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Sex Differences in White Matter Microstructure Following Reading Intervention in Children with Developmental Dyslexia

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Sex Differences in White Matter Microstructure Following Reading Intervention in
Children with Developmental Dyslexia

by

Gehna Gupta

Under the Direction of C. Nikki Arrington, PhD

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

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ABSTRACT

Even though developmental dyslexia (DD) is the most common learning disability, poor response to treatment is well known as a defining feature of this disorder, having adverse effects on children's functioning and mental health. While neuroscience research has made significant advances in studying the neurobiological markers underlying DD, study samples remain unrepresentative of the population as they are typically skewed towards males. The current study helps bridge this gap by identifying sex based white matter differences and their associated changes following a structured reading intervention in third and fourth graders. A series of Linear Mixed Effects models were conducted for comparing sex, hemisphere, time, and white matter microstructure in the tracts of interest. The results indicated significant sex and hemisphere differences in reading tracts of interest. Moreover, significant effects of sex and time were found in the corpus callosum, suggesting that sex plays a role in white matter change following intervention.

INDEX WORDS: Dyslexia, Sex Differences, Reading, Intervention, White Matter, Diffusion

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TABLE OF CONTENTS

LIST OF TABLES		VI
LIST OF FIGURES		VII
1 INTRODUCTION		1
1.1 Neurobiology of DD		3
<i>1.1.1 White Matter Deficits</i>		<i>4</i>
1.2 Neurobiological sex differences in reading and DD		7
1.3 Intervention and white matter changes in DD		9
1.4 Current Study		10
2 METHODS		12
2.1 Study Design		12
2.2 Reading Intervention		13
2.3 Imaging		13
2.4 White Matter Reconstruction		15
2.5 Statistical Analysis		15
3 RESULTS		17
3.1 Superior Longitudinal Fasciculus (SLF) Parietal		17
3.2 Superior Longitudinal Fasciculus (SLF) Temporal		18
3.3 Inferior Longitudinal Fasciculus (ILF)		19
3.4 Uncinate Fasciculus (UF)		21

3.5	Corpus Callosum (CC)	22
4	DICSUSSION	24
4.1	Effect of Time	24
4.2	Effect of Sex	25
4.3	Effect of Hemisphere	26
4.4	The role of CC	28
4.5	Limitations	28
4.6	Conclusion.....	29
	REFERENCES.....	31

LIST OF TABLES

Table 1 Study Demographics.....	13
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LIST OF FIGURES

Figure 1 White matter microstructure and diffusivity in the Superior Longitudinal Fasciculus - Parietal	18
Figure 2 White matter microstructure and diffusivity in the Superior Longitudinal Fasciculus - Temporal	19
Figure 3 White matter microstructure and diffusivity in the Inferior Longitudinal Fasciculus....	21
Figure 4 White matter microstructure and diffusivity in the Uncinate Fasciculus	22
Figure 5 White matter microstructure and diffusivity in the Corpus Callosum – forceps major and minor bundles.....	23

1 INTRODUCTION

Developmental dyslexia (DD) is the most common learning disability, affecting 5-17% of the population (Katusic et al., 2001). DD is diagnosed when a reading disorder affects the visual and phonetic processing of words within the context of normal development of oral and nonverbal skills (Stein, 2018). DD can often have an adverse impact on children's functioning, including low academic achievement, lower self-esteem, decreased confidence, and a higher school dropout rate (Knight, 2021; Zhou, 2022).

Unfortunately, poor response to treatment is well known as a defining feature of learning and reading disorders including DD (American Psychiatric Association [APA], 2013), with research revealing that most treatment interventions for DD result in modest effect sizes (Galuschka et al., 2014; Toffalini et al., 2021). The high prevalence rates of the disorder along with its adverse effects on children's achievement and mental health highlight the need for developing effective treatment and intervention modalities.

One major approach in understanding the manifestation of DD is the proposal of the phonological approach, which attributes the failure of learning to read in children with DD to the lack of orthographic to phonological mapping (Bradley & Bryant et al., 1978; Brady & Shankweiler, 1991; Ramus et al., 2003; Snowling, 1981; Stein, 2018). Proponents of the phonological approach suggest that the inconsistency in matching the visual print to the sound of the letter is a major contributor to reading deficits in DD. Individuals with DD perform poorly on tasks requiring phonological awareness, providing strong evidence for this approach (Ramus et al., 2003). Evidence for the phonological deficit hypothesis in DD comes from intervention and treatment studies (Torgesen et al., 2001; Shaywitz & Shaywitz, 2005; Ehri et al., 2001). Systematic instruction in phonemic awareness, in particular learning letter sound relations and

blending sounds to form words, was established as the most effective treatment for improving reading by the National Reading Panel (National Institute of Child Health and Human Development, 2008). Another advantage of the phonological approach is the direct link between a cognitive deficit and a problem behavior (Ramus et al., 2003), making intervention efforts easier and direct. Research seeking to identify neurobiological markers for the phonological approach has examined the abnormalities in the brain's reading network in individuals with DD.

In the last couple of decades, the field of neuroscience has advanced the understanding and etiology of the disorder in an attempt to gain coherence between various existing theories and foster more effective treatment interventions (Toffalini et al., 2021). The advent of neuroimaging has been instrumental in increasing understanding of the neurological processes underlying DD, classifying it as a primarily neurological disorder. These neuroimaging studies provide evidence for significant differences in the brain profiles of males and females with DD (Krafnick & Evans, 2019; Lambe, 1999; Sandu et al., 2008). However, study samples remain unrepresentative of the population as they are typically skewed towards males (Arnett et al., 2017). One possible reason behind the higher representation of males in both research and diagnostic samples is the differential manifestation of DD symptoms. Females with DD display strengths in verbal conceptualizations, working memory, visuo-spatial processing, and orthographic coding (Krafnick et al., 2019), while struggling with phonological deficits, reduced reading fluency, delayed diagnosis due to compensatory strategies, and increased internalizing symptoms such as anxiety and low self-esteem (Quinn & Wagner, 2015; Hawke et al., 2009; Shaywitz et al., 2002). On the other hand, males with DD typically show more severe reading deficits, particularly in decoding, word recognition, and reading fluency, along with externalizing behaviors such as impulsivity, hyperactivity, or conduct issues, which often make

the disorder more visible and increase the likelihood of early diagnosis (Arnett et al., 2017; Maughan & Carroll, 2006; Rutter et al., 2004). In order to gain a more complete understanding of the neurological basis of DD and develop more efficacious treatments, it is essential to also study the effect of biological sex on DD and its interventions.

1.1 Neurobiology of DD

In typical readers, efficient reading is hypothesized to require effortless interaction between dorsal and ventral pathways of the reading network. The dorsal reading pathway is a temporal-parietal circuit involving the left superior temporal gyrus and inferior parietal lobe (Younger et al., 2018). This dorsal reading pathway plays an important role in phonological processing, in addition to carrying other tasks like understanding sentence syntax, letter recognition, and detecting errors in pronunciation (Dehaene et al., 2015, Pugh et al., 2001, Younger et al., 2018; Xu et al., 2015; Zhou et al., 2015). In contrast, the ventral reading pathway includes the occipitotemporal circuit consisting of the fusiform gyrus and the inferior occipital gyrus. The ventral reading pathway aids in the fast, automatic processing of words through visual attention and word recognition (Sigurdardottir et al., 2021; Zhou et al., 2015). This pathway also works to process word meaning, semantics, and whole words (Dehaene et al., 2015; Price, 2012).

Neuroimaging studies provide evidence for abnormalities in both the dorsal and ventral reading pathways in individuals with DD, including alterations in the tempo-parietal, occipitotemporal, and inferior frontal areas (Yan et al., 2021). Functional magnetic resonance imaging studies have demonstrated altered functional connectivity of the dorsal reading pathway areas responsible for phonological processing in individuals with DD, providing further support for the phonological approach (Di Pietro et al., 2023; Stein, 2014; Zhou et al., 2015).

1.1.1 White Matter Deficits

Diffusion weighted imaging (DWI) studies have been instrumental in establishing the white matter connections underlying the reading network as an important target for understanding brain abnormalities in children and adults with DD. DWI constructs images based on the diffusion of water molecules in the brain and has become the primary research and diagnostic tool for studying white matter microstructure (Ronen et al., 2005). Fractional anisotropy (FA) is one of the most commonly reported metrics of white matter diffusivity (Figley et al., 2022). FA is a scalar value between 0 and 1 that measures the degree of anisotropy (white matter properties across directions) during water diffusion in the MRI, and has been evidenced as a sensitive measure of the brain's microstructural changes such as myelination, fiber tract coherence, and density of fibers (Rouine et al., 2018). In addition to FA, mean diffusivity (MD) describes the overall average diffusion in each of the principal directions and has been implicated by research as a nonspecific but sensitive biomarker for various neurological disorders (Bosch et al., 2012; Clark et al., 2011; Salat, 2014). Since FA acts as a measure of white matter properties in the principal direction, supplementing it with additional white matter metrics, particularly MD, can be helpful to gain comprehensive information about white matter diffusivity and microstructure. In typically developing readers, DWI studies have established important dorsal and ventral white matter tracts that underly the reading network (Vandermosten et al., 2012). The superior longitudinal fasciculus (SLF), is a dorsal white matter tract that connects the tempo-parietal language regions to the ipsilateral frontal regions

(Madhavan et al., 2014). The SLF is hypothesized to be important for language comprehension and production because of its role in connections between Wernicke's and Broca's areas (Barquero et al., 2014; Huber et al., 2018; Lou et al., 2019; Madhavan et al., 2014; Vandermosten et al., 2012). A number of studies have identified differences in white matter microstructure in the SLF bundles in children and adults with DD. Vandermosten et al. (2011) found significantly lower FA in the left SLF of adults with DD, particularly in segments connecting temporal and frontal areas, implicating this pathway in phonological processing deficits associated with the disorder. Other DWI studies provide evidence for decreased FA in both left and right SLF, specifically in the temporal bundle, in individuals with DD (Carter et al., 2009; Odegard et al., 2009; Vandermosten et al., 2012).

The inferior longitudinal fasciculus (ILF) connects the occipital cortex to the anterior temporal lobe and subserves the ventral reading network (Vandermosten et al., 2012). Since the ILF has connections from the occipital area to the ventral occipital-temporal cortex, historically known as "visual word form area", research suggests that it plays an important role in visual memory and perception of word patterns (Ffytche, 2008; Price & Devlin, 2003; Ross, 2008; Yeatman et al., 2013). Studies examining FA and MD of the ILF in people with DD yield diverse findings. Some studies report no significant differences in white matter microstructure in ILF between people with DD and typical readers (Langer et al., 2015; Zhao et al., 2016), whereas others provide evidence for reduced FA and MD in the ILF for dyslexic subjects (Su et al., 2018; Peyrard-Janvid et al., 2019;

Ning et al., 2018). Taken together, evidence suggests that the ILF contributes to orthographical processing and rapid recognition of written language, with disruptions in its microstructure potentially affecting reading fluency and orthographic processing in individuals with DD (Yeatman et al., 2013; Su et al., 2018; Vandermosten et al., 2012).

The uncinate fasciculus (UF) is an anterior white matter tract connecting the dorsal and the ventral pathways of the reading network. The UF connects the orbitofrontal cortex to the anterior temporal lobe (Papagno, 2011). The UF is involved in reading comprehension and verbal memory, suggesting the tract's role in processing complex or higher-level elements of reading (Arrington et al., 2017; Olivé et al., 2022; Schaeffer et al., 2014). Neuroimaging research on the UF's role in reading disorders, while limited, has provided important insights into the tract's role in reading deficits. Knaus et al. (2022) observed reduced hemispheric asymmetry in the UF among children with learning disorders, correlating this alteration with verbal memory abilities that are crucial for reading development. Additionally, a study by Zhao et al (2022) indicated that reduction in UF connectivity was associated with individual differences in visual attention span in participants with DD, postulating the UF's role in attentional processing relevant to reading. These findings suggest that the UF contributes to higher order processes that support reading such as verbal memory and attentional control, and that structural atypicalities in this tract may underlie reading deficits observed in individuals with DD.

Lastly, the corpus callosum (CC) is the brain's largest white matter tract, connecting the left and right hemispheres and facilitating interhemispheric communication essential for reading fluency, comprehension, and visual processing (Dougherty et al., 2007; Frye et al., 2008; Rumsey et al., 1997; Wang et al., 2021). The tract's morphology and white matter microstructure have been linked to reading performance and tasks such as phonological processing (Fabbro et al., 2002; Vandermosten, 2011), and the tract itself has been deemed essential for the phonological to orthographic mapping that takes place during reading (Temple et al., 1990). DWI studies provide evidence for atypicalities in this tract in individuals with DD, including decreased FA, shape differences, and reduced MD (Hynd et al., 1995; Richards et al., 2008; Robichon & Habib, 2000; Hasan et al., 2012; Vandermosten et al., 2009). These findings highlight the critical role of the CC in supporting the neural interhemispheric communication necessary for proficient reading, and highlight how its structural anomalies may contribute to the reading difficulties observed in individuals with DD.

1.2 Neurobiological sex differences in reading and DD

Interestingly, neuroimaging studies reveal significant sex differences in the reading network in typically developing children. FMRI research is suggestive of a greater left lateralized reading and language network in males compared to more bilateral functioning in females (Sato, 2020; Yu et al., 2014). These differences were found to be more pronounced for younger age groups, especially during phonological processing tasks (Sato, 2020; Yu et al., 2014). DWI studies of sex differences examining the reading network are limited, inconclusive, and often times contradictory. However, some studies have found higher FA in left lateralized reading

tracts such as the SLF in typically developing male readers (Kanaan et al., 2012). Additionally, higher FA in the corpus callosum (CC) has been observed in females with typical reading skills, suggesting they demonstrate greater inter-hemispheric communication (Kanaan et al., 2012, Vandermosten, 2012).

Limited neuroimaging research has attempted to understand the neurological basis for sex differences in reading and differential symptom manifestation in DD. Functional neuroimaging studies find that males with DD often show under activation in left hemisphere reading related areas, including inferior frontal gyrus, temporoparietal junction, and occipitotemporal cortex, consistent with the phonological approach to reading (Shaywitz et al., 2002; Altarelli et al., 2013). In contrast, females with DD show less pronounced left-hemisphere dysfunction and instead exhibit more bilateral or right-hemisphere activation patterns, potentially reflecting alternative or compensatory mechanisms (Altarelli et al., 2013; Evans et al., 2014; Rutter et al., 2004).

Structural and DWI research highlights some other important sex differences in the dyslexic population: reduced diffusivity, greater cortical thickness, less gray matter volume, and decreased FA, in left lateralized reading networks in DD samples primarily made up of males (Clark et al., 2011; Gupta et al., 2024; Krafnick & Evans, 2019). Additionally, males with DD show reduced FA in the left SLF and other components of the dorsal language pathway, which are critical for phonological processing (Klingberg et al., 2000; Vandermosten et al., 2012). In contrast, some studies suggest that females with DD may rely more on ventral or bilateral pathways, including the ILF and UF, with greater white matter microstructure and diffusivity in these two tracts (López-Barroso et al., 2014; Su et al., 2018; Zhao et al., 2016). Similar to the ILF and UF, females with DD also display larger or more structurally intact CC compared to

males (Rumsey et al., 1996; Duara et al., 1991), potentially supporting the more bilateral activation patterns frequently observed in functional studies. Additionally, FA in the CC was positively associated with reading fluency, particularly in girls (Hasan et al., 2008), highlighting the role of increased interhemispheric communication during language tasks in females. These findings suggest that sex-specific white matter characteristics may underlie distinct reading strategies and compensatory mechanisms in DD, emphasizing the need for a more sex-informed approach to both research and intervention.

1.3 Intervention and white matter changes in DD

In children with DD, reading improvement is associated with increased activation of the left hemisphere areas associated with the reading network, including the inferior parietal lobule, precuneus, and the fusiform gyrus (Eden et al., 2004; Krafnick et al., 2004). Limited research on post-intervention structural changes (Braid & Richlan, 2022; Perdue et al., 2022) has demonstrated increased diffusivity and white matter microstructure gains in the left ILF and bilateral SLF post intervention (Huber et al., 2018; Partenan et al., 2020, Wang et al., 2016). This suggests that reading intervention that increases phonological awareness and visual word recognition may improve efficiency of white matter connectivity of the ILF and SLF, as indexed by FA and MD. Additionally, Horowitz-Kraus et al. (2014) reported increased FA in the CC following reading intervention in subjects with DD, suggestive of improved communication between hemispheres that supports reading fluency and accuracy. DWI studies like these have been able to link reading skill acquisition to white matter changes in axonal geometry, myelin remodeling, and diffusivity, quantifying white matter plasticity following intervention (Meisler et al., 2023; Huber et al. 2018). Thus, reading intervention may improve the function of white

matter pathways within the reading network in children with DD, possibly due to affecting white matter microstructure and diffusivity.

Research on neurobiological changes following reading intervention in DD has not considered biological sex differences that may moderate behavioral change following intervention. Development of efficacious treatment modalities highlights the need for additional research into the neurobiological factors underlying DD, changes after reading intervention, and the role of sex in this change.

1.4 Current Study

Neuroscientific research has used DWI measures such as FA and MD to identify neurological markers for DD and study structural changes following reading intervention. Such research has been limited in studying biological sex as a factor that plays a role in the manifestation of DD and the white matter changes following reading intervention. The current study helps bridge this gap by identifying sex based white matter differences and their associated changes following a structured reading intervention. Doing so can inform treatment and intervention methods and help mitigate the symptoms associated with the disorder.

Current research provides evidence of changes in white matter in reading related tracts, including the SLF and CC, following reading intervention (Eden et al., 2004; Huber et al., 2018; Krafnick et al., 2004, Partenan et al., 2020, Wang et al., 2016). The role of ventral white matter tracts, ILF and UF, in visual memory, perception of word patterns, reading comprehension, verbal memory, and higher level reading (Arrington et al., 2017; Ffytche, 2008; Olivé et al., 2022; Price & Devlin, 2003; Ross, 2008; Schaeffer et al., 2014; Yeatman et al., 2013) make them an appropriate target for studying white matter change following intervention.

Moreover, research is suggestive of a greater left lateralized reading network in males (Sato, 2020; Yu et al., 2014) as well as structural and functional atypicalities in this left lateralized reading network in dyslexic individuals (Di Pietro et al., 2023; Stein, 2014; Zhou et al., 2015). In contrast, research focusing on sex differences in reading and DD hint at the possible use of a more bilateral reading network in females (Sato, 2020; Yu et al., 2014). Thus, it was hypothesized that:

H1: Males with DD would have greater gains in white matter microstructure and diffusivity (measured by FA and MD) from pre to post intervention, in the left hemisphere reading tracts (SLF posterior, SLF temporal, ILF, and UF), when compared to females.

H2: Conversely, females with DD would have greater gains in microstructure and diffusivity (measured by FA and MD) from pre to post intervention, in the right hemisphere tracts (SLF posterior, SLF temporal, ILF, UF) and CC, when compared to males.

2 METHODS

2.1 Study Design

The current study utilized archival data that was collected between 2013 to 2019 as part of a longitudinal reading intervention study conducted at the Georgia State University/Georgia Institute of Technology Center for Advanced Brain Imaging (CABI), in Atlanta, Georgia. The study, including written informed consent and child assent, was conducted in accordance with Institutional Review Board approval (protocol code H13261 approved on 16 September 2013). Participants included 155 children who were in the third or fourth grade and recruited from public and charter schools in Atlanta. The study was limited to native English speakers. Children completed cognitive and behavioral tests at an initial pre-intervention visit, followed by a 70-hour reading intervention program, with pre- and post-intervention MRI scans. DD diagnosis was determined based on study identified criteria consistent with a standard score below an 85 on any of the following tests, which were completed during baseline testing: Woodcock Johnson 3rd Edition (WJ-3 Broad and Basic Cluster scores; Woodcock et al., 2001), Test of Word Reading Efficiency 2nd Edition (TOWRE-2; Torgesen et al., 2012), and Standardized Reading Inventory Reading Quotient (SRI-2; Newcomer, 1999). Students were screened for intellectual disability and other comorbid disorders including Attention-Deficit Hyperactivity Disorder (ADHD) (*Table 1*). Children with FSIQ < 80 based on the Wechsler Abbreviated Scale of Intelligence – II (WASI-II Full Scale IQ) were excluded. Children with ADHD or SLI were not excluded. Since ADHD and SLI are highly comorbid with DD (25-40%) (McGrath & Stoodley, 2019), including these disorders in the study ensures a representative sample.

Table 1 Study Demographics

	Males (<i>n</i> = 57)	Females (<i>n</i> = 47)
Age	9.25	9.36
Weschler Scale of Intelligence IQ	95.32	92.32
Woodcock Johnson-3 Reading Scores (Broad)	82.41	83.96
% with Attention-Deficit Hyperactivity Disorder	43.86	19.14

2.2 Reading Intervention

Children who met study-based diagnostic criteria for DD were provided with a small group, structured reading intervention, consisting of 70 contact hours. The intervention addressed components of decoding and word identification, comprehension, vocabulary, fluency, and motivational reading, based on previously researched and validated reading intervention models (Lovett et al., 2000; Morris et al., 2012).

2.3 Imaging

All participants completed a pre- and post-intervention MRI scan session. Both sessions included DWI, T2* and T1 MPRAGE sequences on a 3T Siemens scanner at CABI.

Dual DWI sequences were collected using reverse phase encoding (anterior to posterior and posterior to anterior) during each scan session. Reverse phase encoding corrects the geographical distortion in the DWI images by combining data sets from opposite directions

(Hong et al., 2017). The following scanning parameters were used: FoV— 220×220 mm; repetition time TD/TE—8900/97 ms; slices—64; b—1000, 4* b—0; 32 gradient directions; voxel size (isotropic)—2 mm; slice thickness—2 mm.

T2* images (32 slices; 4 mm slice thickness; no gap) and anatomical scans ((MPRAGE; matrix size = 256×256 ; voxel size = $1 \times 1 \times 1$ mm; FoV = 256 mm; TD = 2530 ms; TE = 2.77 ms; flip angle = 7°) were acquired using single shot echo planar imaging (voxel size = $3.438 \times 3.438 \times 4$ mm; matrix size = 64×64 ; TD = 2000 ms; TE = 30 ms; FoV = 220 mm; flip angle = 80°) in an axial-oblique orientation parallel to the intercommissural line. The T2* structural and MPRAGE images were used for co-registration.

An inhouse pipeline consisting of DTIprep was used for quality assurance of the DWI data (Oguz et al., 2014). Diffusion data was corrected for head motion and eddy current distortions using the FSL's eddy correction toolbox by linearly registering the diffusion-weighted volumes to the first b = 0 volume (He et al., 2021). FSL's brain extraction tool was used to remove skull and non-brain tissue. At the end of preprocessing, DTIprep reported the number of good gradients and 10 participants with less than 25 good gradients out of 36 were excluded.

After visual and automated quality assurance of the imaging data, the diffusion MRI data correction software tool TORTOISE version 3 (Allouzi & Irfanoglu, 2018) was used to preprocess the DWI data using the T2* structural file and MPRAGE reorientation file. The TORTOISE command DIFF_PREP computed the b-matrix gradient table. The TORTOISE command DR-BUDDI corrected EPI distortions using blip-up and blip-down data (anterior to posterior and posterior to anterior) and co-registered the DWI images together for each session separately. The b-matrices were then used to reorient DWI into target space.

2.4 White Matter Reconstruction

FreeSurfer 6.0 was used to process structural and diffusion data. FreeSurfer is a suite of tools that provide automatic analysis of anatomical data, including white and gray matter segmentation and correction of topological defects (Fischl, 2012). Visual quality control of reconstruction and segmentation was performed by a trained technician consistent with general practice and the FreeSurfer protocol when necessary (He et al., 2021; Maffei et al., 2021).

White matter tracts of interest were reconstructed using FreeSurfer's Tracts Constrained by Underlying Anatomy (TRACULA). TRACULA uses *a priori* information about anatomical structures relative to white matter pathways, combining it with the FreeSurfer cortical and subcortical segmentations in order to derive tractography of the pathways (Yendiki, 2011). TRACULA preprocessing includes compensation for B0 field inhomogeneity in diffusion weight images as well as co-registration of anatomical and diffusion-weight images (Yendiki, 2011). It utilizes bedpostx by FSL to fit the ball- and- stick model to the diffusion-weight images to reconstruct white matter tracts before extracting standard diffusion measures, including FA and MD, for each pathway (Yendiki, 2011).

The TRACULA pipeline was utilized in this study to construct 15 white matter tracts provided by the software, out of which the FA and MD values were extracted for six tracts corresponding with the reading network: bilateral SLF (temporal and parietal bundles), ILF, UF, as well as the CC (forceps major and minor bundles).

2.5 Statistical Analysis

All statistical analyses were conducted in R (version 4.4.1). Outlier detection was performed using graphs and statistical z-score thresholding.

Linear mixed-effects models (LME) were used to examine the effects of time (pre versus post intervention), hemisphere (left versus right), and sex (male versus female) on FA for each tract of interest. A separate set of LME models were used to assess the same effects on MD. Each model included time, hemisphere, and sex, as well as their interaction terms, as fixed effects. A random intercept was included for each subject to account for repeated measures. All models included correlations between fixed effects.

Post hoc pairwise comparisons were performed using estimated marginal means (emmeans), with Tukey's adjustment for multiple comparisons. Statistical significance was defined as $p < 0.05$.

For each segment of the CC, a distinct LME model was specified, including time and sex (and their interaction) as fixed effects, and a random intercept for each subject. Post hoc comparisons were conducted using emmeans with Tukey correction, and the significance was set at $p < 0.05$.

3 RESULTS

3.1 Superior Longitudinal Fasciculus (SLF) Parietal

LME of the tract SLF - parietal bundle revealed no significant main effects of time or hemisphere on FA. A significant main effect of sex was observed, with higher FA in females compared to males ($t(235) = -2.58, p = 0.01$). No significant interactions were observed between time, hemisphere, or sex. Correlation analyses among fixed effects revealed a strong negative correlation between sex and FA intercept ($r = -0.75, p = 0.01$), suggesting that sex has a substantial influence on FA.

LME of the tract SLF - parietal bundle revealed no significant main effects of time or hemisphere on MD. However, a significant main effect of sex was observed, with males exhibiting significantly higher MD compared to females ($t(139) = -2.78, p = 0.01$). No significant interactions were observed between time, hemisphere, or sex. Fixed effect correlations revealed a strong negative correlation between sex and MD intercept ($r = -0.74, p = 0.01$), suggesting that sex has a substantial influence on MD.

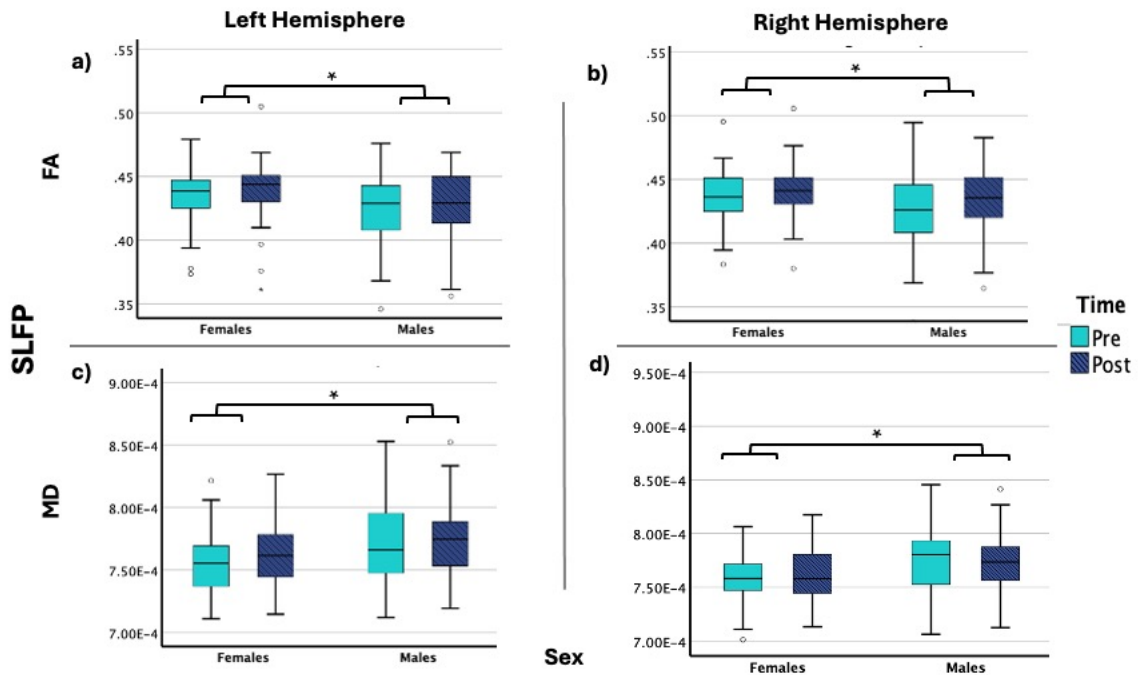


Figure 1 White matter microstructure and diffusivity in the Superior Longitudinal Fasciculus - Parietal

3.2 Superior Longitudinal Fasciculus (SLF) Temporal

LME of the tract SLF - temporal bundle revealed no significant main effect of time on FA. Significant main effects of sex ($t(232) = -2.00, p = 0.04$) and hemisphere ($t(209) = -2.42, p = 0.02$) were observed. Right hemisphere was shown to have a lower FA compared to the left hemisphere ($t(209) = -2.42, p = 0.02$). Additionally, females exhibited significantly higher FA compared to males ($t(232) = -2.00, p = 0.04$). No significant interactions were observed between time, hemisphere, or sex. Correlation analyses among fixed effects revealed a strong negative correlation between sex and FA intercept ($r = -0.75, p = 0.04$) as well as a moderate negative correlation between hemisphere and intercept ($r = -0.48, p = 0.01$), suggesting that sex and hemisphere have a substantial influence on FA.

LME of the tract SLF - temporal bundle revealed no significant main effect of time on MD. Significant main effects of sex ($t(435) = 2.54, p = 0.01$) and hemisphere ($t(290) = -5.27, p < 0.01$) were observed. Right hemisphere reported lower MD compared to the left hemisphere ($t(290) = -5.27, p < 0.01$). Additionally, males exhibited significantly higher MD compared to females ($t(435) = 2.54, p = 0.01$). No significant interactions were observed between time, hemisphere, or sex. Fixed effect correlations revealed a strong negative correlation between sex and MD intercept ($r = -0.74, p < 0.05$), suggesting that sex has a substantial influence on MD.

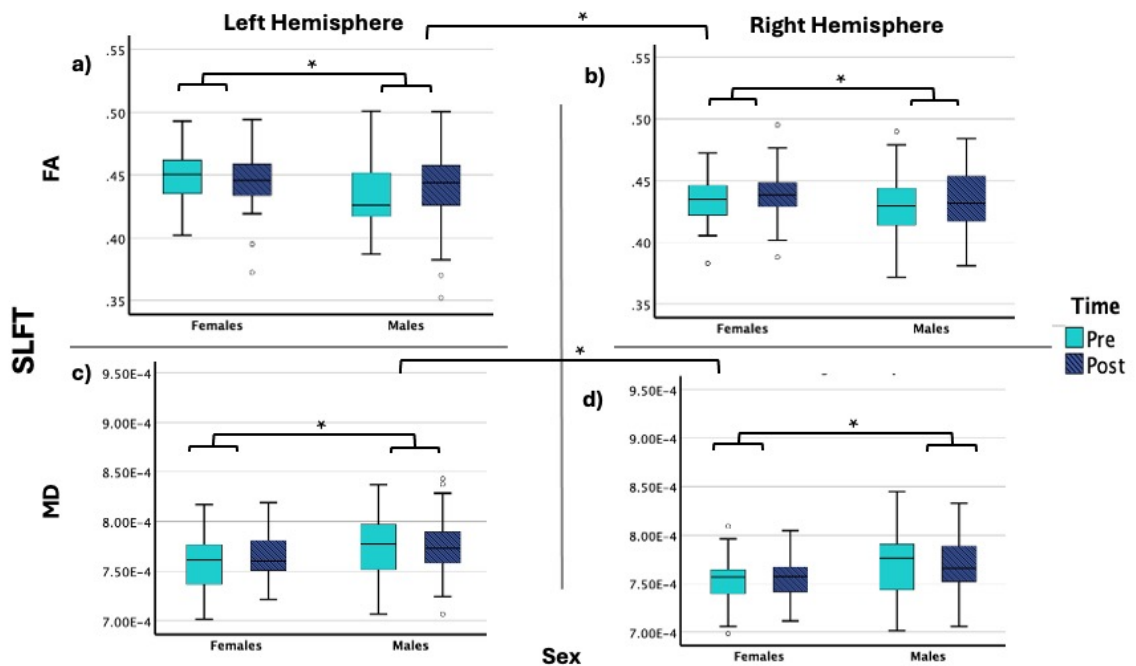


Figure 2 White matter microstructure and diffusivity in the Superior Longitudinal Fasciculus - Temporal

3.3 Inferior Longitudinal Fasciculus (ILF)

LME of the tract ILF revealed no significant main effects of time or hemisphere on FA. A significant main effect of sex was observed, ($t(220) = -2.08, p = 0.04$) along with a significant

interaction between hemisphere and sex ($t(203) = -2.10, p = 0.04$). Post hoc analyses indicated that the effect of hemisphere was significant only in males, with higher FA in the right hemisphere ($p = 0.03$). Additionally, females exhibited significantly higher FA compared to males in the left hemisphere ($p = 0.02$) and no sex differences in the right hemisphere. Correlation analyses among fixed effects revealed a negative correlation between sex and FA intercept ($r = -0.75, p = 0.04$), suggesting that sex has a substantial influence on FA. A moderate negative correlation was observed between the right hemisphere and sex ($r = -0.34, p = 0.04$), indicating that the effect of hemisphere on FA is influenced by sex.

LME of the tract ILF revealed no significant main effects of time or hemisphere on MD. A significant main effect of sex was observed, with males exhibiting significantly higher MD compared to females ($t(120) = -3.03, p = 0.03$). No significant interactions were observed between time, hemisphere, or sex. Fixed effect correlations revealed a strong negative correlation between sex and MD intercept ($r = -0.74, p = 0.03$), suggesting that sex has a substantial influence on MD.

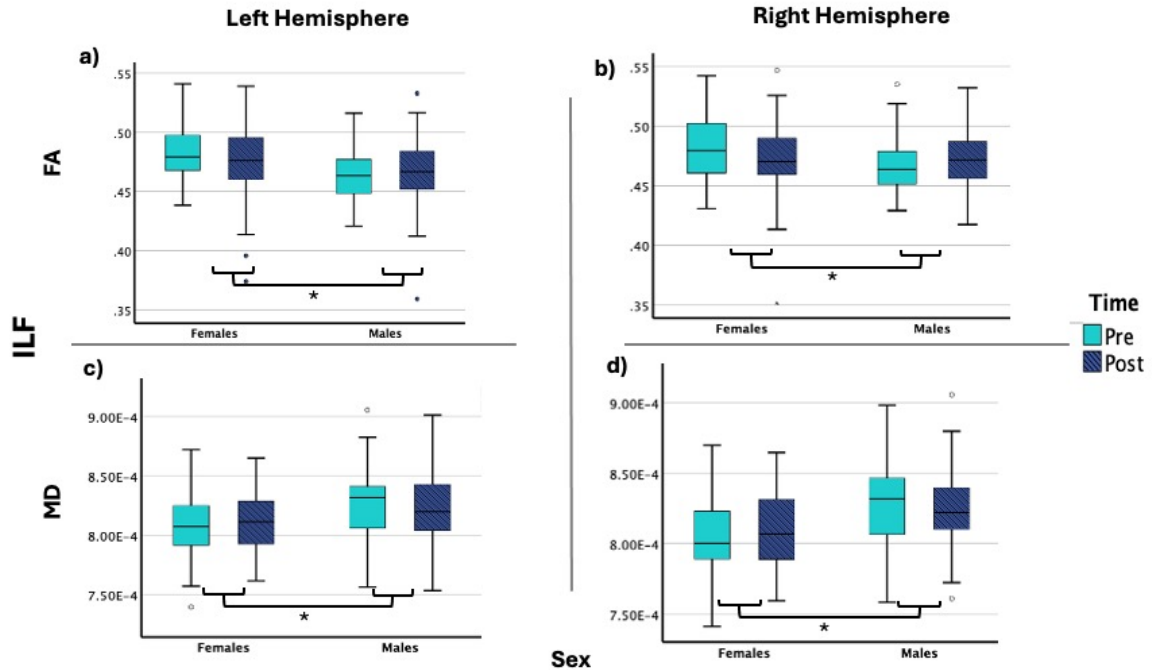


Figure 3 White matter microstructure and diffusivity in the Inferior Longitudinal Fasciculus

3.4 Uncinate Fasciculus (UF)

LME of the tract UF revealed no significant main effect of time or sex on FA. A significant main effect of hemisphere ($t(202) = 3.24, p < 0.01$) was observed with right hemisphere having a significantly higher FA compared to the left hemisphere. No significant interactions were observed between time, hemisphere, or sex. Correlation analyses among fixed effects revealed a moderate negative correlation between hemisphere and FA intercept ($r = -0.60, p < 0.01$), suggesting that hemisphere has a substantial influence on FA.

LME of the tract UF revealed no significant main effect of time or sex on MD. A significant main effect of hemisphere ($t(206) = -3.095, p < 0.01$) was observed with right hemisphere having a significantly lower MD compared to the left hemisphere. No significant interactions were observed between time, hemisphere, or sex. Correlation analyses among fixed

effects revealed a moderate negative correlation between hemisphere and FA intercept ($r = -0.56$, $p < 0.01$), suggesting that hemisphere has a substantial influence on FA.

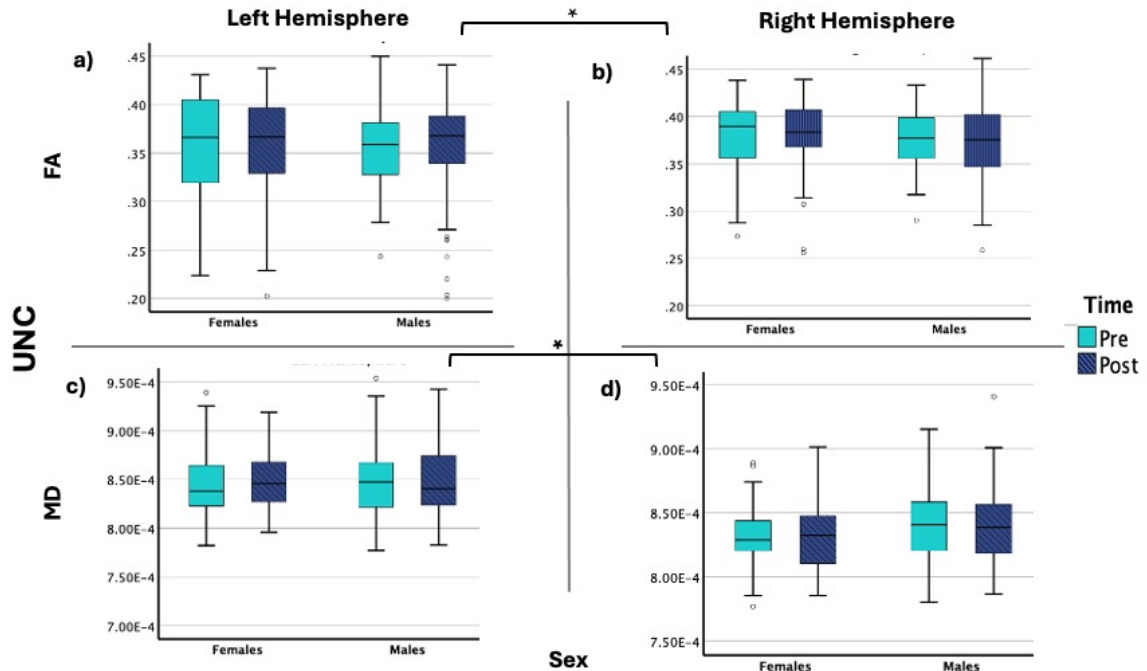


Figure 4 White matter microstructure and diffusivity in the Uncinate Fasciculus

3.5 Corpus Callosum (CC)

Forceps Major

LME of the tract CC - forceps major revealed no significant main effect of time or sex on FA. A significant interaction was observed between time and sex ($t(87) = 2.48$, $p = 0.02$), with a lower FA in males at post, compared to females.

There was no significant main effect of time on MD for CC forceps major. However, a significant main effect of sex was observed, ($t(161) = 3.14$, $p < 0.01$). Post hoc analyses indicated that males exhibited significantly higher MD compared to females. No significant interaction was observed between time and sex. Correlation analyses among fixed effects

revealed a strong negative correlation between sex and FA intercept ($r = -0.74, p < 0.01$), suggesting that sex has a substantial influence on MD.

Forceps Minor

LME of the tract CC - forceps minor revealed no significant main or interaction effects of time or sex on FA. Additionally, no significant main or interaction effects of time or sex on MD.

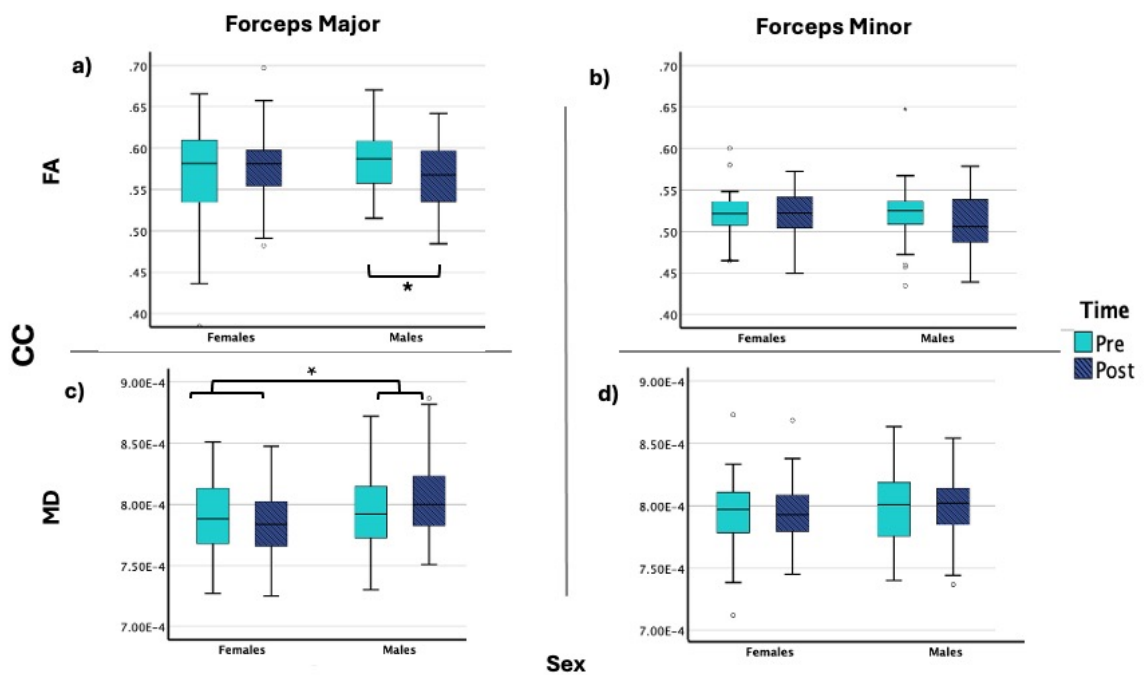


Figure 5 White matter microstructure and diffusivity in the Corpus Callosum – forceps major and minor bundles

4 DISCUSSION

DD is a complex and prevalent learning disorder that impairs reading ability despite normal intelligence and adequate educational opportunities (American Psychiatric Association [APA], 2013). Although neuroscientific literature has established reading related white matter tracts as key biomarkers of both DD and intervention related change (Huber et al., 2018; Wang et al., 2016), study samples are generally biased as they tend to be skewed towards males (Arnett et al., 2017). A growing body of research has provided evidence for sex differences in reading, manifestation of DD symptoms, and white matter microstructure (Shaywitz et al., 2002; Krafnick & Evans, 2019; Yu et al., 2014) but very limited research has attempted to understand the role of sex in neural changes following reading intervention and general brain development. The present study addressed this gap by examining the role of sex and hemisphere in white matter changes across time, highlighting the need for sex-informed approaches in both developmental research and educational interventions.

4.1 Effect of Time

Reading intervention that increases phonological awareness and visual word recognition may improve efficiency of white matter connectivity, particularly FA and MD, in reading related tracts (Huber et al., 2018; Partenan et al., 2020, Wang et al., 2016). Additionally, previous findings indicated a more left-lateralized reading network in males and a possible bilateral or compensatory pathway in females (Yu et al., 2014; Sato, 2020). Based on this, it was hypothesized that males with DD would show greater gains of FA and MD from pre to post intervention in left-hemisphere tracts, while females would demonstrate greater gains in right-hemisphere tracts and the CC.

Contrary to the original hypothesis, no significant interaction or main effect of sex was found across bilateral reading tracts, indicating a lack of change from pre to post intervention. This finding aligns with previous research indicating that white matter changes following intervention are often widespread than localized (Huber et al., 2018; Keller & Just, 2009), while measures such as FA and MD can be relatively insensitive to subtle alterations in white matter in tracts, particularly in children of developing age (Lebel & Beaulieu, 2011; Yeatman et al., 2012). These findings highlight the need for additional research about the specificity of white matter changes during development, along with the role that biological sex plays in these brain changes.

4.2 Effect of Sex

The results indicated varied but interesting patterns for sex differences in both dorsal and ventral white matter reading tracts. Overall, results found a main effect of sex in bilateral SLF (parietal and temporal bundles) and ILF, with females generally reporting higher FA compared to males, averaged across time and hemisphere. These findings align with prior DWI studies reporting greater FA and more robust white matter maturation in females during childhood and adolescence, particularly in tracts associated with language (Inano et al., 2011; Herting et al., 2012). This increased white matter microstructure in reading-related regions among females with DD is consistent with behavioral studies indicating female strengths in verbal conceptualization, working memory, visuospatial processing, and orthographic coding relative to males (Krafnick et al., 2019). These results are suggestive of a stronger white matter microstructure in key reading tracts in females during development, potentially aiding compensatory strategies and contributing to their commonly observed advantages in language-related skills.

In contrast, males demonstrated higher MD compared to females in the same tracts in the current sample. Interestingly, some studies show a correlation between higher MD in reading

related areas and lower reading performance amongst children and adults with DD, potentially reflecting reduced tissue density or compromised white matter diffusivity (Qiu et al., 2008; Christodoulou et al., 2017; Moreau et al., 2023). The pattern of higher MD in males with DD may help explain the finding that males tend to show more severe impairments in decoding, word recognition, and reading fluency compared to females with DD (Arnett et al., 2017; Maughan & Carroll, 2006; Rutter et al., 2004). Moreover, this sex-based difference in microstructure aligns with literature suggesting delayed white matter maturation in males during development and may partly explain the higher prevalence and severity of DD in boys (Arnett et al., 2017; Herting et al., 2012).

These findings highlight the importance of considering sex as a meaningful biological variable when researching white matter changes during development in children with DD. Future research can help clarify the role of sex in reading-related white matter development in both typical and dyslexic populations.

4.3 Effect of Hemisphere

The results also demonstrated a significant influence of hemisphere on FA and MD. In the SLF- temporal bundle, results revealed a significant main effect of hemisphere, averaged across sex and time, with the left hemisphere generally displaying greater FA and MD. Since the SLF is part of the dorsal phonological reading network (Vandermosten, 2012), higher FA in the left hemisphere aligns with prior neuroimaging findings highlighting the left hemisphere's dominant role in language processing and reading, especially during phonological tasks (Catani et al., 2007; Lebel & Beaulieu, 2009). These hemispheric differences may also reflect ongoing maturational changes, as white matter tracts involved in reading typically exhibit increasing FA

with age, particularly in left-lateralized regions that support phonological skills (Lebel & Beaulieu, 2011; Yeatman et al., 2012).

In the ILF tract, results indicated a significant interaction effect between sex and hemisphere, with the effect of hemisphere only relevant in males. Males showed higher FA in the right hemisphere compared to the left, while no such difference was found for females. These results may reflect a compensatory reliance on right-dominant pathways in males with DD, particularly in tracts like the ILF that support higher-order reading processes (Altarelli et al., 2013; Evans et al., 2014). Alternatively, this interaction may also reflect distinct developmental timelines in lateralization, as males often show delayed maturation and lateralization patterns compared to females (Asato et al., 2010; Herting et al., 2012; Lebel & Beaulieu, 2011; Lenroot et al., 2007; Simmonds et al., 2014).

Lastly, there was a significant main effect of hemisphere reported in the UF, averaged across sex and time, with right hemisphere generally displaying higher FA and lower MD. Since the UF is hypothesized to be involved in higher level reading (Arrington et al., 2017; Olivé et al., 2022; Schaeffer et al., 2014), these results might indicate the presence of a compensatory right hemisphere reading tract that utilizes the UF for more advanced and automated reading. Additionally, a higher FA in the right UF may also reflect maturational shifts in cognitive processing during normal development, where reliance on right-hemisphere structures increases with age or reading experience (Brauer et al., 2011; Schmithorst & Holland, 2006). This rightward shift in the UF can be reflective of typical development, especially in readers who engage compensatory or alternative strategies to support reading and comprehension.

In summary, these findings highlight the dynamic nature of white matter development in reading-related tracts, suggesting that both typical maturation and compensatory adaptations

shape hemispheric specialization in children with DD. Future research in sex and hemisphere specific patterns of white matter development in children with DD can help create more targeted neurodevelopmental models and intervention strategies.

4.4 The role of CC

Given the observed influence of hemisphere on white matter microstructure and diffusivity, it is also important to consider the role of the CC and interhemispheric connectivity in supporting these lateralized processes. The CC, particularly the forceps major, is essential for integrating visual and spatial information across hemispheres, which are key components of fluent reading. A significant interaction between time and sex was observed in the CC- forceps major bundle, with males displaying a lower FA in the tract post intervention compared to females. Additionally, males exhibited significantly higher MD in the same tract when compared to females. Lower FA and higher MD in the CC post intervention may indicate improved lateralization in the reading related tracts in males, an effect also demonstrated by previous studies (Eden et al., 2004; Shaywitz et al., 2004; Simos et al. 2007).

These findings suggest that white matter within the CC may play a sex-specific role in reading-related lateralization following intervention, with males showing less interhemispheric communication after intervention. Future intervention research may benefit from studying the differential ways in which females with DD respond to treatment, making intervention more targeted and better suited.

4.5 Limitations

This study has several limitations. The sample size was modest, and the statistical power was further constrained when the data was stratified by sex, hemisphere, and time. This

subdivision resulted in smaller subgroups, which may have limited the ability to detect subtle or interaction effects and increased the risk of Type II errors.

Additionally, white matter changes following intervention are often widespread or whole brained rather than localized (Huber et al., 2018; Keller & Just, 2009). While a whole brain analysis might have been more sensitive towards widespread and subtle changes in white matter after intervention, these analyses typically require large, homogeneous samples and may not accommodate complex interactions (Gilson et al., 2019). Doing tract-based analyses helps study the effect of interacting variables to get a more complete picture of post intervention changes in the brain but may overlook relevant effects occurring in regions outside the selected white matter tracts of interest.

Lastly, the sample consisted of developing children with ongoing neurodevelopmental changes. The observed structural brain differences may not represent stable or enduring patterns. Instead, these findings should be interpreted within the context of developmental plasticity, where white matter microstructure and diffusivity may shift over time due to maturation.

4.6 Conclusion

This study contributes to the growing body of neuroimaging literature examining the neural basis of DD, with a specific focus on sex differences in white matter microstructure after reading intervention. By addressing the role of sex in intervention-based brain changes, this study adds to the limited body of research that studies neural sex differences in reading disorders. While findings did not reveal sex-specific intervention effects in bilateral reading tracts, main effects of sex in key reading related tracts suggest underlying neurobiological differences that may support different compensatory strategies and developmental trajectories. Additionally, the observed intervention changes in the CC suggest a more lateralized reading network in males

following intervention, and a more bilateral reading mechanism in females. Future research should build upon these insights using larger, more diverse samples and multimodal imaging approaches to further understand the complex neurobiological basis of reading disorders. A more complete understanding of the neural basis of reading disorders will be critical in designing personalized, evidence-based interventions that effectively address the needs of all children with DD.

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