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Left lateralized white matter microstructure accounts for individual differences in reading ability and disability[☆]

Sumit N. Niogi, Bruce D. McCandliss [*]

Sackler Institute for Developmental Psychobiology, Weill Medical College of Cornell University, Box 140, 1300 York Ave., New York, NY 10021, United States

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Abstract

Diffusion tensor imaging (DTI) was used to investigate the association between variation in white matter microstructure and individual differences in reading skill within children. Unlike previous DTI studies of reading, our sample examined children in both the average reading range as well as several children in the performance range of reading disability (RD). Results replicate previous findings of a strong correlation between fractional anisotropy (FA) values in a left temporo-parietal white matter region and standardized reading scores of typically developing children. Furthermore, FA values in this same region accounted for differences between children scoring in the average range and children scoring in the RD range, suggesting that the role of white matter tract microstructure is best characterized as an extreme range on a continuum of typical variation. Furthermore, significant correlations between working memory and frontal white matter tract regions were present in this same population, yet were demonstrated to be independent of the relationships found between reading and more posterior regions. Results form a "correlational double dissociation" that demonstrates domain specificity in the influence of white matter tract structures to individual differences in cognitive performance.

Keywords: Development; Reading; Brain; White matter; MRI; Diffusion tensor imaging; DTI; Children; Reading disability; Dyslexia; Double dissociation; Working memory; Short term memory; Fiber-tracking

1. Introduction

Reading is an ability that is typically acquired late in childhood by most children of average intelligence with access to appropriate educational resources. Nonetheless, there is a wide range of variability in reading skills in both adults and children. Considering the more extreme end of poor performance, it is estimated that 5–17% of children in the United States demonstrate significant reading disability (RD) that cannot be accounted for by deficits in general intelligence or educational resources (Shaywitz et al., 1998). Such difficulties often persist into adulthood presenting significantly disabling symptoms (Rutter, 1987). The question of whether such reading specific disabilities represent a quantitatively distinct disorder or the lower end of a spectrum of continuous individual differences remains controversial (for recent reviews, see Shaywitz & Shaywitz, 2005).

Recent neuroimaging research on the neurophysiological correlates of RD has provided converging evidence linking RD to a failure to produce typically observed activation patterns in left lateralized networks of cortical regions. Two classes of generally well-replicated findings in this literature include the observation that adults and children with RD demonstrate reduced activation in left perisylvian regions in response to tasks that require phonological processing (Paulesu et al., 2001, 1996; Rumsey et al., 1997; Shaywitz et al., 1998; Temple et al., 2001), as well as reduced activation in left occipito-temporal regions in response to tasks that require access to visual word forms (Brunswick, McCrory, Price, Frith, & Frith, 1999; Paulesu et al., 2001; Salmelin, Service, Kiesila, Uutela, & Salonen, 1996; Shaywitz et al., 2002). Interestingly, a number of studies have implicated similar regions in brain–behavior correlational investigations of individual differences, both in populations spanning the average range of performance as well as in populations performing in the range of RD. For example, Shaywitz et al. (2002) demonstrated left occipito-temporal activation correlated with

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[*] Corresponding author. Tel.: +1 212 746 5837; fax: +1 212 746 5755.
E-mail address: bdm2001@med.cornell.edu (B.D. McCandliss).

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reading performance, and that such relationships held in both typically developing children as well as in children with RD. Similar results were found in adults with typical reading skills (Garrett et al., 2000). Furthermore, phonological ability and activation of left perisylvian region have been correlated in typically developing children, suggesting the possibility that cortical activation patterns related to those with RD may represent points of increasing severity on a continuum that includes individual differences in the typical range of performance (Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003).

One challenge that arises in interpreting this class of physiological evidence is the fact that subjects with RD cannot be fully equated with subjects from non-impaired populations on task demands and performance variables related to reading skills. Such differences are known to have a dramatic influence on physiological responses used in fMRI, PET, ERP and MEG studies (see Schlaggar et al., 2002 for discussion). In contrast, associations between brain *structure* and cognitive skill avoid this difficulty, potentially providing more direct links to the neurobiological contributions to individual differences in reading ability and disability.

A great deal of structural evidence has associated atypical structure in left lateralized cortical regions to RD, especially at the level of micro-anatomical structure (for review, see Eckert, 2004). In a recent example, Silani et al. (2005) used voxel-based morphometry measures with the same adults who previously demonstrated reduced activations for RD subjects in left temporal and occipital areas during positron emission tomography (PET) scans of reading tasks. The RD group demonstrated reduced gray matter density in these same left lateralized regions. In addition, this study demonstrated similar reductions in white matter density in several regions of the left hemisphere; a pattern that emerged consistently across English, Italian and French samples of participants. This finding of white matter differences between RD and control subjects may hold significant implications for understanding the neural basis of variations in reading ability. For example, several groups have proposed that RD may be characterized as a result of disruptions in functional connectivity between left hemisphere regions required for reading. Differences in white matter tract microstructure provide a neurobiological candidate for accounting for differences in such connections (Horwitz, Rumsey, & Donohue, 1998; Paulesu et al., 1996; Pugh et al., 2000).

With the advent of even more sensitive measures of white matter microstructure, such as magnetic resonance diffusion tensor imaging (DTI), it is now possible to non-invasively assess the contributions of such microstructure differences to individual differences in reading ability and disability (Basser & Jones, 2002).

1.1. *Diffusion tensor imaging*

Magnetic resonance diffusion tensor imaging is a technique to measure white matter integrity non-invasively. DTI operates by examining the diffusion of water in brain tissue (Basser, Mattiello, & LeBihan, 1994). In white matter, water diffuses more readily along the orientation of axonal fibers than in other directions due to obstruction from structural components such as the myelin sheath. Diffusion anisotropy, the degree of directionality of diffusion, can be measured as the variation of the eigenvalues of the diffusion tensor. Fractional anisotropy (FA), a normalized measure of diffusion anisotropy, has been shown to be sensitive to individual differences in white matter integrity and is sensitive to disease conditions that lead to loss of white matter integrity (Mukherjee et al., 2000; Virta, Barnett, & Pierpaoli, 1999; Werring, Clark, Barker, Thompson, & Miller, 1999). White matter tract development is a critical process that continues well beyond infancy into adulthood. The development of these tracts provides the connectivity considered essential for normal cognitive function that integrates processes across segregated regions (Barkovich, 2000; Ben Bashat et al., 2005; Luna & Sweeney, 2001; Paus et al., 2001).

There is mounting evidence that the integrity of white matter tract pathways, as measured by DTI, is systematically related to individual differences in performance across a wide range of cognitive skills (Edwards, Liu, & Blumhardt, 2001; Le et al., 2005; Schmithorst, Wilke, Dardzinski, & Holland, 2005; Urresta, Medina, & Gaviria, 2003). Perhaps the most striking evidence comes from patient studies involving white matter disorders and loss of cognitive function. Loss of white matter integrity due to demyelination has been implicated as an anatomical contributor to a number of neurological disorders associated with loss of cognitive function including schizophrenia, Alzheimer's disease and amyotrophic lateral sclerosis among others (Assaf et al., 2005; Ciccarelli et al., 2003; Kanaan et al., 2005; Nestor et al., 2004). Moderate to strong correlations have been reported between the severity of working memory deficits in Alzheimer patients and the severity of deficits in FA of specific white matter tracts (Fellgiebel et al., 2005; Rose et al., 2000). Recent DTI studies also suggest that severity of cognitive impairment due to closed head brain injury may correlate with severity of damage to white matter integrity (Mathias et al., 2004). Furthermore, individual differences in white matter integrity account for significant inter-individual variation in cognitive performance within typical developing populations. For example, FA in fronto-parietal white matter correlates with performance during working memory tasks, as well as with the magnitude of corresponding brain activations, showing strongest correlations in the anterior corona radiata (Olesen, Nagy, Westerberg, & Klingberg, 2003; Nagy, Westerberg, & Klingberg, 2004). Similarly, Liston et al. (in press) demonstrated that fronto-striatal differences in FA were associated with measures of cognitive control. In this study, DTI parameters reflecting white matter integrity in the anterior corona radiata correlated with reaction times from a go/no-go task.

As a whole, such studies provide examples of associations between variations in white matter tract measures and cognitive ability, yet leave open the possibility that particular white matter pathways are associated with more specific domains of cognitive function. Recent DTI studies of individual variation in reading ability demonstrate that FA values in particular temporo-parietal white matter tract structures correlate with reading ability. The findings across distinct cognitive domains showing cognitive performance correlations with specific white matter structures suggest that certain white matter tracts may demonstrate a form of domain specificity in their influence on individual differences in cognitive performance.

1.2. DTI and reading ability

Klingberg et al. (2000) reported the first DTI study specifically examining the relationship between reading ability and FA. They performed an exploratory whole-brain voxel-based analysis using Statistical Parametric Mapping software (SPM99, Friston et al., 1995) to spatially smooth and then normalize the brains to a common space before analyzing FA values. Results indicated a cluster of voxels in left temporo-parietal white matter, including the superior corona radiata (SCR) in the left temporal lobe, demonstrating lower FA for adults who reported reading difficulty as children. Furthermore, they performed a whole brain search for voxels that correlated reading performance with FA. A strong correlation was found to be significant within both a subset of adults with no history of reading difficulties, as well as within a small subset ($n = 6$) that reported childhood reading difficulties. Taken together, these results suggest that the same white matter tract relationship may account for individual differences extending beyond the normal range, potentially accounting for reading skills in the RD range. It should be noted, however, that only two of the subjects demonstrated scores of less than 1S.D. below the national average, thereby limiting the generalizability of the findings to the disabled range. This same left lateralized region of interest was also significantly correlated with a test of non-verbal intelligence, raising questions about specificity of the relationship between FA of this region and reading skill per se, although multiple regression analyses demonstrated that FA in this region accounted for at least some unique variance in reading skill beyond the variance shared with IQ.

Understanding the developmental implications of these adult findings is less than straightforward as the process of myelination continues through adolescence well into adulthood (Ben Bashat et al., 2005; Hayakawa, Konishi, Kuriyama, Konishi, & Matsuda, 1991; McGraw, Liang, & Provenzale, 2002; Mukherjee et al., 2001; Reiss, Abrams, Singer, Ross, & Denckla, 1996; Richardson, 1982; Schmithorst, Wilke, Dardzinski, & Holland, 2002; Yakovlev, 1967). White matter tract properties have been demonstrated to change in response to changes in experience (Juraska & Kopcik, 1988). Such considerations motivate DTI reading studies in children near the ages when reading is first being mastered. DTI studies conducted during early reading development help to test whether such white matter tract differences are influential early in the reading acquisition process, or appear later, perhaps as a result of years of experience differences that emerge between typical and disabled readers.

Beaulieu et al. (2005) used DTI to examined FA in 32 children, 8–12 years old, representing a wide range of reading abilities, including 2 children who tested below 1S.D. under the population mean. Like Klingberg et al. (2000), they used a voxel-based approach on spatially normalized brains, searching all voxels in the brain for those demonstrating a correlation with reading ability. Results demonstrated one large left lateralized temporo-parietal white matter area, including the SCR, which correlated with reading ability indexed by Word ID ($r = 0.54$), as well as four smaller regions primarily within the left hemisphere. The location of the strongest correlation fell within 6 mm of the region reported by Klingberg et al. (2000). This region was uncorrelated with non-verbal IQ, suggesting some degree of cognitive specificity. A second developmental study (Deutsch et al., 2005), also followed the same voxel-based DTI correlational approach, spatially normalizing brains in a sample of 14 children, 2 of whom scored less than 1S.D. below the national average on a standardized reading test. Reading ability and FA demonstrated a significant correlation within the left temporo-parietal region, including the SCR. Interestingly, this region also correlated with measures of spelling ability and a rapid naming task that did not involve reading, yet was uncorrelated with IQ. This pattern of findings provides further evidence for the nature of cognitive specificity of the influence of the reported white matter region on individual differences.

Together, these reading studies provide converging evidence in support of a structure–function relationship implicating left lateralized white matter tract microstructure and variability near the typical range of reading skill. Unfortunately, given the lack of sampling of individuals with skills in the range of reading impairments, the implications of such findings for RD are unknown.

The current study seeks to specifically include a broad range of children, including multiple children who scored less than 1S.D. below the national average. Taking advantage of the fact that several regions have been implicated in previous studies, the approach of this study is to assess FA values of a restricted set of a priori defined anatomical regions of interest (ROIs). These regions are defined on individual subjects' unmodified data, thereby avoiding potential disadvantages associated with voxel-based approaches (e.g. large multiple comparisons, potential artifacts or loss of sensitivity introduced via smoothing and spatial normalization). Tisserand et al. (2002) suggest that while voxel-based approaches are quick, reproducible among groups, and applicable to large datasets, the most accurate method for analysis is an anatomically based manual ROI approach. Studies also demonstrate that substantial inter-subject anatomical spatial variability exists after spatial normalization using SPM99, which potentially influences results (Ardekani et al., 2005). In the current study, we also seek to establish stronger evidence for specificity of structure–function relationships involving white matter areas by contrasting reading measures with other cognitive measures associated with frontal control structures that also continue to develop in late childhood and early adolescence.

2. Methods

2.1. Participants

Children were selected from a larger study investigating the neural basis of individual differences in reading ability and disability. The study included 31 children who (a) completed a neuroimaging session without significant motion or image artifacts during the DTI sequence, (b) demonstrated right handedness, (c) demonstrated proficiency with English, (d) whose families fell above the poverty line as defined by a family income-to-needs ratio and (e) whose parents reported

Table 1
Characteristics of the overall subjects and the two subgroups defined as those scoring above 1S.D. (non-impaired) or below 1S.D. (reading disabled) on Word ID

	Number	Male	Female	Age	Word ID	Non-verbal IQ	Income-to-needs ratio
Total	31	15	16	7.95 ± 0.91	86.8 ± 11.5	92.1 ± 12.9	3.41 ± 2.38
Non-impaired	20	7	13	7.75 ± 0.66	93.8 ± 7.33	93.8 ± 12.7	3.30 ± 1.48
Reading disabled	11	8	3	8.31 ± 1.19	77.7 ± 4.08	89.1 ± 13.4	3.60 ± 3.56

Reading disabled (RD) children were those that scored 1S.D. below the mean in Word ID test (score ≤ 85) and non-impaired readers (NI) were everyone else. There were roughly equal number of males and females in the study, and slightly more children in the NI group than the RD group. While the RD group has a lower mean non-verbal IQ less than the NI group, there is no significant difference between the groups ($p = 0.365$). Socio-economic status was controlled for by only selecting children with an income-to-needs ratio greater than 1 indicating that they were above the poverty line.

no other psychiatric diagnosis other than learning disability or ADHD. Written informed consent from parents and assent from children were obtained for all participants. The age range of the 31 participants was 6.5–10.3 years old (15 male and 16 female). Based on questionnaires given to each subject's parent regarding psychiatric, neurological or developmental problems the child may have been previously diagnosed with, four children in the reading disability range and two children in the non-impaired range had an attention deficit hyperactivity disorder (ADHD) diagnosis. During subsequent testing, two children in the non-impaired group demonstrated test scores consistent with clinical depression. These two cases were not excluded from the analyses as they had not been diagnosed by a clinician. Table 1 provides a summary of the population parameters for the participants.

As part of the larger study, each subject was given a series of standardized tests, including the Letter Word Identification subtest (Word ID), Word Attack subtest (Woodcock–Johnson III Tests of Achievement, American Guidance Service), the Wechsler Abbreviated Scale of Intelligence (WASI) and Matrix Reasoning subtest to measure non-verbal IQ. The Memory for Digits (Digit Recall) subtest measured children's working memory abilities (Comprehensive Test of Phonological Processing, CTOPP).

2.2. *MRI acquisition and analysis*

All magnetic resonance imaging protocols were approved by the Internal Review Board of Weill Cornell Medical College prior to testing. Diffusion tensor magnetic resonance imaging was acquired with a 1.5 T GE Scanner (GE Healthcare, Milwaukee, WI) using 26 gradient directions at $b = 1000\,\text{s/mm}^2$, 6 images with $b = 0\,\text{s/mm}^2$, 30 slices (5 mm thickness) with 128 × 128 resolution, and a field of view of 220 mm resulting in a pixel size of 1.71875 mm (Zhang et al., 2003). Images were post-processed offline using DTIStudio software (S. Mori, Johns Hopkins University) to obtain fractional anisotropy (FA) maps, average non-diffusion weighted images ($b = 0\,\text{s/mm}^2$), average diffusion coefficient images (ADC, $b = 1000\,\text{s/mm}^2$) and primary eigenvectors of the diffusion tensor.

To avoid several assumptions and potential confounds associated with spatial normalization of white matter tracts, a region of interest (ROI) approach was adopted to test five specific regions within each hemisphere selected in an a priori fashion from previous studies reporting correlations between FA and reading ability and/or working memory scores in individuals. Including ROIs from reading as well as working memory studies permits a test of the domain specificity of the contribution of white matter microstructure to individual differences in different domains of cognitive performance. These selected structures included the following right and left hemispheres structures: (a) the centrum semiovale (CS), (b) the superior corona radiata (SCR), (c) the superior longitudinal fasciculus (SLF), (d) the posterior limb of the internal capsule (PLIC) and (e) anterior corona radiata (ACR). The SCR has been shown to have significant group differences between typical and poor readers, and has also demonstrated strong correlations with reading performance in three studies (Beaulieu et al., 2005; Deutsch et al., 2005; Klingberg et al., 2000). The CS also overlaps part of the cluster that showed a significant group difference in the study by Klingberg et al. (2000). The SLF is a structure that connects Wernicke's and Broca's regions, and has been implicated by Klingberg et al. (2000) as being critical to the connectivity of visual and phonological processing areas. The PLIC has been shown in two studies to have voxels that correlate white matter anisotropy to reading performance (Beaulieu et al., 2005; Klingberg et al., 2000). Finally, FA values in the ACR have been shown to correlate with working memory performance (Nagy et al., 2004; Olesen et al., 2003).

These ROIs were selected using the Reproducible Objective Quantification Scheme (ROQS), a semi-automated process that segments white matter structures based on user-selected seed pixels. This technique has been shown to have higher inter- and intra-rater reliability than manual tracings of anatomical regions (Niogi et al., 2004). ROQS operates in a four-step process using directionally encoded information from the principal eigenvector to segment structures that the user first selects by assigning a seed pixel. The second step is to determine thresholds and selection criteria based on properties of the seed. During this step, the ROQS algorithm determines the x, y and z components of the principal eigenvector of the seed pixel, where the principal eigenvector denotes the direction of maximal diffusivity. ROQS restricts the selection to pixels with the same maximum component (x, y or z) of the principal eigenvector of the seed pixel. The third step is to create a binary mask such that pixels that fit the criteria determined in the second step are assigned a value of one and all other pixels are assigned a value of zero. The final step is for ROQS to determine the boundary of the structure. This occurs by drawing a vector from the seed pixel to a pixel with a value of zero. A chain-algorithm is then applied to determine and connect all boundary pixels. The final ROI includes all pixels within this boundary. The benefit of the ROQS analysis is that regions conforming to the boundaries of the tracts are selected using an objective, reproducible algorithm, in a fashion specific to each subject. The average and standard deviation of the FA is calculated for each ROI. Fig. 1 provides examples of ROQS ROIs for each structure.

One disadvantage of ROQS is that each subject contributes a uniquely sized and shaped ROI for a given structure. To complement this, a second ROI selection procedure was employed using standard sized ellipse shaped ROIs. Selection and analysis was implemented with software written by the first author in Interactive Data Language v6.0 (IDL, Research Systems Inc., Boulder, CO). Ellipses were prescribed on axial color-coded anisotropy maps at the center of each structure. The size and dimensions of the ellipse was kept constant for each tract across subjects. Fig. 1 provides examples of manually placed ellipse ROIs for each structure.

Subsequently, a correlation of FA for each ROI to Word ID, Word Attack, Matrix Reasoning, age and Digit Recall was calculated. Additionally, a lateralization index (LAT) was determined for each ROI using the following formula:

$$\text{LAT} = \frac{\text{right} - \text{left}}{\text{right} + \text{left}} \times 100$$

A negative lateralization score indicates the FA is relatively left lateralized across two symmetric ROIs while a positive lateralization score reflects relative right lateralization. Values close to zero suggest a lack of lateralization.

Subjects were then separated into two groups, children with RD and non-impaired children (NI), based on performance on Word ID. The RD group was defined as participants scoring less than 1S.D. below the normative mean of the standardized test (Word ID ≤ 85) while the NI group consisted of everyone else (Word ID > 85). Group differences were then calculated on measures of Word ID, Word Attack, Matrix Reasoning, lateralization index and FA of each ROI.

Non-parametric statistical tests were used to calculate correlations and group comparisons. Significance for correlations was calculated using a two-tailed Spearman's rank–order rho statistic, and group comparisons were carried out using Wilcoxon signed rank tests. Multiple linear regression analyses were

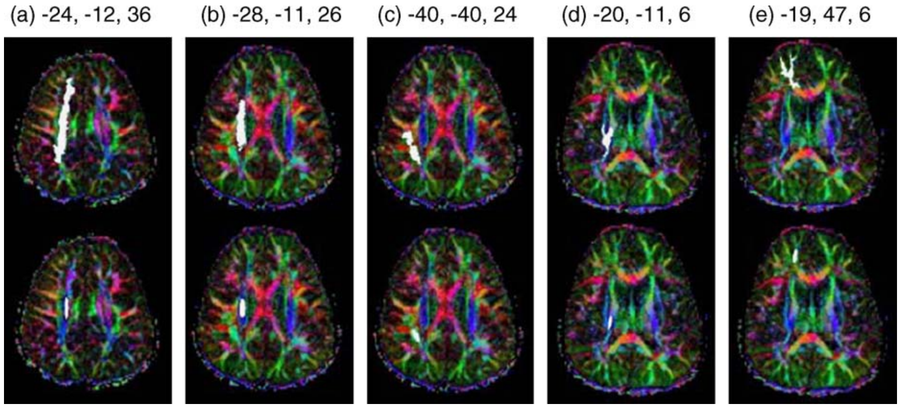

Fig. 1. The 5 ROIs of the study are illustrated for the left hemisphere of a single subject (the corresponding right hemisphere ROIs are not shown). On top are the corresponding ROQS ROIs that algorithmically trace the boundary of the structure on a 2D slice. On bottom are ellipses prescribed for the same structures. While the latter method maintains the size of the ROI across all subjects, ROQS adheres to the border of the structure on a subject-by-subject basis. Both types of analysis produced very similar FA scores which did not differ significantly. ROQS has the added benefit of being a more efficient method for ROI delineation. Shown are example left hemisphere ROIs. The corresponding right hemisphere structure was analyzed as well. Structures: (a) centrum semiovale; (b) superior corona radiata; (c) superior longitudinal fasciculus; (d) posterior limb of the internal capsule and (e) anterior corona radiata.

employed to test for the significance of differences between observed correlations as a direct test for a "correlational double dissociation" between specific structures and specific functions associated with reading and working memory.

2.3. Fiber-tracking

Fiber-tracking of white matter tracts was performed to illustrate the extent and pathways of the fiber tracts passing through the two primary ROIs, implicated in previous reports of white matter tract correlations with reading and working memory, using DTI-Query software v1.01 (Sherbondy, Akers, Mackenzie, Dougherty, & Wandell, 2005, Stanford University, CA). The fiber-tracking algorithm uses a streamlined technique similar to those developed by other groups (Mori, Crain, Chacko, & van Zijl, 1999). Starting from manually selected seed point within the respective region of interest, the algorithm determines the direction of greatest diffusion of the seed voxels and proceeds to match the direction of greatest of diffusion for neighboring voxels until a threshold of $\text{FA} = 0.15$ is met or the curvature of the connection between neighboring voxels increases to more than 70°.

3. Results

As shown in Table 2, correlations between cognitive measures and FA measures were analyzed using SPSS (SPSS Inc., Chicago, IL). FA from the ROQS ROIs did not differ significantly from the ellipse ROIs suggesting results were robust across individually shaped and sized ROIs. Consequently, further consideration of ROI results below is restricted to the ROQS ROI values.

As shown in Fig. 2a, a significant correlation between FA and Word ID was observed in the SCR of the left hemisphere ($r = 0.64$, $p < 0.001$) and the CS of the left hemisphere ($r = 0.58$, $p < 0.05$). No other ROI approached a significant level of correlation with Word ID. No regions correlated significantly with Word Attack when using non-parametric tests, although when using a two-tailed Pearson correlation, FA in the left SCR correlated significantly with Word Attack ($r = 0.37$, $p < 0.05$). The lateralization index for the SCR is significantly correlated with Word ID in the SCR ($r = 0.61$, $p < 0.001$) (see Fig. 3). Lateralization index of the other ROIs did not correlate significantly with any cognitive measure.

As illustrated in Fig. 2b, working memory, as indexed by Digit Recall, correlated bilaterally with FA in the ACR (right hemisphere, $r = 0.66$, $p < 0.001$; left hemisphere, $r = 0.61$, $p < 0.001$; bilateral average, $r = 0.65$, $p < 0.001$). No other ROI was significantly correlated with Digit Recall. Furthermore, no significant correlation in any of the ROIs was found with Matrix Reasoning or age.

Given that these sets of correlations together form an apparent "correlational double dissociation" between FA values in distinct white matter structures differentially linked to reading and working memory, a series of multiple linear regression analyses was carried out to examine whether these sets of significant correlations were significantly different from the observed

Table 2
Correlation coefficients of the fractional anisotropy of each ROI and lateralization index to Word ID, Word Attack and Digit Recall

Structure	Word ID	Word Attack	Digit Recall
CS right	0.38	0.14	0.35
CS left	0.58	0.25	-0.11
SCR right	-0.18	-0.02	-0.22
SCR left	0.64	0.37*	0.15
SLF right	-0.22	0.10	0.16
SLF left	-0.12	0.03	-0.16
ACR right	-0.18	-0.30	0.66
ACR left	-0.08	-0.11	0.61
PLIC right	0.28	0.05	0.17
PLIC left	-0.21	0.02	-0.19
LAT SCR	-0.61	-0.28	-0.26
LAT CS	-0.23	-0.12	0.32

Significant correlations are shaded in gray ($p < 0.05$, two-tailed Spearman's rho statistic). Word ID correlated strongly with the left CS ($p = 0.024$), left SCR ($p < 0.001$), and LAT SCR ($p < 0.001$). *Word Attack correlated significantly only with the left SCR using a Pearson's correlation ($p = 0.041$). Digit Recall correlated significantly bilaterally in the ACR ($p \leq 0.001$ for both hemispheres). There were no significant correlations to non-verbal IQ or age for any of the structures ($p > 0.05$). *Abbreviations:* centrum semiovale (CS); superior corona radiata (SCR); superior longitudinal fasciculus (SLF); anterior corona radiata (ACR); posterior limb of the internal capsule (PLIC); lateralization index (LAT).

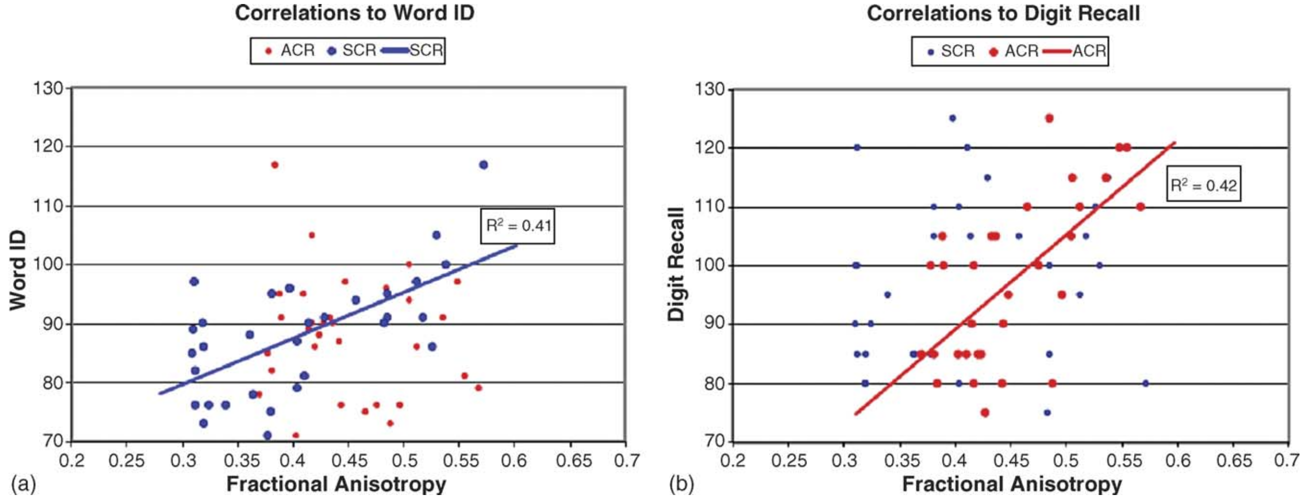

Fig. 2. Bivariate scatterplot of the relationship of FA values for the bilateral average of left and right ACR (in red) and left SCR (in blue) to (a) Word ID and (b) Digit Recall. When correlated with Word ID (a), there exists a significant correlation in the SCR ($R^2 = 0.41$, $p = 0.001$) but an insignificant correlation with the ACR ($R^2 = 0.02$, $p = 0.48$). When correlated with Digit Recall (b) there exists a significant correlation in the ACR ($R^2 = 0.42$, $p < 0.001$) but an insignificant correlation with the SCR ($R^2 = 0.02$, $p = 0.43$).

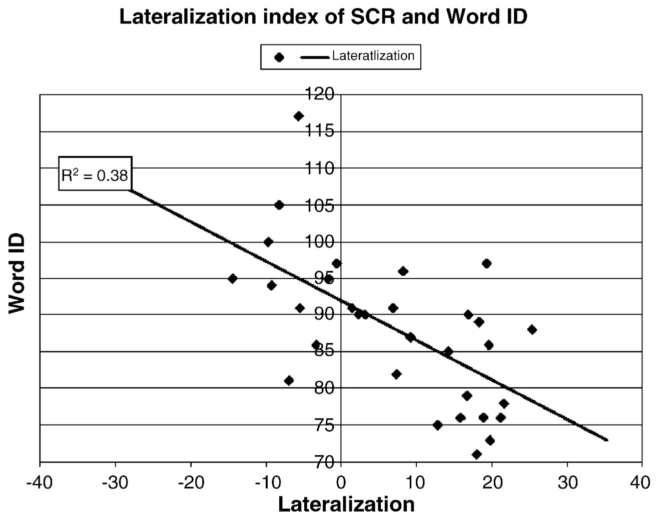

Fig. 3. Lateralization index of the superior corona radiata (SCR) correlates strongly with Word ID ($R^2 = 0.38$, $p < 0.001$). This relationship exists in superior–inferior fibers at the level of the corpus callosum, but not in centrum semiovale (CS) which also contain superior–inferior fibers about 10 mm above the SCR. Negative values indicate left lateralization while positive values indicate right lateralization.

non-significant correlations. Our goal was to construct a direct statistical test of the correlational double dissociation hypothesis by assessing whether the left SCR FA values accounted for additional variance in reading scores after controlling for working memory, and conversely to assess whether ACR FA values accounted for additional variance in the working memory after controlling for reading scores. This analysis also provided the opportunity to partial out the effects of age and non-verbal intelligence in the initial step.

Specifically, each multiple regression analysis consisted of three blocks of independent variables and FA of the relevant structure as the dependent measure. The first block contained age and non-verbal IQ as variables that are controlled for. The second block adds the "irrelevant" measure. In the case of the SCR, the irrelevant measure is Digit Recall; and in the ACR, the irrelevant measure is Word ID. The final block adds the "pertinent" parameter that loads on to the specific region. In the case of the SCR the pertinent parameter is Word ID, while in the ACR it is Digit Recall. As seen in Table 3, the SCR demonstrates a significant and substantial R^2 change in the final block when adding Word ID as an independent variable ($\Delta R^2 = 0.407$, $p < 0.001$). Likewise, as Table 4 demonstrates, adding Digit Recall in the final step demonstrated a significant change in R^2 the ACR ($\Delta R^2 = 0.497$, $p < 0.001$). These results demonstrate that read-

Table 3
Multiple regression analysis using three blocks to assess specificity of reading performance attributed to FA of the SCR

Model	R	R^2	Adjusted R^2	S.E. of the estimate	Change statistics				
					R^2 change	F change	d.f.1	d.f.2	Significant F change
1	0.318	0.101	0.029	0.07947	0.101	1.403	2	25	0.265
2	0.318	0.101	−0.011	0.08110	0.000	0.006	1	24	0.938
3	0.713	0.509	0.423	0.06125	0.407	19.071	1	23	0.000

The first block contains independent variables to be controlled for, age and non-verbal IQ (Matrix Reasoning). The second block contains the control variables and the proposed "irrelevant" measure, Digit Recall. The third block contains the previous independent variables and the "pertinent" parameter, Word ID. There exists only a significant R^2 change when including Word ID in the regression analysis. Model 1: non-verbal IQ, age; Model 2: non-verbal IQ, age, Digit Recall; Model 3: non-verbal IQ, age, Digit Recall, Word ID.

Table 4
Multiple regression analysis using three blocks to assess specificity of working memory attributed to FA of the ACR

Model	R	R^2	Adjusted R^2	S.E. of the estimate	Change statistics				
					R^2 change	F change	d.f.1	d.f.2	Significant F change
1	0.069	0.005	−0.075	0.05527	0.005	0.060	2	25	0.941
2	0.078	0.006	−0.118	0.05638	0.001	0.029	1	24	0.866
3	0.709	0.503	0.416	0.04073	0.497	22.981	1	23	0.000

The first block contains independent variables to be controlled for, age and non-verbal IQ (Matrix Reasoning). The second block contains the control variables and the proposed “irrelevant” measure, Word ID. The third block contains the previous independent variables and the “pertinent” parameter, Digit Recall. There exists only a significant R^2 change when including Digit Recall in the regression analysis. Model 1: non-verbal IQ, age; Model 2: non-verbal IQ, age, Word ID; Model 3: non-verbal IQ, age, Word ID, Digit Recall.

ing performance measured by Word ID loads above and beyond working memory to the superior–inferior fibers of the SCR. Conversely, working memory indexed by Digit Recall loads onto the frontal association fibers of the ACR independently of reading performance. Furthermore, both analyses revealed that the “irrelevant” cognitive measures in the first two blocks accounted for no significant variance in FA.

Group differences between the RD and NI group were assessed using a Wilcoxon signed rank test. Significant differences existed between the groups in Word ID ($p < 0.001$), Word Attack ($p = 0.044$), lateralization index of the SCR ($p = 0.018$) lateralization index of the CS ($p < 0.004$), FA in the left SCR ($p = 0.007$) and FA in the left CS ($p < 0.001$). Matrix Reasoning, Digit Recall, age, income-to-needs ratio and the other ROIs did not demonstrate significant group differences ($p > 0.05$).

Significant correlations existed in the RD group between Digit Recall and the ACR FA (bilateral average, $r = 0.66$, $p < 0.05$). Significant correlations existed in the NI group between Word ID and lateralization index of the SCR ($r = 0.46$, $p < 0.01$), Word ID and FA in the left SCR ($r = 0.51$, $p < 0.05$), and Digit Recall and both hemispheres of the ACR (bilateral average, $r = 0.69$, $p < 0.005$).

Fiber tractography was performed to illustrate the distinct nature of the two ROIs that independently accounted for individual reading performance differences in reading and working memory measures, respectively. Fig. 4 illustrates the primary direction of each fiber tract. The SCR has fibers that run primarily in the superior–inferior direction, while the ACR consists of association pathways that run primarily in the anterior–posterior direction. As visualized, the two structures demonstrated no connection.

4. Discussion

This study investigated the relationships between individual differences in children’s reading ability and white matter tract microstructure during early reading development. Our approach involved the use of a broader range of reading skills than previously reported, with the specific aim of including a substantial number of children tested in the range of RD. We also used an anatomically defined ROI analysis informed by previously reported findings for adults and children, allowing us to perform hypothesis testing on a limited set of regions specified in an a priori fashion based on each subject’s anatomy. Furthermore, ROI analysis avoids the potential influence of spatial smoothing and spatial registration associated with voxel-based analyses (Ardekani et al., 2005; Jones, Symms, Cercignani, & Howard, 2005; Tisserand et al., 2002) which often render FA findings ambiguous as to whether they reflect differences in microstructure or differences in gross anatomical shape and size. In this study we employed two methods of ROI analysis, each with specific strengths and weaknesses. The first technique, ROQS (Niogi et al., 2004), utilized a program that algorithmically defines the ROI conforming to the boundary of the structure. While this technique has been demonstrated to offer increased reproducibility, the sizes and shapes of the ROIs differ across

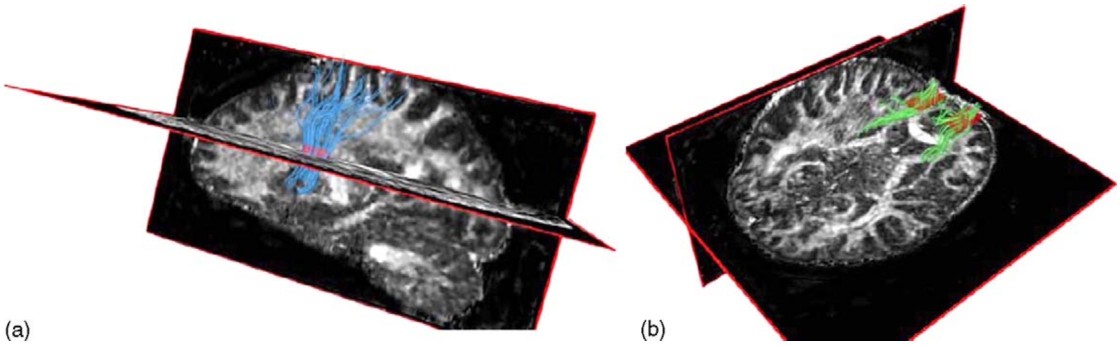

Fig. 4. Fiber tractography of the (a) left SCR and (b) ACR. The red prism indicates a volume of interest defining the seed voxels. As seen here, the SCR contains primarily fiber tracts that run in the superior–inferior direction while the ACR contains fibers that run anterior–posterior in the frontal region of the brain. The white matter integrity of the fiber tracts of the left SCR correlate significantly with reading performance. White matter integrity of the fiber tracts of the ACR bilaterally correlate significantly with working memory. As seen here, the two white matter bundles are not connected and show specific relationships to different domains of cognitive ability.

subjects. The manual technique of prescribing an ellipse does not have the latter concern, but is prone to more inter-rater variability than ROQS. Both techniques produced similar FA values as well as equivalent statistical relationships with cognitive measures for each ROI, suggesting that the pattern of observed results is unlikely to be attributable to subtle differences in ROI selection.

Results across the entire sample of 31 children, as well as a subset analysis of children testing within the normal range of reading performance, replicated several of the previously reported findings. FA values in two *left* temporo-parietal regions, the left SCR and the left CS were each highly correlated with standardized word identification skills, while homologous structures on the right demonstrated no such correlation. This result is consistent with findings from adults (Klingberg et al., 2000) as well as in two independent samples of children performing primarily in the typical range of reading skills (Beaulieu et al., 2005; Deutsch et al., 2005).

Correlations with decoding ability (Word Attack) and white matter tract microstructure measures failed to reach significance when a non-parametric Spearman's rho was used, although we did note a significant correlation when a parametric approach was used as well as a significant group comparison between reading disability and non-impaired groups in the SCR. Other reports of left SCR show correlations with both Word ID and Word Attack in adults (Klingberg et al., 2000) and children (Beaulieu et al., 2005; Deutsch et al., 2005). The location of this left SCR region is consistent with previous studies demonstrating significant correlations between reading scores and FA. The average location of our anatomically based ROIs ($x = -28$, $y = -11$, $z = 24$) fell within 9 mm of the average of the three previously reported ROIs (Beaulieu et al., 2005; Deutsch et al., 2005; Klingberg et al., 2000).

Furthermore, this study replicates previous findings establishing that such correlations are distinct from associations with more general non-verbal IQ measures. As in previous studies, age and non-verbal intelligence were uncorrelated with any of the reported ROIs. As indicated by multiple linear regression analysis, FA scores in left SCR accounted for unique variance in reading scores even after working memory, age and non-verbal intelligence were controlled for.

These results provide strong converging evidence for a systematic correlation between microstructure of white matter tracts in left temporo-parietal regions and individual differences in reading ability. Specifically, individual variation in white matter microstructure within the left SCR accounts for approximately 40% of the variance in standardized scores of reading ability across studies of both adults and children. This finding, originally reported in adults, has now been replicated in three independent samples of children, suggesting that this form of structure–function relationship is influential during the early years of reading acquisition, rather than reflecting the influence of years of altered experiences associated with poor reading versus average reading ability from childhood to adulthood.

Furthermore, replicating such relationships using a priori anatomically based ROI analyses suggest that previous findings are not likely attributable to the influence of spatial smoothing or individual differences in spatial alignment of white mater tract regions that are largely unconstrained in SPM99 normalization procedures.

The current results also extend previous findings in several important ways. This is the first study to examine such white matter effects in and adequately sampled RD population. This extension provides an important test of dimensional models of RD that portray reading disabilities as an extreme range of a continuum that accounts for individual variability in reading performance, and extends such models by proposing white matter microstructure in left hemisphere regions as a potential mechanism accounting for such broad individual differences. Previous DTI studies of reading primarily sampled individuals in the typical range of reading ability, and included at most 2 RD individuals who surpassed a threshold of testing more than 1S.D. below the national mean. This corresponds to approximately the 16th percentile of performance, which is in accord with the upper range of prevalence estimates for RD in the United States. (Shaywitz et al., 1998). The current study, which includes 11 such cases, provides the possibility of testing whether the same white matter microstructure regions that account for approximately 40% of the typical variation in reading ability also account for differences between RD and non-impaired populations.

Group tests comparing RD and non-impaired children demonstrated significant differences in FA scores within only the left SCR and the left CS. Such results directly parallel correlational findings that demonstrated sensitivity to individual differences across the entire group. These findings support the notion that the contribution of white matter tract microstructure to RD reflects a more extreme range on a continuum with individual differences displayed by typically developing readers.

Across each of the reported studies, including the present results, correlations between reading and white matter tract structures were predominantly in the left hemisphere, suggesting a potentially important role for lateralization of function. For example, both Klingberg et al. (2000) and Deutsch et al. (2005) found significant reading-FA correlations in the left SCR, but not in any right hemisphere region. Beaulieu et al. (2005), however showed a reading-FA correlation in a similar region on the left, but also found a smaller corresponding region in right hemisphere that was also significantly correlated with reading ability. Such findings provide indirect, albeit mixed, evidence in support of the left lateralization of structure–function relationships in the domain of reading. Several potential factors, however, could lead to null findings within the right hemisphere without necessarily indicating significant lateralization of function. To address this question more directly, the current study established a "lateralization index" score for each subject, which directly contrasted FA values on a subject-by-subject basis in the left and right SCR ROIs, as well as the left and right CS ROIs. Lateralization index scores were significantly correlated with standardized tests of Word ID specifically in the SCR ROIs. Interestingly, no such correlation was found in the lateralization index of the CS ROIs demonstrating a potentially stronger role of the superior–inferior fibers at the level of the body of the corpus callosum for the observed lateralization effects. This provides the first direct evidence that the degree to which subjects demonstrated lateralization of white matter tract microstructure was systematically correlated with reading performance. Furthermore, as a group, the RD subjects demonstrated considerable right lateralization in SCR ROIs. Such findings are potentially consistent with other neuroimaging results that demonstrate atypical over-activation of right temporo-parietal readings or under-activation of left temporo-parietal readings in RD populations performing reading tasks, as well as right lateralization of temporo-parietal sources (Shaywitz et al., 1998; Simos, Breier, Fletcher, Bergman, & Papanicolaou, 2000).

In summary, the results from the reading measures indicate that a specific portion of white matter tracts are systematically related to individual differences in the average range of reading ability, and that this same relationship is on a continuum which accounts for differences between RD and NI populations. Patterns of lateralization of the implicated regions may play an important role accounting for approximately 38% of variance in reading scores; with right lateralized scores associated with lower reading scores and reading disabilities. The particular region most typically and robustly implicated across studies appears to be an area of the left temporo-parietal region, identified by our methods as corresponding to the left SCR – a region dominated by fiber tracts oriented in the superior–inferior direction. Klingberg et al. (2000) indicate anterior-posterior fiber tracts in this general region. Furthermore, Nagy et al. (2004) report a correlation between reading speed and a left temporal cluster that they report contain some association fibers in the anterior–poster direction. These reports of anterior–posterior fibers associating with reading stand in contrast to our current findings which specifically demonstrate integrity of superior–inferior fibers accounting for differences in reading ability, and show no such association when anterior–posterior fibers are directly examined using a method that allows the direction of fibers to be verified on a subject-by-subject basis. This result is consistent with both the Beaulieu et al. (2005) and Deutsch et al. (2005) studies, which clearly identify a similar region dominated by superior–inferior fibers, and provide no direct support for anterior–posterior fibers associated with reading ability.

There is no clear consensus for the role such left lateralized superior–inferior fiber tracts play in the connectivity of cortical regions associated with reading. One potentially fruitful direction for future research may involve combinations of DTI and functional magnetic resonance imaging (fMRI) analysis of reading-related activation to investigate such issues (e.g. Olesen et al., 2003).

Correlations between white matter microstructure and performance in specific cognitive domains raise broader questions with implications for basic research. For example, is the association between left SCR microstructure and reading highly specific to that particular cognitive domain? Previous results showing independence of correlations between left SCR and other global cognitive measures such as non-verbal IQ suggest that these white matter tract structures are at least somewhat specific to reading ability, and null results in other white matter tract regions suggest that reading ability is not necessarily associated with whole-brain differences in white matter tract structure. However, both of these claims of specificity are limited by the nature of the evidence, as they rely on the absence of findings to establish specificity.

To provide more direct evidence for the specificity of structure–function relationships between particular white matter regions and particular domains of cognitive function, the current study was expanded to include a measure of working memory. The *anterior corona radiata*, previously implicated to have FA values correlated with working memory performance in children was therefore included as an ROI for analysis (Olesen et al., 2003). Results of the working memory analysis replicated previous findings, demonstrating a significant correlation between performance on a standardized working memory task and FA values in bilateral ACR regions.

This aspect of the study extends findings of a prior study demonstrating two separate correlations within the same population—reading performance with left temporal white matter and a working memory with frontal white matter (Nagy et al., 2004). Nagy et al. (2004) used a non-standardized reading time measure as an index of reading ability and showed a correlation to only one large cluster in the left temporal lobe, and used a non-standardized visual–spatial working memory task that correlated with frontal white matter, using SPM (Friston et al., 1995). No direct test, however, was presented to directly examine the specificity of these two relationships. By contrasting measures of reading and working memory across several ROIs previously associated with each of these domains, we sought to assess the possibility of a “correlational double dissociation” within a single population of subjects. It is important to note that these two structures, the SCR and ACR, are well separated. The region of the ACR correlating with working memory is about 20 mm inferior and 58 mm anterior to the ROI of the SCR. Moreover, the ACR fibers run in the anterior–posterior direction whereas the SCR run primarily in the superior–inferior direction. Results of both correlational analyses and a series of multiple linear regression analyses indicate that within the same sample of children, reading skill is specifically correlated with FA values in left SCR regions, and working memory skill is specifically correlated with FA values in bilateral ACR regions. Conversely, FA values in the ACR regions account for no significant variance in reading scores, and FA values in the left SCR region account for no significant variance in the working memory measure. Taken together, results of the two multiple regression analyses provide direct support for a “correlational double dissociation” pattern in the same indicates that particular regions of white matter tracts are specifically associated with individual differences in separable domains of cognitive function. The presence of such a correlational double dissociation suggests that the link between individual differences in specific domains of cognitive performance, such as reading and working memory, are likely mediated by individual microstructure differences in specific white matter tract circuitry.

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