, 2003). Children and adolescents likely have more experience with speeded information processing as they grow older (i.e., timed tests) and such experience may mediate structural changes in white matter. Training designs that account for both brain maturation and experience would be useful in addressing this concern (Durston et al., 2006).

We found that increased white matter organization is important in accounting for age-related change in visual–spatial information processing speed. Recent developmental models have emphasized the increasing specialization of neural activation as underlying cognitive change (Brown et al., 2005; Durston and Casey, 2006a, 2006b). Using fMRI paradigms, scientists have focused on whether a primary developmental process is contraction from distributed to regionally specified cortical networks (Durston and Casey, 2006a, 2006b), or whether both progressive and contractive changes in neural representation occur depending on the cognitive function examined (Brown et al., 2005, 2006). Our work is relevant to understanding a potential mechanism underlying such changes in representation. Specifically, our findings are consistent with the hypothesis that greater white matter organization and presumably efficiency in signal conduction, mediates improved information processing speed and ultimately cognitive development. Maturational processes, including glial proliferation, myelination, and increase fiber density and packing may boost axonal signaling, and subsequently yield greater efficiency in cognitive performance. Hence, maturation of white matter connections between and within specific regions is likely important for age-related changes in neural representation and improved performance. Developmental models of cortical specialization should incorporate the role of white matter maturation in mediating changes in cognition (Liston et al., 2006).

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