

Variations in the neurobiology of reading in children and adolescents born full term and preterm



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ABSTRACT

Diffusion properties of white matter tracts have been associated with individual differences in reading. Individuals born preterm are at risk of injury to white matter. In this study we compared the associations between diffusion properties of white matter and reading skills in children and adolescents born full term and preterm. 45 participants, aged 9–17 years, included 26 preterms (born <36 weeks' gestation) and 19 full-terms. Tract fractional anisotropy (FA) profiles were generated for five bilateral white matter tracts previously associated with reading: anterior superior longitudinal fasciculus (aSLF), arcuate fasciculus (Arc), corticospinal tract (CST), uncinate fasciculus (UF) and inferior longitudinal fasciculus (ILF). Mean scores on reading for the two groups were in the normal range and were not statistically different. In both groups, FA was associated with measures of single word reading and comprehension in the aSLF, AF, CST, and UF. However, correlations were negative in the full term group and positive in the preterm group. These results demonstrate variations in the neurobiology of reading in children born full term and preterm despite comparable reading skills. Findings suggest that efficient information exchange required for strong reading abilities may be accomplished via a different balance of neurobiological mechanisms in different groups of readers.

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1. Introduction

Reading is a multi-faceted process in which visual letter strings are linked to sounds and meaning in order to extract information from written text. Reading abilities vary substantially within the general population (Lyon et al., 2003; Shanahan, 2008). Functional neuroimaging studies have documented that reading engages a widely distributed network of cortical and cerebellar regions and that patterns of activation differ significantly between good and poor readers (Bitan et al., 2007; Bouhali et al., 2014; Graves et al., 2010; Hoeft et al., 2006; Martin et al., 2015; McCandliss et al., 2003; Seghier and Price, 2010; Shaywitz et al., 2006; Stoodley and Stein, 2013). In such a complex network, it is likely that the level of performance would depend not only on the adequacy of cortical responses but also on efficiency of information transmission among these cortical regions through long-range white matter pathways. Indeed, measures of anatomical connectivity, as assessed using diffusion magnetic resonance imaging (dMRI), have also been shown to

be associated with reading. Initially, it was found that fractional anisotropy (FA) in bilateral temporo-parietal white matter was reduced in poor adult readers compared to controls (Klingberg et al., 2000). Subsequent analyses found similar results in children (Beaulieu et al., 2005; Deutsch et al., 2005; Lebel and Beaulieu, 2009; Nagy et al., 2004; Niogi and McCandliss, 2006). It is now well established that microstructural properties of various white matter tracts in the brains of adults and children are associated with individual differences in reading abilities (Ben-Shachar et al., 2007; Frye et al., 2011; Hoeft et al., 2011; Myers et al., 2014; Travis et al., 2015b; Vandermosten et al., 2012b; Wandell and Yeatman, 2013).

In this study, we sought to examine the pattern of associations between white matter microstructure and reading skills in a clinical pediatric population. Children born preterm constitute an intriguing population to study because they are at risk for relatively poor reading skills that persist through childhood (Aarnoudse-Moens et al., 2009; Kovachy et al., 2014) and adolescence (Grunau et al., 2004). Adverse outcomes in individuals born preterm have been attributed to white matter injuries and dysmaturity at birth (Back and Miller, 2014; Back et al., 2007; Back and Rosenberg, 2014; Volpe, 2009) that lead to persistent differences in white matter properties through childhood and adolescence (Allin et al., 2011; Eikenes et al., 2011; Feldman et al., 2012a; Mullen et al., 2011; Skranes et al., 2007; Travis et al., 2015a; Yung

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et al., 2007). White matter microstructure has been associated specifically with individual differences in reading and reading-related skills in older children and adolescents born preterm (Andrews et al., 2010; Feldman et al., 2012b; Frye et al., 2010; Mullen et al., 2011). However, it remains unclear how closely the associations between white matter properties and reading skills in children born preterm resemble those observed in the general childhood population. To pursue this issue, we applied dMRI and tractography and mapped the correlations between white matter anisotropy and reading skills along white matter pathways in a sample of children born full term or preterm.

We limited our inquiry to white matter tracts that have been associated with reading abilities in previous studies of children and adolescents. Likely candidates for involvement in reading include the superior longitudinal fasciculus and arcuate fasciculus, which are considered the dorsal stream of the language and reading network, involved in mapping sound to articulatory-based representations (Brauer et al., 2013; Hickok and Poeppel, 2004; Monzalvo and Dehaene-Lambertz, 2013; Vandermosten et al., 2012b). The superior longitudinal fasciculus has been associated with reading abilities in children (Frye et al., 2011; Steinbrink et al., 2008) and in adolescents born preterm (Frye et al., 2010). The arcuate fasciculus has been associated with reading or reading-related abilities in children sampled from the general population (Gullick and Booth, 2015; Lebel and Beaulieu, 2009; Vandermosten et al., 2012a; Yeatman et al., 2011), and with rapid naming in adolescents born preterm (Mullen et al., 2011). Longitudinally, microstructural changes in diffusion properties of the arcuate fasciculus across 3 school years predicted children's reading scores (Yeatman et al., 2012a). Similarly, volumetric changes in the arcuate fasciculus between kindergarten and 3rd grade predicted children's reading abilities in the 3rd grade (Myers et al., 2014).

The corticospinal tract has been implicated in reading, though this tract is not conventionally considered part of the language or reading system. Studies have argued that fibers going through the different temporal-parietal voxels in which FA is associated with reading belong to the corona radiata, centrum semiovale, and/or posterior limb of the internal capsule based on analysis of the principle diffusion direction or fiber tracking through the relevant voxels (Beaulieu et al., 2005; Deutsch et al., 2005; Frye et al., 2011; Niogi and McCandliss, 2006). A superior region of the corona radiata was also a predictor of reading skills in kindergarteners (Myers et al., 2014) and a segment of the centrum semiovale showed changes in FA after successful reading remediation (Keller and Just, 2009). (Frye et al. (2011)) found that the associations within the superior longitudinal fasciculus and arcuate were suggestive of alterations in white matter organization and axonal size, whereas the associations within the corticospinal tract were suggestive of alterations in pathway complexity.

Additional pathways that have been linked to reading skills include the ventral pathways of the language and reading network, involved in mapping sound to meaning (Hickok and Poeppel, 2004) and orthography to phonology and semantics (Vandermosten et al., 2012b). Diffusion properties of the uncinata fasciculus, a tract that courses between the anterior temporal lobe and the frontal lobe (Von Der Heide et al., 2013), were associated with reaction time to written words in adults sampled from the general population (Cummine et al., 2015) and with a related language ability, receptive vocabulary, in adolescents born preterm (Mullen et al., 2011). Significant associations in adults have been found between measures of single word reading and properties of the left inferior longitudinal fasciculus, a tract that courses from the occipital lobe to the anterior temporal lobe, in some (Lebel et al., 2013; Steinbrink et al., 2008) but not all studies (Frye et al., 2011). Developmentally, longitudinal change across 3 school years in the diffusivity of the inferior longitudinal fasciculus was another significant predictor of reading skill in children (Yeatman et al., 2012a).

Reading is generally considered to have two fundamental components: (1) Decoding, the ability to accurately name written words and/or pseudowords, and (2) Comprehension, the ability to derive

meaning from words, phrases and sentences and to form interpretations (Hoover and Gough, 1990). Most studies to date of associations between white matter properties and reading in children have focused on single word reading (Beaulieu et al., 2005; Deutsch et al., 2005; Dougherty et al., 2007; Hoeft et al., 2011; Nagy et al., 2004; Niogi and McCandliss, 2006; Odegard et al., 2009; Rimrodt et al., 2010) or sublexical processing, such as phonological awareness (Deutsch et al., 2005; Dougherty et al., 2007; Yeatman et al., 2011). Based on these findings, we hypothesized that in the full term group, we would find statistically significant associations between measures for single-word reading and FA in tracts that have been associated with reading in other studies of the general population: superior longitudinal fasciculus and/or arcuate fasciculus (Hoeft et al., 2011; Klingberg et al., 2000; Myers et al., 2014; Saygin et al., 2013; Thiebaut de Schotten et al., 2014; Yeatman et al., 2012a; Yeatman et al., 2011), corticospinal tract (Deutsch et al., 2005; Frye et al., 2011; Lebel and Beaulieu, 2009; Niogi and McCandliss, 2006), inferior longitudinal, and uncinata fasciculus (Cummine et al., 2015; Yeatman and Feldman, 2013). We further hypothesized that we would find significant associations between FA and single-word reading in the preterm group within the same pathways (Feldman et al., 2012b; Frye et al., 2010; Mullen et al., 2011). We included comprehension to examine distinct patterns of association with each reading component, as has been found in relation to cerebellar tracts (Travis et al., 2015b). Moreover, as a skill, reading comprehension has been found to demonstrate persistent impairment in children born preterm (Kovachy et al., 2014). In secondary analyses, we interrogated axial and radial diffusivity within segments of significant association with FA. We also determined if significant associations occurred in similar or different locations within the tract.

By examining patterns of associations in both full term and preterm groups within the same study we were able to explore whether each group would demonstrate similar or different patterns of associations with reading. Based on findings from our own research and those of others, results from previous studies suggest that individuals in the preterm group would demonstrate mostly positive associations with reading abilities (Andrews et al., 2010; Feldman et al., 2012b; Frye et al., 2010; Mullen et al., 2011), and individuals in the full term group would demonstrate positive or negative associations (Beaulieu et al., 2005; Deutsch et al., 2005; Dougherty et al., 2007; Feldman et al., 2012b; Frye et al., 2008; Frye et al., 2011; Klingberg et al., 2000; Lebel and Beaulieu, 2009; Lebel et al., 2013; Odegard et al., 2009; Yeatman et al., 2012a). In this study, variations in the patterns of associations between white matter microstructure and reading in the preterm and full term groups would suggest variations in the underlying neurobiology of reading, possibly related to white matter injury or dysmaturity from prematurity (Back and Miller, 2014; Back et al., 2007; Back and Rosenberg, 2014; Volpe, 2009). It might be that different neurobiological factors impact reading abilities in the two populations. Alternatively, it might be that the balance of the same critical neurobiological factors can be altered based on a child's early medical history and subsequent development.

2. Materials and methods

2.1. Participants

Participants were enrolled in the Palo Alto site of a multi-site study and completed MRI scanning at Stanford University. Preterm birth was defined as gestational age of <36 weeks and birth weight < 2500 g. Full term was defined as gestational age of ≥ 37 weeks. The range of gestational ages for the current preterm sample was 26.0–34.5 weeks and the range for the full term sample was 37.0–40.0 weeks. Exclusion criteria for all participants included active seizure disorder, hydrocephalus, receptive vocabulary score < 70, sensorineural hearing loss, and non-native speaker of English. Only the participants who completed the reading battery and

underwent the MRI scanning were included in the present analyses. Approval for the study was granted by the Stanford University Institutional Review Board. A parent or legal guardian provided informed written consent and children provided written assent. Participants were compensated for participation.

Participants were between the ages of 9–17 years old at the time of scanning, and were born either full term (FT: $n = 19$; 9 males, mean age = 12.9 ± 2.2) or preterm (PT: $n = 26$, 13 males mean age = 12.8 ± 2.3). Full term controls were volunteers. One child born full term from the original sample ($n = 20$) with an incidental finding of an arachnoid cyst was excluded from present analyses. Two preterm subjects from the original sample ($n = 28$) were excluded from the present analyses because one subject showed tract anomalies described in a previous case study (Yeatman and Feldman, 2013) and the second had not performed behavioral tests for reading. The association of reading and cerebral white matter properties has been previously analyzed in a subset of this cohort using TBSS, a different analytic approach (Feldman et al., 2012b). In addition, cerebellar white matter structure and function have been analyzed in this cohort (Leitner et al., 2015; Travis et al., 2015b).

Demographic data for the groups are presented in Table 1. The groups did not differ significantly in age, gender, handedness, or maternal education, which was used here as a proxy for socioeconomic status (SES). Maternal education level was dichotomized with “low” defined as less than a college degree and “high” as at least a college degree. By design, the preterm sample had significantly decreased gestational age and birth weight compared to the full term sample. One full term and three preterm subjects were left-handed, and three full term and two preterm subjects were ambidextrous, as measured by the Edinburgh Handedness Inventory (Oldfield, 1971). Medical information was available for 25 of 26 preterm subjects. Medical complications at birth in the preterm group were as follows: six with abnormal findings on head ultrasound or MRI (\geq grade 2 intraventricular hemorrhage, echodensities or cystic lesions), two with mildly abnormal findings (grade 1 hemorrhage or choroid plexus cyst); 12 had respiratory distress syndrome, five developed bronchopulmonary dysplasia (BPD) or chronic lung disease; four had patent ductus arteriosus (PDA); none had necrotizing enterocolitis; one was small for gestational age (\leq 3rd percentile birth weight for gestational age). A neuroradiologist unaware of the child's medical conditions evaluated the T1- and T2-weighted MRI scans of the preterm group, using a white matter scoring system used previously in infants (Inder et al., 2003) and older children (Feldman et al., 2012a). Of the 26 preterm subjects, 13 had normal scans, 10 had mild-moderate injury, and 3 had moderate to severe injury (Feldman et al., 2012a). The three children observed to have moderate to severe injury were among the 6 children born preterm who had a history of abnormal neonatal head ultrasound or MRI. The remaining three children who had a

history of abnormal neonatal head ultrasound or MRI either had mild-to moderate injury (2 subjects) or had a normal scan (1 subject).

2.2. Reading measures

Reading abilities were assessed with the Woodcock-Johnson III Tests of Achievement ((WJ-III; (Woodcock et al., 2001)). We chose to consider the two fundamental components of reading separately on the possibility that different patterns of association might be found. Decoding skills, or the ability to translate written letters into speech sounds and recognize written words, was assessed using the Basic Reading Skills Cluster, a composite score encompassing two subtests: (1) Word Identification, untimed overt reading of real words, and (2) Word Attack, untimed overt reading of pseudo-words. Comprehension skill, or understanding of text, was assessed using the Passage Comprehension subtest. This subtest assesses comprehension using a cloze procedure in which participants are asked to read covertly 1–2 sentences and fill in the blank(s) orally. Raw scores were converted to age-adjusted standard scores based on the participant's chronological age at the time of testing.

2.3. MRI acquisition

MRI data were acquired on a 3T Signa Excite scanner (GE Medical Systems, Milwaukee, WI) at Stanford University. T1 images included three high resolution inversion recovery (IR)-prep 3D fast spoiled-gradient (FSPGR) scans collected in the axial plane. The first T1 (field of view (FOV) = 240×156 mm, matrix size = 256×192 , 1.2 mm slices) was subsequently averaged with two additional T1 scans (FOV = 240×180 mm, matrix size = 260×192 , 0.9 mm slices).

For dMRI and tractography, a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence was used to acquire 60 slices, in 30 different diffusion directions ($b = 900$, FOV = 240×240 mm, matrix size = 128×128 , voxel size = $1.875 \times 1.875 \times 2$ mm, TE = 80 ms, TR = 6500 ms). The sequence was repeated 4 times for improved SNR. 10 non-diffusion weighted ($b = 0$) volumes were collected as well.

2.4. Data preprocessing

The T1 images were co-registered to each other using a mutual information maximization algorithm (SPM5, <http://www.fil.ion.ucl.ac.uk/spm/>) and subsequently averaged for improved contrast. A trained research assistant manually identified the anterior and posterior commissures on the midsagittal plane, and these points were used to align the averaged anatomical image to a canonical ac-pc orientation, using a rigid body transformation also implemented in SPM5 with no warping applied.

Diffusion MR images were pre-processed with open-source software, mrDiffusion (<http://white.stanford.edu/newlm/index.php/MrDiffusion>) implemented in MATLAB R2012a (Mathworks, Natick, MA). Eddy current distortions and subject motion in the diffusion weighted images were corrected by a 14-parameter constrained non-linear co-registration algorithm based on the expected pattern of eddy-current distortions, given the phase-encoding direction of the acquired data (Rohde et al., 2004). No subjects or image volumes were excluded due to excessive head motion. The degree of translational head motion was analyzed and found to be <1.5 mm in all image planes for all full term and preterm participants, and statistical analyses confirmed that preterm and full term groups did not significantly differ on the basis of head motion. Diffusion data were aligned to the T1 anatomical scans that had been averaged and rotated to align with the ac-pc plane. Alignment between dMRI and T1 data was achieved by registering the b0 images to the resampled T1 image using the same mutual information maximization algorithm used for T1 image co-registration (SPM5, <http://www.fil.ion.ucl.ac.uk/spm/>).

Table 1
Demographic characteristics and mean scores on the reading measures in the full term and preterm groups.

	Full term ($n = 19$) M \pm (SD) or n (%)	Preterm ($n = 26$) M \pm (SD) or n (%)	t or χ^2
Demographic characteristics			
Age	12.90 \pm 2.16	12.80 (2.27)	0.149
Males	9 (47%)	13 (50%)	0.03
Low SES	6 (32%)	3 (11%)	2.76
White	10 (53%)	18 (67%)	1.29
Handedness	60.53 \pm 42.23	62.31 \pm 57.64	-0.11
Gestational age, weeks	39.17 \pm 1.13	28.17 \pm 2.23	21.59*
Birth weight, g	3154 \pm 407	1159 \pm 427	15.90*
Reading standard scores ^a			
Decoding (basic reading cluster)	106.7 (10.0)	105.3 (13.4)	0.402
Comprehension (passage comprehension)	108.1 (14.0)	102.5 (12.7)	1.4

* $p < .01$.

^a Woodcock-Johnson Tests of Achievement – 3rd Edition.

For each voxel in the aligned and resampled volume, tensors were fit to the diffusion measurements using a robust least-squares algorithm, Robust Estimation of Tensors by Outlier Rejection (RESTORE), which is designed to remove outliers at the tensor estimation step (Chang et al., 2005). A continuous tensor field was estimated using trilinear interpolation of the tensor elements. We computed the eigenvalue decomposition of the diffusion tensor and the resulting three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) were used to compute fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) in each voxel (Basser and Pierpaoli, 1996).

2.5. Fiber tracking and segmentation

Fiber tracking and tract segmentation were performed using open source software, Automated Fiber Quantification (AFQ; <https://github.com/yeatman/AFQ>) implemented in MATLAB R2012a (Mathworks, Natick, MA).

AFQ consists of three major processing steps: (1) whole-brain tractography (2) automatic tract segmentation and cleaning, and (3) fiber quantification (Yeatman et al., 2012b). Whole brain tractography was performed using a deterministic streamlines tracking algorithm (STT) (Chang et al., 2005; Conturo et al., 1999; Mori et al., 1999), with a fourth-order Runge-Kutta path integration method (Press et al., 2002). The fiber tracking algorithm was seeded with a white matter mask defined as all the voxels with FA value >0.2 in the entire brain volume. Tracking proceeded in all directions and stopped when FA dropped below 0.15 or when the angle between the extension of a line in the direction of the current step and the direction of the next step was $>30^\circ$.

Tract segmentation was achieved using a multiple waypoint ROI procedure as defined by Wakana et al. (2007) and automated in AFQ (Yeatman et al., 2012b). During AFQ processing, an estimated non-linear transformation (Friston and Ashburner, 2004) was applied to automatically transform predefined ROIs from the Montreal Neurological Institute (MNI) template into an individual's native space. In this approach, ROIs are defined such that they isolate the central portion of the tract where fibers are most coherently bundled. Fibers are considered to belong to a specific tract only if they pass through both waypoint ROIs as specified in Wakana et al. (2007). Using this procedure, we isolated for each individual 5 bilateral pathways in the participant's native space: two dorsal association pathways, the anterior superior longitudinal fasciculus (aSLF) left (-L) and right (-R) and the arcuate fasciculus (Arc-L and Arc-R); one projection pathway, the corticospinal tract (CST-L and CST-R); and two ventral association pathways, the inferior longitudinal fasciculus (ILF-L and ILF-R) and the uncinate fasciculus (UF-L and UF-R). To be consistent with an influential scheme for segmenting the superior longitudinal fasciculus (Catani et al., 2005),

we employ the term aSLF to refer the segment of the SLF that connects between the posterior frontal cortex and the parietal lobe and the arcuate fasciculus to refer to the long or direct segment of the superior longitudinal fasciculus, which connects directly between the posterior inferior frontal cortex and the temporal cortex. These pathways were selected due to their documented association with reading abilities in adults and children (Deutsch et al., 2005; Frye et al., 2011; Klingberg et al., 2000; Lebel and Beaulieu, 2009; Myers et al., 2014; Niogi and McCandliss, 2006; Yeatman et al., 2012a; Yeatman et al., 2011) including in individuals born preterm (Frye et al., 2010; Mullen et al., 2011). Tracts were cleaned automatically using a statistical outlier rejection algorithm for removing outlier fibers (Chang et al., 2005). Fig. 1 shows the tracts, including the defining ROIs, in a representative full term participant.

For every subject, tracts were visualized and inspected by a trained investigator (KET) to ensure that the automatic fiber cleaning procedure produced pathways consistent with anatomical guidelines (Mori et al., 2005). In one full term participant the aSLF still included looping fibers that re-crossed both ROIs. These fibers were removed using Quench, a gesture based segmentation and visualization tool (<http://white.stanford.edu/newlm/index.php/QUENCH>). No other tracts required manual editing. The same investigator (KET) also verified that ROI placement for fiber segmentation was anatomically accurate in the small proportion of subjects in whom the Arc-R (6 FT; 3 PT) and the CST-R (1 PT) were not reliably identified. This procedure ensured that failure to detect these tracts was unlikely to be a consequence of inaccurate ROI placement, but likely resulted from the limitations of the tracking algorithm.

2.6. Fiber tract quantification

FA was calculated at 30 equidistant nodes along a central portion of each fiber tract bounded by the same two ROIs used for tract segmentation. This procedure allowed us to assess associations with reading measures in comparable tract locations in each group. Tract extremities beyond these ROIs were not included in the analysis. This procedure generates, for every tract and every individual, an FA tract profile that describes the variations in FA along the central portion of the tract. At each node, diffusion properties were calculated by taking a weighted average across all fibers belonging to this tract. Each fiber's contribution to the average was weighted by the probability that a fiber was a member of the fascicle, computed as the Mahalanobis distance from the tract core (Yeatman et al., 2012b). This procedure minimizes the contribution of fibers located further from the fiber tract core that are more likely to reflect a mixture of gray and white matter or of different tracts, and thereby minimizes the effect of partial voluming on diffusion parameters. The decision to analyze 30 nodes along the tract rather than tract

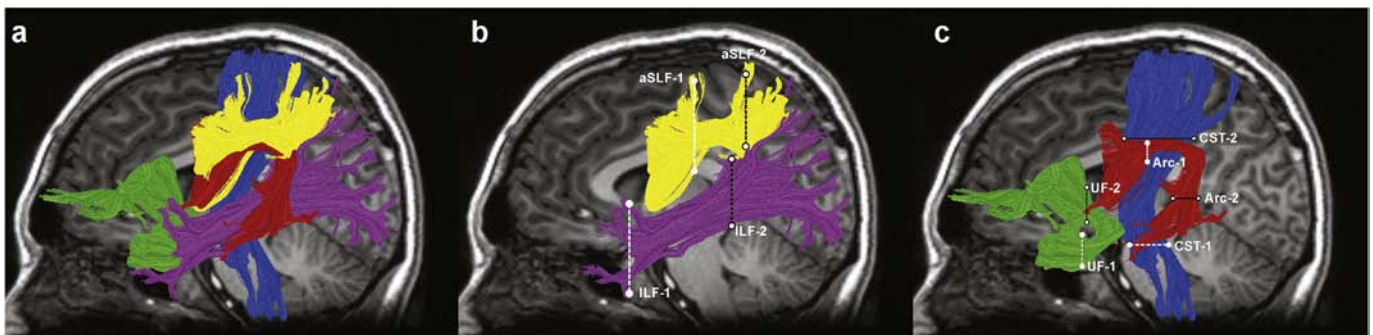


Fig. 1. Tractography methods demonstrated for major cerebral white matter tracts, displayed within the left hemisphere. Tracts are displayed on mid-sagittal T1 images from a representative full term subject. Right hemisphere tract renderings not shown. Panel a illustrates all five tracts: Anterior Superior Longitudinal Fasciculus (aSLF) in yellow, Arcuate Fasciculus (Arc) in red, Uncinate Fasciculus (UF) in green, Corticospinal Tract (CST) in blue, and Inferior Longitudinal Fasciculus (ILF) in purple. Panels b and c include dashed lines to represent the location of the regions of interest (ROIs) used to isolate each cerebral tract; ROI 1, white; ROI 2, black. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

means is it increases the chance of detecting significant associations within the tracts and it allows us to compare those locations within and across groups.

2.7. Statistical approach

2.7.1. Analyses of demographic variables

Chi-square tests and two-tailed *t*-tests for independent samples were used to examine differences between the full term and preterm samples on demographic variables and on reading scores. Associations between the reading measures in each group were assessed using Pearson correlations.

2.7.2. Associations of FA with reading

Spearman correlations were calculated in each group separately between individual's FA tract profiles (FA measured at 30 locations along the trajectory of each tract) and their decoding or comprehension standardized scores. Spearman rank correlations were used due to evidence for non-normal distribution in tract FA measures in a preliminary exploration of the data. To control for the multiple associations performed along the tracts, a family-wise error corrected cluster size and a critical *r*_s-value were computed using a nonparametric permutation testing method for each tract (Nichols and Holmes, 2002). The correlation in a given tract segment was considered significant if (1) significant correlation at an uncorrected level of $p < 0.05$ occurred in a sufficient number of adjacent nodes (range 6–7 nodes) to meet the criteria for a family-wise error corrected cluster size or (2) the correlation was greater than the critical *r*_s-value and occurred within a minimum cluster size of at least 3 nodes with $p < 0.05$ (uncorrected).

We controlled for the number of correlations calculated within each group (5 tracts × 2 hemispheres × 2 different reading measures = 20 total), using a separate false discovery rate (FDR) (Benjamini and Hochberg, 1995) at $q < 0.05$ for the preterm and full term groups. To assure that none of the associations were driven by age, we computed partial Spearman correlations between the relevant reading measure (decoding and/or comprehension) and mean FA of significant clusters, while controlling for age at scan. To be thorough, we also examined whether associations may have been driven by pseudo-correlations arising from gender differences in either measures of FA or reading. This was achieved first by determining whether there were gender differences in reading measures using *t*-tests for independent samples calculated within each group (full term or preterm) separately. We next determined whether there were gender differences in tract FA measures using a 2-way analysis of variance (ANOVA) in which Gender (male versus female) served as the between group measure and mean tract FA from significant clusters served as the within subjects variable. To determine the significance of the difference between the correlation coefficients in the two groups, we used the Fisher *r* to *Z* transformation. To examine the specificity of the FA-reading correlations to either decoding or comprehension, we computed partial Spearman correlations between each of the reading measures independently (decoding or comprehension) and mean FA from clusters of significant association, while controlling for the other reading measure (comprehension or decoding, respectively).

Within regions of significant association between FA and reading, we conducted secondary exploratory analyses to evaluate the contribution of AD and RD to the correlation. This step was achieved by calculating Spearman correlations between each of the reading measures and the mean AD or mean RD from clusters demonstrating significant FA-reading correlations. Associations were considered significant at $p < 0.05$.

To investigate whether differences in the direction or magnitude of the correlations within each group reflect differences in the range of FA values between the two groups, we compared the range of FA values in each group within each segment of significant association.

3. Results

3.1. Behavioral results

Table 1 includes the mean scores for decoding and comprehension for the full term and preterm groups. Both groups performed solidly within the normal range. Notably, the groups did not differ significantly on either decoding or comprehension $p > 0.05$. Decoding and comprehension scores were correlated with each other in both the full term ($r = 0.744$, $p < 0.001$) and preterm groups ($r = 0.747$, $p < 0.001$).

3.2. Associations of FA and reading measures

Table 2 shows the white matter tracts and segments in which correlations between FA and standard scores on the reading measures were significant in the full term and preterm groups. In the full term group, we found significant negative correlations between FA and decoding in five segments along five white matter tracts: aSLF-L, bilateral CST, and bilateral UF. Similarly, the full term group showed significant negative associations between FA and comprehension in three segments along three tracts: aSLF-L, Arc-L and UF-L. We found no segments of association within the ILF-L, ILF-R or Arc-R. Fig. 2 depicts the significant associations within the full term group. Each panel includes a representation of the tract with a superimposed heat map indicating the strength of the associations along the tract. The panels also include scatter plots showing the distribution of individual FA and reading scores at the peak node of each tract, i.e., the one showing the strongest association along the tract between reading and FA. Only the association between FA and decoding is displayed on heat maps for tracts in which both reading measures demonstrated significant correlations with FA (aSLF-L, UF-L). All of these associations remained statistically significant after controlling for age, with the exception of the Arc-L (Supplemental material Table 1). No significant gender differences were observed for either reading measures (decoding or comprehension) or FA from significant clusters ($p > 0.05$), confirming that associations were unlikely to be driven by gender in the full term group (Supplemental Fig. 1).

In the preterm group, FA was significantly associated with reading in several tract locations, but the direction of association was positive, in contrast with the negative associations detected in the full term group. Specifically, FA was significantly positively correlated with decoding at six locations along five tracts: two segments of the aSLF-L, one segment of the aSLF-R, Arc-L, CST-L and CST-R (Table 2). FA was also significantly positively associated with comprehension in this group in four locations along three tracts: two segments of the aSLF-L and one segment of the CST-R and the UF-L (Table 2). Similar to the full term group, we found no associations with reading in the ILF-L, ILF-R or Arc-R. Fig. 3 depicts the significant associations within the preterm group. Again, each panel includes a representation of the tract with a superimposed heat map indicating the strength of the association and a scatter plot of individual FA and reading measures at the peak node. Heat maps are again displayed only for associations between FA and decoding in tracts where both reading measures demonstrated significant correlations with FA (aSLF-L, CST-R). All of the associations remained significant after controlling for age (Supplemental material Table 1). No significant gender differences were observed for either reading measures (decoding or comprehension) or FA from significant clusters ($p > 0.05$), confirming that associations were unlikely to be driven by gender in the preterm group (Supplemental Fig. 1).

Associations between mean FA and reading measures within the significant segments of both groups remained statistically significant after controlling for multiple comparisons at a 5% criterion for false discovery rate.

Having found negative associations in the full term group and positive associations in the preterm group, we tested whether the differences between the correlation coefficients of the two groups were statistically significant. We restricted the analyses to those tracts in

Table 2
Spearman correlations between mean FA of significant segments and reading measures for full term and preterm groups.

	Decoding (SS) Full term		Comprehension (SS) Full term		Decoding (SS) Preterm		Comprehension (SS) Preterm	
White matter tract ^a	rs	Peak node (range)	rs	Peak node (range)	rs	Peak node (range)	rs	Peak node (range)
aSLF-L	−0.566 ^{b,d}	27 (26–29)	−0.745 ^{b,d}	27 (25–30)	0.466 ^{b,d}	24 (22–29)	0.417 ^{c,d}	28 (23–29)
aSLF-R	–	–	–	–	0.464 ^{c,d}	7 (4–10)	0.491 ^{b,d}	6 (2–8)
Arc-L	–	–	−0.647 ^{b,d}	9 (8–10)	0.403 ^{b,d}	13 (12–14)	–	–
Arc-R	–	–	–	–	0.606 ^{b,d}	10 (9–11)	–	–
CST-L	−0.657 ^{b,d}	2 (1–14)	–	–	0.493 ^{b,d}	23 (23–27)	–	–
CST-R	−0.690 ^{b,d}	9 (1–13)	–	–	0.551 ^{b,d}	26 (23–27)	0.448 ^{b,d}	26 (24–27)
UF-L	−0.548 ^{b,d}	20 (17–22)	−0.613 ^{b,d}	20 (17–22)	–	–	0.562 ^{c,d}	14 (11–17)
UF-R	−0.662 ^{b,d}	17 (14–21)	–	–	–	–	–	–

SS = standard score; aSLF = anterior superior longitudinal fasciculus; Arc = arcuate; ILF = inferior longitudinal fasciculus; CST = corticospinal tract; UF = uncinate fasciculus; L = left; R = right.

^a FA extracted from the peak node within a cluster of ≥ 3 nodes demonstrating significant associations.

^b Significant for correlations coefficient, corrected.

^c Significant for cluster size, corrected.

^d Significant at 5% false discovery rate (FDR) criterion.

which both groups had significant associations with one or both reading measures. In the aSLF-L, the associations in the two groups were statistically different for decoding ($z = -3.51$, $p < 0.0005$) and for comprehension ($z = -4.6$, $p < 0.0001$). The associations between FA and decoding were also significantly different between the groups in the CST-L ($z = -4.08$, $p < 0.0001$), CST-R ($z = -4.47$, $p < 0.0001$) and UF-L ($z = -4.15$, $p < 0.0001$).

The associations of mean FA and reading measures within significant clusters were generally not specific to one or the other reading measure, with one exception: In the aSLF-L, associations between mean FA (nodes 25–30) and comprehension remained significant after controlling for decoding ($rs = -0.552$, $p = 0.018$). All other correlations with comprehension were no longer significant after controlling for decoding, and vice versa, in both groups. In the CST-R, the partial

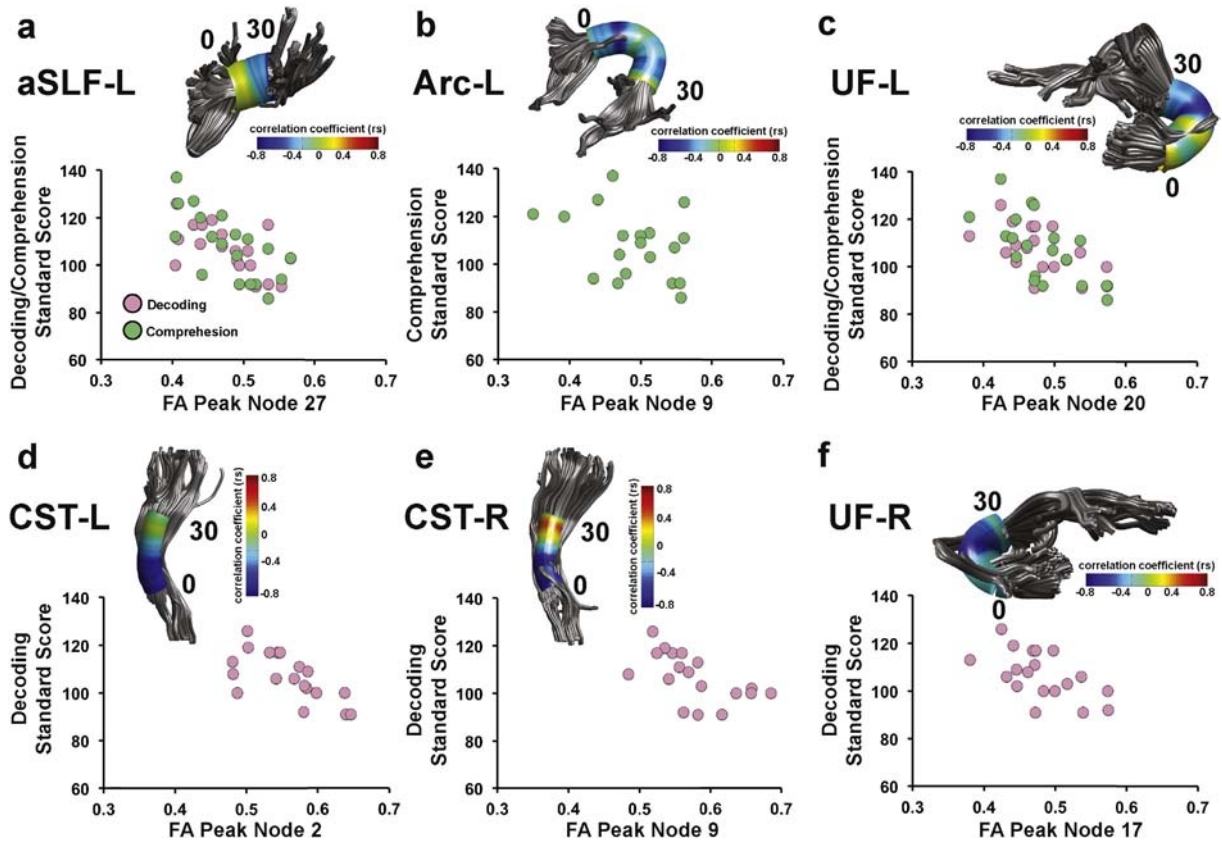


Fig. 2. Associations between peak node FA and reading measures in full term subjects. Each panel (a–f) includes a rendering of a specific tract with the strength of the Spearman correlation between FA at 30 equidistant nodes along the tract and either decoding (a, c–f) or comprehension (a–c) represented as a heat-map cylinder surrounding the tract. Each panel also includes a scatter plot representing the strength of the association between FA of the peak node and decoding (pink circles) and/or comprehension (green circles) standard scores. Panels show the results for the following tracts: aSLF-L (a), Arc-L (b), UF-L (c), CST-L (d), CST-R (e), and UF-R (f). FA is negatively associated with decoding within the aSLF-L (a), UF-L (c), CST-L (d), CST-R (e) and UF-R (f). FA is negatively associated with comprehension within the aSLF-L (a), Arc-L (b) and UF-L (c). Color bars represent Spearman correlation coefficients. FA = fractional anisotropy; aSLF = anterior Superior Longitudinal Fasciculus; Arc = arcuate; UF = uncinate fasciculus; CST = corticospinal tract; L = left; R = right; rs = Spearman correlation coefficient. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

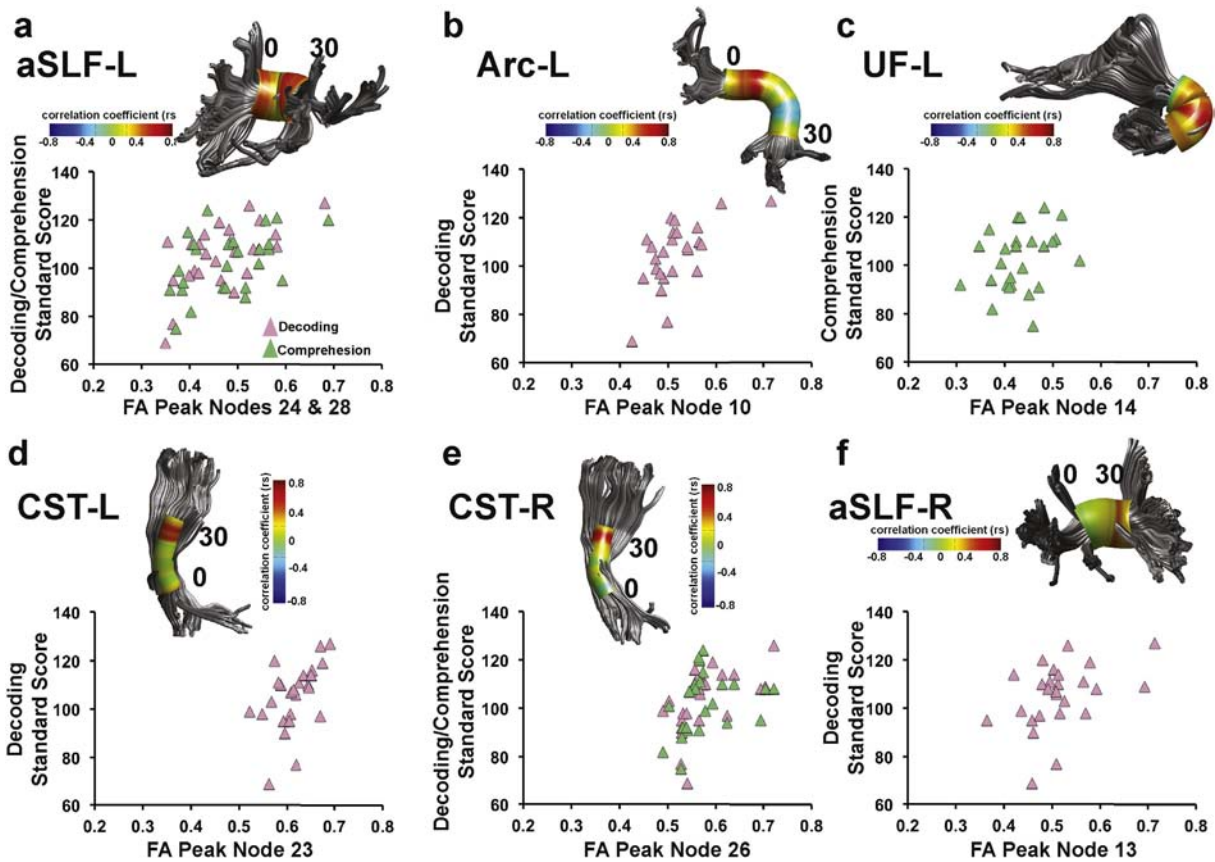


Fig. 3. Associations between peak node FA and reading measures in preterm subjects. Each panel (a–f) includes a rendering of a specific tract with the strength of the Spearman correlation between FA at 30 equidistant nodes along the tract and either decoding (a, b, d–f) or comprehension (a, c, e) represented as a heat-map cylinder surrounding the tract. Each panel also includes a scatter plot representing the strength of the association at 30 equidistant nodes along the tract between FA of the peak node and decoding (pink triangles) and/or comprehension (green triangles) standard scores. Panels show the results for the following tracts (arranged for ease of comparison to Fig. 2): aSLF-L (a), Arc-L (b), UF-L (c), CST-L (d), CST-R (e), and aSLF-R (f). Decoding standard scores are positively associated with FA of the aSLF-L (a), Arc-L (b), CST-L (d) and CST-R (e) and aSLF-R (f). Comprehension standard scores are positively associated with FA of the aSLF-L (a), UF-L (c) and CST-R (e). Color bar represents Spearman correlation coefficients. FA = fractional anisotropy; aSLF = anterior Superior Longitudinal Fasciculus; Arc = arcuate; UF = uncinate fasciculus; CST = corticospinal tract; L = left; R = right; r_s = Spearman correlation coefficient. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

correlation between mean FA and decoding after controlling for comprehension approached statistical significance ($r_s = 0.3839$, $p = 0.064$).

3.3. Secondary analyses

3.3.1. Associations of AD and RD with reading

The pattern of associations between reading measures and mean AD (or mean RD) in segments of significant association with FA are presented in Supplemental material Table 2. In general, most FA associations could be attributed to RD, not AD correlations, in both groups. In the full term group, decoding was significantly associated with RD in five of the five relevant segments (aSLF-L, CST-L, CST-R, UF-L, and UF-R). Decoding was significantly associated with AD only in the aSLF-L. In addition, within the full term group, comprehension was significantly correlated with RD in three of the three relevant segments (aSLF-L, Arc-L and UF-L). Again, comprehension was also significantly correlated with AD in the aSLF-L.

Similar results were acquired in the preterm group, even though the direction of the correlations was inverted. Decoding was significantly correlated with RD in five of the six relevant segments (two segments of the aSLF-L, Arc-L, CST-L and CST-R), and was only correlated with AD in one of the six segments (Arc-L). Comprehension was significantly correlated with RD in four of the four segments (two segments of aSLF-L, CST-R, and UF-L), and was not correlated with AD in any of the four relevant segments.

To determine whether these findings could be explained by a different range of FA values in the two groups (and a U-shaped or reverse U-

shaped association of FA and reading skill), we compared the mean and range of FA values within the segments in which we found significant associations of either of the reading measures and FA in each group. The results are shown in Table 3. While the mean scores were statistically different in the aSLF-R, Arc-L, and UF-L and UF-R, FA was higher in the preterm than full term group in the aSLF-R and the Arc-L, but higher in the full term than preterm group in the UF-L and UF-R. Importantly, the ranges of FA values were at least partially overlapping in all segments.

4. Discussion

This study evaluated the associations between FA of several white matter tracts and reading skills in two groups—full term and preterm children and adolescents—whose mean scores in both decoding and comprehension were very similar on standardized testing. We identified significant associations of FA and reading skill in both groups within segments of the aSLF-L, Arc-L, bilateral UF and bilateral CST, but not in either the ILF-L or ILF-R. A novel finding from this study was that the direction of association was opposite in the two groups. Associations of FA and both decoding and comprehension were consistently negative within the full term group and consistently positive within the preterm group. Partial correlation analyses confirmed that both negative and positive associations observed for the full term and preterm group remained significant after controlling for age, with the exception of the Arc-L in the full term group. The different directions of associations could not be explained by different and non-overlapping values of FA in the two groups. A second novel finding was that the locations along the

Table 3
Mean fractional anisotropy (FA) of peak nodes and range of FA values for segments of white matter tracts with significant associations between FA and reading scores in the full term (FT) and preterm (PT) groups.

Tract (nodes)	FT peak node mean FA (95% CI)	FT FA range	PT peak node mean FA (95% CI)	PT FA range	t-Stat	p-Value
aSLF-L (4–8)	0.474 (0.45–0.50)	0.39–0.55	0.480 (0.45–0.51)	0.36–0.69	–0.27	0.79
(26–29)	0.476 (0.45–0.50)	0.40–0.55	0.478 (0.44–0.51)	0.35–0.68	–0.08	0.94
aSLF-R (12–14)	0.469 (0.45–0.49)	0.39–0.58	0.514 (0.48–0.54)	0.37–0.71	–2.33	0.02
Arc-L (8–11)	0.472 (0.45–0.50)	0.33–0.55	0.514 (0.49–0.54)	0.42–0.67	–2.65	0.01
CST-L (1–14)	0.601 (0.58–0.62)	0.50–0.68	0.612 (0.59–0.63)	0.48–0.73	–0.73	0.47
(23–27)	0.579 (0.56–0.60)	0.51–0.64	0.584 (0.58–0.63)	0.52–0.67	–1.69	0.10
CST-R (1–13)	0.593 (0.57–0.61)	0.51–0.65	0.608 (0.59–0.63)	0.52–0.67	–1.17	0.25
(24–27)	0.575 (0.56–0.59)	0.51–0.65	0.585 (0.56–0.61)	0.50–0.71	–0.695	0.49
UF-L (11–17)	0.405 (0.39–0.42)	0.36–0.47	0.380 (0.36–0.40)	0.30–0.49	2.07	0.04
(17–22)	0.477 (0.46–0.50)	0.39–0.56	0.429 (0.41–0.45)	0.31–0.53	3.61	0.003
UF-R (14–21)	0.423 (0.40–0.44)	0.35–0.49	0.388 (0.37–0.41)	0.25–0.48	2.36	0.023

aSLF = anterior superior longitudinal fasciculus; Arc = arcuate; ILF = inferior longitudinal fasciculus; CST = corticospinal tract; UF = uncinate fasciculus; L = left; R = right; CI = confidence interval.

tracts in which these significant associations were found in the two groups overlapped in one segment of the aSLF-L, Arc-L, and UF-L but were in different locations in the CST-L and CST-R.

4.1. Associations of white matter properties and reading in the full term group

In the full term group, FA was associated with decoding in five segments of white matter tracts consistent with previous literature: (1) the aSLF-L (Frye et al., 2011; Lebel et al., 2013; Steinbrink et al., 2008); (2) CST-L and CST-R (Deutsch et al., 2005; Frye et al., 2011; Myers et al., 2014; Niogi and McCandliss, 2006); and the UF-L and UF-R (Cummine et al., 2015; Lebel et al., 2013; Steinbrink et al., 2008). FA in the full term group was also associated with comprehension in segments of the aSLF-L, Arc-L, and UF-L. We did not find associations of reading with either the ILF-L or ILF-R, as has been seen in other studies (Lebel et al., 2013; Steinbrink et al., 2008; Yeatman et al., 2012a). Failure to find associations with the ILF is most likely related to methodological differences in the reading tasks and/or dMRI analyses and to variations in age and reading abilities among samples. The findings indicate that significant associations are not ubiquitous in all white matter tracts of the brain.

Partial correlations between FA and each reading component (while controlling the other component) did not find evidence for selective associations between decoding or comprehension and specific tracts. This lack of selectivity may stem from the use of standardized tests of decoding and comprehension that do not completely dissociate the cognitive processes that participants use in the tasks. For example, participants may have used similar strategies in decoding written words, which is an essential component of both tests. This interpretation is supported by the fact that the association between decoding and comprehension in each group of subjects was very strong. However, selectivity was found using these same tests in a recent analysis of the cerebellar peduncles (Travis et al., 2015b). Future studies using tasks that probe reading components more specifically and assessing larger samples will be able to examine the level of selectivity in the reading pathways more thoroughly.

The associations of FA and reading in the full term group were consistently negative. Several previous studies have reported positive associations of FA and reading within cerebral white matter (Beaulieu et al., 2005; Deutsch et al., 2005; Klingberg et al., 2000; Lebel and Beaulieu, 2009; Lebel et al., 2013; Myers et al., 2014). However, other studies

have found negative associations between FA and reading or reading-related abilities (Dougherty et al., 2007; Feldman et al., 2012b; Frye et al., 2008; Frye et al., 2011; Odegard et al., 2009; Yeatman et al., 2012a). More recently, Yeatman et al. (2012a) found that a sample of typically developing children with above-average reading skills initially had lower FA values that increased over time, whereas children with below-average reading skills had higher initial FA that declined over time. Negative associations have also been found between FA and other cognitive abilities, including those for language (Schmithorst et al., 2011), mathematics and executive functions (Rollins et al., 2014).

We hypothesize that the negative associations of FA and reading reflect neurobiological factors that facilitate information exchange in reading. FA is a summary measure that arises from multiple tissue properties that may co-vary in different combinations and proportions across distinct regions of a single white matter tract, across tracts, and across clinical populations (De Santis et al., 2014). Further, several of the tissue properties known to influence FA (e.g., crossing fibers, myelination, axonal count, and axonal densities) can have counteracting effects on FA, but may still be relevant for promoting efficient and rapid transmission of neural information for reading processes (Jones et al., 2013). For example, an increase in number of crossing fibers or axon diameters within the major tracts of the reading network could facilitate information exchange to different cortical regions and yet would lead to decreased FA within that tract. In the present study, negative associations of FA and reading were driven primarily by increased radial diffusivity. Increased radial diffusivity would be consistent with an increase in the number of crossing fibers or larger axon diameter.

4.2. Associations of white matter properties and reading in the preterm group

Consistent with our results in this study, other studies of white matter and reading in children and adolescents born preterm have found positive associations (Andrews et al., 2010; Feldman et al., 2012b; Frye et al., 2010; Mullen et al., 2011). However, this pattern is opposite from that in the full term group. Opposite going correlations between FA and reading within the preterm and full term groups could arise if different neurobiological factors influence the development and maintenance of functional connections important for reading in the two groups. For example, children born full term may achieve efficient communication between distant brain regions via overgrowth followed by pruning of inappropriate axons (Yeatman et al., 2012a). In this scenario,

better performance would be associated with fewer but larger fibers capable of faster conduction speeds (Arbuthnott et al., 1980; Goldman and Albus, 1968; Horowitz et al., 2015) and reduced FA (Dougherty et al., 2007). In contrast, preterm born children may achieve similar levels of reading performance via alternative mechanisms such as myelination of existing axons. Here, better function would be associated with more myelin and higher FA (Fields, 2008). Another possibility is that multiple factors are converging in white matter to allow efficient information exchange for reading in both full term and preterm groups, but our methods detect them differentially in the aftermath of early white matter injury or dysmaturity in the preterm group. For example, if the preterm group experienced early white matter damage in some tracts, they may develop reading with initially lower FA values, and reading will then result in an increase in FA, similar to the good readers in the longitudinal sample of (Yeatman et al., 2012a) who were found to begin reading with lower FA values but later to exhibit higher FA at older ages.

4.3. Segments of significant associations along the tracts

Within each of the groups, associations with the two reading components localized to similar tracts. However, across groups, the significant association of FA of the CST-L and CST-R and decoding localized to different and non-overlapping segments of the tracts. The segments were near the proximal end in the full term group and near the distal end in the preterm group. Though throughout the brain, the vast majority of voxels include some amount of crossing fibers (Jeurissen et al., 2013), these two segments of the CST differ in terms of the expected amount of crossing fibers. In a sample of adolescents born preterm, the proximal end was relatively dominated by fibers going in a single direction, while the distal end had a high density of crossing fibers (Groeschel et al., 2014). If reading skill in the full term group was related to the density of crossing fibers, even a small number of crossing fibers in a predominantly single fiber region could lead to negative associations. By contrast, the association would not be apparent in the preterm group. If the preterms have a reduced number of crossing fibers and better reading is associated with increased myelin, then the association might become significant in regions of crossing fibers. Alternatively, group differences in the direction of association may arise from other differences across the two groups, such as the size of axons. The pertinent neurobiological factors explaining the different direction of associations may even vary within and across tracts in the two groups.

We found differences in one segment of the aSLF between groups. While we again think that these findings represent different neurobiological factors or a different balance of factors, the findings are more difficult to interpret because the density of crossing fibers at each end has not been well established (Groeschel et al., 2014).

4.4. Limitations

Modeling diffusion with a tensor model constitutes a limitation of this study because it does not quantify the amount of potential crossing fibers. In addition, FA, RD and AD are limited in their ability to assess specific tissue properties, because each parameter is affected by multiple tissue properties, including myelin, directional coherence, axonal density and axonal diameter. In the future, strategies for understanding the direction of associations between microstructural properties of white matter and reading will likely require the use of multiple converging methods for analysis of white matter. Techniques for quantifying the amount of crossing fibers (Tuch et al., 2002; Wedeen et al., 2008) will likely prove important for determining which associations may be driven by the amount of crossing fibers (De Santis et al., 2014). Such research is also expected to provide insight into the contributions of fibers crossing the tracts analyzed here to neural processes for reading. New quantitative techniques for estimating myelin content (Lutti et al., 2014; Mezer

et al., 2013) and axon diameter (Assaf et al., 2008; Barazany et al., 2009) are also important for distinguishing among neurobiological factors contributing to variations in reading skills.

Our study was also limited in the specificity of the reading measures used. We chose to use age-standardized tests, which was important due to the relatively large age range here, but may have failed to single out specific components of the reading process. We also studied children and adolescents across a wide age-range. Future studies using fine-tuned behavioral contrasts of skills essential for reading (Hulme and Snowling, 2014) at specific stages of learning to read (Monzalvo and Dehaene-Lambertz, 2013; Thiebaut de Schotten et al., 2014) could allow more precise inferences into the types of information that course along the various white matter tracts at different developmental time points. Finally, the sample size here was modest. A larger sample would be better powered to reveal associations that were not apparent in this study.

4.5. Conclusion and implications

This study found that FA of segments within several white matter tracts of the brain (aSLF, Arc, CST, and UF) was associated with decoding and comprehension in children born full term and preterm. However, the direction of the association was different in the two groups and found in different segments of white matter tracts. These results suggest that different neurobiological factors or a different balance of neurobiological factors are associated with reading in the two groups. White matter diffusion properties represent a complex interaction of biological and experiential forces. The children born preterm may have experienced injury and subsequent dysmaturity to their white matter. The dynamic forces sculpting their white matter beyond the newborn period, by necessity, would take different forms from the forces at play within full term healthy individuals. The children born preterm in this study were nonetheless able to develop reading skills that were comparable to full term peers on standardized testing.

Children born preterm typically perform below their full term peers in reading skills (Aarnoudse-Moens et al., 2009; Frye et al., 2010; Kovachy et al., 2014; Mullen et al., 2011). The results of this study suggest that distinctive neurobiological factors may influence reading abilities in this population. These findings leave open the possibility that children born preterm would benefit from customized reading instruction or particular types of remediation if they show early delays. To date, reading instruction and remediation are solely based on behavioral profiles. In the future, it may be possible to refine the approaches based on both behavior and neurobiological factors.

These findings should be generalized across different samples of children born full term and preterm. In addition, longitudinal studies are essential to explore whether group differences are found at the very earliest stages of reading, suggesting that they may be the result of biological factors and early experience, or whether they develop as the children progress in learning to read, suggesting that they are the result of education. Evaluations of education and intervention in children born preterm versus full term, both in terms of behavioral and neurobiological outcomes, will determine if these children benefit from distinctive programs of education and remediation.

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