Brain connectivity in non-reading impaired children and children diagnosed with developmental dyslexia

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ABSTRACT

Diffusion Tensor Imaging (DTI) was used to investigate the relationship between white matter and reading abilities in reading impaired and non-reading impaired children. Seventeen children (7 non-reading impaired, 10 reading impaired) participated in this study. DTI was performed with 2 mm isotropic resolution to cover the entire brain along 30 noncollinear directions. Voxelwise analyses were conducted on data processed through Tract Based Spatial Statistics (TBSS). The data replicated previous results seen across multiple studies and extended findings to include measures of both real word and pseudoword decoding. Negative correlations were observed in the left posterior corpus callosum between fractional anisotropy (FA) values and both measures of decoding. Positive correlations between FA values and real word and pseudoword decoding were observed in the left superior corona radiata. This extension of findings regarding correlations between the corona radiata and reading skills suggests an important direction for future research into the neurological substrates of reading.

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Functional brain imaging studies have identified a distributed network of brain regions located in both the left and right hemispheres as being involved in skilled reading. In particular, decoding words is associated with three left hemisphere brain regions: (a) the juncture of the posterior temporal and anterior occipital lobes, (b) the juncture of the superior temporal and inferior parietal lobes, and (c) a region of the inferior frontal lobe (e.g., Pugh, Mencl, Jenner, et al., 2000). When reading, typically developing children engage both frontal and posterior regions of this network (Epelbaum et al., 2008; Hoeft et al., 2007; Horwitz, Rumsey, & Donohue, 1998; McCandliss, Cohen, & Dehaene, 2003; Pugh, Mencl, Jenner, et al., 2000; Shaywitz et al., 2002). Whereas, in contrast, individuals with dyslexia do not engage the posterior portions of it (Hoeft et al., 2007; Shaywitz & Shaywitz, 2004).

In addition to the research that has focused on the functionality of distributed cortical areas, researchers have also used Diffusion Tensor Imaging (DTI) to test the notion that reading difficulties are associated with a disconnection between temporo-parietal and frontal regions (Horwitz et al., 1998; Paulesu et al., 1996; Pugh, Mencl, Shaywitz, et al., 2000; Temple, 2002). DTI is a magnetic resonance imaging technique that can measure the impact of biological structures, such as white matter, on the nonrandom (i.e., anisotropic) diffusion of water within a system, such as the brain (for a review see, Beaulieu, 2002). A common value calculated from the resulting images is fractional anisotropy (FA), which provides a normalized measure of the magnitude of the direction of the anisotropic diffusion within a given voxel (Basser, 1995; Niogi & McCandliss, 2006). These values range from zero to one, with higher values being related, in part, to the tendency of the white matter within a given voxel to be oriented primarily in the same direction. However, high FA values are related to other characteristics of white matter within a voxel, such as fiber crossings (Ben-Shachar, Dougherty, & Wandell, 2007; Smith et al., 2006; Snook, Paulson, Roy, Phillips, & Beaulieu, 2005).

Given the importance of left hemisphere cortical regions for skilled reading, it was initially hypothesized that individuals with dyslexia would demonstrate less integrity along the left superior longitudinal fasciculus, a white matter tract which connects the anterior and posterior components of the left hemisphere reading network. Using DTI, Klingberg et al. (2000) provided initial support for this hypothesis by observing a decrease in FA values in bilateral temporo-parietal white matter in a group of adults with reading difficulties when compared to non-impaired readers. Furthermore, the levels of FA values in left temporo-parietal areas were correlated with measures of phonological decoding in both impaired and non-impaired readers. Additionally, Deutsch et al. (2005) replicated these findings with children. Such findings could be interpreted as

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evidence for the importance of the integrity of the left superior longitudinal fasciculus for reading.

However, other researchers have failed to observe white matter projections along the anterior–posterior axis to be related to reading and instead have observed superior–inferior projections to be associated with reading ability. For example, in a study of 8–12-year-old children, who had a wide range of reading abilities, Beaulieu et al. (2005) reported the largest cluster of voxels observed to correlate with phonological decoding to be located on the posterior limb of the internal capsule, a thalamic projection along the superior–inferior axis. More recently, Niogi and McCandliss (2006) replicated these findings in 6–10-year-old children by having observed FA values in the left internal capsule, semiovale and superior corona radiata, to have been positively correlated with reading ability in non-reading impaired as well as reading impaired children. They concluded that reading ability is dependent on left lateralized white matter tracts located in the temporo-parietal region that projects in the superior–inferior direction opposed to white matter tracts, such as the superior longitudinal fasciculus, which projects along the anterior–posterior axis (see also, Dougherty et al., 2007).

Thus, past research has clearly established that there is a relationship between reading ability and white matter tracts located in the left hemisphere. Yet, some findings seem to highlight white matter regions nested within the left hemisphere reading network, specifically the superior longitudinal fasciculus (Deutsch et al., 2005; Klingberg et al., 2000), while other data point to the relationship of reading to white matter areas extending out of the thalamus that project along the superior–inferior axis (Beaulieu et al., 2005; Niogi & McCandliss, 2006). Therefore, we were interested in the extent to which we would replicate one or both of these previous findings.

In addition to finding different cortical tracts to be related to basic reading skills, researchers have used different measures of these reading skills to obtain their results. For example, Klingberg et al. (2000) observed correlations between FA values located in the left temporo-parietal region and measures of both real word and pseudoword decoding. However, although Niogi and McCandliss (2006) observed correlations between decoding real words and FA values in left hemisphere brain regions, they failed to observe correlations between decoding pseudowords and FA values. As such, there presently is a need for additional research to help resolve these varying results regarding real word and pseudoword decoding.

Finally, prior researchers have frequently constrained analyses to areas of the left temporo-parietal lobes. Such analyses are extremely important and have allowed researchers to have gained a deeper understanding of the relationship of reading to cortical projections within these areas, but these analyses do not allow for the identification of other white matter regions that may be related to reading ability. For example, when FA values in the corpus callosum were analyzed, a relationship between these values and reading was observed in posterior regions of this structure (Dougherty et al., 2007). In addition to attempting to replicate past correlations observed between temporo-parietal regions and reading (Beaulieu et al., 2005; Deutsch et al., 2005; Klingberg et al., 2000; Niogi & McCandliss, 2006), it is also valuable to replicate the relationship of reading to other brain regions, such as the posterior corpus callosum (Dougherty et al., 2007).

To accomplish these goals, the present study involved the computation of the correlation between measures of real word and pseudoword decoding and FA values obtained through DTI in both non-impaired readers as well as children diagnosed with developmental dyslexia. Furthermore, Tract Based Spatial Statistics (TBSS; Smith et al., 2006) were applied in order to conduct whole brain analyses intended to identify the extent to which reading abilities related to white matter tracts in areas other than temporo-parietal brain regions. TBSS has several advantages, one being that this analytic approach was designed with group analyses in mind and is well suited to converting images obtained from different individuals to a standard space. Additionally, the analytic approach was designed to constrain analyses to white matter tracts observed across all participants.

1. Methods

1.1. Participants

Ethical review boards at the participating institutions approved all procedures. Informed written parental consent and child assent were obtained for all participants. Seventeen children, 10–14 years old, who did not show evidence for hearing loss, neurological disorders, psychiatric problems, ADHD, or English as a second language, participated in the study. Children were screened for attention difficulties through parent and teacher reports. Additionally, psychiatric and emotional problems were identified based on a review of the child's medical history and parent reports. Of the participants, 8 were female and 16 were determined to be right handed as per administration of the Edinburgh Handedness Inventory (Oldfield, 1971).

Ten of the 17 participants were children whose diagnosis of dyslexia and reading intervention occurred at a hospital center for learning disabilities (Avrit et al., 2006). Within this intervention program, small groups of 4–6 children received explicit instruction and guided practice in phonological decoding and comprehension strategies from certified academic language therapists for approximately 90 min a day for 4 days each week over 2 academic years. In addition to the 10 children diagnosed with dyslexia, 7 approximately age- and gender-matched children were recruited from the community to serve as non-impaired readers. Parent interviews and assessment of reading and related skills, as shown in Table 1, confirmed that the control participants had experienced no difficulties learning to read.

1.2. Behavioral assessment

All participants' reading and related skills were confirmed before participation in this study and are presented in Table 1. On the day that they were scanned, non-impaired readers were administered a test battery which assessed intellectual aptitude, phonological awareness, word reading, and phonological decoding. Measures of reading and related skills were obtained from all participants in the dyslexia sample within 3 months of MR scanning. The participant's phonological decoding scores were measured by the polysyllabic nonword reading portion of the phonics subtest of the Decoding Skills Test (DST; Richardson & DiBenedetto, 1985). This test is a criterion-referenced instrument, which is administered by having participants read aloud isolated pseudowords (e.g., thrain). A score of .70 correct represents adequate decoding proficiency. Word reading or word recognition was measured by the basic reading subtest of the Wechsler Individual Achievement Test Second Edition (WIAT-II; PsychCorp, 2002). This subtest requires participants to read aloud isolated words that increase in length and decrease in frequency. The WIAT-II is an individually administered test designed to assess academic achievement for individuals aged 4–85 years old (Lichtenberger & Smith, 2005).

As shown in Table 1, prior to MRI, the children with dyslexia and the non-impaired readers still differed in their word reading abilities $t(15) = 2.56$, $p = .02$, but not in phonological decoding or phonological awareness, $t(15) = 1.42$, $p = .18$; $t(15) = .90$, $p = .39$. There was also a marginally significant difference in intellectual ability between the non-impaired readers and the children with dyslexia, $t(15) = 2.23$, $p = .04$.

Table 1
Group profiles at pre-treatment and before MRI.

	Non-impaired readers ($n = 7$)	Children with dyslexia ($n = 10$)	
	Pre-MRI	Pre-treatment	Pre-MRI
Age in months	146.43 (13.91)		147.8 (17.97)
Gender[a]	.43	.50	.50
Full-scale IQ	111 (6.83)	101.70 (9.38)	
Phonological awareness SS[b]	109 (7.55)	88.3 (11.53)	103.90 (13.64)
Phonological decoding PC[c]	.84 (.15)	.30 (.25)	.72 (.20)
Word recognition SS[d]	109.14 (6.39)	83.9 (9.45)	95 (13.50)

Note: SS = Standard Score. PC = Percent Correct. Standard deviations are in provided parentheses.

[a] Percent female.
[b] Comprehensive test of phonological processing.
[c] Decoding Skills Test.
[d] Wechsler Individual Achievement Test II.

1.3. Image acquisition

All participants were prepared for the scanning environment by first training in a full-scale mock-up MR scanner. Whole brain images were then acquired on a 3-T Siemens Trio Tims MR scanner using a 12-channel radio frequency head coil. Structural images were acquired from 160 1 mm sagittal slices using a multiplanar rapidly acquired gradient echo sequence (flip angle = 9°; TE = 2.91 ms; TR = 2250 ms; inplane resolution = 1 mm × 1 mm; matrix size = 256 × 240). DTI was performed using an echo planar imaging sequence (flip angle = 90°; TE = 90 ms; TR = 9600 ms or 8500 ms; inplane resolution = 2 mm × 2 mm; field of view = 256 mm; matrix size 128 × 128). Sixty-four 2 mm slices were acquired with no interslice gap. The diffusion tensor acquired for each slice included 5 images without diffusion weighting ($b = 0$ s/mm^2) and diffusion weighted images along 30 noncollinear directions ($b = 700$ s/mm^2). While this study was in the data collection phase the scanner software was upgraded.

Consequently, a modification was made to the DTI scanning sequence so that it would run on the upgraded scanner software. This modification resulted in some participant's sequence having a TR of 8500 ms. Seven of the impaired readers and 4 of the non-impaired readers were scanned after the software upgrade and consequently their sequence had a TR of 8500 ms.

1.4. MR data analysis

The 5 non-diffusion weighted ($b = 0$ s/mm^2) images were visually inspected for participant motion and scanner induced artifacts. Each participant's first non-diffusion weighted image with minimal motion artifacts was chosen to align the following images in order to correct for head motion and the effects of gradient coil eddy currents. For all but two of the participants this was the first $b0$ image, and for the remaining participants this was the second $b0$ image. Eddy currents in the

Table 2
Areas of significant correlation between participants' scores on the polysyllabic nonword reading portion of the phonics subtest of the Decoding Skills Test, a measure of phonological decoding, or the WIAT-II basic reading subtest, a measure of word recognition and the FA values on the FA skeleton. Coordinates for the voxel of maximum intensity are reported in MNI and all differences have been corrected for multiple comparisons across space with the family-wise error rate set to $p < .05$.

White matter tract	MNI coordinates (x, y, z)	Number of voxels	r	t value
Decoding Skills Test				
Left superior corona radiata	−20, −8, 37	173	.75	4.39
Right inferior fronto-occipital fasciculus	16, 30, −19	161	.89	7.41
Left inferior fronto-occipital fasciculus	−11, 26, −10	138	.82	5.54
Right uncinate fasciculus	38, −1, −31	137	.81	5.26
Left superior corona radiata	−15, −9, 44	111	.70	3.78
Right inferior longitudinal fasciculus/inferior fronto-occipital fasciculus	43, −40, −11	91	.76	4.57
Left posterior corpus callosum	−11, −35, 24	97	−.70	−3.79
WIAT				
Left corticopontine tract/superior thalamic radiation	−20, −10, 34	222	.76	4.59
Right posterior limb of the internal capsule	27, −24, 14	202	.67	3.47
Left superior corona radiata	−13, −9, 47	193	.75	4.45
Right superior corona radiata	21, 4, 45	74	.75	4.35
Left posterior corpus callosum	−6, −35, 20	74	−.71	−3.91
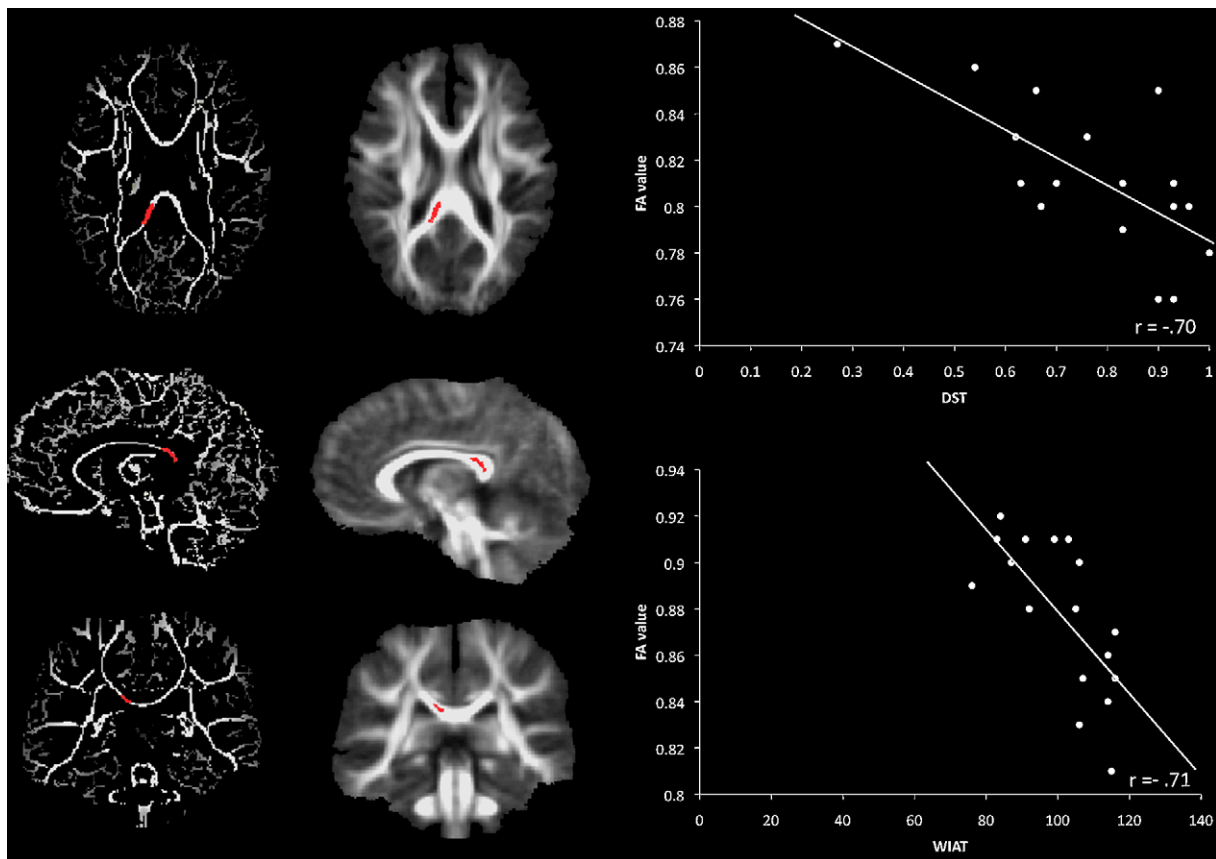
Fig. 1. Overlap observed between the correlations of the DST and WIAT-II to FA values in the posterior corpus callosum overlaid on the mean FA skeleton (left) and mean FA (right) images. The scatterplots reflect the correlation between the FA value of the maximum intensity voxel of the clusters corresponding to the overlap area and scores on the DST (top) and WIAT-II (bottom).

gradient coils can result in some diffusion weighted images appearing stretched or sheared. The eddy correct tool in the FMRIB FDT toolbox corrected for these distortions, as well as participant head motion, by employing an affine registration to a reference volume (Behrens et al., 2003). Brain extraction was performed on the chosen non-diffusion weighted image using BET (Smith, 2002) to create a mask that excluded non-brain voxels from further processing steps. Then, DTIFit was used to calculate the diffusion tensors, which allows for the computation of the principle diffusion direction, the mean diffusivity, and each voxel's fractional anisotropy (FA) value (Behrens et al., 2003).

Following procedures outlined in Smith et al. (2006), Tract Based Spatial Statistics version 1.2 (TBSS) were performed to place each participant's FA images into a standard space allowing for voxel-wise statistical analyses of the FA values to be conducted across participants. Each participant's FA images were aligned to all other FA images and the "most representative" image was identified as the target image. The target image was affine-aligned into MNI152 standard space, and using a combination of the nonlinear registration FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b) and the affine transformed target FA image, all participants' images were transformed into 1 mm^3 MNI152 space. Then, a mean FA image was created and used to generate a mean FA skeleton. The mean FA skeleton was thresholded at an FA value of .2 to restrict further analyses to points within white matter tracts, which have been successfully aligned across all participants. Finally, each participant's aligned FA image was projected onto the mean FA skeleton. This enables the participant's FA image to be aligned with the skeleton even though there was not a perfect nonlinear preregistration (Smith et al., 2006).

1.5. Group analysis of FA values

Analysis of the participants' phonological decoding and word recognition scores, and their FA values at the voxel level were conducted using a permutation-based approach (Nichols & Holmes, 2002) with cluster-based thresholding to account for the family-wise error rate ($t > 2.13$, $p < .05$). The clusters that satisfied this criterion were then visually inspected to confirm that they were contained within the computed FA skeleton, and their anatomical locations were then manually labeled using a white matter atlas (Mori, Wakana, Nagae-Poetscher, & van Zijl, 2005). Furthermore, the primary eigenvectors were projected onto the mean FA skeleton using TBSS and were visually inspected to confirm the primary orientation of all significant regions

corresponded to the orientation of the tract labels determined through the use of the white matter atlas. Clusters are reported in terms of the MNI coordinate system (x, y, z) for the voxel with the strongest correlation coefficient in that cluster.

2. Results

2.1. Correlations between FA values and phonological decoding

Participants' phonological decoding scores of polysyllabic non-words (DST; Richardson & DiBenedetto, 1985) were correlated with the participants' FA values. The results of these analyses are presented in Table 2 and revealed 7 clusters of voxels that were significantly correlated with phonological decoding. Voxel-wise multiple regression analyses revealed that age and gender did not have a significant contribution to the correlations observed between decoding pseudowords and FA values.

Clusters with strong positive correlations were located on 2 locations of the left superior corona radiata (−20, −8, 37; −15, −9, 44), the left (−11, 26, −10) and right (16, 30, −19) inferior fronto-occipital fasciculus, the right uncinate fasciculus (38, −1, −31), and an area that was determined to be located on either the right inferior longitudinal fasciculus or the inferior fronto-occipital fasciculus (43, −40, −11). Negative correlations were observed between the participant's FA values and the left posterior corpus callosum (−11, −35, 24).

2.2. Correlations between FA values and word recognition

Participants' word recognition scores were also correlated with their FA values. The results of these analyses are presented in Table 2
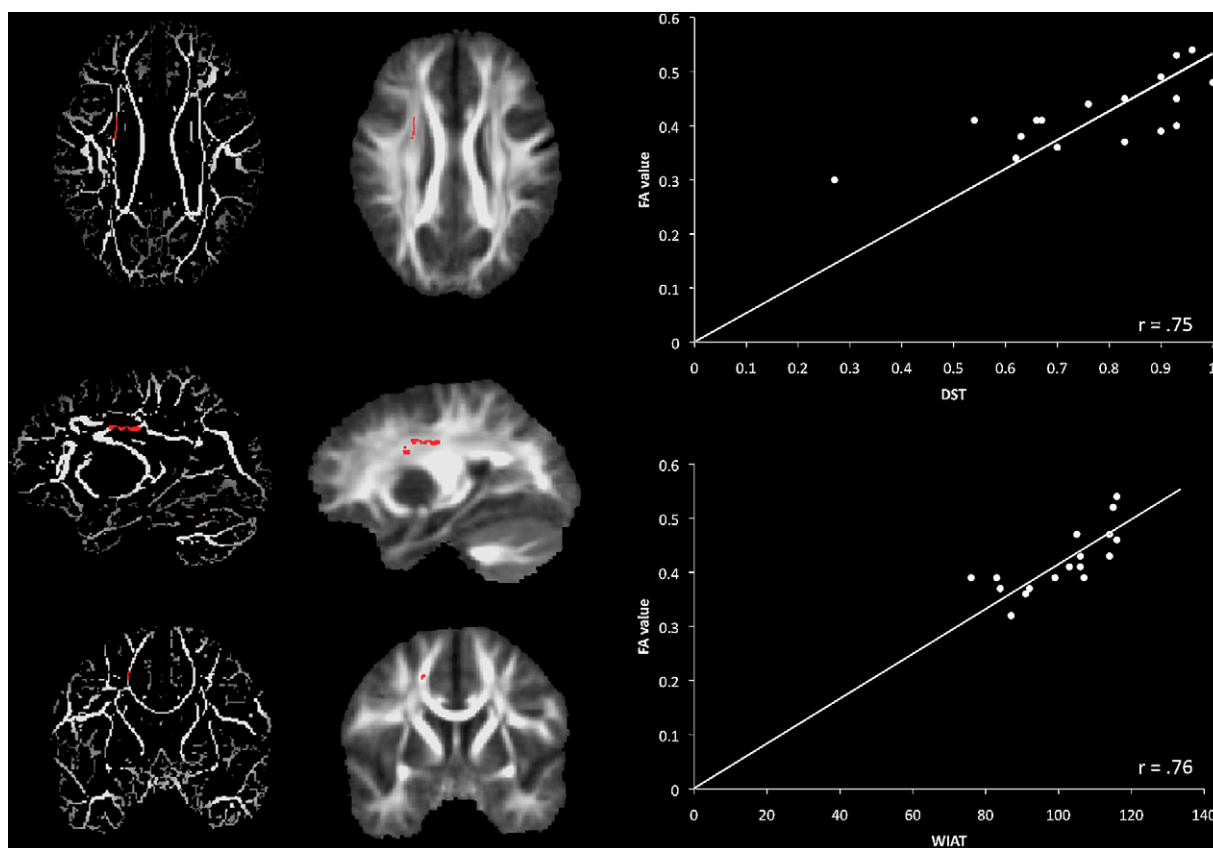
Fig. 2. Overlap observed between the correlations of the DST and WIAT-II to FA values in the left superior corona radiata overlaid on the mean FA skeleton (left) and mean FA (right) images. The scatterplots reflect the correlation between the FA value of the maximum intensity voxel of the clusters corresponding to the overlap area and scores on the DST (top) and WIAT-II (bottom).
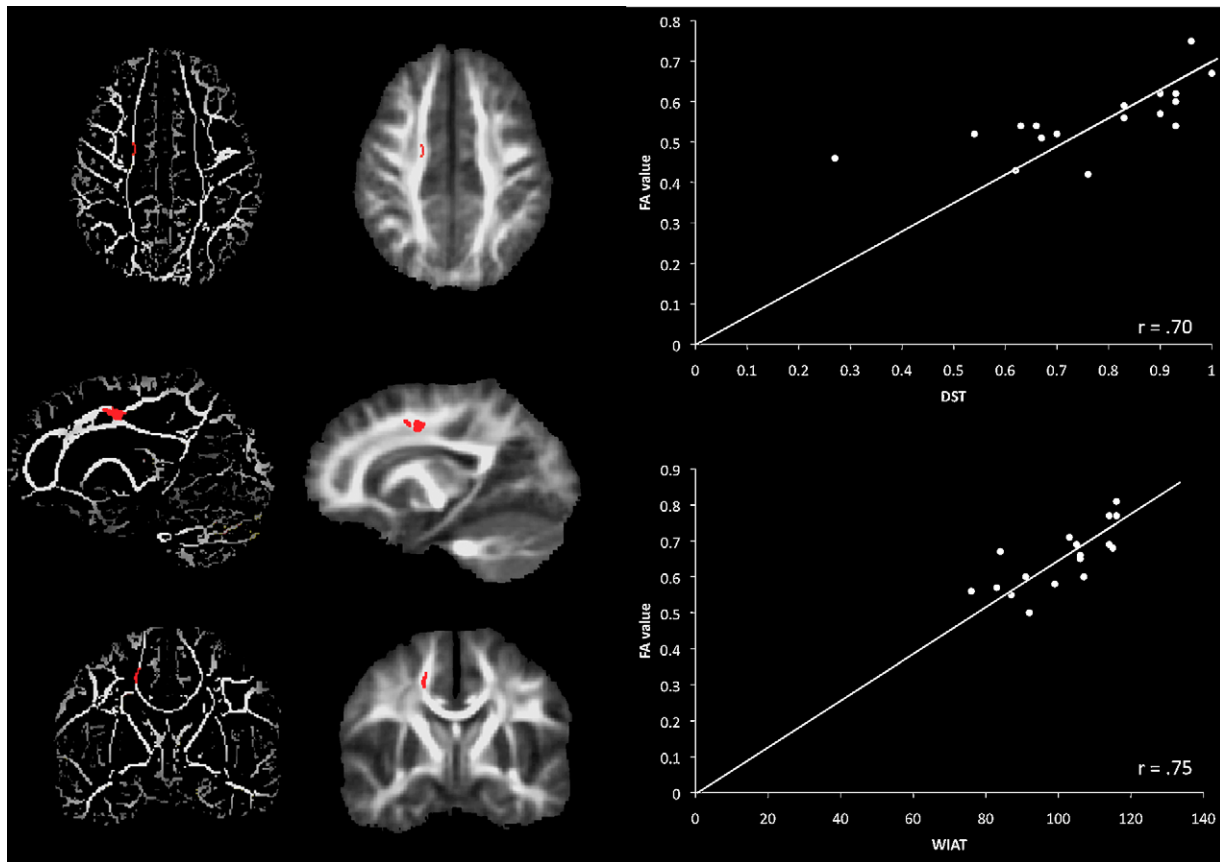
Fig. 3. Overlap observed between the correlations of the DST and WIAT-II to FA values in an area of the left superior corona radiata overlaid on the mean FA skeleton (left) and mean FA (right) images. The scatterplots reflect the correlation between the FA value of the maximum intensity voxel of the clusters corresponding to the overlap area and scores on the DST (top) and WIAT-II (bottom).

and revealed 5 clusters of voxels that were significantly correlated with WIAT-II basic reading scores. Voxelwise multiple regression analyses demonstrated that age and gender did not have a significant contribution to the correlations observed between decoding pseudowords and FA values. A cluster on the left (−13, −9, 47) and right (21, 4, 45) superior corona radiata exhibited strong positive correlations between FA values and basic reading scores. Additionally, positive correlations were observed in a cluster of voxels on the left corticopontine tract/superior thalamic radiation (−20, −10, 34) and the right posterior limb of the internal capsule (27, −24, 14). Negative correlations were observed in a cluster on the left posterior corpus callosum (−6, −35, 20).

2.3. Overlap analyses

Additionally, we investigated the extent to which the clusters that showed significant correlations between the two different reading measures and FA values overlapped with one another. These areas of overlap are presented in Figs. 1–3 along with scatterplots of the correlation observed between each reading measure and FA values within the voxel of peak intensity for the cluster observed with that reading measure. The pseudoword (DST) and real word (WIAT-II) decoding scores were both negatively correlated with FA values measured in the same region of the left posterior corpus callosum (−4, −33, 19) which encompassed 25 voxels (Fig. 1). In addition, the two areas in the left superior corona radiata that demonstrated positive correlations between FA values and the DST and the WIAT-II overlapped with one another. One of these overlapping areas contained 125 voxels (−21, 0, 27; Fig. 2) and was located more inferior

to the other cluster (−14, −9, 42) which encompassed 108 voxels (see Fig. 3).

3. General discussion

The present study replicates previous findings investigating the relationship between white matter tract coherence (i.e., FA values) and reading abilities (Beaulieu et al., 2005; Deutsch et al., 2005; Dougherty et al., 2007; Klingberg et al., 2000; Niogi & McCandliss, 2006). In particular, the majority of the white matter tracts observed to correlate with real word and pseudoword decoding were located in the left hemisphere. Although past research has provided converging evidence that white matter tracts located in left temporo-parietal regions are associated with reading ability, conflicting findings have been reported.

First, some previous researchers have observed a relationship between reading ability and white matter tracts along the anterior–posterior axis (i.e., Klingberg et al., 2000) while others have observed these relationships along tracts that project on the superior–inferior axis (i.e., Beaulieu et al., 2005). In the present study, we observed correlations between FA values and decoding skills within clusters of voxels along tracts primarily oriented in the superior–inferior direction. Furthermore, in line with the findings of Niogi and McCandliss (2006), we observed correlations with reading in areas along the left superior corona radiata, and did not observe a correlation between FA values located on the posterior limb of the left internal capsule and reading ability.

Second, different patterns of results have also been reported in regards to the extent to which correlations between FA values and

measures of decoding obtained using real words are also observed when decoding is measured using pseudowords. Pseudowords require phonological decoding whereas real words can be read by sight using knowledge from memory. Given that past researchers have interpreted their DTI findings in relation to decoding ability, overlap between the correlations observed across these measures is of great importance. We focus on those areas that showed convergence across the two measures of decoding ability. For example, Klingberg et al. (2000) observed correlations between FA values in the left temporo-parietal region and measures of both real word and pseudoword decoding to be located in the same left hemisphere white matter regions. However, Niogi and McCandliss (2006) observed correlations between decoding real words and FA values in left hemisphere brain regions, but failed to observe correlations between decoding pseudowords and FA values. We observed FA values in two regions of the left superior corona radiata to be positively correlated with measures of reading obtained using real words and pseudowords.

Third, the present study replicates numerous past findings inspite of its small sample size. For example, by having conducted full brain analyses using TBSS we were able to replicate Dougherty et al. (2007) who observed a negative correlation between phonological awareness and FA values located in the posterior corpus callosum and extend these findings to decoding skills. Additionally, these data replicate the positive correlations observed between reading ability and FA values in left hemisphere white matter tracts that project along the superior–inferior axis opposed to the anterior–posterior axis (Beaulieu et al., 2005; Dougherty et al., 2007; Niogi & McCandliss, 2006). The main areas observed to be positively correlated with reading ability in the present study were located on the left superior corona radiata, which is a white matter tract that projects from the thalamus to the sensory cortices. Because the corona radiata does not seem to connect commonly identified brain regions involved when reading, several researchers have acknowledged that integrating it into current theories of reading is not an easy proposition (Beaulieu et al., 2005; Dougherty et al., 2007). Nevertheless, the weight of the evidence supporting the correlations of the coherence of the corona radiata and reading skill suggests an important direction for future research into the neurological substrate underlying reading.

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