White matter properties underlying reading abilities differ in 8-year-old children born full term and preterm

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32   **Highlights:**

- 33   •   Reading correlated with fractional anisotropy in dorsal tracts in term-born children
- 34   •   Reading was not associated with myelin content in term children
- 35   •   Reading was not correlated with fractional anisotropy in children born preterm
- 36   •   Reading correlated with myelin content in dorsal and ventral tracts in preterms

Abstract:

Diffusion magnetic resonance imaging (dMRI) studies find differences in associations between reading and white matter fractional anisotropy (FA) in children born full term (FT) versus preterm (PT). Use of complementary neuroimaging modalities may reveal neurobiological factors driving these associations. We used two MRI methods to interpret associations of reading abilities and white matter properties in FT and PT children. Participants ($N=79$: 36 FT and 43 PT) were administered the Gray's Oral Reading Test at age 8 years. We segmented two dorsal and two ventral white matter tracts associated with reading abilities and quantified (1) FA from dMRI and (2) R1 from quantitative relaxometry, as a proxy for myelin content. We examined correlations between reading scores and neuroimaging metrics, assessing trajectories along the tracts. Mean reading scores fell in the typical range in both groups. Reading positively correlated with FA in segments of the left arcuate and the left and right superior longitudinal fasciculi in FT children, but not in PT children. Reading positively correlated with R1 in segments of the left superior longitudinal, right uncinate, and left inferior longitudinal fasciculi in PT children, but not in FT children. The significantly different patterns of associations between reading abilities and white matter properties across FT and PT groups suggest variations in the neurobiology of typical reading abilities.

Keywords: reading, fractional anisotropy, myelination, relaxometry, children, preterm

1. Introduction

Children learn to read around 6 years of age and within 3 years use reading to learn. Reading abilities correlate with academic and occupational attainment and physical and mental health (Arnold et al., 2005; Snowling et al., 2007). Poor readers in early primary grades rarely catch up with good readers. Early detection and intervention are therefore critical for prevention of the long-term adverse outcomes of poor reading. Research on the neurobiological foundations of reading abilities may reveal basic underlying processes associated with individual differences in reading. Ultimately, understanding the neurobiology supporting reading abilities can contribute to strategies for early detection of reading difficulties and customizing reading instruction for individuals based on neurobiological characteristics.

Characteristics of white matter pathways in the brain are associated with reading abilities in school-aged children (Wandell & Yeatman, 2013). Studies using diffusion magnetic resonance imaging (dMRI) in children have consistently found associations between reading abilities and fractional anisotropy (FA) in dorsal white matter pathways, specifically the arcuate fasciculus (Arc) and superior longitudinal fasciculus (SLF) (Saur et al., 2008; Wang et al., 2017; Yeatman et al., 2012). These tracts have been implicated in the transmission of phonological information for converting visual forms to spoken words (Hickok & Poeppel, 2007). Associations have also been found between reading and FA in ventral pathways, including the inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF) (Andrews et al., 2010; Bruckert et al., 2019; Dodson et al., 2018; Saur et al., 2008). These tracts have been implicated in transmission of semantic and orthographic information, used for understanding meaning (Yeatman et al., 2012). The goal of this study was to examine whether consistently reported associations between reading abilities and white matter characteristics in specific pathways in

typically developing full term (FT) born children differ from associations in a group with known high risk for both reading deficits and white matter differences, namely children born preterm (PT).

Both positive and negative associations of reading and FA have been reported. Positive associations would be consistent with increases in myelination, leading to faster nerve impulse propagation along axons (Cykowski et al., 2010; Gao et al., 2009; Jones et al., 2013; Lebel et al., 2013) and contributing to maturation of cognitive functions (Casey et al., 2005; Nagy et al., 2004; Toga et al., 2006). Negative associations between reading abilities and FA (Dougherty et al., 2007; Odegard et al., 2009; Travis et al., 2016) challenge this interpretation. FA indexes multiple tissue properties beyond the degree of myelination, including axon diameter, number of crossing fibers, axon density, and fiber coherence (Jones et al., 2013; Pierpaoli & Basser, 1996). If rapid or efficient information transfer characterizes competent performance, negative associations implicate properties other than myelin, such as increased axonal diameter or number of crossing fibers, in increasing signal propagation. The use of more than one imaging technique is a strategy to determine whether reading-white matter associations are best explained by myelination or other white matter microstructural properties.

Associations of reading and white matter properties differ in very PT children, defined as birth at < 32 weeks' gestation, compared to FT children, defined as birth at ≥ 37 weeks' gestation. As a group, PT children have poorer reading abilities than FT children (Aarnoudse-Moens et al., 2009; Kovachy et al., 2015). Their deficits have been attributed to white matter injury and dysmaturity, part of a complex of encephalopathic changes incurred at birth (Back, 2017; Volpe, 2009). Resultant injuries can be identified on neonatal dMRI scans as altered FA (Li et al., 2015). Birth group differences in FA persist throughout childhood to adulthood

(Eikenes et al., 2011; Groeschel et al., 2014). White matter changes in PT children are thought to impact neurocognitive function by altering structural and functional connectivity (Lubsen et al., 2011). Our team found different patterns of associations between reading and FA in two different cohorts of FT and PT children (Bruckert et al., 2019; Dodson et al., 2018; Travis et al., 2016). These findings suggest that a different balance of white matter properties may lead to individual differences in reading in the two birth groups.

Further interrogation of reading-white matter associations would be assisted using complementary MRI methods that are sensitive to specific tissue properties, including myelin content and axonal properties. Quantitative R1 measurement with MRI (qR) is a technique that estimates the longitudinal relaxation rate of water protons in a magnetic field. R1, the inverse of the time constant ($R1 = 1/T1$), is considered a proxy for myelin content within white matter areas of the brain (Stüber et al., 2014). Developmental changes in R1 suggest that this metric reflects myelin content (Yeatman et al., 2014). Our team has reported that values of R1 in the cerebellar peduncles were related to reading abilities in FT children (Bruckert et al., 2020). A recent study showed, however, that two brain imaging metrics of myelin content in cerebral tracts were associated with age but not with reading abilities in typically developing FT children (Geeraert et al., 2020). A gap in the literature is whether reading abilities in FT and PT children would show similar or different patterns of associations with metrics sensitive to myelin content in cerebral white matter pathways, as they do with diffusion metrics.

The present study assessed a sample of FT and PT children, who were part of a longitudinal study of reading development from ages 6 to 8 years (Bruckert et al., 2019; Dodson et al., 2018). When these children turned 8-year-old, R1 became available at our imaging center. We collected both dMRI and R1 in children whose reading abilities had been assessed. The

study had two aims. First, we wanted to assess the associations between reading abilities and FA of white matter pathways in the two birth groups (FT and PT) at age 8 years, evaluating dorsal pathways, Arc and SLF, and ventral pathways, UF and the ILF, based on evidence implicating these tracts in reading (Duffau, 2015; Herbet et al., 2018; Saur et al., 2008; Vandermosten et al., 2012). We hypothesized that, consistent with previously reported results at age 6 in this sample of FT and PT children, we would observe positive associations between reading abilities and FA in FT children at age 8, but not in PT children (Bruckert et al., 2019; Dodson et al., 2018). Second, we wanted to assess the associations between reading abilities and R1 of the same pathways. Based on a previous study that found no associations between reading abilities and two myelin-sensitive metrics in their FT participants (Geeraert et al., 2020), we hypothesized that we would not observe associations between reading and R1 in the FT group. Given that the encephalopathy of prematurity (white matter injury and dysmaturity) seen in PT children results from injury to the myelin producing oligodendrocyte precursor cells (Back, 2017; Volpe, 2009), we hypothesized a positive association between reading and the myelin-sensitive metric (R1) in the PT group.

2. Materials and Methods

2.1. Participants

A sample ($N=95$) of children born FT ($n=45$) or PT ($n=50$) were recruited at age 6 years between 2012 to 2015 as part of a longitudinal study (Bruckert et al., 2019; Dodson et al., 2018). The participants reported here had to have complete reading measures and useable dMRI data at age 8 years. Of the 36 FT participants with complete reading and dMRI data at age 8 years, $n=24$

had usable qR data. Of the 43 PT participants with complete reading and dMRI data at age 8 years, $n=29$ had useable qR data.

Inclusion in the PT group required a gestational age (GA) < 32 weeks, the GA below which neonates are at greatest risk for white matter injury (Back, 2017). Children were recruited from the Lucile Packard Children's Hospital Stanford High-Risk Infant Follow-Up Clinic, local parent groups, and the surrounding San Francisco Bay Area. Exclusion criteria included neurological, sensory, or cognitive factors unrelated to prematurity that could account for white matter differences or could impact learning to read English, including congenital anomalies, active seizure disorder, hydrocephalus, sensorineural hearing loss, visual impairment, intelligence quotient <80, and non-English speakers. Socioeconomic status was measured using a modified 4-Factor Hollingshead Index (Hollingshead, 1975). A neuroradiologist assessed T1-weighted scans for evidence of white matter injury.

The Stanford University Institutional Review Board approved the experimental protocol (#IRB-22233). A parent or legal guardian provided informed written consent. Children provided assent. Participants were compensated for participation.

2.2. Reading Measure

For the current study, we analyzed the Oral Reading Index (ORI) generated from the Gray's Oral Reading Tests, 5th Edition (Wiederholt & Bryant, 2012) as the measure of reading. The ORI asks children to read short paragraphs aloud and then answer questions about what they read. A composite score, composed of fluency (rate and accuracy) and comprehension is reported as a standard score (mean=100, standard deviation=15). Study assessments were completed in English.

2.3. MRI Data Acquisition and Processing

172 MRI data were acquired on a 3T Discovery MR750 scanner (General Electric Healthcare,
173 Milwaukee, WI, USA) equipped with a 32-channel head coil (Nova Medical, Wilmington, MA,
174 USA) at the Center for Cognitive and Neurobiological Imaging at Stanford University
175 (www.cni.stanford.edu). Participants were scanned without sedation. High-resolution T1-
176 weighted anatomical images were collected using an inversion recovery-prep 3D fast-spoiled
177 gradient (FSPGR) sequence collected in the sagittal plane (0.9 x 0.9 x 0.9 mm³ voxel size). The
178 T1-weighted volume was used as an anatomical reference for the alignment of the dMRI images.

179 dMRI data were acquired with a diffusion-weighted, dual-spin echo, echo-planar imaging
180 sequence with full brain coverage. Diffusion weighted gradients were applied at 30 non-
181 collinear directions with a b-value=1,000 s/mm². Three volumes were acquired at $b=0$ at the
182 beginning of the scan. We collected 70, 2mm-thick, axial slices in each participant (TR=8300
183 ms; TE=83.1 ms; FOV=220 mm; matrix size of 256 x 256; 0.8594 x 0.8594 x 2 mm³ voxel size).
184 R1 maps were acquired with spoiled gradient echo (SPGR) images at a four flip angles ($\alpha = 4^\circ$,
185 10° , 20° , and 30° ; TR=14 ms; TE=2 ms) (Fram et al., 1987). SPGR scans were acquired
186 sequentially, without breaks to ensure that scan parameters were similar across flip angles. A
187 0.9375 x 0.9375 x 1.5 mm³ voxel size was chosen to acquire the four SPGR scans in a reasonably
188 short time frame, appropriate for a pediatric clinical sample. To obtain an unbiased R1 map, we
189 acquired a spin-echo inversion-recovery (SEIR) sequence with echo-planar imaging (EPI) read-
190 out, measured at lower resolution (1.875 x 1.875 x 4 mm³ voxel size). Four inversion times were
191 measured (2400, 1200, 400 and 50 ms; TR = 3 s; TE = 47 ms). Unbiased R1 maps obtained
192 from SEIR-EPI scans were used to correct for Radio Frequency (RF) transmit bias in the higher-
193 resolution SPGR scans as described and validated by others (Mezer et al., 2013, 2016). R1 maps
194 were directly aligned to the dMRI.

Image preprocessing and registration steps, deterministic tractography, fiber tract identification, segmentation, and quantification are described in the **Supplemental Information**. We computed FA from dMRI scans and calculated R1 from quantitative scans. We characterized white matter metrics from two dorsal (Arc-L and bilateral SLF) and two ventral (bilateral ILF and bilateral UF) tracts. We selected these pathways *a priori*, based on previous evidence implicating their involvement in reading. The right arcuate fasciculus, however, was excluded *a priori* from our analyses, given the previously described limitations of deterministic tractography for segmenting it (Catani et al., 2007; Lebel and Beaulieu, 2009; Mishra et al., 2010; Travis et al., 2015a; Yeatman et al., 2011).

Figure 1 shows the left hemisphere tracts in a representative participant. We generated FA and R1 tract profiles to describe variations in each of the white matter tissue parameters at 30 equidistant locations along the central portion of each fiber tract, bounded by the same regions of interest used for tract segmentation. For greater sensitivity, relative to mean values, we calculated and analyzed the association of reading (ORI) with values of the relevant metric (FA or R1) along the trajectory of the tract.

2.4. Statistical Approach

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS version 25.0 and 26.0, IBM Corp., 2018). Statistical significance was set at $p < 0.05$. Adherence to the normal distribution of clinical and neurobiological data was assessed using the Shapiro–Wilk test. Based on normality, we used parametric tests for all associations. A False Discovery Rate (FDR) of 5% was set for zero-order associations to account for multiple comparisons across seven tracts (Benjamini & Hochberg, 1995).

2.4.1. Associations between reading and white matter microstructure metrics

First, to identify associations between reading abilities and white matter microstructural properties, we computed Pearson's correlations between ORI and FA, and between ORI and R1, for 30 equidistant nodes along each of the four tracts within the FT and the PT groups, separately. We calculated the associations separately because previous studies found differences in the patterns of associations in separate groups of FT and PT children (Bruckert et al., 2019; Dodson et al., 2018b; Travis et al., 2016). The tract profile analysis utilized a nonparametric permutation-based method to control for 30 along-tract comparisons, producing a family-wise error corrected cluster size and a critical r -value for each tract (Nichols & Holmes, 2002). Along-tract correlations were considered significant if (1) correlations at an uncorrected level of $p < 0.05$ occurred in adjacent nodes $\geq$ the critical cluster size (range 6-9 nodes) or (2) correlations $\geq$ the critical r -value occurred within a minimum cluster size ≥ 3 nodes. For both FA and R1, we computed the mean r -value from the longest tract segment meeting these criteria and controlled for the FDR at $p < 0.05$, to correct significance across seven tracts per group.

Second, we tested whether the strength of associations between reading abilities and white matter microstructural properties differed by birth group (FT vs. PT). Following an independent-samples correlation coefficients comparison principle, we transformed the Pearson's correlation coefficients (r values) into z scores. Specifically, we used the r value of the mean of FA or R1 of the adjacent nodes in the longest region of the tract with significant correlations with ORI. We transformed and compared the mean r value of each ORI-FA or ORI-R1 significant nodes set in a given birth group with the same set of nodes (not significant) from the other group. For example, the mean r value of ORI-FA significant correlation in the SLF-L nodes 1-6 in the FT group was compared to the (non-significant) mean r value of ORI-FA in the SLF-L nodes 1-6 of the PT group. Fisher's r -to- z transformation allowed statistical comparison

of the observed z -test statistics. We used the Psychometrica online calculator (<https://www.psychometrica.de/correlation.html>) to perform the r -to- z transformations and the VassarStats online calculator (<http://vassarstats.net/rdiff.html>) to determine the significance of differences between correlation coefficients estimated in the two groups.

3. Results

3.1. Participant Characteristics

Participant characteristics are shown in **Table 1**. By study design, groups differed in GA (FT = 39.6 ± 1.6 weeks, PT = 29.3 ± 2.1 weeks, $t=24.61$, $p<0.001$) and birthweight (FT = 3325 ± 431 grams, PT = 1310 ± 429 grams, $t=20.73$, $p<0.001$). There were no statistically significant differences in mean-tract FA, mean-tract R1, or proportion of female/male participants between the two groups. FT participants were, on average, 1 month younger than PT participants at the time of testing (FT = 8.1 ± 0.2 years, PT = 8.2 ± 0.2 years, $t=-2.13$, $p=0.04$). Standard scores, which account for age at testing, for reading (ORI) are reported. Hollingshead Index differed in the larger sample (FT = 57.2 ± 11.0 , PT = 51.7 ± 12.7 , $t=2.1$, $p=0.04$), but not in the R1 subsample (FT = 57.1 ± 11.8 , PT = 54.3 ± 12.6 , $t=0.9$, $p=0.37$). Although the difference was statistically significant in the larger sample, both samples were relatively high SES and there was no significant difference in the participants with R1, therefore we did not include SES in our analyses. Four of the 43 PT participants had mildly abnormal T1-weighted scans. The mean ORI scores were significantly higher in the FT compared to the PT group (FT = 102.0 ± 12.6 , PT = 95.8 ± 10.8 , $t=2.3$, $p=0.02$), though both groups scored within the average range.

3.2. Associations between reading abilities and FA

3.2.1. Correlations between ORI and FA

As expected, significant positive correlations between ORI and FA were identified in large segments of the Arc-L (nodes 2-10; $r_{\text{mean}}=0.52$, $p=0.001$), SLF-L (nodes 13-20; $r_{\text{mean}}=0.54$, $p=0.001$), and SLF-R (nodes 1-22; $r_{\text{mean}}=0.62$, $p<0.001$) in the FT group (**Table 2, Figure 2**).

These associations remained significant after FDR correction for multiple comparisons. We found no significant correlations between ORI and FA in the PT group, as predicted.

3.2.2. Correlations between ORI and FA as a function of birth group

The difference in the strength of associations between ORI and FA in these three tracts was statistically significant between the two birth groups after correction for multiple comparisons: Arc-L (nodes 2-10: $z_{\text{mean}}=2.30$, $p=0.021$), SLF-L (nodes 13-20: $z_{\text{mean}}=2.70$, $p=0.007$), and SLF-R (nodes 1-22: $z_{\text{mean}}=2.85$, $p=0.004$) (**Table 2**).

3.3. Associations between reading abilities and R1

3.3.1. Correlations between ORI and R1

We found no significant correlations between ORI and R1 in the FT group, as expected. In PT children, as predicted, significant positive correlations between ORI and R1 were identified in the SLF-L (nodes 1-5; $r_{\text{mean}}=0.42$, $p=0.02$), UF-R (nodes 13-19; $r_{\text{mean}}=0.45$, $p=0.02$), and ILF-L (nodes 20-23 $r_{\text{mean}}=0.53$, $p<0.01$) (**Table 2, Figure 2**). These associations remained significant after FDR correction for multiple comparisons.

3.3.2. Correlations between ORI and R1 as a function of birth group

The difference in the strength of the association between the ORI and R1 was statistically significant between the two birth groups in the UF-R (nodes 13-19, $z_{\text{mean}}=1.77$, $p=0.038$) and the ILF-L (nodes 20-23, $z_{\text{mean}}=1.93$, $p=0.026$) (**Table 2**) after correction for multiple comparisons.

3.4. Secondary Analyses: Associations between FA and R1

To further understand the variation in the patterns of association, we assessed the degree of association between FA and R1 in the tracts of interest, using their mean-tract value. We found no statistically significant associations within the FT group (**Supplemental Table 1**). In the PT group, however, associations between R1 and FA were positive and statistically significant in the SLF-R, UF-L, UF-R, and ILF-R (**Supplemental Table 1**). These findings suggest that myelin content is insufficient to drive FA in the PT group.

4. Discussion

In this investigation of 8-year-old FT and PT children with comparable reading abilities, we evaluated correlations between reading abilities and two concurrent white matter microstructure metrics, FA from dMRI and R1 from quantitative MRI. Consistent with previous findings and current hypotheses, we found positive associations between reading abilities and FA within dorsal pathways (Arc-L, SLF-L, SLF-R) in FT children, but not in PT children. The strength of the associations between reading abilities and FA between the two groups was also significantly different. In contrast, we found positive associations between reading abilities and R1 in segments of some of a dorsal (SLF-L) and two ventral (UF-R, ILF-L) pathways in PT children, but not in FT children. The strength of the associations between reading abilities and R1 between the two groups was also significantly different in the UF-R and ILF-L.

4.1. Correlations between reading abilities and white matter metrics

We observed significant positive associations between reading abilities and FA within dorsal tracts in FT children. These results are consistent with those of many other studies (Saur et al., 2008; Wang et al., 2017; Yeatman et al., 2012). We did not find, however, positive correlations in the PT children. This finding is also consistent with previous studies of this same sample of

children at a younger age. We previously reported that FA at age 6 was related to reading abilities at age 6 and at age 8 years in FT children, but not in PT children (Bruckert et al., 2019; Dodson et al., 2018).

Interestingly, we did not observe associations of reading and R1 for the FT group. R1 within white matter tracts is considered a proxy for myelin content of the tract (Stüber et al., 2014). Our finding suggests that myelin content is unlikely to be driving the associations between FA and reading in FT children. While myelin content may be associated with maturity and transmission efficiency, it appears not to be the principal factor associated with individual differences in reading in FT born individuals, based on the results in this study and those in related work (Geeraert et al., 2020). These findings are consistent with studies that report negative associations of FA and reading (Dougherty et al., 2007; Odegard et al., 2009; Travis et al., 2016), because myelin content is likely to cause positive FA associations, not negative ones. Moreover, recent studies that obtained dMRI and quantitative MRI scans at several points during an intensive reading intervention for poor readers found widespread increases in FA and no change in R1 after the initial phase of intervention, associated with improvements in reading (Huber et al., 2018, 2021). The time frame of FA increase and absence of change in R1 made it unlikely that the intervention permitted a major increase in myelination. Alternative microstructural properties that might lead to positive associations between reading and FA include axonal diameter, fiber tract coherence, axonal packing, or number of crossing fibers. Rapid change in FA may relate to changes in characteristics of glial cells, that may also play a role in individual differences in reading (Huber et al., 2018). Alternative MRI sequences or analyses may be useful for assessing the strength of the association between reading and other white matter or glial metrics.

We found that individual differences in reading among PT children were not associated with FA at these two ages. These findings are interesting because the PT group had average reading scores, though the mean scores were lower than that of the FT group. Positive associations between reading abilities and FA in the same pathways have been found at older ages in PT children (Travis et al., 2016).

In this sample of PT children, R1 was associated with individual variation in reading abilities. PT birth leads to encephalopathic changes that include perinatal injury to oligodendrocyte precursors, the cell line that later myelinates axons, and/or to aberrant regeneration and repair of the oligodendrocytes and, consequently, to white matter tracts (Back, 2017; Volpe, 2009). Long-term neurodevelopmental outcomes in PT children are currently thought to result from these processes. Thus, R1 may be associated with the severity of the initial injury and/or the degree of recovery and compensation of white matter after the initial injury. Such factors would explain why associations between reading and R1 were found in the PT group only. In addition, associations between FA and R1 were significant in four of the seven tracts examined in this study only in the PT group. While myelin content would contribute to FA, R1 is also sensitive to other factors, such as iron content and lipid composition, that also contribute to FA (Stüber et al., 2014). Other properties contributing to FA, but not to R1, including axonal diameter, fiber coherence, and proportion of crossing fibers, may reduce the association between reading and FA in the PT group. These factors may have been negatively impacted by preterm birth and its aftermath.

4.2. Tracts in which associations were found

We observed ORI-FA associations in dorsal pathways in the FT group and ORI-R1 associations in both dorsal and ventral pathways in the PT group. The variation in location of significant

associations could be explained by differences related to behavior, or to developmental differences resulting from injury or recovery from PT birth. Associations between reading abilities and dorsal tract FA in the FT group may be due to the age of the participants, the modest sample size, and/or different measurement properties of the dorsal and ventral tracts in this study. Our identification of associations between reading abilities and R1 in some dorsal and some ventral tracts in PT children suggests that the ventral tracts are also important for reading abilities in this birth group. The variation of the identity of the tracts in which associations between reading abilities and white matter microstructural properties were found in FT and PT children is further evidence for variation in the neurobiology of reading in these two birth groups, despite both groups being in the typical range of reading abilities.

4.3. Limitations

Limitations include a modest sample size and reading scores within the normal range in both groups. Future studies in larger samples with greater diversity in reading abilities could confirm the findings described here and explore whether associations exist in other white matter pathways. An additional limitation was the use of only two MRI modalities. As new modalities become available, they could be integrated with the methods here to gain further insights into the factors associated with reading.

4.4. Conclusions

In summary, by combining complementary structural neuroimaging approaches, we identified relations between reading abilities and concurrent white matter properties that differed in two birth groups — FT and PT children. The associations between reading and FA but not R1 in the FT group implicate axonal features, such as axonal diameter and packing, in individual variations of reading abilities. The associations between reading and R1 but not FA in the PT

group implicate myelin content as the primary factor associated with reading abilities. Further exploration of white matter pathways using multiple imaging techniques will contribute to understanding reading-brain associations in different birth groups.

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REFERENCES

- Aarnoudse-Moens, C. S. H., Weisglas-Kuperus, N., van Goudoever, J. B., & Oosterlaan, J. (2009). Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics*, *124*(2), 717–728.
- Andrews, J. S., Ben-Shachar, M., Yeatman, J. D., Flom, L. L., Luna, B., & Feldman, H. M. (2010). Reading performance correlates with white-matter properties in preterm and term children. *Dev Med Child Neurol*, *52*(6), e94-100. <https://doi.org/10.1111/j.1469-8749.2009.03456.x>
- Arnold, E. M., Goldston, D. B., Walsh, A. K., Reboussin, B. A., Daniel, S. S., Hickman, E., & Wood, F. B. (2005). Severity of emotional and behavioral problems among poor and typical readers. *Journal of Abnormal Child Psychology*, *33*(2), 205–217.
- Back, S. A. (2017). White matter injury in the preterm infant: Pathology and mechanisms. *Acta Neuropathologica*, *134*(3), 331–349. <https://doi.org/10.1007/s00401-017-1718-6>
- Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*(1), 289–300. JSTOR.
- Bruckert, L., Borchers, L. R., Dodson, C. K., Marchman, V. A., Travis, K. E., Ben-Shachar, M., & Feldman, H. M. (2019). White Matter Plasticity in Reading-Related Pathways Differs in Children Born Preterm and at Term: A Longitudinal Analysis. *Frontiers in Human Neuroscience*, *13*, 139. <https://doi.org/10.3389/fnhum.2019.00139>
- Bruckert, L., Travis, K. E., Mezer, A. A., Ben-Shachar, M., & Feldman, H. M. (2020). Associations of Reading Efficiency with White Matter Properties of the Cerebellar

423 Peduncles in Children. *Cerebellum (London, England)*, 19(6), 771–777.
424 <https://doi.org/10.1007/s12311-020-01162-2>

425 Casey, B. J., Tottenham, N., Liston, C., & Durston, S. (2005). Imaging the developing brain:
426 What have we learned about cognitive development? *Trends in Cognitive Sciences*, 9(3),
427 104–110. <https://doi.org/10.1016/j.tics.2005.01.011>

428 Cykowski, M. D., Fox, P. T., Ingham, R. J., Ingham, J. C., & Robin, D. A. (2010). A study of the
429 reproducibility and etiology of diffusion anisotropy differences in developmental
430 stuttering: A potential role for impaired myelination. *NeuroImage*, 52(4), 1495–1504.
431 <https://doi.org/10.1016/j.neuroimage.2010.05.011>

432 Dodson, C. K., Travis, K. E., Borchers, L. R., Marchman, V. A., Ben-Shachar, M., & Feldman,
433 H. M. (2018a). White matter properties associated with pre-reading skills in 6-year-old
434 children born preterm and at term. *Developmental Medicine and Child Neurology*, 60(7),
435 695–702. <https://doi.org/10.1111/dmcn.13783>

436 Dodson, C. K., Travis, K. E., Borchers, L. R., Marchman, V. A., Ben-Shachar, M., & Feldman,
437 H. M. (2018b). White matter properties associated with pre-reading skills in 6-year-old
438 children born preterm and at term. *Developmental Medicine and Child Neurology*, 60(7),
439 695–702. <https://doi.org/10.1111/dmcn.13783>

440 Dougherty, R. F., Ben-Shachar, M., Deutsch, G. K., Hernandez, A., Fox, G. R., & Wandell, B.
441 A. (2007). Temporal-callosal pathway diffusivity predicts phonological skills in children.
442 *Proceedings of the National Academy of Sciences*, 104(20), 8556–8561.
443 <https://doi.org/10.1073/pnas.0608961104>

444 Duffau, H. (2015). Stimulation mapping of white matter tracts to study brain functional
445 connectivity. *Nature Reviews. Neurology*, 11(5), 255–265.
446 <https://doi.org/10.1038/nrneurol.2015.51>

447 Eikenes, L., Løhaugen, G. C., Brubakk, A.-M., Skranes, J., & Håberg, A. K. (2011). Young
448 adults born preterm with very low birth weight demonstrate widespread white matter
449 alterations on brain DTI. *NeuroImage*, 54(3), 1774–1785.
450 <https://doi.org/10.1016/j.neuroimage.2010.10.037>

451 Fram, E. K., Herfkens, R. J., Johnson, G. A., Glover, G. H., Karis, J. P., Shimakawa, A., Perkins,
452 T. G., & Pelc, N. J. (1987). Rapid calculation of T1 using variable flip angle gradient
453 refocused imaging. *Magnetic Resonance Imaging*. [https://doi.org/10.1016/0730-](https://doi.org/10.1016/0730-725X(87)90021-X)
454 [725X\(87\)90021-X](https://doi.org/10.1016/0730-725X(87)90021-X)

455 Gao, W., Lin, W., Chen, Y., Gerig, G., Smith, J. K., Jewells, V., & Gilmore, J. H. (2009).
456 Temporal and Spatial Development of Axonal Maturation and Myelination of White
457 Matter in the Developing Brain. *American Journal of Neuroradiology*, 30(2), 290–296.
458 <https://doi.org/10.3174/ajnr.A1363>

459 Geeraert, B. L., Chamberland, M., Lebel, R. M., & Lebel, C. (2020). Multimodal principal
460 component analysis to identify major features of white matter structure and links to
461 reading. *PloS One*, 15(8), e0233244. <https://doi.org/10.1371/journal.pone.0233244>

462 Groeschel, S., Tournier, J.-D., Northam, G. B., Baldeweg, T., Wyatt, J., Vollmer, B., &
463 Connelly, A. (2014). Identification and interpretation of microstructural abnormalities in
464 motor pathways in adolescents born preterm. *NeuroImage*, 87, 209–219.

465 Herbet, G., Zemmoura, I., & Duffau, H. (2018). Functional Anatomy of the Inferior Longitudinal
 466 Fasciculus: From Historical Reports to Current Hypotheses. *Frontiers in Neuroanatomy*,
 467 12, 77. <https://doi.org/10.3389/fnana.2018.00077>
 468 Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature*
 469 *Reviews Neuroscience*, 8(5), 393–402.
 470 Hollingshead, A. (1975). *Four Factor Index of Social Status*. Yale University Department of
 471 Psychology.
 472 Huber, E., Donnelly, P. M., Rokem, A., & Yeatman, J. D. (2018). Rapid and widespread white
 473 matter plasticity during an intensive reading intervention. *Nature Communications*, 9(1),
 474 2260. <https://doi.org/10.1038/s41467-018-04627-5>
 475 Huber, E., Mezer, A., & Yeatman, J. D. (2021). Neurobiological underpinnings of rapid white
 476 matter plasticity during intensive reading instruction. *NeuroImage*, 243, 118453.
 477 <https://doi.org/10.1016/j.neuroimage.2021.118453>
 478 Jones, D. K., Knösche, T. R., & Turner, R. (2013). White matter integrity, fiber count, and other
 479 fallacies: The do's and don'ts of diffusion MRI. *NeuroImage*, 73, 239–254.
 480 <https://doi.org/10.1016/j.neuroimage.2012.06.081>
 481 Kovachy, V. N., Adams, J. N., Tamaresis, J. S., & Feldman, H. M. (2015). Reading abilities in
 482 school-aged preterm children: A review and meta-analysis. *Developmental Medicine and*
 483 *Child Neurology*, 57(5), 410–419. <https://doi.org/10.1111/dmcn.12652>
 484 Lebel, C., Shaywitz, B., Holahan, J., Shaywitz, S., Marchione, K., & Beaulieu, C. (2013).
 485 Diffusion tensor imaging correlates of reading ability in dysfluent and non-impaired
 486 readers. *Brain and Language*, 125(2), 215–222.
 487 <https://doi.org/10.1016/j.bandl.2012.10.009>

488 Li, K., Sun, Z., Han, Y., Gao, L., Yuan, L., & Zeng, D. (2015). Fractional anisotropy alterations
489 in individuals born preterm: A diffusion tensor imaging meta-analysis. *Developmental*
490 *Medicine & Child Neurology*, 57(4), 328–338. <https://doi.org/10.1111/dmcn.12618>

491 Lubsen, J., Vohr, B., Myers, E., Hampson, M., Lacadie, C., Schneider, K. C., Katz, K. H.,
492 Constable, R. T., & Ment, L. R. (2011). Microstructural and Functional Connectivity in
493 the Developing Preterm Brain. *Seminars in Perinatology*, 35(1), 34–43.
494 <https://doi.org/10.1053/j.semperi.2010.10.006>

495 Mezer, A., Rokem, A., Berman, S., Hastie, T., & Wandell, B. A. (2016). Evaluating quantitative
496 proton-density-mapping methods. *Human Brain Mapping*.
497 <https://doi.org/10.1002/hbm.23264>

498 Mezer, A., Yeatman, J. D., Stikov, N., Kay, K. N., Cho, N., Dougherty, R. F., Perry, M. L.,
499 Parvizi, J., Hua, L. H., Butts-Pauly, K., & Wandell, B. (2013). Quantifying the local
500 tissue volume and composition in individual brains with MRI. *Nature Medicine*, 19(12),
501 1667–1672. <https://doi.org/10.1038/nm.3390>

502 Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of White Matter is Associated
503 with the Development of Cognitive Functions during Childhood. *Journal of Cognitive*
504 *Neuroscience*, 16(7), 1227–1233. <https://doi.org/10.1162/0898929041920441>

505 Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional
506 neuroimaging: A primer with examples. *Human Brain Mapping*, 15(1), 1–25.
507 <https://doi.org/10.1002/hbm.1058>

508 Odegard, T. N., Farris, E. A., Ring, J., McColl, R., & Black, J. (2009). Brain connectivity in non-
509 reading impaired children and children diagnosed with developmental dyslexia.

510 *Neuropsychologia*, 47(8–9), 1972–1977.
 511 <https://doi.org/10.1016/j.neuropsychologia.2009.03.009>
 512 Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy.
 513 *Magnetic Resonance in Medicine*, 36(6), 893–906.
 514 <https://doi.org/10.1002/mrm.1910360612>
 515 Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., Umarova, R.,
 516 Musso, M., Glauche, V., Abel, S., Huber, W., Rijntjes, M., Hennig, J., & Weiller, C.
 517 (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy*
 518 *of Sciences of the United States of America*, 105(46), 18035–18040.
 519 <https://doi.org/10.1073/pnas.0805234105>
 520 Snowling, M. J., Muter, V., & Carroll, J. (2007). Children at family risk of dyslexia: A follow-up
 521 in early adolescence. *Journal of Child Psychology and Psychiatry*, 48(6), 609–618.
 522 Stüber, C., Morawski, M., Schäfer, A., Labadie, C., Wähnert, M., Leuze, C., Streicher, M.,
 523 Barapatre, N., Reimann, K., Geyer, S., Spemann, D., & Turner, R. (2014). Myelin and
 524 iron concentration in the human brain: A quantitative study of MRI contrast.
 525 *NeuroImage*, 93 Pt 1, 95–106. <https://doi.org/10.1016/j.neuroimage.2014.02.026>
 526 Toga, A. W., Thompson, P. M., & Sowell, E. R. (2006). Mapping Brain Maturation. *FOCUS*,
 527 4(3), 378–390. <https://doi.org/10.1176/foc.4.3.378>
 528 Travis, K. E., Ben-Shachar, M., Myall, N. J., & Feldman, H. M. (2016). Variations in the
 529 neurobiology of reading in children and adolescents born full term and preterm.
 530 *Neuroimage Clin*, 11, 555–565. <https://doi.org/10.1016/j.nicl.2016.04.003>

- Vandermosten, M., Boets, B., Poelmans, H., Sunaert, S., Wouters, J., & Ghesquière, P. (2012). A tractography study in dyslexia: Neuroanatomic correlates of orthographic, phonological and speech processing. *Brain*, 135(3), 935–948. <https://doi.org/10.1093/brain/awr363>
- Volpe, J. J. (2009). Brain injury in premature infants: A complex amalgam of destructive and developmental disturbances. *The Lancet Neurology*, 8(1), 110–124.
- Wandell, B. A., & Yeatman, J. D. (2013). Biological development of reading circuits. *Current Opinion in Neurobiology*, 23(2), 261–268.
- Wang, Y., Mauer, M. V., Raney, T., Peysakhovich, B., Becker, B. L. C., Sliva, D. D., & Gaab, N. (2017). Development of Tract-Specific White Matter Pathways During Early Reading Development in At-Risk Children and Typical Controls. *Cerebral Cortex (New York, N.Y.: 1991)*, 27(4), 2469–2485. <https://doi.org/10.1093/cercor/bhw095>
- Wiederholt, J. L., & Bryant, B. R. (2012). Gray oral reading tests—Fifth edition (GORT-5). *Austin, TX: Pro-Ed*.
- Yeatman, J. D., Dougherty, R. F., Ben-Shachar, M., & Wandell, B. A. (2012). Development of white matter and reading skills. *Proc Natl Acad Sci U S A*, 109(44), E3045-53. <https://doi.org/10.1073/pnas.1206792109>
- Yeatman, J. D., Wandell, B. A., & Mezer, A. A. (2014). Lifespan maturation and degeneration of human brain white matter. *Nature Communications*, 5, 4932. <https://doi.org/10.1038/ncomms5932>

Figure Legends

Figure 1. Left hemisphere tract renderings are displayed on a mid-sagittal T1 image from a representative PT participant. Right hemisphere tract renderings not shown. **(A)** The arcuate fasciculus is shown in blue, **(B)** the superior longitudinal fasciculus is shown in green, **(C)** the uncinate fasciculus is shown in yellow, **(D)** the inferior longitudinal fasciculus is shown in orange. Dashed lines represent the location of the regions of interest (ROIs) used to segment each pathway from the whole-brain tractogram.

Figure 2. Associations between along-tract FA and ORI in FT children and along-tract R1 and ORI in PT children at age 8 years. Each panel includes a rendering of a specific tract with the strength of the Pearson's correlation (r) between the white matter metric (FA or R1) and ORI at 30 equidistant nodes along the tract represented as a heat-map cylinder surrounding the tract. Each panel also includes a scatter plot representing the strength of the association between ORI and the mean of FA or R1 of the adjacent nodes in the longest region of the tract with significant correlations. Panels show the results for ORI-FA correlations in the FT participants in the AF-L **(A)**, SLF-L **(B)**, SLF-R **(C)**, and for ORI-R1 correlations in the PT participants in the SLF-L **(D)**, UF-L **(E)**, and ILF-L **(F)**. Only tracts in which statistically significant correlations were identified are shown.

Abbreviations: R1 = Relaxation rate (s^{-1}); ORI = Oral Reading Index; AF-L = Left Arcuate Fasciculus; SLF-L = Left Superior Longitudinal Fasciculus; SLF-R = Right Superior Longitudinal Fasciculus; UF-R = Right Uncinate Fasciculus; ILF-L = Left Inferior Longitudinal Fasciculus; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 1
Sample characteristics.

	<i>Full term</i> <i>n (%) or M (SD)</i>	<i>Preterm</i> <i>n (%) or M (SD)</i>	<i>X² or t</i>	<i>p</i>
Demographic measures				
Total <i>N</i>	36	43		
Sex: Female	20 (56%)	15 (35%)	3.39	0.065
Age at Testing, years	8.1 (SD 0.2)	8.2 (SD 0.2)	-2.13	0.028
Birthweight, grams	3325 (SD 431)	1310 (SD 429)	20.73	<0.001
Gestational Age at birth in weeks	39.6 (SD 1.5)	29.3 (SD 2.1)	24.61	<0.001
Hollingshead Index ^a	57.2 (SD 11.0)	51.7 (SD 12.7)	2.05	0.044
Neonatal Head Ultrasound or MRI findings (<i>n</i> = 36)				
Grade I Intraventricular hemorrhage (IVH)	-	8 (22%)	-	-
Grade II IVH	-	1 (3%)	-	-
Grade III IVH	-	1 (3%)	-	-
Small Periventricular Lesions	-	1 (3%)	-	-
Mild White Matter Injury	-	5 (14%)	-	-
Transient Vascular Malformation	-	1 (3%)	-	-
Enlarged Ventricles	-	3 (8%)	-	-
Neurocognitive Measures				
Oral Reading Index ^b	102.0 (SD 12.6)	95.8 (SD 10.8)	2.34	0.022

^a Modified Hollingshead Index, socioeconomic status.

^b Oral Reading Index Scaled Score, Gray Oral Reading Tests, 5th Edition.

Table 2

Pearson's correlations between ORI and mean FA or mean R1 of the segment of the tract in which significant associations were found in along-tract analyses in one group.

Tract	ORI-FA						ORI-R1					
	FT		PT		FT vs. PT		FT		PT		FT vs. PT	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>z</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>z</i>	<i>p</i>
Dorsal												
Arc-L (nodes 2-10)	0.52	0.001*	0.03	0.83	2.28	0.021	-	-	-	-	-	-
SLF-L (nodes 13-20)	0.54	0.001*	-0.03	0.82	2.70	0.007	-	-	-	-	-	-
SLF-L (nodes 1-5)	-	-	-	-	-	-	0.01	0.97	0.42	0.022*	1.59	0.056
SLF-R (nodes 1-22)	0.62	<0.001*	-0.05	0.74	2.85	0.004	-	-	-	-	-	-
Ventral												
UF-R (nodes 13-19)	-	-	-	-	-	-	0.03	0.91	0.45	0.015*	1.77	0.038
ILF-L (nodes 20-23)	-	-	-	-	-	-	0.02	0.91	0.53	0.003*	1.93	0.026

Abbreviations: FT = full-term; PT = preterm; FA = fractional anisotropy; R1 = myelin-derived metric; ORI = Oral Reading Index; Arc = Arcuate; SLF = Superior longitudinal; UF = Uncinate; ILF = Inferior longitudinal; L = left; R = right; bold = significant; * = False Discovery Rate-corrected for multiple comparisons.

A. ORI-FA in Full term

D. ORI-R1 in Preterm

Supplemental Information

Image Preprocessing: The T1w images were first aligned to the canonical ac-pc orientation. Diffusion weighted images were pre-processed with Vistasoft (<http://github.com/vistalab/vistasoft/mrDiffusion>), an open-source software package implemented in MATLAB R2012a (Mathworks, Natick, MA). The dual-spin echo dMRI sequence used here greatly reduces eddy-current distortions obviating the need for eddy-current correction (1). Subject motion during the diffusion weighted scan was corrected using a rigid body alignment algorithm (2). Each diffusion weighted image was registered to the mean of the $b=0$ images and the mean $b=0$ image was registered automatically to the participant's T1w image, using a rigid body transformation (implemented in SPM8, <http://www.fil.ion.ucl.ac.uk/spm/>; no warping was applied). The combined transform that resulted from motion correction and alignment to the T1w anatomy was applied to the raw data once, and the transformed images were resampled to $2 \times 2 \times 2\text{mm}^3$ isotropic voxels. This step was performed because non-isotropic voxels may bias the tensor fit and distort both tracking and measurements of diffusion properties (3). Diffusion gradient directions were then adjusted to fit the resampled diffusion data (4).

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 (5). A continuous tensor field was estimated using trilinear interpolation of the tensor elements. The eigenvalue decomposition of the diffusion tensor was calculated and the resulting three eigenvalues (λ_1 , λ_2 , λ_3) were used to

compute fractional anisotropy (FA), mean diffusivity (MD; i.e., the mean of λ_1 , λ_2 , and λ_3), radial diffusivity (RD, i.e., the mean of λ_2 and λ_3) and axial diffusivity (AD, i.e., λ_1) (6).

Quantitative T1 (relaxation time, seconds) maps were calculated using mrQ, (<https://github.com/mezera/mrQ>), an open-source software package implemented in MATLAB R2012a (Mathworks, Natick, MA). T1 fitting and bias correction was calculated using methods described in (7,8). These procedures involve measuring the local transmit-coil inhomogeneities which are calculated by minimizing the difference between the unbiased T1 map calculated from the low-resolution SEIR-EPI images (9) and the T1 map fit from the high-resolution multiple flip angle SPGR images. Minimization was achieved using a nonlinear least-squares (NLS) solution that assumes transmit-coil inhomogeneities to be smooth in space (10).

To co-register a subject's quantitative relaxometry (qR) images to their dMRI data, we used the Advanced Normalization Tools (ANTs) software package (11). This tool was used to warp the qR images to the non-diffusion weighted b=0 images, as these images have relatively similar contrast (12). This warping procedure is used to minimize mis-registration errors due to EPI distortions in the dMRI data. EPI distortions were minimal due to the 2x ASSET acceleration used for the readout of the diffusion-weighted images. After applying the diffeomorphic warp, image registration was manually inspected using the mrView software (13). Manual inspection of the aligned images confirmed that the registration was accurate in all subjects. From the qR maps, we then derived R1, the inverse of T1 ($R1 = 1/T1$).

Quantification of White Matter Tissue Properties

Automated Fiber Quantification (AFQ; <https://github.com/jyeatman/AFQ>; (14)), a software package implemented in MATLAB R2012a (Mathworks, Natick, MA), was used to isolate and characterize white matter metrics from two dorsal tracts: the Arc-L and bilateral SLF, and two bilateral ventral white matter tracts: the ILF and UF. We selected these pathways *a priori* based on evidence implicating their involvement in phonological and semantic processes (15–18). Due to previously described limitations of deterministic tractography for segmenting the right Arc (19–23), we excluded it from analysis *a priori*. Using AFQ software, we generated an FA or R1 tract profile that described the variations in either tissue parameter (FA and R1) along the central portion of the tract. Specifically, tract FA or tract R1 profiles each were calculated at 30 equidistant locations along the central portion of each fiber tract bounded by the same two ROIs used for tract segmentation. The core of the tract was calculated by defining 30 sample-points along the tract and computing the robust mean position of the corresponding sample points. The robust mean for all tracts except the SLF was computed by estimating the 3-dimensional Gaussian covariance of the sample points and removing fibers that are either located more than 5 standard deviations away from the mean position of the tract, or that differed more than 4 standard deviations in length from the mean length of the tract. In the SLF, these parameters resulted in the inclusion of many fibers not consistent with the known anatomy of the SLF. Therefore, for the SLF, fibers that were 4 standard deviations away from the mean position of the tract, or that differed more than 1 standard deviation in length from the mean length of the tract were removed. This computation constituted the final automatic cleaning stage of the

segmented tracts. Tract profiles were then averaged to produce a single mean FA or R1 value for each tract. Importantly, the FA and R1 measurements were obtained for the same tract regions.

References

1. Reese TG, Heid O, Weisskoff RM, Wedeen VJ. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magnetic Resonance in Medicine*. 2003;49(1):177–82.
2. Rohde GK, Barnett AS, Basser PJ, Marenco S, Pierpaoli C. Comprehensive Approach for Correction of Motion and Distortion in Diffusion-Weighted MRI. *Magnetic Resonance in Medicine*. 2004;
3. Oouchi H, Yamada K, Sakai K, Kizu O, Kubota T, Ito H, et al. Diffusion anisotropy measurement of brain white matter is affected by voxel size: Underestimation occurs in areas with crossing fibers. *American Journal of Neuroradiology*. 2007;28(6):1102–6.
4. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. *Magnetic Resonance in Medicine*. 2009;61(6):1336–49.
5. Chang LC, Jones DK, Pierpaoli C. RESTORE: Robust estimation of tensors by outlier rejection. *Magnetic Resonance in Medicine*. 2005;53(5):1088–95.
6. Basser PJ, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance - Series B*. 1996;111(3):209–19.
7. Mezer A, Yeatman JD, Stikov N, Kay KN, Cho NJ, Dougherty RF, et al. Quantifying the local tissue volume and composition in individual brains with magnetic resonance imaging. *Nature Medicine*. 2013;19(12):1667–72.
8. Mezer A, Rokem A, Berman S, Hastie T, Wandell BA. Evaluating quantitative proton-density-mapping methods. *Human Brain Mapping*. 2016;
9. Barral JK, Gudmundson E, Stikov N, Etezadi-Amoli M, Stoica P, Nishimura DG. A robust methodology for in vivo T1 mapping. *Magnetic Resonance in Medicine*. 2010;
10. Chang LC, Cheng GK, Basser PJ, Pierpaoli C. Linear least-squares method for unbiased estimation of T1 from SPGR signals. *Magnetic Resonance in Medicine*. 2008;

11. Avants BB, Tustison N, Song G. Advanced Normalization Tools (ANTS). Insight Journal. 2011;
12. Berman S, West KL, Does MD, Yeatman JD, Mezer AA. Evaluating g-ratio weighted changes in the corpus callosum as a function of age and sex. *NeuroImage*. 2017;
13. Tournier JD, Calamante F, Connelly A. MRtrix: Diffusion tractography in crossing fiber regions. *International Journal of Imaging Systems and Technology*. 2012;
14. Yeatman JD, Dougherty RF, Myall NJ, Wandell BA, Feldman HM. Tract Profiles of White Matter Properties: Automating Fiber-Tract Quantification. *PLoS ONE*. 2012;7(11):e49790.
15. Duffau H. Stimulation mapping of white matter tracts to study brain functional connectivity. *Nat Rev Neurol*. 2015 May;11(5):255–65.
16. Herbet G, Zemmoura I, Duffau H. Functional Anatomy of the Inferior Longitudinal Fasciculus: From Historical Reports to Current Hypotheses. *Front Neuroanat*. 2018;12:77.
17. Saur D, Kreher BW, Schnell S, Kümmerer D, Kellmeyer P, Vry M-S, et al. Ventral and dorsal pathways for language. *Proc Natl Acad Sci USA*. 2008 Nov 18;105(46):18035–40.
18. Vandermosten M, Boets B, Wouters J, Ghesquière P. A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neurosci Biobehav Rev*. 2012 Jul;36(6):1532–52.
19. Catani M, Allin MPG, Husain M, Pugliese L, Mesulam MM, Murray RM, et al. Symmetries in human brain language pathways correlate with verbal recall. *Proc Natl Acad Sci USA*. 2007 Oct 23;104(43):17163–8.
20. Lebel C, Beaulieu C. Lateralization of the arcuate fasciculus from childhood to adulthood and its relation to cognitive abilities in children. *Human Brain Mapping*. 2009;30(11):3563–73.
21. Mishra A, Anderson AW, Wu X, Gore JC, Ding Z. An improved Bayesian tensor regularization and sampling algorithm to track neuronal fiber pathways in the language circuit. *Med Phys*. 2010 Aug;37(8):4274–87.
22. Travis KE, Adams JN, Ben-Shachar M, Feldman HM. Decreased and Increased Anisotropy along Major Cerebral White Matter Tracts in Preterm Children and Adolescents. *PloS one*. 2015;10(11):e0142860.
23. Yeatman JD, Dougherty RF, Rykhlevskaia E, Sherbondy AJ, Deutsch GK, Wandell BA, et al. Anatomical properties of the arcuate fasciculus predict phonological and

reading skills in children. Journal of cognitive neuroscience. 2011;23(11):3304–3317.

Supplemental Table 1

Pearson's correlations between mean-tract FA and mean-tract R1 in dorsal and ventral tracts within the full term (FT) and the preterm (PT) groups.

Tract	FA-R1			
	FT		PT	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Dorsal				
Arc-L	-0.33	0.13	-0.03	0.88
SLF-L	0.21	0.33	0.03	0.88
SLF-R	-0.08	0.72	0.44	0.02*
Ventral				
UF-L	0.08	0.72	0.41	0.03*
UF-R	-0.15	0.49	0.62	<0.001*
ILF-L	-0.20	0.36	0.30	0.11
ILF-R	0.3	0.16	0.43	0.02*

Abbreviations: FT = full term; PT = preterm; FA = fractional anisotropy; R1 = myelin-derived metric; ORI = Oral Reading Index; Arc = Arcuate; SLF = Superior longitudinal; UF = Uncinate; ILF = Inferior longitudinal; L = left; R = right; bold = significant; * = False Discovery Rate-corrected for multiple comparisons.