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Identifying brain and behavioral predictors of language and reading development in typically developing and at-risk children

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Dissertation

IDENTIFYING BRAIN AND BEHAVIORAL PREDICTORS OF LANGUAGE AND READING DEVELOPMENT IN TYPICALLY DEVELOPING AND AT-RISK CHILDREN

by

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Dedication

To my parents who have always loved and supported me. They fostered my love of science beginning at an early age: taking me to dinosaur and bat exhibits, buying me my first chemistry set and microscope, and encouraging me to question and search for answers. They never complained when I realized we were out of ink late at night, when I had a report due the next morning. They attended countless award ceremonies, always clapping the loudest. They sacrificed for my education, and allowed me to attend a school 350 miles away (although it felt like 3,500 miles to my mother). I am eternally grateful to you both.

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ABSTRACT

Learning to read is essential, yet many children do not receive a diagnosis of developmental dyslexia (DD) until second or third grade. The aim of this dissertation is to identify brain and behavioral predictors of DD so that diagnosis and intervention can begin sooner.

Experiment 1 examines infants with familial risk of DD longitudinally. Infants completed non-sedated diffusion-weighted imaging (DWI) between 4- and 18-months of age and cognitive-linguistic assessment at four years. Infants at-risk of DD displayed reduced fractional anisotropy (FA) and increased radial diffusivity (RD) in the left arcuate fasciculus (AF) and reduced FA and axial diffusivity (AD) of the splenium of the corpus callosum (CC) compared to peers without a familial risk. Both the left AF and CC are implicated in reading and reading-related tasks, and atypicalities have been observed in children and adults with DD. RD may reflect myelination and AD is thought to indicate pathway complexity suggesting infants at-risk of DD exhibit reduced myelination of the left AF and reduced pathway complexity of the CC at or shortly after birth. The left AF assessed in infancy predicted four-year-old vocabulary skills while the CC predicted four-year-old print knowledge.

Experiment 2 explores the association between white matter microstructure of the left AF and CC and neural activity during phonological processing assessed via functional magnetic resonance imaging (fMRI). Preschoolers with and without a familial risk of DD completed DWI and an fMRI alliteration task where children indicated via button-press whether two words started with the same initial sound. Positive correlations were observed between FA of the left AF and CC and neural activity in the left medial temporal gyrus and the left lingual gyrus, two regions implicated in phonological processing.

Experiment 3 examines whether white matter microstructure of the CC assessed in preschool is associated with school-age reading fluency in children with and without a familial risk of DD. Similar to children and adults with DD, preschoolers with a familial risk of DD displayed greater FA and AD of the CC compared to controls. Furthermore, AD of the CC predicted school-age reading fluency.

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List of Abbreviations

AD	Axial Diffusivity
AF	Arcuate Fasciculus
AFQ	Automated Fiber-Tract Quantification
CC	Corpus Callosum
CELF	Clinical Evaluation of Language Fundamentals, Fourth Edition
CELF Preschool-2	Clinical Evaluation of Language Fundamentals Preschool – Second Edition
CTOPP	Comprehensive Test of Phonological Processing
DD	Developmental Dyslexia
DWI	Diffusion-Weighted Imaging
EEG	Electroencephalography
ERP	Event-Related Potentials
FA	Fractional Anisotropy
FDR	False Discovery Rate
fMRI	Functional Magnetic Resonance Imaging

GORT-5	Gray Oral Reading Tests, Fifth Edition
KBIT-2	Kaufman Brief Intelligence Test, Second Edition
MRI	Magnetic Resonance Imaging
NEPSY-II	NEPSY, Second Edition
PPVT-4	Peabody Picture Vocabulary Test, Fourth Edition
RD	Radial Diffusivity
RAN/RAS	Rapid Automatized Naming and Rapid Alternating Stimulus
ROI	Region of Interest
SES	Socioeconomic Status
SPSS	Statistical Package for the Social Sciences
TOPEL	Test of Preschool Early Literacy
WRMT	Woodcock Reading Mastery Tests-Revised

Introduction

Learning to read is one of the major milestones in a child's life, and is essential for scholastic achievement, and future employment. Nonetheless, many children struggle while learning to read, and as many as 11.6% percent of children are diagnosed with developmental dyslexia (DD) (Snowling & Lervag, 2016). DD is a brain-based specific learning disability characterized by deficits in reading and reading-related skills, such as phonological awareness (the ability to manipulate phonemes, the smallest units of speech), spelling, and/or rapid visual/verbal manipulation of letters and/or words despite adequate intelligence (Petersen & Pennington, 2012). Children with DD are often viewed by educators and peers as lazy or simply "acting out," and consequently may develop anxiety and other psychopathology (Habib & Naz, 2015). Compared to their peers, not only are children with DD less likely to complete high school and/or college, but also are more likely to enter the juvenile justice system (Svensson et al., 2003).

The dilemma is that even though early intervention is the gold standard of treatment, DD is typically not diagnosed until second or third grade (Vaughn et al., 2010). Children essentially need to struggle and fail prior to the recognition and diagnosis of the fundamental disorder. However, recent data suggest that DD is highly heritable and that the majority of genes implicated in DD are also involved in neuronal migration and axonal development as well as neural activity in language-related brain structures (Pennington & Lefly, 2001; Nopola-Hemmi et al., 2001; Meng et al., 2005; Galaburda et al., 2006; Peterson & Pennington, 2012; Darki et al., 2012; Pinel et al., 2012; Wang et al., 2016). Moreover, children with a parent or sibling with DD have a 34-56% chance of also receiving a diagnosis of DD (Pennington & Lefly, 2001).

The Reading Brain

Imaging studies suggest that the reading circuit in typically developing individuals consists of two left lateralized posterior systems, one which is ventral and one which is dorsal (Pugh et al., 2000). The ventral component consists of the left lateral extrastriate areas and the occipitotemporal area; it is activated during word and pseudoword reading tasks. The dorsal system includes the angular gyrus in the inferior parietal lobule, and the posterior aspect of the superior temporal gyrus (Wernicke's area); it is implicated in mapping the sounds of language (phonemes) onto printed text (graphemes). A third component, the anterior circuit consists of the inferior frontal gyrus (Broca's area); it is crucial for sequencing and control of speech-gestural recoding and is implicated in silent reading and naming (Pugh et al., 2000).

The Neural Basis of Developmental Dyslexia

Children and adults with DD display both structural and functional anomalies. Recently Linkersdörfer and colleagues (2012) conducted a meta-analysis of nine VBM studies of children and adults with DD, and observed that the largest reduction in cortical grey matter was in the left fusiform extending into the left inferior temporal gyrus in readers with DD. Additional reductions in grey matter were seen bilaterally in the supramarginal gyri and cerebellum in individuals with DD. Children with DD also show atypical activations when engaged in reading tasks. The temporoparietal region has been reported to have atypical functional activation, as measured with functional magnetic resonance imaging (fMRI), in DD compared to typical readers (Temple et al., 2001; Shaywitz et al., 2002; Hoeft et al., 2007; Richlan et al., 2009). Reduced bilateral occipitotemporal activation was also observed in a meta-analysis of children with DD (Richlan, 2011). Additionally, older children and adults with DD also display increased right hemispheric activity during reading and reading-related tasks compared to controls (Waldie et al., 2013). The absence of activation differences in frontal and right hemisphere regions between typically developing and children with DD may suggest that these differences, often found in adults, reflect compensatory strategies.

School-age children and adults with DD also display altered white matter connectivity. Diffusion-weighted imaging (DWI) is a structural magnetic resonance imaging technique, which permits reconstruction and measurement of white matter tract integrity. Compared to typical adult readers, those with DD display reduced fractional anisotropy (FA), a summary measure of white matter fiber architecture, in the left temporoparietal area (Klingberg et al., 2000; Deutsch et al., 2005; Rimrodt et al., 2010). “FA is the normalized standard deviation of the three eigenvalues and indicates the degree to which the isodiffusion ellipsoid is anisotropic (i.e., one or two eigenvalues are larger than the mean of all three eigenvalues)” (Yeatman et al., 2011, p. 4). Based on the literature and on preliminary findings, special attention will be paid to the left arcuate fasciculus (AF) and the corpus callosum (CC).

The role of the arcuate fasciculus in reading and developmental dyslexia. The left AF is a white matter tract that directly connects two well-documented regions of the reading network, the temporoparietal region and the left inferior frontal gyrus (Frye et al., 2011; Vandermosten et al., 2012). Intraoperative subcortical stimulation of the left AF in adults resulted in phonemic paraphasias (i.e., incorrect substitution of phonemes) (Duffau et al., 2002), and stroke patients with lesions in the left AF also experience phonological deficits (Rolheiser et al., 2011).

The left AF is implicated in reading and reading related tasks including phonological processing, reading fluency, speech production, language comprehension, and speech repetition (Fridriksson et al., 2013; Rauschecker et al., 2009). In fact, learning to read results in increased integrity of the left AF in previously illiterate adults (de Schotten et al., 2014).

Recently, Vandermosten and colleagues (2012) segmented the left AF into three regions: arcuate fasciculus-anterior, arcuate fasciculus-direct, and arcuate fasciculus-posterior in 20 adults with DD and 20 controls. When compared to controls, adults with DD displayed reduced FA within the left arcuate fasciculus-direct. In addition to assessing FA, Vandermosten et al. (2012) also measured axial diffusivity (AD) and radial diffusivity (RD). AD measures the magnitude of microstructure oriented in the direction of the principal axis, while RD measures the magnitude of microstructure in the direction perpendicular to the principal axis (Frye et al., 2011). Reductions in FA were accompanied by increases in RD, but not AD, which they interpreted as suggesting reduced myelination in adults with DD. Furthermore, they observed that the left arcuate fasciculus-direct, the midsection of the AF, was positively correlated with phonemic awareness skills across groups. They also found a negative correlation between the FA of the right arcuate fasciculus-direct and phonemic awareness skills suggesting increased left lateralization in the arcuate fasciculus-direct is associated with enhanced phonological processing abilities.

Adults and children with DD display reduced FA within the left AF relative to typically developing readers (Klingberg et al., 2000; Catani et al., 2008; Vandermosten et al., 2012). FA of the entire left AF also correlates with phonological awareness in school-age children (Yeatman et al., 2011), and the volume of the left AF correlates with phonological awareness in kindergarteners

(Saygin et al., 2013). Furthermore, in a sample of 58 children between ages 5-9, white matter volume changes within the left AF predict reading outcomes during the developmental period when children become fluent readers (Yeatman et al., 2012). Similarly, the volume of the left AF and superior corona radiata assessed in 38 children between five- and six-years predicted third grade reading abilities (Myers et al., 2014).

A recent study observed FA of the left AF and bilateral inferior fronto-occiptial fasciculi correlates with phonological awareness in Dutch speaking pre-readers with (N=36) and without a familial risk of DD (N=35) (Vandermosten et al., 2015). Children completed behavioral testing at the start of kindergarten and an MRI scan at the end of the academic year. Children can be considered pre-readers since none of the participating schools included reading instruction in kindergarten. Regression analyses suggest phonological awareness skills predict FA in left AF and bilateral inferior fronto-occiptial fasciculi across pre-readers with and without a familial risk of DD. Moreover, pre-readers with a familial risk of DD display reduced FA in the left inferior fronto-occiptial fasciculus and a trend toward reduced FA in the posterior left AF compared to pre-readers without a familial risk of DD.

The role of the corpus callosum in reading and developmental dyslexia. Even though a number of studies indicate atypical white matter connectivity in DD, the corpus callosum (CC), the largest interhemispheric white matter tract remains understudied (Frye et al., 2008). The CC may be a particularly important neural pathway in DD since children and adults with DD likely need to rely on the CC to recruit right hemisphere homologs during reading and reading-related tasks as a compensatory mechanism (Rumsey et al., 1996; Klingberg et al., 2000; Dougherty et al., 2006; Niogi & McCandaliss, 2006; Hoeft et al., 2011).

The CC's role in DD is complex due to its diverse morphology. The midbody of the CC is implicated in processing primary sensory and higher order auditory information along with premotor and primary motor cortices (Aboitiz, 1992; Hofer & Frahm, 2006; Paul, 2010). Large axons within the midbody of the CC facilitate rapid sensory integration essential to perceive temporal cues in auditory and visual stimuli which are needed for phonological processing and ultimately fluent reading. Individuals with DD (which included 12 children, 3 adults, and 9 compensated adults) display reduced FA values within the midbody of the CC (Fine, et al., 2007).

In contrast, posterior regions of the CC, such as the splenium display greater FA values in adults and children with DD than typically developing controls (Frye et al., 2008; Odegard et al., 2009; Vandermosten et al., 2012; Hasan et al., 2012). In typical development, the splenium consists of small densely packed axons; thus, splenium enlargement suggests a greater number of axons and greater interhemispheric connectivity (Paul, 2010). Furthermore, compared to typically developing adults (N=18), individuals with DD (N=9) display increased FA and AD in the splenium (Frye et al., 2008). In particular, only letter word identification was negatively correlated with FA and AD within the splenium across controls and readers with DD. Reduced splenium interhemispheric connectivity may suggest reduced connectivity between the ventral occipital areas through occipital interhemispheric callosal fibers, and may result in greater lateralization of orthographic processing. This is consistent with the fact that typically developing individuals show left lateralized activation of the ventral occipital area, near the so-called visual word form area (Cohen et al., 2000), while individuals with DD display bilateral activation of this area during reading (Shaywitz et al., 2007).

Recently Hasan and colleagues (2012) similarly observed that compared to controls (N=26), children and adolescents with DD (N=24) display increased FA in the splenium of the CC. However, they observed that the posterior midbody of the CC was negatively correlated with measures of single word reading and reading comprehension. The authors argue that increases in myelination and/or axial integrity within the posterior midbody of the CC may enhance interhemispheric communication, which may reflect greater compensatory mechanisms in children and adults with DD. This is in line with previous work suggesting increased values of FA in the posterior aspect of the CC is associated with reduced lateralization of the left hemisphere (Westerhausen et al., 2006).

Since the CC is a bilateral structure, damage to territory on either the left side of the brain (or restricted inputs to those regions from damage to regions that project to those areas), can change the number (or integrity) of fibers traveling to the right side of the brain. This suggests that DWI measures of the

CC are to some extent a reflection of both the relative integrity of the origin and destination of the fibers, as well as differential degree of connectivity between the two sides. When the origin and receiving sides of the cortex are symmetric, one would presume that the degree of lateralization of function would be lowest.

It is sometimes claimed that increases of interhemispheric connectivity mediate recovery in a subgroup of individuals with DD by enhancing right hemispheric activation beyond normal levels. (Shaywitz et al., 2007; Fine et al., 2007; Frye et al., 2008; Paul, 2010; Waldie et al., 2013). Since this hyperactivation is generally observed past infancy, it would be of interest to see whether enhanced CC connectivity is intrinsic in children and infants at risk of DD prior to the majority of reading development. If enhanced connectivity precedes compensation, in certain callosal areas, this would help to differentiate the roles of the CC in reading acquisition vs. its recovery.

Genetic Basis of Developmental Dyslexia

DD is highly heritable; estimates suggest that DD occurs in 65% of monozygotic twin boys and 63% in monozygotic twin girls (Hawke et al., 2005). A recent meta-analysis consisting of 420 children with DD reports that children with a first degree relative with DD have a 45% chance of also being diagnosed with DD (Snowling & Lervag, 2016). A number of DD susceptibility genes have been identified, including *DCDC2*, *DYX1CI*, *ROBO1*, *KIAA0319,* and the majority of these genes play a role in neuronal migration and axonal development (Fisher et al., 2002; Olson, 2006; McGrath et al., 2006; Galaburda et al., 2006; Kere, 2014). Experimental manipulation of these genes in rodent models results in localized gray matter malformations, such as ectopias, which result in atypical cortical connectivity (Fitch et al, 2013). Cortical ectopias have previously been shown in postmortem studies of adults with DD (Galaburda et al., 1985). Furthermore, *DCDC2* deletion in humans with DD has been linked to reduced FA, a measure of fiber tract integrity, in the left AF and the genu of the corpus callosum (Marino et al., 2014). This is consistent with the notion that some factors causing DD are present prior to learning to read and possibly at birth.

Language and Reading. Ample evidence suggests an intimate relationship between the development of DD and language impairment, which isdiagnosed when a child’s language development lags behind his/her other cognitive skills despite exhibiting average or above-average nonverbal abilities

(Bishop & Hayiou, 2009). In fact, a number of genes implicated in DD, *DCDC2*, *KIAA0319, FOXP2*, *CNTNAP2*, are also implicated in language impairment (Eicher et al., 2013; Powers et al., 2013). Furthermore, markers within *KIAA0319*, *FOXP2*, *CNTNAP2*, and *ZNF385D* are contribute to comorbid diagnoses of DD and language impairment (Eicher et al., 2013).

A recent study examined the relationship between speech production, language, and literacy in children with and without a familial risk of DD (Carroll et al., 2014). Interestingly, speech production was more highly correlated with phonological processing in children with a familial risk of DD than controls. Children with a familial risk of DD displayed speech production deficits compared to control children. 45% of children with a familial risk of DD developed word reading deficits. Poor readers displayed weaknesses in language, phonological processing, and early literacy measures, but no deficits in speech production. This suggests that speech processing deficits may be a marker of familial risk, but is not associated with the manifestation of DD.

Impaired nonword repetition has been implicated in both in language disorders and DD. In 2011, Baird and colleagues set out to disentangle this relationship, and examined children who had language impairment or were siblings of children with language impairment. Nonword repetition was impaired in children who currently or previously displayed language impairment. Reading decoding, spelling, and comprehension skills correlated severity of language impairment. Interestingly, nonword repetition differentiated children with language impairment with and without reading impairment (defined as deficits in decoding or spelling). The authors suggest nonword repetition may be marker for language impairment that co-occurs with reading, spelling, and decoding deficits.

A recent meta-analysis reviews oral language deficits in children with a familial risk of DD (Snowling & Melby-Lervag, 2016). Infants and toddlers with a familial risk of DD who are ultimately diagnosed with DD display poorer articulatory skills, vocabulary knowledge, and grammar than peers with a familial risk of DD who do not develop DD (Snowling & Melby-Lervag, 2016). Preschoolers with a familial risk of DD who ultimately are diagnosed with DD display poorer auditory processing skills, letter knowledge, and reduced sensitivity to rapid auditory processing compared to at-risk peers who do not receive a diagnosis of DD (Snowling & Melby-Lervag, 2016). Furthermore, at-risk preschoolers demonstrate poorer articulatory skills, vocabulary knowledge, and phonological processing skills than control children (Snowling & Melby-Lervag, 2016). At-risk school-age children display reduced nonverbal vocabulary than control children (Snowling & Melby-Lervag, 2016). Interestingly by school-age, deficits in articulatory accuracy, vocabulary knowledge, letter knowledge, and grammar are resolved in at-risk children (Snowling & Melby-Lervag, 2016). At-risk children who are later diagnosed with DD still display deficits in vocabulary knowledge at school-age compared to peers (Snowling & Melby-Lervag, 2016).

Although there is an intimate link between language and reading abilities, not all children with language impairment are later diagnosed with DD. In 2009, Bishop and Hayiou-Thomas aimed to identify protective factors in children with language impairment without DD. Children with language impairment without DD display deficits in vocabulary knowledge, sentence comprehension, and memory for sentences (Bishop & Hayiou-Thomas, 2009). Interestingly, rapid serial naming performance was within the normal range for children with language impairment but not DD (Bishop & Hayiou-Thomas, 2009). It appears that the ability to name pictures and digits rapidly may serve as a protective factor in the development of DD.

Experiment 1: Infant White Matter Microstructure Predicts Pre-Reading Skills in Children At-Risk of Developmental Dyslexia

Introduction

It has been established that children with a familial risk of DD exhibit neural differences from their peers without a family history of DD even prior to learning how to read (Raschle et al., 2011; Raschle et al., 2012; Vandermosten et al., 2015; Wang et al., 2016). Recently Langer and colleagues observed that infants with and without a familial risk of DD already display differences in the left AF (2015). Specifically, infants with a familial risk of DD display reduced FA within the left AF compared to age-matched peers without a familial risk of DD. This is in line with results in children and adults with DD who also display reduced FA of the left AF compared to typically developing controls (Klingberg et al., 2000; Catani et al., 2008; Vandermosten et al., 2012). The current study addresses an open question: whether differences in white matter connectivity observed in infancy are associated with subsequent pre-reading skills.

Electroencephalography studies in infants at-risk of developmental dyslexia. Event-related potentials (ERP) assessed in infancy have been shown to predict later language and reading skills in children with and without a familial risk of DD (Molfese et al., 2002; Lyytinen et al., 2004; Guttorm et al., 2005; van Zuijen et al., 2013). For example, newborn infants with a family history of DD display neural activity localized to the right hemisphere, which is the non-dominant hemisphere for language processing when presented with differing vowel durations in an oddball paradigm compared to infants without a family history of DD (Lyytinen et al., 2004). In contrast, infants without a family history of DD display neural responses localized to the left hemisphere, which is similar to typically developing adults. Furthermore, infants with a family history of DD who display enhanced right hemisphere activity displayed significantly poorer receptive language skills at 2.5 years and poorer verbal memory at age five.

In a follow-up study, newborns with a familial risk of DD who display right localized neural activation score significantly lower on measures of phonological awareness, rapid automatized naming, and letter knowledge at 6.5 years (Guttorm et al., 2005). Specifically, infants with a family history of DD (N=26) and without a family history of DD (N=12) who display greater left hemisphere localization predict better receptive language skills at 2.5 years and verbal memory skills at age five. Often enhanced right neural activity during reading and reading-related tasks is thought to reflect compensatory mechanisms in struggling readers (Shaywitz et al., 2007; Fine et al., 2007; Frye et al., 2008; Paul, 2010; Waldie et al., 2013). The aforementioned study suggests that enhanced right neural activity in children who later develop DD may predate reading instruction and therefore may serve as a risk factor for later DD.

One prospective longitudinal study recorded auditory ERPs within 36 hours of birth (Molfese et al., 2002). Based on their ERP analysis, researchers correctly identified the reading abilities of over 81% of 38 newborns eight years later (Molfese et al. 2002). At age eight, these children completed letter and word decoding tests. Children were divided into three groups based on their reading scores: children with DD (N=17), poor readers (N=7), and controls (N=24). Six amplitude and latency measures correctly identified 85.7% of poor readers (6/7), 82.4% of children with DD (14/17) and 79.2% of controls (19/24). For example, control children displayed faster latencies and a larger N1 component at birth than poor readers and children with DD. In contrast, children with DD and poor readers displayed larger N2 amplitudes at birth than the control children. In addition, poor readers displayed larger P2 amplitudes than the control children.

Van Zuijen and colleagues (2013) observed impaired speech-sound processing in 39% (10 of 26) two-month-old infants with a family history of DD who later became non-fluent second grade readers. Infants who became fluent readers (from both control groups and at-risk groups) elicited an ERP mismatch negativity response at two-months to consonant-vowel-consonant words presented in an oddball paradigm indicating that they differentially process speech stimuli. Interestingly, non-fluent at-risk children did not show a mismatch response in infancy. This suggests neural responses elicited by speech stimuli at two-months can differentiate infants with a familial risk of DD who become fluent readers from those that become non-fluent readers in second grade.

Although EEG studies investigating predictors of reading development in at-risk infants is encouraging, it is important to note several limitations. Many EEG predictions lack specificity, the ability of a measure to correctly identify individuals without a disease, and as a result are susceptible to a significant percentage of false positives resulting in the over-diagnosis of DD in at-risk children. A recent study using EEG to diagnosis children with ADHD reported a specificity of only 57% (Sangal & Sangal, 2014). EEG studies may also lack sensitivity, the ability of a measure to correctly identify individuals with a disease, which may result in a number of children not receiving a warranted diagnosis. For instance, van Zujien and colleagues (2013) observed the absence of a mismatch negativity response was predictive of deficits in reading fluency in only 39% (10 of 26) of infants who later were later classified as non-fluent readers meaning 16 infants would wrongly be diagnosed. It has been argued that the mismatch negativity component is inconsistent across studies in infants and children (Bishop, 2007). This would result in the excessive allocation of services. Additionally, ERP lack adequate spatial resolution especially for deep structures, which results in rough estimates of where processes are occurring based on postsynaptic potentials generated by cortical structures.

Development of the arcuate fasciculus during infancy. To my knowledge, there have been no longitudinal studies of white matter connectivity beginning in typically developing infants. Infants (N=23) with a mean age of ten weeks display leftward asymmetry of the arcuate fasciculus (Dubois et al., 2009).

Both voxel-based analysis of FA (Dubois et al., 2009) and tractography (Dubois et al., 2015) reveal a left-to-right asymmetry in the AF in infants. Unfortunately, both of these studies did not report RD or AD, making it difficult to interpret whether this asymmetry is due to different rates of myelination or differences in axonal integrity, respectively.

Recently, O'Muircheartaigh and colleagues (2014) conducted a large cross-sectional study examining the relationship between white matter development and cognitive abilities in infants and children between three months and four years. They found correlations between expressive and receptive language abilities and white matter volume underlying frontal and temporal cortices and anterior and posterior CC. Furthermore, these measures of myelin volume fraction were more strongly associated with language abilities with increasing age. It is important to note that this investigation did not implement tractography; therefore, it is difficult to assess whether the entire tract or specific regions along these white matter bundles are associated with later language abilities.

Longitudinal studies are needed to determine whether increased connectivity results in more successful language acquisition. Moreover, longitudinal investigations are needed in high-risk clinical populations to assess whether these individuals undergo different developmental trajectories. At the same time, we will begin to piece together the properties of normal development.

The power of measuring white matter tracts, over time, is illustrated by a recent longitudinal study that explored the developmental trajectories of white matter tracts (confirmed by tractography) in infants at-risk of autism spectrum disorder (Wolff et al., 2012). Infants with high familial risk of autism spectrum disorder exhibit greater FA values in bilateral limbic, association, and projection fiber tracts at six months. However, this early-enhanced developmental trajectory was reversed such that FA values of children with autism spectrum disorder were lower than controls by 24 months. Interestingly, AD and RD values did not differ between groups suggesting that the difference in FA was due to- the relative proportion of RD and AD and not to either measure alone. This suggests that individuals who are later diagnosed with autism spectrum disorder undergo an altered course of neural development that precedes the manifestation of clinical symptoms. This study highlights the dynamism of development as well as the feasibility and utility of characterizing neural differences in infants at high risk of a neurodevelopmental disorder.

Recently Swanson and colleagues (2015) have observed that splenium microstructure predicts spoken language production in two-year-old children. Infants completed diffusion-tensor imaging and behavioral assessments at 6, 12, and 24 months of age. Additionally, the MacArthur-Bates Communicative Development Inventory was completed by parents at 24 months to quantify the number of words infants produced at that time. Infants with high language production at 24 months generally had higher FA in the splenium when compared with children with lower language production. Furthermore, infants with a high word production showed accelerated FA development in the splenium sometime between the 12- and 24-month time point. Swanson et al. (2015) denote a limitation of the aforementioned study is that it remains unknown whether later language and reading skills are similarly predicted by rate of splenium development. One explanation of this finding is that the splenium passes through the posterior hub of the default network (Damaraju et al., 2014;

Gao et al., 2009; Gao et al., 2013; Pruett et al., 2015). The default network supports orienting to salient stimuli. Therefore, Swanson et al. (2015) suggest that the splenium may support early language skills through its role in visual orienting. Previously, visual orienting has been shown to support spoken word acquisition, specifically label mapping; therefore, the splenium may be an important neurobiological region for emerging language production in infancy through its role in visual orienting (Keehn et al., 2013; Koegel et al., 2009; Vouloumanos et al., 2014).

The Gaab lab has recently shown that infants with a familial risk of DD already show differences in white matter architecture in the first year of life (Langer et al., 2015). Diffusion scans were acquired in 14 infants with and 18 infants without a familial risk of DD during natural sleep. Infants also completed the Mullen Scales of Early Learning on the same day of imaging. Two measures, manual tractography and automated fiber-tract quantification (AFQ) of the left AF performed to visualize group differences along the tract rather than relying on mean diffusivity measures, allowing for more precise group differences. Both methods exhibited high reliability (r=.77, p=.002). Infants with a familial risk of

DD displayed reduced age-corrected FA in the left AF compared to infants without a familial risk of DD. Age-corrected FA of the left AF was also positively correlated with expressive language skills measured via the Mullen Scales of Early Learning. Diffusivity measures of the left AF have predicted reading and reading-related skills in children (Yeatman et al., 2011; Saygin et al., 2013; Vandermosten et al., 2015) and formerly illiterate adults show increases in the left AF diffusivity after learning to read (de Schotten et al., 2014). Langer et al. (2015) show that infants with a familial risk of DD already show the characteristic alterations in the left AF observed in children and adults with a diagnosis of DD. Longitudinal follow-up is needed to ascertain whether infant white matter diffusivity is predictive of later language and reading measures.

The aim of the current study was to assess whether three indices of white matter microstructure in the left AF and in the splenium of the CC predict subsequent pre-reading skills in preschoolers. A subset of infants was included in Langer et al.'s 2015 sample. AFQ was employed to segment the left AF and CC. AFQ segments the forceps major of the CC, which connects homologous regions of the occipital lobe via the splenium, rather than segmenting the splenium separately (Yeatmen et al., 2012). For simplicity and to mirror the prior literature, the forceps major of the CC will be referred to as the splenium of the CC.

It is hypothesized that infants with and without a familial risk of DD will already differ in diffusivity measures. Infants at familial risk of DD are predicted to display abnormal diffusion measures in the splenium of the CC and the left AF. Based on prior research in infants (Langer et al., 2015) and children at-risk of DD (Vandermosten et al., 2015; Wang et al., 2016) and children (Yeatmen et al., 2011; Yeatmen et al., 2012; Wang et al., 2016) and adults (Vandermosten et al., 2012) with a diagnosis of DD, it is predicted that infants with a familial risk of DD will display reduced FA in the left AF compared to infants without a familial risk of DD. The focus of this investigation is on the left AF and does not examine the right AF since the right AF is less reliably tracked at this developmental stage. It is also hypothesized that infants with a familial risk of DD will display atypical diffusion measures in the splenium of the CC. The direction of this prediction is not specified since prior literature has shown increased FA and AD in children and adults with DD (Frye et al., 2008; Odegard et al., 2009), but no study has explored this relationship in preschoolers or infants. Furthermore, it is hypothesized that across groups, diffusion measures of the left AF and the splenium of the CC will predict pre-reading skills at age four (Yeatmen et al, 2011; Saygin et al., 2013; Swanson et al., 2015; Wang et al., 2016).

Methods

Participants. Sixty-four infants (33 with and 31 without a familial risk of DD) between four and 18 months of age (mean age of 10.2 months) were recruited. A subset of this participants were previously reported in Langer et al., 2015. Infants were classified as having a family history of DD (*n*=33): a first-degree relative with DD (*n*=22), a second-degree relative with DD (*n*=8), or a first-degree relative with a history of reading difficulties (*n*=3). Family members with a history of reading difficulties without a diagnosis completed the Nelson Denny reading test and scored at or below the 25th percentile. Infants were classified as not having a family history of DD (*n*=31) if they had no relatives with a diagnosis of DD or history of reading problems. 51 infants had completed DWI (25 with and 26 without a familial risk of DD) with a mean age of 9.82 months. 22 males participated in the study (10 with and 12 without a familial risk of DD).

Informed consent was obtained from the child's legal guardian. Parents also completed a series of questionnaires assessing perinatal and early development, socioeconomic status (SES), and home literacy. Infants were matched for age, sex, and SES. All infants were born on or after 37 weeks' gestation and had no history of neurological disease or trauma, nor any reported vision or hearing difficulties. Twenty-two infants (12 with and 10 without a familial risk of DD) completed follow-up cognitive-linguistic testing at four-years of age (mean age of 50.76 months). Twelve males (7 with and 5 without a familial risk of DD) participated in the study. Sixteen children were right handed (10 with and 6 without a familial risk of DD). Five children were left handed (1 with and 4 without a familial risk of DD). One child with a familial risk of DD was classified as ambidextrous.

Mullen Scales of Early Learning. Infants were assessed with the Mullen Scales of Early Learning (Mullen, 1995) during their initial visit. The Mullen Scales of Early Learning is designed to assess gross and fine motor skills, visual receptive abilities, and receptive and expressive language skills from birth through 59 months. The Mullen Scales of Early Learning has been independently normed on a representative sample of 1800 children in the US. The two subtests of interest were Receptive Language, which assesses comprehension of verbal language, and Expressive Language, which assesses verbal production abilities.

Novel MRI protocol for scanning naturally sleeping infants. Dr. Gaab's lab has developed a complex and innovative protocol for acquiring MRI scans while infants sleep naturally without sedation (Raschle et al., 2012). These include considering naptime, asking parents to play MRI sounds at home to habituate the child to the sounds, keeping them active immediately prior to the scan, including home items to make them more comfortable, using ear protection to minimize scanner noise, and using a memory foam mattress to minimize scanner motion and increase comfort.

Image acquisition. The image acquisition parameters were previously reported in Langer et al., 2015. Scans are acquired with a 3.0 Tesla SIEMENS Trio Tim whole-body MRI scanner utilizing multi-echo magnetization-prepared rapid gradient echo sequences with prospective motion correction (mocoMEMPRAGE) for structural T1-weighted images and echo planar image (EPI) sequence of 30 gradient directions for DWI via a 32-channel radio frequency head coil. The following structural MRI imaging parameters were used: flip angle: 7 degrees; TE: 1450 ms; TA: 2270 ms; TA: 4:51 min; field of view (FOV) = 220 x 220 mm; in-plan acceleration (GRAPPA) factor of 2; spatial resolution = 1.1 x 1.11 x 1.0 mm (176 slices). The DWI parameters were: flip angle: 90 degrees; TE: 88 ms; TR: 8320 ms; TA: 5:59 min; FOV: 256 x 256 mm; b = 1000 s/mm^2.

Image processing. Imaging processing was previously described in Wang et al., 2016. The T1-weighted structural image was used to generate a brain mask by removing non-brain tissue using the Brain Extraction Tool (BET) (Smith, 2002) from Functional MRI of the Brain (FMRIB) software library (Oxford, UK). DWI data were converted to NRRD (teem.sourceforge.net/nrrd/) format using DicomToNrrdConverter software from Slicer4 (www.slicer.org). DWI quality control procedures were implemented using DTIprep software (Liu et al., 2010) along with visual inspection. Motion artifacts were defined by a translation threshold of 2 mm and rotation threshold of 0.5 degrees through rigid registration-based volume-by-volume measures. Volumes with motion artifacts were excluded from diffusion tensor estimation. Following quality control, DWI data were processed using mrDiffusion, a toolbox from the VISTALab (Standford Vision and Imaging Science and Technology) diffusion MRI software suite (www.vistalab.com) including eddy-current correction and tensor-fitting estimation (Rohde et al., 2004).

Automated fiber quantification. AFQ (https://github.com/jyeatman/AFQ) was implemented to segment the left AF and splenium of the CC (Yeatmen et al., 2012). AFQ employed the following procedure: 1. whole-brain tractography with a deterministic streamlines tracking algorithm (Mori et al., 1999; Basser et al., 2000) with an FA threshold of 0.2 and angle threshold of 40 degrees; 2. region-of-interest-based fiber-tract segmentation; 3. fiber-tract "cleaning" via a statistical outlier rejection algorithm; 4. diffusion quantification at each node throughout the tract. AFQ segmented tracts into 100 equidistant units along the trajectory of the tract rather than calculating mean diffusion across an entire tract, resulting in more precise localization of group differences (Yeatman et al., 2012). This method allowed us to calculate FA, RD, and AD across each tract and at each of the 100 nodes for each subject. For each tract of interest, 100 nodes along the tract were resampled to 50 nodes by discarding the portion of the fiber tract where individual fibers deviate from the core fascicle toward their destination in the brain. This approach normalized the fiber endpoints across participants and improves co-registration of each fiber tract (Yeatman et al., 2011; Wang et al., 2016).

Follow-up behavioral assessment. At age four, participants completed a cognitive-linguistic battery. 22 participants (12 with and 10 without a familial risk of DD) have completed follow-up testing (mean age of 50.76 months). Twelve males (7 with and 5 without a familial risk of DD) participated in the study. Sixteen children were right handed (10 with and 6 without a familial risk of DD). Five children were left handed (1 with and 4 without a familial risk of DD). One child with a familial risk of DD was classified as ambidextrous. To date, the majority of the remaining children with infant data and missing follow-up data, are still under four-years-old. These children will be invited to participate after their fourth birthday.

- *Kaufman Brief Intelligence Test, Second Edition* (KBIT-2) (Kaufman, 2004) assesses children’s nonverbal intelligence.

- *Peabody Picture Vocabulary Test - Fourth Edition (PPVT-4)* (Dunn & Dunn, 2007) assesses children's receptive vocabulary skills.
- *Clinical Evaluation of Language Fundamentals Preschool – Second Edition (CELF Preschool-2)* (Wiig, Secord, & Semel, 2004) assesses participants' general language abilities, receptive and expressive language, semantic development and ability to comprehend and produce syntactic structures.
- *Test of Preschool Early Literacy (TOPEL)* **(**Lonigan, Wagner, Torgesen, & Rashotte, 2007**)** assesses each child's print knowledge, definitional vocabulary, and phonological awareness via elision and blending tasks.
- *NEPSY – Second Edition (NEPSY-II) (Speeded Naming*) (Brooks, Sherman, & Strauss, 2009) assesses each child's ability to perceive a visual symbol, such as a picture, and retrieve the name for it accurately and rapidly.

Statistical analyses. Statistical analyses were executed in the programs R (version 3.1.0 64 bit) (Ihaka & Gentlemen, 1996) and Statistical Package for the Social Sciences (SPSS) (version 20) (IBM, 2011). Between-subjects'

ANOVAs were computed with age of infant, SES, and sex as covariates, and diffusion values as the dependent measure. Familial risk of DD was the between-subjects' variable.

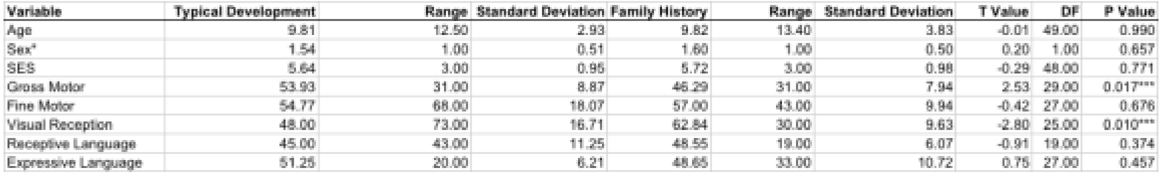
While controlling for age, sex, and SES, a series of partial correlations were run between the diffusion measures of the left AF and splenium of the CC and the cognitive-linguistic behavioral measures in infants with and without a familial risk of DD. Independent sample *t*-tests were also employed to explore mean differences between infants with and without a family history of DD. False discovery rate (FDR) corrections were employed to control for the number of comparisons (Yekutieli & Benjamini, 1999).

For the follow-up data, linear multiple regression analyses were also employed to assess the optimal set of predictors (i.e., family history, FA, AD and RD in the left AF and CC, expressive and receptive language as measured with the Mullen Scales of Early Learning (Mullen, 1995)) to predict print knowledge, phonological awareness, speeded naming, and vocabulary skills assessed at age four.

Results

Infant behavioral results. Infants with and without a familial risk of DD did not differ in terms of age (*t*=-.01, df=49, p=.990, Cohen's d=.003), sex (χ^2=.20, df=1, p=.657, Cohen's d=.112), SES as measured via maternal education (*t*=-.29, df=48, p=.771, Cohen's d=.084). Moreover, these children did not differ on the following subtests of the Mullen Scales of Early Learning: fine motor (*t*=-.42, df=27, p=.676, Cohen's d=.162, power=.06), receptive language (*t*=-.91, df=19, p=.374, Cohen's d=.418, power=.17), and expressive language (*t*=.75, df=27, p=.457, Cohen's d=.289, power=.08). Infants with and without a familial risk of DD differed on the gross motor subscale (*t*=2.53, df=29, p=.017, Cohen's d=.940, power=.61) and visual reception (*t*=-2.80, df=25, p=.010, Cohen's d=1.120, power=.68). See Table 1.1 for further information.

Table 1.1. Infant Demographic and Psychometric Results.



Variable	Typical Development	Range	Standard Deviation	Family History	Range	Standard Deviation	T Value	DF	P Value
Age	9.81	12.50	2.93	9.82	13.40	3.83	-0.01	49.00	0.990
Sex*	1.54	1.00	0.51	1.60	1.00	0.50	0.20	1.00	0.657
SES	5.64	3.00	0.95	5.72	3.00	0.98	-0.29	48.00	0.771
Gross Motor	53.93	31.00	8.87	46.29	31.00	7.94	2.53	29.00	0.017***
Fine Motor	54.77	68.00	18.07	57.00	43.00	9.94	-0.42	27.00	0.676
Visual Reception	48.00	73.00	16.71	62.84	30.00	9.63	-2.80	25.00	0.010***
Receptive Language	45.00	43.00	11.25	48.55	19.00	6.07	-0.91	19.00	0.374
Expressive Language	51.25	20.00	6.21	48.65	33.00	10.72	0.75	27.00	0.457

*Since sex is a dichotomus variable, chi square analysis is reported.

Preschool behavioral results. Children with and without a familial risk of DD did not differ in any behavioral measure at the four-year-old follow-up visit: KBIT-2 nonverbal intelligence (*t*=-.12, df=22, p=.908, Cohen's d=.051, power=.02), TOPEL print knowledge (*t*=1.17, df=21, p=.255, Cohen's d=.511, power=.22), TOPEL definitional vocabulary (*t*=-1.17, df=21, p=.257, Cohen's d=.51, power=.23), TOPEL phonological awareness (*t*=-.36, df=20, p=.724, Cohen's d=.161, power=.05), NEPSY-II speeded naming (*t*=-.54, df=17, p=.595, Cohen's d=.262, power=.08), CELF Preschool-2 core langauge (*t*=-1.76, df=21, p=.094, Cohen's d=.768, power=.36), CELF Preschool-2 receptive langauge (*t*=-1.49, df=19, p=.153, Cohen's d=.684, power=.34), CELF Preschool-2 expressive langauge (*t*=-.32, df=18, p=.754, Cohen's d=.151, power=.05), CELF Preschool-2 language content (*t*=-.90, df=20, p=.378, Cohen's d=.402, power=.15), CELF Preschool-2 language structure (*t*=-1.10, df=17, p=.288, Cohen's d=.534, power=.10), PPVT-4 (*t*=-.66, df=21, p=.515, Cohen's d=.288, power=.08). See Table 1.2 for further information.

Table 1.2. Follow-Up Psychometric Results.

Measure	Typical Development	Range	Standard Deviation	Family History	Range	Standard Deviation	T Value	DF	P Value
Nonverbal Intelligence	103.55	33.00	10.16	104.15	53.00	14.46	-0.12	22.00	0.908
Print Knowledge	114.70	10.00	12.88	106.31	13.00	19.58	1.17	21.00	0.255
Definitional Vocabulary	104.30	10.00	12.28	109.54	13.00	9.31	-1.17	21.00	0.257
Phonological Awareness	105.00	9.00	17.21	107.31	13.00	13.05	-0.36	20.00	0.724
Speeded Naming	12.50	10.00	2.51	13.00	9.00	1.22	-0.54	17.00	0.595
Core Langauge	104.00	10.00	16.29	114.23	13.00	11.71	-1.76	21.00	0.094
Receptive Language	104.33	9.00	14.55	112.92	12.00	11.87	-1.49	19.00	0.153
Expressive Language	110.75	8.00	15.73	112.75	12.00	12.37	-0.32	18.00	0.754
Language Content	108.44	9.00	15.62	113.23	13.00	9.32	-0.90	20.00	0.378
Language Structure	106.88	8.00	15.24	114.00	11.00	13.04	-1.10	17.00	0.288
Vocabulary	113.50	10.00	18.90	118.08	13.00	14.33	-0.66	21.00	0.515

Diffusion-weighted imaging results. For the left AF, infants with and without a familial risk of DD differed in FA in 7 nodes (*t*=2.056, p<.05) (Figure 1.3) and in radial diffusivity in 35 nodes (*t*=-4.192, p<.05) (Figure 1.4). The pattern was that infants with a familial risk of DD exhibited reduced FA, and increased RD of the left AF compared to infants without a familial risk of DD.

For the splenium of the CC, infants with and without a familial risk of DD also differed in FA in 15 nodes (*t*=2.927, p<.05) (Figure 1.5) and in AD in 7 nodes (*t*=3.969, p<.05) (Figure 1.6). The pattern was that infants with a familial risk of DD displayed reduced FA and reduced AD of the CC compared to infants without a familial risk of DD.

Figure 1.1. Single subject left arcuate fasciculus. The left AF is displayed for a representative participant.

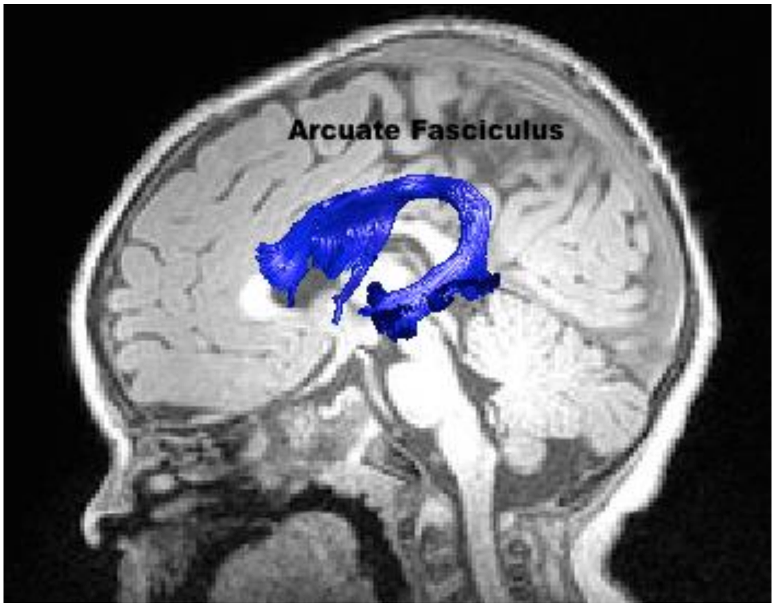


Figure 1.2. Single subject splenium of the CC. The splenium (forceps major) of the CC is displayed for a representative participant.

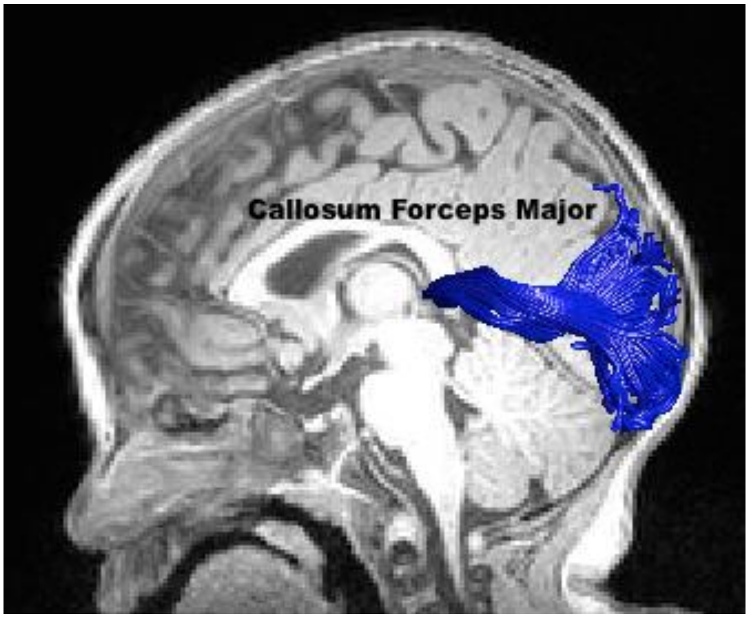


Figure 1.3. Infants with a familial risk of DD (FHD+) displayed reduced FA in the left AF compared to infants without a familial risk of DD (FHD-) (p<.05). Regions of the left AF that significantly differed (p<.05, corrected) in FA between infants with and without a risk of DD are displayed in red.

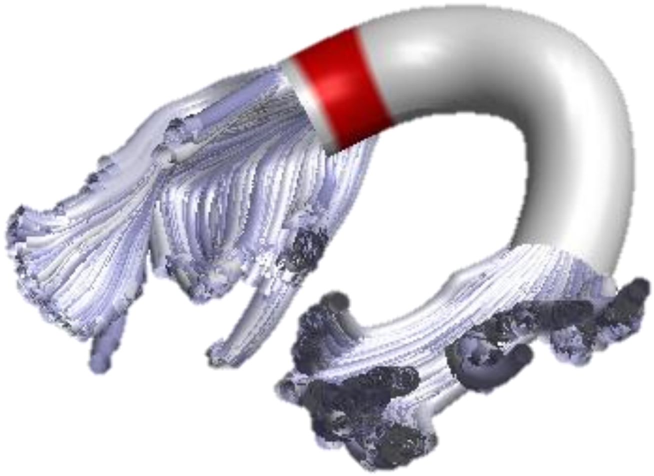


Figure 1.4. Infants with a familial risk of DD (FHD+) displayed increased RD in the left AF compared to infants without a familial risk of DD (FHD-) (p<.05). Regions of the left AF that significantly differed (p<.05, corrected) in RD between infants with and without a risk of DD are displayed in red.

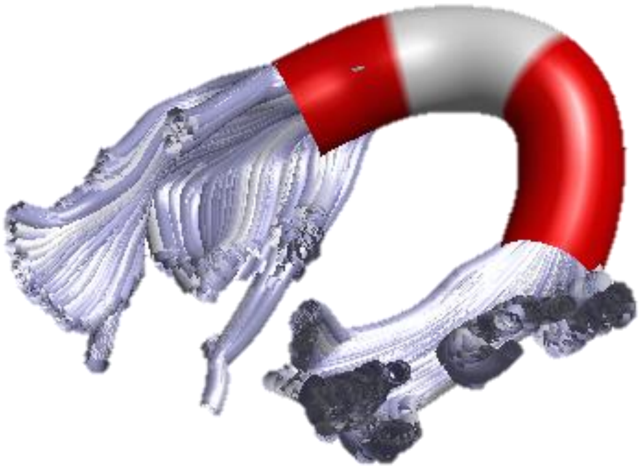


Figure 1.5. Infants with a familial risk of DD (FHD+) displayed reduced FA in the splenium of the CC compared to infants without a familial risk of DD (FHD-) ($p<.05$). Regions of the splenium of the CC that significantly differed ($p<.05$, corrected) in FA between infants with and without a risk of DD are displayed in red.

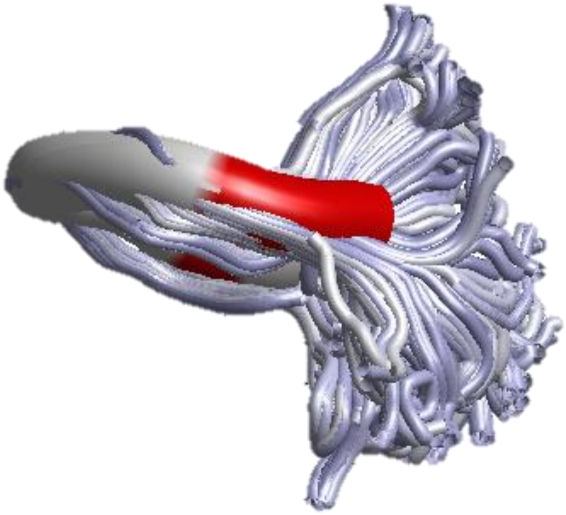
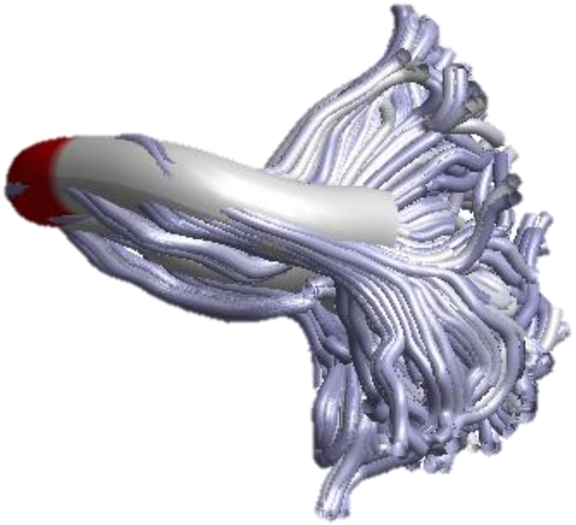


Figure 1.6. Infants with a familial risk of DD (FHD+) displayed reduced AD in the splenium of the CC compared to infants without a familial risk of DD (FHD-) (p<.05). Regions of the splenium of the CC that significantly differed (p<.05, corrected) in AD between infants with and without a risk of DD are displayed in red.



Brain-behavior results. Infants' white matter connectivity predicted vocabulary and print knowledge across groups. Specifically, during infancy FA of the left AF (which connects the left temporoparietal region to the left inferior frontal gyrus) in infancy was positively correlated with PPVT-4 (r=.574, p<.05, uncorrected) across children with and without a familial risk of DD (Figure 1.7).

In contrast, RD of the left AF in infancy was negatively correlated with PPVT-4 (r=-.651, p<.05, uncorrected) across children with and without a familial risk of DD (Figure 1.8). Moreover, AD of the splenium of the CC in infancy was positively correlated with TOPEL print knowledge during preschool (r=.656, p<.05, uncorrected) across children with and without a familial risk of DD (Figure 1.9).

Figure 1.7. FA of the left AF measured in infancy is positively correlated with PPVT-4 assessed in preschool (p<.05). Infants with a familial risk of DD (FHD+) are displayed in red and infants without a familial risk of DD (FHD-) are displayed in blue. PPVT-4 standard scores are displayed.

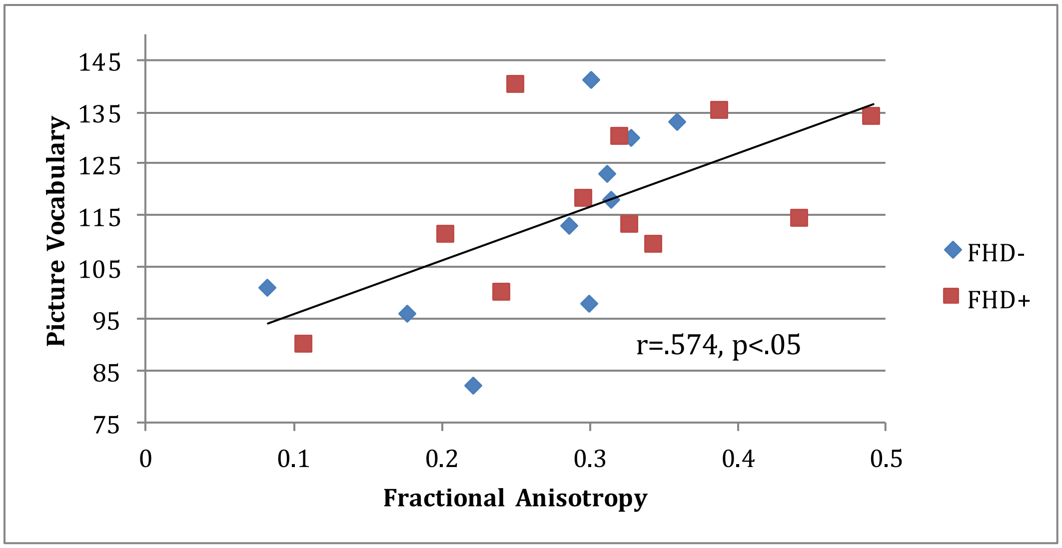


Figure 1.8. RD of the left AF measured in infancy is negatively correlated with PPVT-4 assessed in preschool (p<.05). Infants with a familial risk of DD (FHD+) are displayed in red and infants without a familial risk of DD (FHD-) are displayed in blue. PPVT-4 standard scores are displayed.

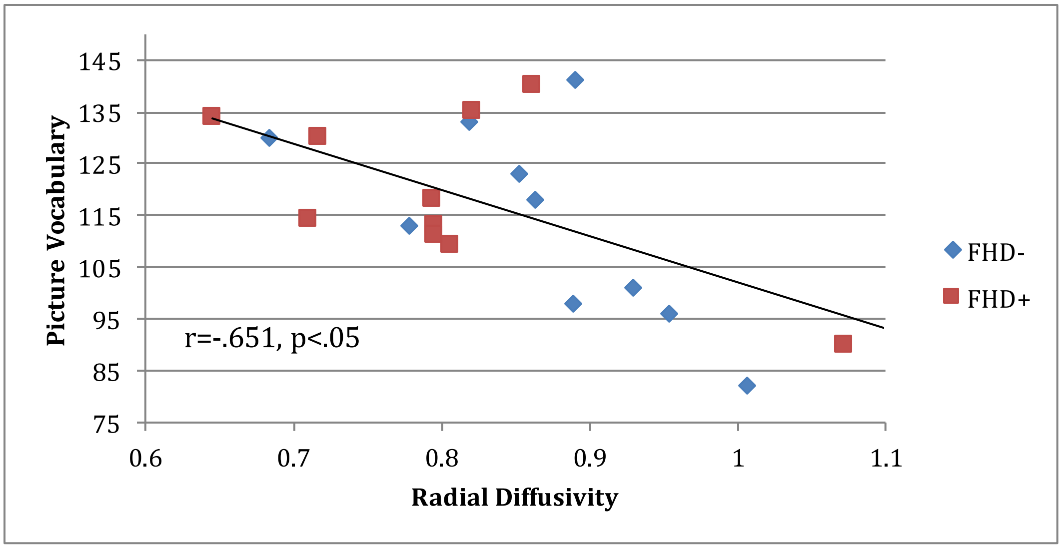
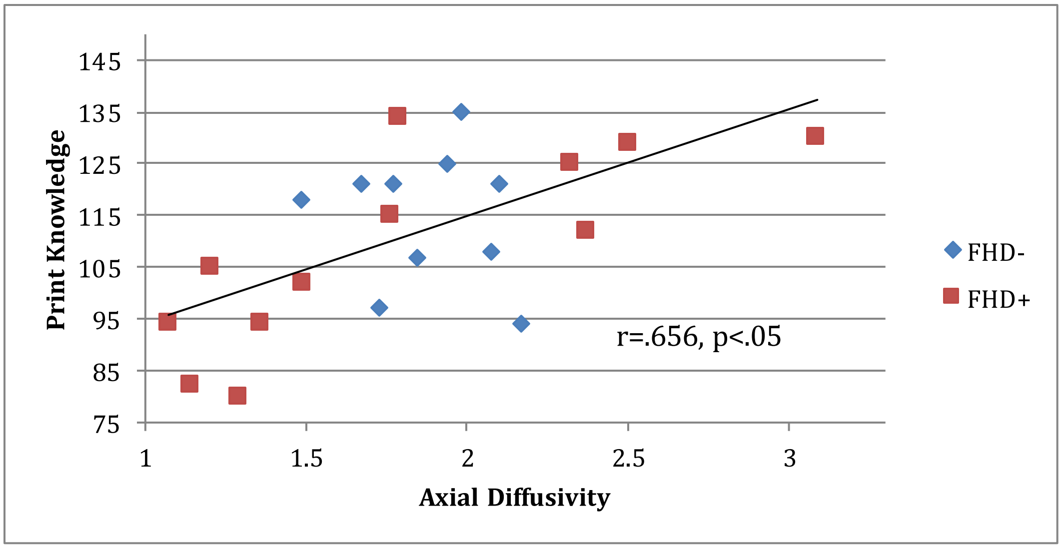


Figure 1.9. AD of the splenium of the CC measured in infancy is positively correlated with TOPEL print knowledge assessed in preschool (p<.05). Infants with a familial risk of DD (FHD+) are displayed in red and infants without a familial risk of DD (FHD-) are displayed in blue. TOPEL Print Knowledge subtest standard scores are displayed.



Since FA and RD of the left AF correlated with vocabulary and AD of the CC correlated with print knowledge series of stepwise multiple regression analyses were conducted. The model included the predictor variables: age, sex, SES as reflected by maternal education, family history, and diffusion measures.

The criterion variables were vocabulary as assessed by the PPVT-4 and print knowledge as assessed by TOPEL.

The model predicting vocabulary from RD of the left AF accounted for 26.4% of the variance (power=.76), and RD of the AF was the sole significant predictor (*t*=-2.395, p=.029, beta=.514). The model excluded: family history (*t*=1.080, p>.05), age (*t*=.432, p>.05), sex (*t*=-1.130, p>.05), SES (*t*=-1.261, p>.05). Note that the models predicting vocabulary from FA of the left AF did not account for a significant amount of the variance.

The model predicting print knowledge from AD of the splenium of the CC accounted for 46% of the variance (power=.98), and AD of the CC was the only significant predictor (*t*=4.129, p=.001, beta=.678). The model excluded: family history (*t*=-.547, p>.05), age (*t*=.129, p>.05), sex (*t*=-1.606, p>.05), SES (*t*=1.399, p>.05). Note that the models predicting print knowledge from FA of the splenium did not account for a significant amount of the variance.

Discussion

The goals of the current study were to determine whether infants with and without a familial risk of DD differ in measures of white matter connectivity and to assess whether measures of white matter connectivity in infancy are associated with subsequent pre-reading skills. In line with previous findings in children and adults with DD (Vandermosten et al., 2012; Rumsey et al., 1996; Dougherty et al., 2006; Niogi & McCandaliss, 2006; Hoeft et al., 2011), the current study found that infants with a familial risk of DD already exhibit atypical white matter connectivity in the left AF and splenium of the CC compared to peers without a familial risk of DD (Langer et al., 2015; Catani et al., 2008). Specifically, infants with a familial risk of DD displayed reduced FA and increased RD of the left AF and reduced FA and reduced AD of the splenium of the CC compared to controls without a familial risk of DD.

In terms of behavioral group differences, it is interesting that gross motor skills were the only behavioral measure in which infants with and without a familial risk of DD significantly differed. A significant proportion of children with DD display language deficits during the first years of life (Pennington & Bishop, 2009). Prior research has suggested that in addition to reading deficits, children with DD also exhibit gross motor deficits (Fawcett & Nicholson, 1995; Fawcett et al., 1996; Viholainen et al., 2006; Getchell et al., 2007). Children with a diagnosis of DD performed significantly lower than control children on the Total Balance subtest of the Movement Assessment Battery for Children (Getchell et al., 2007). Those authors suggest that cerebellar dysfunction may account for impaired performance in the DD group. A longitudinal study observed that preschoolers with a familial risk of DD and slow early motor development had smaller vocabularies and poorer inflectional morphology at ages 3.5 and 5.5 years (Viholainen et al., 2006). Furthermore, familial risk of DD with delayed motor milestones was associated with slower reading of words and pseudowords at the end of first grade.

Gross motor deficits have been reported in various neurodevelopmental disorders, and thus, may not be a specific predictor of DD, but rather neurodevelopmental disorders in general. Children with attention deficit/hyperactivity disorder often show motor impairments in fine motor skills, slow reaction time, and online motor control when completing complex tasks (Kaiser et al., 2015). Infants at-risk of autism spectrum disorder also display gross motor delays when compared to control infants (Bhat et al., 2012). Furthermore, 38% of at-risk infants who displayed gross motor delays at 6-

months later displayed communication delays at 18-months (Bhat et al., 2012). A recent study tracked 30 children with gross motor delays and/or abnormalities from infancy until early school-age (Hatakenaka et al., 2016). The aim of the investigation was to determine whether early gross motor delay is predictive of disorders such as attention-deficit/hyperactivity disorder, autism spectrum disorder, speech and language disorder, intellectual developmental disorder, and epilepsy. Of the 30 children evaluated with gross motor delays and/or abnormalities, 28 were given neurodevelopmental diagnoses. Furthermore, the investigators observed high comorbidity rates among the neurodevelopmental disorders (Hatakenaka et al., 2016).

FA is a summary measure thought to reflect axonal ordering, axonal density, and myelination, but is not specific to an individual factor (Jones et al., 2012). Animal studies have shown that increased RD is associated with reduced myelination, and decreased AD is associated with axonal degeneration or increased fiber complexity (i.e., cross fibers) (Song et al., 2005; Harsan et al., 2007; Frye et al., 2011)._ However, their underlining biological properties are still under debate (Wheeler-Kingshott & Cercignaani, 2009). This suggests that infants with a familial risk of DD who displayed decreased FA and increased RD in the left AF compared to infants without a familial risk may have reduced myelination of axons resulting in slower transmission of action potentials between neurons (Klingberg et al., 200; Glasser & Rillings, 2008). The left AF is implicated in reading and reading related tasks, such as phonological processing, reading fluency, speech production, language comprehension, and speech repetition (Fridriksson et al., 2013; Rauschecker et al., 2009). In fact, learning to read results in increased integrity of the left AF in previously illiterate adults (de Schotten et al., 2014). de Schotten's 2014 study consisted of three groups: adult illiterates who did not have access to schooling, ex-illiterates who similarly did not have access to schooling but attended adult courses, and literates who attended 2-7 years of early education. Both ex-literates and literates displayed increased FA in the left FA than the illiterate group; however, ex-literates and literates did not differ in terms of FA of the left AF.

This is the first study to compare CC morphometry between infants with and without a familial risk of DD. The youngest sample in a prior study investigating differences in the CC between children with DD and controls consisted of children between 7-12 years (Dougherty et al., 2007). The studies which included older children and/or adults with a familial risk of DD reported that DD displayed increased FA and AD compared to typically developing controls (Dougherty et al., 2007; Frye et al., 2008; Odegard et al., 2009; Vandermosten et al., 2012; Hasan et al., 2012).

In contrast, the current study observed that infants with a familial risk of DD displayed reduced FA and AD in the splenium of the CC compared to infants without a familial risk of DD. The splenium of the CC links bilateral occipital lobes through the splenium of the CC (Thomas et al., 2009).

These differences of CC development may seem to contradict previous findings in children and adults with DD. However, the trajectory of CC connectivity may very well be different in young infants vs. older children vs. teenagers and adults. A previous study tracks the development of the left AF and left inferior longitudinal fasciculus over a three-year period in children 7-12 (Yeatmen et al., 2012). Children with above-average reading skills initially had low FA in the aforementioned tracts that increased over the three-year period. In contrast, children with below-average reading skills, FA of these tracts diminished over time. This highlights the importance of longitudinal studies with multiple imaging time points beginning in infancy.

In the current study, white matter connectivity measured in infancy was associated with preschool vocabulary skills. Specifically, FA of the left AF was positively correlated with vocabulary skills in four-year-olds whereas RD of the left AF was negatively correlated with vocabulary skills in four-year-olds. Moreover, multiple regression analyses revealed RD of the left AF accounted for over 26% of the variance in later vocabulary skills. Although the relationship between FA and RD appears counterintuitive, it is important to remember that these measures are inversely proportional. A reduction in RD is thought to reflect an increase in myelination (Song et al., 2005; Harsan et al., 2007; Frye et al., 2011). Children who develop superior vocabulary skills may have faster transmission of action potentials along the left AF, a region that connects the left temporoparietal region to the left inferior frontal gyrus than children with poorer vocabulary abilities.

The left AF has been repeatedly implicated in various aspects of reading including word learning (Lopez-Barroso et al., 2013). Lopez-Barroso previously observed a negative correlation between RD of the left AF and word learning in adults. The current study similarly observes a negative correlation between RD of the left AF and vocabulary skills. Furthermore, RD of the AF was the best predictor of later vocabulary skills. In fact, multiple regression analyses revealed RD of the left AF accounted for 26.4% of the variance in later vocabulary skill.

White matter connectivity measured in infancy was also associated with preschool print knowledge skills. AD of the splenium of the CC was positively correlated with subsequent print knowledge. Multiple regression analyses revealed AD of the CC accounted for 46% of the variance in subsequent print knowledge skills. Decreases in AD are associated with axonal degeneration and increased fiber pathway complexity (Song et al., 2005; Harsan et al., 2007; Frye et al., 2011). Children who develop superior print knowledge may display greater lateralization of language than children with poorer print knowledge abilities.

The current investigation focuses on the most posterior section of the CC where majority of the fibers project to the occipital lobe. These CC fibers transverse the posterior hub of the default network and project to primary and higher-order visual cortices (Putnam et al., 2010). Recent work suggests this pattern of connectivity facilitates orienting to salient information during infancy (Elison et al., 2013). Visual orienting has been shown to facilitate language acquisition through language labeling, and consequently the CC may support emerging language through its role in language in visual orienting (Swanson et al., 2015). Swanson and colleagues observed that infants with superior language production at 24 months displayed the greatest change over time in FA of the CC and a tread toward RD suggesting that in myelination and axon packing density may be driving the FA results. Language production was assessed via parental report with the MacArthur-Bates Communicative Development Inventory, which is not normed for children greater than 24 months.

The current study observed a positive correlation with AD of the CC and print knowledge which was objectively assessed via the TOPEL which assess letter knowledge and early knowledge about written conventions and form. Children are asked to identify specific letters and written words, name specific letters, identify letters associated with specific sounds, and say the sounds associated with specific letters. Increases in AD may reflect reduced pathway complexity, such as less crossing fibers.

Frye and colleagues (2008) also observed differences in FA and AD in the splenium, the most posterior section of the CC, between adults with and without a diagnosis of DD. Adults with DD displayed greater FA and AD in the CC compared to age-matched controls. Moreover, FA and AD of the splenium were positively correlated with phonological awareness, alternate rapid naming, and alternate phonological awareness in typically developing controls but not individuals with DD. The current study also observes a positive correlation with print knowledge across groups, and AD of the splenium of the CC is the best predictor of subsequent print knowledge abilities.

The current study also has limitations. The first limitation being the relatively small sample of children with and without a familial risk of DD with follow-up data. The low number of participants does not reflect attrition but rather that the study is ongoing, and a significant percentage of infants have not yet turned four-years-old. Another limitation is that the current study has imaging data from only one-time point. Future studies are needed with multiple imaging time points such that the developmental trajectories of at-risk infants of DD can be elucidated. Furthermore, future studies are needed to determine whether atypicalities in the left AF and splenium are specific to DD or whether they may be predictive of neurodevelopmental disorders in general. One last limitation is that AFQ software only tracks the anterior and posterior regions of the CC, and thus, one cannot speculate about groups differences in central regions of the CC, such as the body. Prior research has suggested that individuals with DD may differ from controls in the body of the CC (Fine et al., 2007; Dougherty et al., 2007; Hasan et al., 2012). Future studies are needed to determine whether the body of the CC is associated with reading and reading-related skills in infants and preschoolers.

In summary, the current study observes differences in white matter microstructure between infants with and without a familial risk of DD in two neural tracts implicated in reading: the left AF and the splenium of the CC. Furthermore, FA and RD of the left AF assessed in infancy predicted vocabulary skills in four-year-old children, and AD of the splenium of the CC assessed in infancy predicted print knowledge skills in four-year-old children. Interestingly, diffusivity measures were the sole predictor variable in regression models predicting vocabulary and print knowledge illustrating the importance of neuroanatomical information in pre-reading skills.

Experiment 2: Evidence that White Matter Microstructure is Correlated with Neural Activation: Phonological Processing in Preschoolers With and Without a Familial Risk of Developmental Dyslexia

Introduction

Children and adults with DD differ in terms of both white matter microstructure and neural activity compared to typically developing peers (Temple et al., 2001; Shaywitz et al., 2002; Fine et al., 2007; Hoeft et al., 2007; Frye et al., 2008; Odegard et al., 2009; Rimrodt et al., 2010; Richlan et al., 2009; Richlan et al, 2011; Hasan et al., 2012; Richlan et al., 2013). The left AF is implicated in reading and reading related tasks including phonological processing, reading fluency, speech production, language comprehension, and speech repetition (Fridriksson et al., 2013; Rauschecker et al., 2009). FA of the left AF has been shown to correlate with phonological awareness in school-age children (Yeatman et al., 2011). Additionally, the volume of the left AF has been shown to correlate with phonological awareness in kindergarteners (Saygin et al., 2013). Furthermore, intraoperative subcortical stimulation of the left AF in adults also resulted in phonemic paraphasias (i.e., incorrect substitution of phonemes) (Duffau et al., 2002), and stroke patients with lesions in the left AF also experience phonological deficits (Rolheiser et al., 2011).

The CC has also been implicated in phonological processing (Frye et al., 2008). Frye and colleagues (2008) observed increased FA and AD of the splenium of the CC in adults with DD compared to age-matched controls. They observed a positive correlation between measures of phonological awareness and FA and AD of the splenium in typically developing adults but not patients with DD. The authors note that although the correlations between diffusion measures and measures of phonological awareness were not observed in the DD group, diffusion measures on average were greater in the DD group. The lack of correlation between diffusivity measures of the splenium of the CC and phonological awareness measures in adults with DD may be due to the fact that microstructure values were at ceiling in adults with DD, possibly due to a compensatory interhemispheric pathway.

Recent research has similarly shown that infants and preschoolers with a familial risk of DD differ from typically developing peers in both brain structure and function prior to learning to read (Raschle et al., 2011; Raschle et al., 2012; Saygin et al., 2013; Raschle et al., 2014; Vandermosten et al., 2015; Langer et al., 2015; Wang et al., 2016). Despite ample prior research, it remains unclear how white matter microstructure of the left AF and splenium of the CC relates to the blood-oxygen-level dependent signal, during phonological processing, which is predictive of later reading.

Magnetic resonance imaging studies of preschoolers and kindergarteners at-risk of developmental dyslexia. Previously, our lab has shown that preschoolers with a familial risk of DD (N=10) display reduced cortical grey matter in a number of regions implicated in reading compared to preschoolers without a family history of DD (N=10) (Raschle et al., 2011). In subsequent experiments, our lab has shown that preschoolers with a familial risk of DD display an altered pattern of fMRI neural activity during phonological and rapid auditory processing tasks which was similar to children and adults with a diagnosis of DD (Raschle, et al., 2012; Raschle et al., 2014). Specifically, during an alliteration task neural activity was recorded via fMRI (Raschle et al., 2012). Preschoolers with a familial risk of DD displayed reduced neural activation in bilateral occipitotemporal and left temporoparietal regions compared to children without a familial risk of DD. Furthermore, left occipitotemporal and temporoparietal regional activity positively correlated with phonological processing skills assessed behaviorally (Raschle et al., 2012).

In contrast, a recent longitudinal study examined the development of the reading network in kindergarten (Yamada et al., 2011). Kindergarteners were classified as either on-track (N=7) or at-risk of later reading difficulties (N=7) based on standard school screenings. Participants completed a one-back fMRI task with letter and letter-like stimuli. At-risk children displayed less activity in bilateral temporoparietal regions than on-track children. However, after just three months of reading instruction, on-track children displayed left lateralized activation in the temporoparietal region. In contrast, at-risk children displayed bilateral activity in the temporoparietal region along with recruitment of frontal regions. This study suggests that typical reading development is characterized by the initial engagement of bilateral structures followed by left lateralization whereas atypical reading development is associated with the recruitment of bilateral frontal regions.

A recent DWI study sheds light on the timing of the growth of three neural tracts implicated in reading (Wang et al., 2016). They examined the neural basis of reading development in pre-readers, beginning readers, and fluent readers cross-sectionally and longitudinally in children with and without a familial risk of DD. AFQ was employed to assess FA of left AF, left inferior longitudinal fasciculus, and the left superior longitudinal fasciculus (Yeatman et al., 2012). AFQ assesses FA at multiple regions along a tract rather than providing a summary average measure of FA. Wang et al. 2016's cross-sectional cohort consisted of 78 children (45 children with a familial risk of DD) divided among three groups: children who recognized fewer than nine single words were classified as pre-readers, kindergarteners through grade two were classified as early readers, and children in third, fourth, and fifth grade were classified as fluent readers. Of the 78 children, only 45 children (22 with a familial risk of DD) had more than one imaging time point and thus composed the longitudinal cohort.

Pre-readers, beginning readers, and fluent readers with a familial risk of DD displayed reduced FA of the left AF. In contrast, no group differences were seen in the left inferior longitudinal fasciculus during the pre-reading stage. However, during the early reading and fluent reading stages, children without a familial risk of DD displayed greater FA in the left inferior longitudinal fasciculus than children at familial risk of DD. In contrast, children without a familial risk of DD displayed greater FA in the left superior longitudinal fasciculus than at-risk children during the pre-reading and beginning reading stages; no group differences were observed during the fluent reading stage. Children with a familial risk of DD also displayed a right lateralization of the FA of the AF during the pre-reading and beginning reading stages, whereas children without a familial risk of DD displayed left lateralization. No group differences were observed during the fluent reading stage in the left AF or at any stage of reading in the left inferior longitudinal fasciculus or left superior longitudinal fasciculus.

Wang et al. (2016) examined the rate of white matter development of the left AF and left inferior longitudinal fasciculus and found a positive correlation irrespective of group membership. This suggests that maturation of white matter pathways plays a crucial role in both typical and atypical reading development. In fact, combining familial risk status, mean FA-development rate of the left AF and left superior longitudinal fasciculus, rapid automatized naming: Objects standard score, and KBIT-2 nonverbal intelligence standard score accounted for 56% of the variance in reading comprehension. Furthermore, FA-development rate of the left superior longitudinal fasciculus, rapid automatized naming: Objects standard score, and KBIT-2 nonverbal intelligence standard score, and family history accounted for 62% of the variance in reading fluency. Of the three neural tracts investigated it appears that the left longitudinal fasciculus was driving the effect. This was somewhat surprising since the left AF has repeatedly shown to correlate with reading and reading-related skills in children and adults (Vandermosten et al., 2012; de Schotten et al., 2012; Gullick & Booth, 2015). Interestingly, a subset of children with familial risk of DD who subsequently developed into good readers displayed a faster rate of white matter development in the right superior longitudinal fasciculus suggesting a potential right hemisphere compensatory mechanism.

The aim of the current study is to examine the relationship between neural activity during a phonological processing task assessed via fMRI and white matter microstructure in the left AF and splenium of the CC assessed via DWI. AFQ was employed to segment the left AF and CC. AFQ segments the forceps major of the CC, which connects homologous regions of the occipital lobe via the splenium, rather than segmenting the splenium separately (Yeatmen et al., 2012). For simplicity and to mirror the prior literature, the forceps major of the CC will be referred to as the splenium of the CC.

Methods

Participants. Forty-two children (21 children with and 21 children without a familial risk of DD) with a mean age of 69.95 months with fMRI and DWI data were selected from the Boston Longitudinal Study of Dyslexia. Children were classified as having a family history of DD (*n*=21): a first-degree relative with DD (*n*=19), a second-degree relative with DD (*n*=1), or a first-degree relative with history of reading difficulties (*n*=1). Children were classified as not having a family history of DD (*n*=21) if they had no relatives with a diagnosis of DD or history of reading problems. Eighteen males (10 with and 8 without a familial risk of DD) participated in the study. Thirty-six children were classified as right handed (17 with and 19 without a familial risk of DD). Six children were classified as left handed (4 with and 2 without a familial risk of DD. Informed consent was obtained from the child's legal guardian and assent was obtained from the child. Parents also completed a series of questionnaires assessing perinatal and early development, socioeconomic status (SES), and home literacy. Children were matched for age, sex, and SES. All children were born on or after 37 weeks' gestation and had no history of neurological disease or trauma, nor any reported vision or hearing difficulties.

Behavioral assessment. Children completed a cognitive-linguistic assessment, including KBIT-2 nonverbal intelligence, Woodcock Reading Mastery Tests (WRMT) letter identification, WRMT word identification, Rapid Automatized Naming and Rapid Alternating Stimulus (RAN/RAS) objects, RAN/RAS colors, Comprehensive Test of Phonological Processing (CTOPP) elision, CTOPP blending, CTOPP nonword repetition, Clinial Evaluation of Language Fundamentals (CELF) core language, CELF expressive language, CELF receptive language, and CELF language structure.

fMRI task procedure. Phonological processing was assessed via a block design, and was previously reported in Raschle et al. 2012. Children were presented sequentially with two common object words during the experimental task in either a male or female voice. Pictures of the objects were presented simultaneously. During an alliteration task, children were asked to indicate via button-press whether or not the words began with the same initial sound. The control task also presented children with two common object words presented sequentially in either a male or female voice. Children were presented with pictures of the objects simultaneously. Here, children were asked to indicate via button-press whether or not the words were spoken by the same or different voice. A diagram of the fMRI task is presented in Figure 2.1.

Figure 2.1. fMRI Task Design. During the experimental task, fist sound matching, participants were presented with two words aurally and visually. Children indicated via button-press whether the two words began with the same initial sound (Raschle et al, 2012, p. S2).

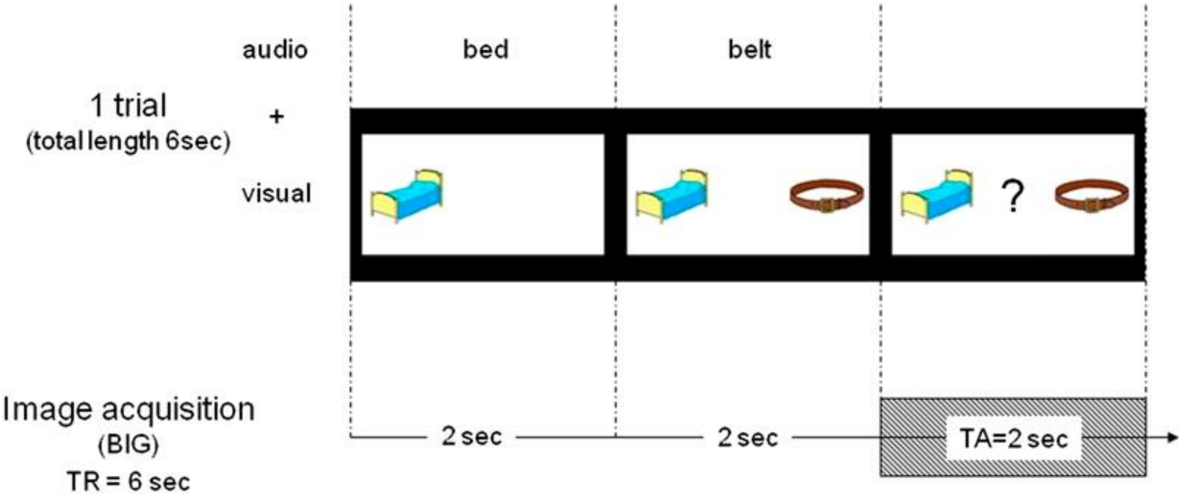


Image acquisition. The functional image acquisition parameters were previously reported in Raschle et al., 2012. For both the experimental and control tasks, 56 functional whole-brain images were acquired with a 32-slice EPI interleaved acquisition via a SIMENS 3T Trio whole-body MRI scanner with the following imaging parameters: TR: 6,000 ms; TA: 1,995 ms; TE: 30 ms; flip angle: 90^{o}; field of view (FOV): 256 mm; voxel size: 3 x 3 x 4 mm; slice thickness: 4 mm. Prior to the first block, additional functional images were obtained and later discarded to allow for T1 equilibration. Stimuli were presented via Presentation software (Version 0.70, www.neurobs.com). Prior to completing fMRI tasks, children completed a 60 min preparation session in a mock scanner.

The structural image acquisition parameters were previously reported in Wang et al., 2016. Scans were acquired with a 3.0 Tesla SIEMENS Trio Tim whole-body MRI scanner utilizing multi-echo magnetization-prepared rapid gradient echo sequences with prospective motion correction (mocoMEMPRAGE) for structural T1-weighted images and echo planar image (EPI) sequence of 30 gradient directions for DWI via a 12-channel radio frequency head coil. The following structural MRI imaging parameters were used: flip angle: 7 degrees; TE: 1450 ms; TA: 2270 ms; TA: 4:51 min; field of view (FOV) = 220 x 220 mm; in-plan acceleration (GRAPPA) factor of 2; spatial resolution = 1.1 x 1.11 x 1.0 mm (176 slices). The DWI parameters were: flip angle: 90 degrees; TE: 88 ms; TR: 8320 ms; TA: 5:59 min; FOV: 256 x 256 mm; b = 1000 s/mm^2.

Image processing. T1 images underwent preprocessing in the VBM8 toolbox (http://www.fil.ion.ucl.ac.uk/spm/) of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Images were segmented into gray matter, white matter, and cerebral spinal fluid using an adaptive Maximum A Posterior approach (Rajapakse et al. 1997). Segmented images were then affine transferred from native space from Montreal Neurological Institute (MNI) space based on age- and sex-matched Tissue Probability Maps generated by the Template-O-Matic toolbox (Wilke et al., 2008). A diffemorphic anatomical registration using exponentiated lie algebra (DARTEL) approach was implemented to normalize the affine-registered gray matter and white matter through six iterations of high dimensional warping processes via nonlinear registration (Ashburner, 2007). Pediatric DARTEL templates were utilized during DARTEL normalization, which were created based on the structural images of 149 children with a similar age and sex ratio. Following DARTEL registration, the deformation fields, which record transformational matrices from the native space to the MNI space, were saved for each structural image.

Prior to statistical modeling, a rigorous procedure was implemented to reduce motion artifact using the Artifact detection tool (http://www.nitrc.org/projects/artifact_detect). Images with excessive head motion were automatically selected with a translational threshold of 3 mm and/or a rotation threshold of 0.05 mm. The remaining images were then visually inspected for motion allowing for images with missing voxels, stripes, ghosting, or intensity differences to be identified and discarded.

The general linear model was implemented to assess the fixed-effects within each participant. Experimental regressors were implemented: first sound matching, voice matching, and rest were modeled in a block-design and were entered into the general linear model with run effect and an intercept term with as nuisance covariates. Motion regressors were also included in the model to regress out outlier images and partial out the overall motion effect. A default value of a high-pass filter of 128 seconds was also included to remove confounding influences of the BOLD signal due to physiological noise from cardiac and respiratory cycles. Contrast maps for the experimental > control (i.e., first sound matching > voice matching) were built and computed for each participant. Second-level *t*-tests were computed to assess neuronal changes underlying phonological processing.

During functional imaging preprocessing, the initial volumes were removed from each run to allow for T1 equilibration effects. The remaining images were spatially realigned to the first image and coregistered to the corresponding structural images. Deformation fields generated via the DARTEL wrapping process were applied to normalize the functional images to MNI space, which were them smoothed using a Gaussian kernel with full-width at half maximum of eight mm.

Diffusion imaging processing was previously described in Wang et al., 2016. The T1-weighted structural image was used to generate a brain mask by removing non-brain tissue using the Brain Extraction Tool (BET) (Smith, 2002) from Functional MRI of the Brain (FMRIB) software library (Oxford, UK). DWI data were converted to NRRD (teem.sourceforge.net/nrrd/) format using DicomToNrrdConverter software from Slicer4 (www.slicer.org). DWI quality control procedures were implemented using DTIprep software (Liu et al., 2010) along with visual inspection. Motion artifacts were defined by a translation threshold of 2 mm and rotation threshold of 0.5 degrees through rigid registration-based volume-by-volume measures. Volumes with motion artifacts were excluded from diffusion tensor estimation. Following quality control, DWI data were processed using mrDiffusion, a toolbox from the VISTALab (Standford Vision and Imaging Science and Technology) diffusion MRI software suite (www.vistalab.com) including eddy-current correction and tensor-fitting estimation (Rohde et al., 2004).

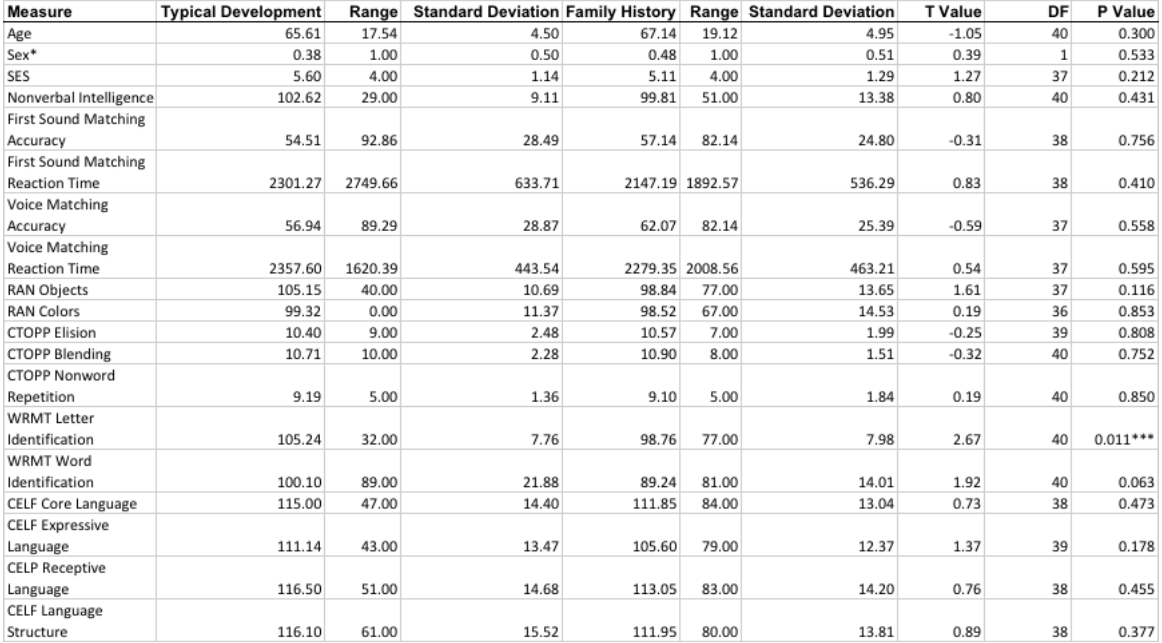
Automated fiber quantification. AFQ (https://github.com/jyeatman/AFQ) was implemented to segment the left AF and splenium of the CC (Yeatmen et al., 2012). AFQ employed the following procedure: 1. whole-brain tractography with a deterministic streamlines tracking algorithm (Mori et al., 1999; Basser et al., 2000) with an FA threshold of 0.2 and angle threshold of 40 degrees; 2. region-of-interest-based fiber-tract segmentation; 3. fiber-tract “cleaning” via a statistical outlier rejection algorithm; 4. diffusion quantification at each node throughout the tract. AFQ segmented tracts into 100 equidistant units along the trajectory of the tract rather than calculating mean diffusion across an entire tract, resulting in more precise localization of group differences (Yeatman et al., 2012). This method allowed us to calculate FA, RD, and AD across each tract and at each of the 100 nodes for each subject. For each tract of interest, 100 nodes along the tract were resampled to 50 nodes by discarding the portion of the fiber tract where individual fibers deviate from the core fascicle toward their destination in the brain. This approach normalized the fiber endpoints across participants and improves co-registration of each fiber tract (Yeatman et al., 2011; Wang et al., 2016).

Statistical analyses. Regions of interest (ROIs) analyses were performed to assess the relationship between neural activation during FSM and two neural tracts implicated in reading, left AF and splenium of the CC. Functional ROIs were obtained from Raschle et al., 2012 for the left superior temporal sulcus, left medial temporal gyrus, and lingual gyrus. Previously, these regions significantly differed between preschoolers with and without a familial risk of DD (Raschle et al., 2012). Pearson correlations were calculated between fMRI and DWI measures while controlling for age. *FDR* corrections were applied to control for multiple comparisons, and all reported significant results survived *FDR* correction (Yekutieli & Benjamini, 1999).

Results

Behavioral Results. Children with and without a familial risk of DD did not differ in terms of age (*t*=-1.05, df=40, p=.300, Cohen's d=.332), sex (χ^2=.39, df=1, p=.533, Cohen's d=.194), SES (*t*=1.27, df=37, p=.212, Cohen's d=.418), or KBIT-2 nonverbal intelligence (*t*=.80, df=40, p=.431, Cohen's d=.253, power=.14). Additionally, groups did not differ on in scanner performance: first sound matching accuracy (*t*=-.31, df=38, p=.756, Cohen's d=.101, power=.04), first sound matching reaction time (*t*=.83, df=38, p=.410, Cohen's d=.269, power=.17), voice matching accuracy (*t*=-.59, df=37, p=.558, Cohen's d=.194, power=.08), voice matching reaction time (*t*=.54, df=37, p=.595, Cohen's d=.178, power=.08). Children with a familial risk displayed reduced WRMT letter identification (*t*=2.67, df=40, p=.011, Cohen's d=.844, power=.68) compared to controls. Groups did not differ in terms of RAN/RAS objects (*t*=1.61, df=37, p=.116, Cohen's d=.381, power=.34) RAN/RAS colors (*t*=.19, df=36, p=.853, Cohen's d=.063, power=.02), CTOPP elision (*t*=-.25, df=39, p=.808, Cohen's d=.080, power=.05), CTOPP blending (*t*=-.32, df=40, p=.752, Cohen's d=.101, power=..05), CTOPP nonword repetition (*t*=.19, df=40, p=.850, Cohen's d=.060, power=.02), WRMT word identification (*t*=1.92, df=40, p=.063, Cohen's d=.607, power=.47), CELF core language (*t*=.73, df=38, p=.473, Cohen's d=.237, power=.10), CELF expressive language (*t*=1.37, df=39, p=.178, Cohen's d=.439, power=.23), CELF receptive language (*t*=.76, df=38, p=.455, Cohen's d=.247, power=.15), and CELF language structure (*t*=.89, df=38, p=.377, Cohen's d=.289, power=.13). See Table 2.1 for further information.

Table 2.1. Demographic and Psychometric Results.



Measure	Typical Development	Range	Standard Deviation	Family History	Range	Standard Deviation	T Value	DF	P Value
Age	65.61	17.54	4.50	67.14	19.12	4.95	-1.05	40	0.300
Sex*	0.38	1.00	0.50	0.48	1.00	0.51	0.39	1	0.533
SES	5.60	4.00	1.14	5.11	4.00	1.29	1.27	37	0.212
Nonverbal Intelligence	102.62	29.00	9.11	99.81	51.00	13.38	0.80	40	0.431
First Sound Matching Accuracy	54.51	92.86	28.49	57.14	82.14	24.80	-0.31	38	0.756
First Sound Matching Reaction Time	2301.27	2749.66	633.71	2147.19	1892.57	536.29	0.83	38	0.410
Voice Matching Accuracy	56.94	89.29	28.87	62.07	82.14	25.39	-0.59	37	0.558
Voice Matching Reaction Time	2357.60	1620.39	443.54	2279.35	2008.56	463.21	0.54	37	0.595
RAN Objects	105.15	40.00	10.69	98.84	77.00	13.65	1.61	37	0.116
RAN Colors	99.32	0.00	11.37	98.52	67.00	14.53	0.19	36	0.853
CTOPP Elision	10.40	9.00	2.48	10.57	7.00	1.99	-0.25	39	0.808
CTOPP Blending	10.71	10.00	2.28	10.90	8.00	1.51	-0.32	40	0.752
CTOPP Nonword Repetition	9.19	5.00	1.36	9.10	5.00	1.84	0.19	40	0.850
WRMT Letter Identification	105.24	32.00	7.76	98.76	77.00	7.98	2.67	40	0.011***
WRMT Word Identification	100.10	89.00	21.88	89.24	81.00	14.01	1.92	40	0.063
CELF Core Language	115.00	47.00	14.40	111.85	84.00	13.04	0.73	38	0.473
CELF Expressive Language	111.14	43.00	13.47	105.60	79.00	12.37	1.37	39	0.178
CELP Receptive Language	116.50	51.00	14.68	113.05	83.00	14.20	0.76	38	0.455
CELF Language Structure	116.10	61.00	15.52	111.95	80.00	13.81	0.89	38	0.377

*Since sex is a dichotomus variable, chi square analysis is reported.

Neuroimaging Results. Preschoolers with a familial risk of DD displayed hypoactivation during phonological processing in the cerebellum, left temporoparietal, and bilateral occipitotemporal areas (Figure 2.2). FA of the left AF was positively correlated with left medial temporal gyrus (Figure 2.3) and left lingual gyrus (Figure 2.5) activity during phonological processing across groups. FA of the splenium of the CC was positively correlated with left medial temporal gyrus (Figure 2.4) and left lingual gyrus (Figure 2.6) activity during phonological processing across groups.

Figure 2.2. Group Differences during Phonological Processing. First Sound Matching > Voice Matching. Preschools without a familial risk of DD display greater neural activity in left temporoparietal, bilateral occipitotemproal, and cerebellum compared to controls. (p<.005, uncorrected).

Figure 2.3. FA of the left AF is positively correlated with left medial temporal gyral activation during phonological processing. Children with a familial risk of DD (FHD+) are displayed in red and children without a familial risk of DD (FHD-) are displayed in blue.

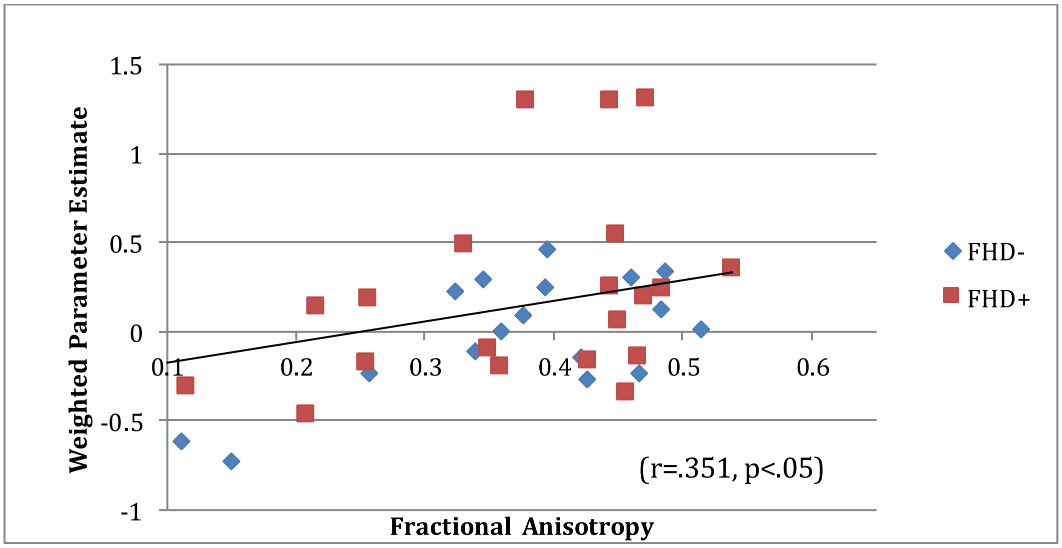


Figure 2.4. FA of the splenium of the CC is positively correlated with left medial temporal gyral activation during phonological processing. Children with a familial risk of DD (FHD+) are displayed in red and children without a familial risk of DD (FHD-) are displayed in blue.

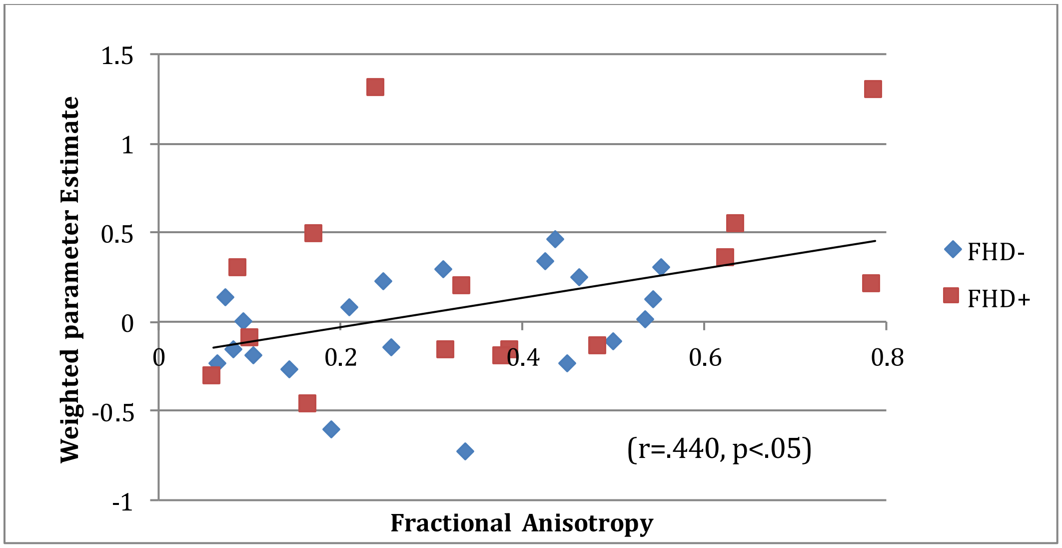


Figure 2.5. FA of the left AF is positively correlated with left lingual gyral activation during phonological processing. Children with a familial risk of DD (FHD+) are displayed in red and children without a familial risk of DD (FHD-) are displayed in blue.

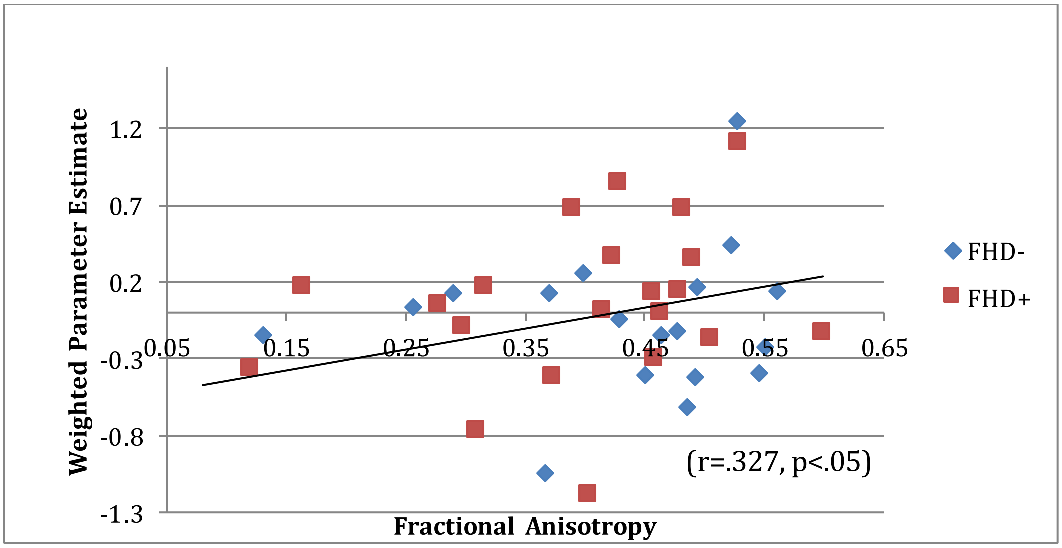
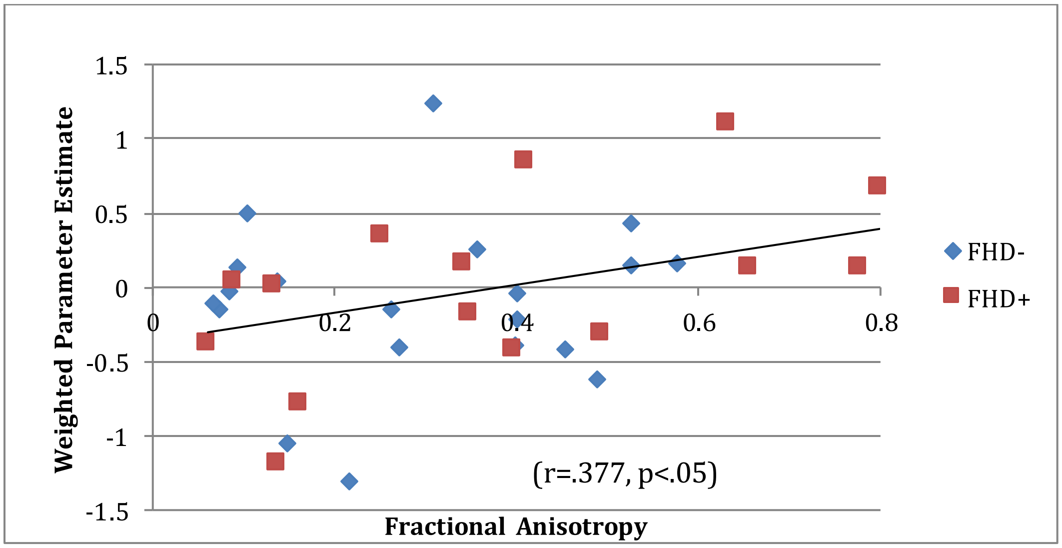


Figure 2.6. FA of the splenium of the CC is positively correlated with left lingual gyral activation during phonological processing**.** Children with a familial risk of DD (FHD+) are displayed in red and children without a familial risk of DD (FHD-) are displayed in blue.



Discussion

The aim of the current study was to assess whether the neural correlates of phonological processing are associated with white matter microstructure of the left AF and splenium of the CC. It was observed that neural activity in left medial temporal gyrus and left lingual gyrus during a phonological processing task was positively correlated with FA of the left AF and the splenium of the CC.

Raschle and colleagues (2012) previously observed preschoolers at-risk of DD displayed reduced neural activation in bilateral occipitotemporal, left temporoparietal and cerebellar regions compared to children without a familial risk of DD during an alliteration task. Furthermore, left occipitotemporal and left temporoparietal regional activity positively correlated with phonological processing skills assessed behaviorally. The current investigation replicates these findings in a different sample of children.

The left AF was positively correlated with the left medial temporal gyrus and the left lingual gyrus activity during phonological processing. Previous research has implicated the left AF in phonological processing (Duffau et al., 2002; Rolheiser et al., 2011; Fridriksson et al., 2013). Individuals who suffered a stroke in the left AF exhibited phonological deficits (Rolheiser et al., 2011). Furthermore, intraoperative subcortical stimulation of the left AF in adults resulted in phonemic paraphasias (i.e., incorrect substitution of phonemes) (Duffau et al., 2002).

The splenium of the CC was positively correlated with the left medial temporal gyrus and the left lingual gyrus activity during phonological processing. Prior studies have implicated the CC in phonological processing (Temple et al., 1989; Dougherty et al., 2007; Frye et al., 2008). Case studies of children with callosal agenesis report that even patients with normal intelligence display specific deficits in in rhyming tasks (Temple et al., 1989). Furthermore, prior research has indicated that the CC is positively correlated with measures of phonological awareness (Dougherty et al., 2007). Frye and colleagues (2008) also observed a positive correlation between measures of phonological awareness and FA and AD of the splenium in typically developing adults but not patients with DD. The authors note that although the correlations between diffusion measures and measures of phonological awareness were not observed in the DD group, diffusion measures on average were greater in the DD group. The lack of correlation between diffusivity measures of the splenium of the CC and phonological awareness measures in adults with DD may be due to the fact that microstructure values are at ceiling in adults with DD, possibly due to a compensatory interhemispheric pathway.

The current study also has limitations. The first limitation is the relatively small sample of children with and without a familial risk of DD. The sample size may not have had enough power to identify group differences between children with and without a familial risk of DD. Furthermore, another limitation is that AFQ software only tracks the anterior and posterior regions of the CC, and thus, one cannot speculate about groups differences in central regions of the CC, such as the body. Prior research has suggested that individuals with DD may differ from controls in the body of the CC (Fine et al., 2007; Dougherty et al., 2007; Hasan et al., 2012). Future studies are needed to determine whether the body of the CC is associated with reading and reading-related skills in infants and preschoolers.

In summary, the current study established that measures of white matter microstructure of the left AF and the splenium of the CC are associated with neural activity during phonological processing in brain areas implicated in reading and reading-related skills.

Experiment 3: White Matter Connectivity of Corpus Callosum Assessed in Preschool Predicts Reading Fluency in School-Age Children at Risk of Developmental Dyslexia

Introduction

Reading fluency, the ability to read accurately and at a rate that enables comprehension is crucial for skilled reading (Wolf & Katzir-Cohen, 2001; Christodoulou et al., 2013). Reading fluency deficits, such as slow and/or inaccurate text reading, are persistent and widespread in both adolescents and adults with a history of DD among those who have received intervention (Leinonen et al., 2001; Ziegler et al., 2003). In contrast to efficacious interventions targeting phonological decoding dysfluent reading is particularly challenging to remediate (Torgesen et al., 2001; Torgesen & Hudson, 2006). In particular, beyond elementary school, attempts to improve fluency deficits in individuals with DD tend to produce only minimal improvement (Wexler et al., 2008). Furthermore, fluency deficits in DD are not restrictive to the English language but rather play a prominent role across languages (Ziegler et al., 2003; Katzir et al., 2004). Despite the breadth of evidence that reading fluency is crucial for efficient reading and that fluency remains a severe problem in adolescents and adults with a history of DD, there is little research investigating the neural structures critical for fluent reading as it relates to particular structural abnormalities of the CC in adults and children with DD.

Neuroimaging studies of reading fluency. In 2013, Christodoulou et al. compared the neural correlates of reading fluency in adults with and without DD. An fMRI sentence reading paradigm was employed that varied fluency demands by increasing the rate at which sentences were presented while participants made semantic plausibility judgments. Readers with DD were slower and less accurate than their typically developing counterparts. Furthermore, readers with DD's accuracy declined disproportionately as rates increased. A large bilateral network of cortical, subcortical, and cerebellar systems was activated across groups. Readers with DD showed less of an increase in activity, as a function of reading rate, in the left prefrontal and left superior temporal cortices, anterior cingulate, and brainstem/cerebellar areas than typically developing readers.

A recent fMRI study compared reading fluency in typically developing and children with DD between 8 and 13 years-of-age (Langer et al., 2013). Of note, the authors define reading fluency as reading speed with accurate comprehension and not reading accuracy (i.e., participants did not read aloud). The rate of the comfortable reading speed was individually determined prior to fMRI testing by using a computer program to time participants read three paragraphs silently. After completing the paragraph, participants were asked comprehension questions to ensure they completed the reading with care. Each child's accelerated reading speed was calculated by multiplying his comfortable reading speed by 35%. Children also completed a "slow" condition in which stimulus duration was fixed (1350 ms). The fMRI task required children to match an image following the presentation of a sentence at varying speeds. The control task consisted of word-like groups of the letter “n” along with one oddball letter (either “f,” “p,” or “x”). The target oddball letter was always displayed in one of the last two groups of the letter “n” of the sentence to ensure all letters were viewed. Readers with typical development displayed increased activation in reading network components such as the fusiform gyrus during all reading contrasts compared to rest. Interestingly, children with DD utilize the same network (i.e., the fusiform gyrus) during fluent reading as their typically developing peers but to a lesser extent. During the comfortable reading speed condition, children with typical development displayed increased activity in temporoparietal and frontal regions compared to their peers with DD. During the accelerated reading condition, children with typical development displayed increased neural activity in multiple components of the reading network, which was absent in children with DD. The authors suggest that since multiple components of the reading network are recruited during fluent reading, interventions to improve reading fluency skills should target all aspects of reading rather than solely focusing on repetition of sentence reading.

In 2013, Lebel et al. explored the relationship between reading fluency of extended text and white matter connectivity in healthy adolescents and young adults with a wide range of reading abilities. Using voxel-based DWI, they observed significant positive correlations between the reading fluency subtest of the Gray Oral Reading Test (GORT-5) and FA of the right and middle of the cerebellum, left thalamus, right anterior limb of the internal capsule, bilateral superior longitudinal fasciculi, anterior CC, corona radiate, and the splenium of the CC. The wide spread neural structures associated with reading fluency extend beyond the left temporoparietal and left thalamus, which suggest that the right hemisphere may also be involved in fluency tasks. Unfortunately, Lebel and colleagues (2013) only reported correlations with FA making it difficult to interpret the biological mechanism implicated in the association with reading fluency.

One prior study examined differences in the volume and area of the CC between family members with DD compared to better readers of the same family (Fine et al., 2007). Regression analyses revealed that total CC volume, intelligence, and gender predicted 23% of the variance in reading achievement (a composite measure of GORT-5 reading fluency and accuracy). Segmentation of the CC suggested that the midbody of the CC uniquely predicted both reading fluency and accuracy. A limitation of the study is the relative small number of participants with DD (12 children and 3 adults of a sample of 68 participants). Furthermore, only reporting volumetric differences between family members with DD and typical readers makes it difficult to speculate the underlying biological mechanism driving the effect.

The corpus callosum and reading. The CC is a neural pathway that is often implicated in DD or characterized as a neural region which improves DD. It has been argued that those with DD may utilize some component(s) of the CC as a compensatory mechanism which in turn recruits right hemisphere homologs during reading and reading-related tasks (Rumsey et al., 1996; Klingberg et al., 2000; Dougherty et al., 2007; Niogi & McCandaliss, 2006; Hoeft et al., 2011). The best support for this notion is that posterior regions of the CC, such as the splenium, display greater FA values in adults and children with DD than typically developing controls (Frye et al., 2008; Odegard et al., 2009; Vandermosten et al., 2012; Hasan et al., 2012). Frye and colleagues (2008) observed increased FA and AD of the splenium of the CC in adults with DD compared to age-matched controls. They also observed a negative correlation between FA and AD of splenium of the CC and measures of letter-word identification in both adults with DD and controls. In children and adults with DD, abnormal organization of the splenium of the CC may reflect reduced connectivity between ventral occipital areas through occipital interhemispheric callosal fibers, which in turn would result in greater lateralization of orthographic processing. In contrast, they observed a positive correlation between measures of phonological awareness and FA and AD of the splenium in typically developing adults but not children and adults with DD. The authors note that although the correlations between diffusion measures and measures of phonological awareness were not observed in the DD group, diffusion measures on average were greater in the DD group. The lack of correlation between diffusivity measures of the splenium of the CC and phonological awareness measures in adults with DD may be due to the fact that microstructure values are at ceiling in adults with DD, possibly due to a compensatory interhemispheric pathway.

Hasan and colleagues (2012) also reported that compared to controls, children and adolescents between 10.5 and 16 years with DD display increased FA in the posterior aspect of the CC. However, they observed that FA of the posterior midbody of the CC and not the splenium was negatively correlated with measures of single word reading and reading comprehension. The authors argue that increases in myelination and/or axial integrity within the posterior midbody regions of the CC may enhance interhemispheric communication, which may reflect greater compensatory mechanisms in children and adults with DD.

Dougherty et al. (2007) assessed the relationship between diffusivity measures of splenium and measures of phonological awareness in children between 7-12 years with a wide range of reading abilities. FA of the splenium was negatively correlated with phonological awareness and RD of the splenium was positively correlated with phonological awareness. Since RD is thought to reflect myelination, one plausible explanation is that good readers have a greater proportion of large diameter axons than poor readers in posterior sections of the CC. In contrast, Odegard and colleagues (2009) observed that measures of real word and pseudoword decoding were negatively correlated with FA of the posterior CC in 10-14 year-old children with DD and typically developing controls.

The CC has repeatedly been implicated in reading and reading-related skills, but the direction of these relationships have been quite variable. The aim of the current study is to investigate the relationship between white matter connectivity of the splenium of the CC in preschool and reading fluency assessed in school-age children with and without a familial risk of DD. AFQ was employed to segment the CC. AFQ segments the forceps major of the CC, which connects homologous regions of the occipital lobe via the splenium, rather than segmenting the splenium separately (Yeatmen et al., 2012). For simplicity and to mirror the prior literature, the forceps major of the CC will be referred to as the splenium of the CC. It is hypothesized that children with a familial risk of DD will differ in diffusivity measures of the splenium of the CC compared to children without a familial risk of DD. Furthermore, diffusivity measures of the splenium of the CC will predict reading fluency skills in school-age children irrespective of group status.

Methods

Participants. Twenty-four preschoolers (13 with and 11 without a familial risk of DD) with a mean age of 66.02 months with DWI and reading fluency data were selected from the Boston Longitudinal Study of Dyslexia. Children were classified as having a family history of DD (*n*=13): a first-degree relative with DD (*n*=11), a second-degree relative with DD (*n*=2). Children were classified as not having a family history of DD (*n*=11) if they had no relatives with a diagnosis of DD or history of reading problems. Eleven males (5 with and 6 without a familial risk of DD) participated in the study. Twenty-one children were classified as right handed (11 with and 10 without a familial risk of DD). Three children were classified as left handed (2 with and 1 without a familial risk of DD). Informed consent was obtained from the child's legal guardian and assent was obtained from the child. Parents also completed a series of questionnaires assessing perinatal and early development, socioeconomic status (SES), and home literacy. Children were matched for age, sex, and SES. All children were born on or after 37 weeks' gestation and had no history of neurological disease or trauma, nor did they report vision or hearing difficulties. Children completed follow-up cognitive-linguistic testing at school-age, approximately two years later (mean age of 90.75 months).

Behavioral assessment. During children's initial visit, they completed a cognitive-linguistic assessment: KBIT-2 nonverbal intelligence, WRMT letter identification, WRMT word identification, RAN/RAS objects, RAN/RAS colors, CTOPP elision, CTOPP blending, CTOPP nonword repetition, CELF core language, CELF expressive language, CELF receptive language, and CELF language structure. Children's reading fluency and reading comprehension skills were measured during their follow-up visit, approximately two years later via the GORT-5.

Image acquisition. The image acquisition parameters were previously reported in Wang et al., 2016. Scans were acquired with a 3.0 Tesla SIEMENS Trio Tim whole-body MRI scanner utilizing multi-echo magnetization-prepared rapid gradient echo sequences with prospective motion correction (mocoMEMPRAGE) for structural T1-weighted images and echo planar image (EPI) sequence of 30 gradient directions for DWI via a 12-channel radio frequency head coil. The following structural MRI imaging parameters were used: flip angle: 7 degrees; TE: 1450 ms; TA: 2270 ms; TA: 4:51 min; field of view (FOV) = 220 x 220 mm; in-plan acceleration (GRAPPA) factor of 2; spatial resolution = 1.1 x 1.11 x 1.0 mm (176 slices). The DWI parameters were: flip angle: 90 degrees; TE: 88 ms; TR: 8320 ms; TA: 5:59 min; FOV: 256 x 256 mm; b = 1000 s/mm^2.

Image processing. Imaging processing was previously described in Wang et al., 2016. The T1-weighted structural image was used to generate a brain mask by removing non-brain tissue using the Brain Extraction Tool (BET) (Smith, 2002) from Functional MRI of the Brain (FMRIB) software library (Oxford, UK). DWI data were converted to NRRD (teem.sourceforge.net/nrrd/) format using DicomToNrrdConverter software from Slicer4 (www.slicer.org). DWI quality control procedures were implemented using DTIprep software (Liu et al., 2010) along with visual inspection. Motion artifacts were defined by a translation threshold of 2 mm and rotation threshold of 0.5 degrees through rigid registration-based volume-by-volume measures. Volumes with motion artifacts were excluded from diffusion tensor estimation. Following quality control, DWI data were processed using mrDiffusion, a toolbox from the VISTALab (Standford Vision and Imaging Science and Technology) diffusion MRI software suite (www.vistalab.com) including eddy-current correction and tensor-fitting estimation (Rohde et al., 2004).

Automated fiber quantification. AFQ (https://github.com/jyeatman/AFQ) were implemented to segment the splenium of the CC (Yeatmen et al., 2012).

AFQ employed the following procedure: 1. whole-brain tractography with a deterministic streamlines tracking algorithm (Mori et al., 1999; Basser et al., 2000) with an FA threshold of 0.2 and angle threshold of 40 degrees; 2. region-of-interest-based fiber-tract segmentation; 3. fiber-tract “cleaning” via a statistical outlier rejection algorithm; 4. diffusion quantification at each node throughout the tract. AFQ segmented tracts into 100 equidistant units along the trajectory of the tract rather than calculating mean diffusion across an entire tract, resulting in more precise localization of group differences (Yeatman et al., 2012). This method allowed us to calculate FA, RD, and AD across each tract and at each of the 100 nodes for each subject. For each tract of interest, 100 nodes along the tract were resampled to 50 nodes by discarding the portion of the fiber tract where individual fibers deviate from the core fascicle toward their destination in the brain. This approach normalized the fiber endpoints across participants and improves co-registration of each fiber tract (Yeatman et al., 2011; Wang et al., 2016).

Statistical analyses. Statistical analyses were executed in the programs R (version 3.1.0 64 bit) (Ihaka & Gentlemen, 1996) and Statistical Package for the Social Sciences (SPSS) (version 20) (IBM, 2011). Between-subjects’ ANOVAs were computed with age of child, SES, and sex as covariates, and diffusion values as the dependent measure. Familial risk of DD was the between-subjects’ variable.

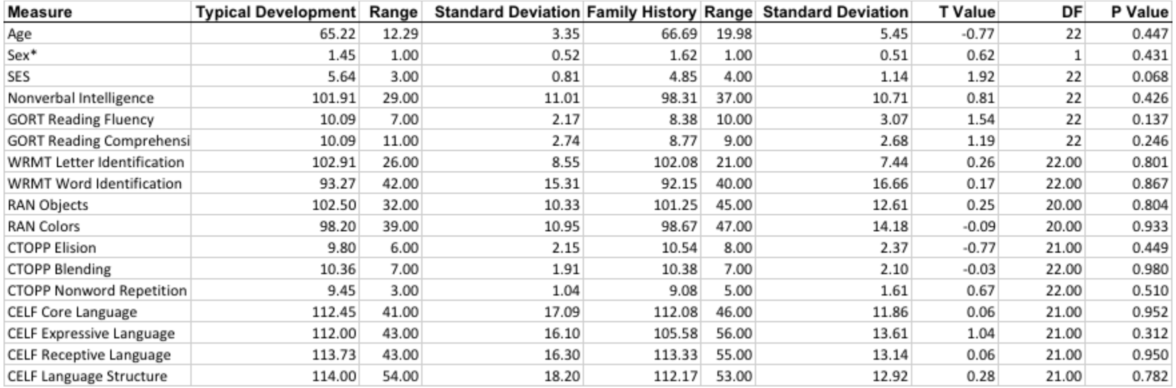
While controlling for age, sex, and SES, a series of partial correlations were run between the diffusion measures of the splenium of the CC and reading fluency and comprehension scores assessed at school-age in children with and without a familial risk of DD. Independent sample *t*-tests were also employed to explore mean differences between preschoolers with and without a family history of DD. *FDR* corrections were employed to control for the number of comparisons (Yekutieli & Benjamini, 1999).

Backward linear multiple regression analyses were also employed to assess the optimal set of predictors (i.e., family history, FA, AD and RD in the CC, nonverbal intelligence, and SES to predict reading fluency and reading comprehension assessed at school-age. Backward stepwise (likelihood ratio) logistic regression was also utilized to assess whether the aforementioned predictors could distinguish fluent and dysfluent readers. Children were classified as dysfluent readers if their GORT-5 reading fluency score was at or below the 25th percentile (which equates with a standard score of 8). Children were classified as fluent readers if their GORT-5 reading fluency score was at or above the 37th percentile (which equates with a standard score of 9).

Results

Behavioral results. Children with and without a familial risk of DD did not differ in terms of age (t=-.77, df=22, p=.447, Cohen's d=.328), sex (χ^2=.62, df=1, p=.431, Cohen's d=.326), SES as measured via maternal education (t=1.92, df=22, p=.068, Cohen's d=.819), or KBIT-2 nonverbal intelligence (t=.81, df=22, p=.426, Cohen’s d=.345, power=.13). Furthermore, children with and without a familial risk of DD did not differ in terms of WRMT letter identification (*t*=.26, df=22, p=.801, Cohen’s d=.111, power=.05), WRMT word identification (*t*=.17, df=22, p=.867, Cohen’s d=.072, power=.03), RAN/RAS objects (*t*=.25, df=20, p=.804, Cohen’s d=.112, power=.06), RAN/RAS colors (*t*=-.09, df=20, p=.933, Cohen’s d=.040, power=.04) CTOPP elision (*t*=-.77, df=21, p=.449, Cohen’s d=.336, power=.11), CTOPP blending (*t*=-.03, df=22, p=.980, Cohen’s d=.013, power=.02), CTOPP nonword repetition (*t*=.67, df=22, p=.510, Cohen’s d=.256, power=.20), CELF core langauge (*t*=.06, df=21, p=.952, Cohen’s d=.026, power=.02), CELF expressive language (*t*=1.04, df=21, p=.312, Cohen’s d=.454, power=.14), CELF receptive language (*t*=.06, df=21, p=.950, Cohen’s d=.026, power=.04), CELF language structure (*t*=.28, df=21, p=.782, Cohen’s d=.122, power=.05), GORT-5 reading fluency (*t*=1.54, df=22, p=.137, Cohen’s d=.657, power=.35) or GORT-5 reading comprehension (*t*=1.19, df=22, p=.246, Cohen’s d=.507, power=.12) assessed via the GORT-5 at follow-up. See Table 3.1 for further information.

Table 3.1. At-Risk Readers' Demographic and Psychometric Results.

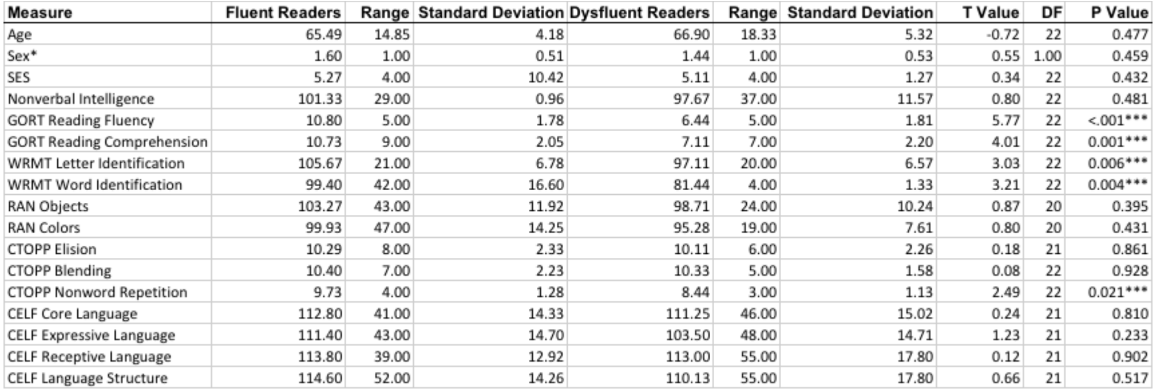


Measure	Typical Development	Range	Standard Deviation	Family History	Range	Standard Deviation	T Value	DF	P Value
Age	65.22	12.29	3.35	66.69	19.98	5.45	-0.77	22	0.447
Sex*	1.45	1.00	0.52	1.62	1.00	0.51	0.62	1	0.431
SES	5.64	3.00	0.81	4.85	4.00	1.14	1.92	22	0.068
Nonverbal Intelligence	101.91	29.00	11.01	98.31	37.00	10.71	0.81	22	0.426
GORT Reading Fluency	10.09	7.00	2.17	8.38	10.00	3.07	1.54	22	0.137
GORT Reading Comprehensi	10.09	11.00	2.74	8.77	9.00	2.68	1.19	22	0.246
WRMT Letter Identification	102.91	26.00	8.55	102.08	21.00	7.44	0.26	22.00	0.801
WRMT Word Identification	93.27	42.00	15.31	92.15	40.00	16.66	0.17	22.00	0.867
RAN Objects	102.50	32.00	10.33	101.25	45.00	12.61	0.25	20.00	0.804
RAN Colors	98.20	39.00	10.95	98.67	47.00	14.18	-0.09	20.00	0.933
CTOPP Elision	9.80	6.00	2.15	10.54	8.00	2.37	-0.77	21.00	0.449
CTOPP Blending	10.36	7.00	1.91	10.38	7.00	2.10	-0.03	22.00	0.980
CTOPP Nonword Repetition	9.45	3.00	1.04	9.08	5.00	1.61	0.67	22.00	0.510
CELF Core Language	112.45	41.00	17.09	112.08	46.00	11.86	0.06	21.00	0.952
CELF Expressive Language	112.00	43.00	16.10	105.58	56.00	13.61	1.04	21.00	0.312
CELF Receptive Language	113.73	43.00	16.30	113.33	55.00	13.14	0.06	21.00	0.950
CELF Language Structure	114.00	54.00	18.20	112.17	53.00	12.92	0.28	21.00	0.782

*Since sex is a dichotomus variable, chi square analysis is reported.

Fifteen children were classified as fluent readers (6 children with and 9 children without a familial risk of DD) and 9 children were classified as dysfluent readers (7 children with and 2 children without a familial risk of DD). Fluent and dysfluent readers did not differ in terms of age (*t*=-.72, df=22, p=.477, Cohen's d=.307), sex (χ^2=.55, df=1, p=.459, Cohen's d=.306), SES as measured via maternal education (*t*=.34, df=22, p=.432, Cohen's d=.145), or KBIT-2 nonverbal intelligence (*t*=.80, df=22, p=.481, Cohen's d=.341, power=.09). Fluent readers displayed greater GORT-5 reading fluency (*t*=5.77, df=22, p<.001, Cohen's d=2.460, power=.91), GORT-5 reading comprehension (*t*=4.01, df=22, p=.001, Cohen's d=1.710, power=.77), WRMT letter identification (*t*=3.03, df=22, p=.006, Cohen's d=1.292, power=.71), WRMT word identification (*t*=3.21, df=22, p=.004, Cohen's d=1.369, power=.71), and CTOPP nonword repetition (*t*=2.49, df=22, p=.021, Cohen's d=1.062, power=.55) than dysfluent readers. Fluent and dysfluent readers did not differ in terms of RAN/RAS objects (*t*=.87, df=20, p=.395, Cohen’s d=.389, power=.17), RAN/RAS colors (*t*=.80, df=20, p=.431, Cohen’s d=.358, power=.14), CTOPP elision (*t*=.18, df=21, p=.861, Cohen’s d=.079, power=.03), CTOPP blending (*t*=.08, df=22, p=.928, Cohen’s d=.034, power=.04), CELF core langauge (*t*=.24, df=21, .810, Cohen’s d=.105, power=.05), CELF expressive language (*t*=1.23, df=21, p=.233, Cohen’s d=.537, power=.22), CELF receptive language (*t*=.12, df=21, p=.902, Cohen’s d=.052, power=.04), or CELF langauge structure (*t*=.66, df=21, p=.517, Cohen’s d=.288, power=.11).

Table 3.2. Fluent and Dysfluent Readers’ Demographic and Psychometric Results.



Measure	Fluent Readers	Range	Standard Deviation	Dysfluent Readers	Range	Standard Deviation	T Value	DF	P Value
Age	65.49	14.85	4.18	66.90	18.33	5.32	-0.72	22	0.477
Sex*	1.60	1.00	0.51	1.44	1.00	0.53	0.55	1.00	0.459
SES	5.27	4.00	10.42	5.11	4.00	1.27	0.34	22	0.432
Nonverbal Intelligence	101.33	29.00	0.96	97.67	37.00	11.57	0.80	22	0.481
GORT Reading Fluency	10.80	5.00	1.78	6.44	5.00	1.81	5.77	22	<.001***
GORT Reading Comprehension	10.73	9.00	2.05	7.11	7.00	2.20	4.01	22	0.001***
WRMT Letter Identification	105.67	21.00	6.78	97.11	20.00	6.57	3.03	22	0.006***
WRMT Word Identification	99.40	42.00	16.60	81.44	4.00	1.33	3.21	22	0.004***
RAN Objects	103.27	43.00	11.92	98.71	24.00	10.24	0.87	20	0.395
RAN Colors	99.93	47.00	14.25	95.28	19.00	7.61	0.80	20	0.431
CTOPP Elision	10.29	8.00	2.33	10.11	6.00	2.26	0.18	21	0.861
CTOPP Blending	10.40	7.00	2.23	10.33	5.00	1.58	0.08	22	0.928
CTOPP Nonword Repetition	9.73	4.00	1.28	8.44	3.00	1.13	2.49	22	0.021***
CELF Core Language	112.80	41.00	14.33	111.25	46.00	15.02	0.24	21	0.810
CELF Expressive Language	111.40	43.00	14.70	103.50	48.00	14.71	1.23	21	0.233
CELF Receptive Language	113.80	39.00	12.92	113.00	55.00	17.80	0.12	21	0.902
CELF Language Structure	114.60	52.00	14.26	110.13	55.00	17.80	0.66	21	0.517

Diffusion-weighted imaging results. Preschoolers with and without a familial risk of DD differed in FA of the splenium of the CC in 19 nodes (*t*=-2.671, p<.05) (Figure 3.1). Additionally, preschoolers with and without a familial risk of DD differed in AD of the splenium of the CC in 15 nodes (*t*=-2.522, p<.05) (Figure 3.2). Specifically, preschoolers with a familial risk of DD display greater FA and AD of the splenium of the CC compared to preschoolers without a familial risk of

DD. These findings are in line with previous studies in children (Hasan et al., 2012) and adults (Frye et al., 2008) with a diagnosis of DD.

Figure 3.1. Preschoolers with a risk of DD (FHD+) display greater FA of the splenium of the CC compared to preschoolers without a familial risk of DD (FHD-). Children with a familial risk of DD are displayed in red and children without a familial risk of DD are displayed in blue.

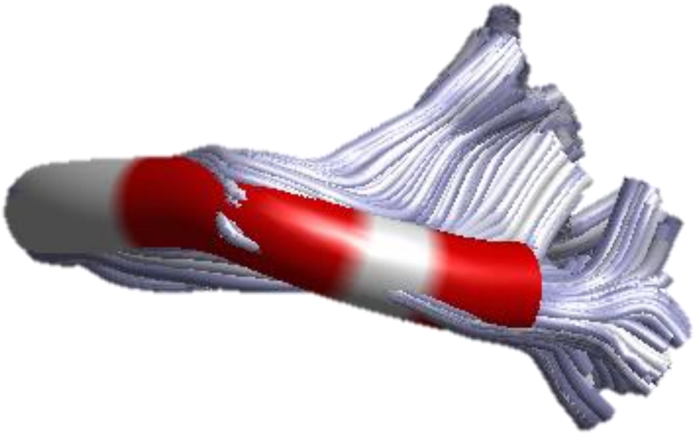
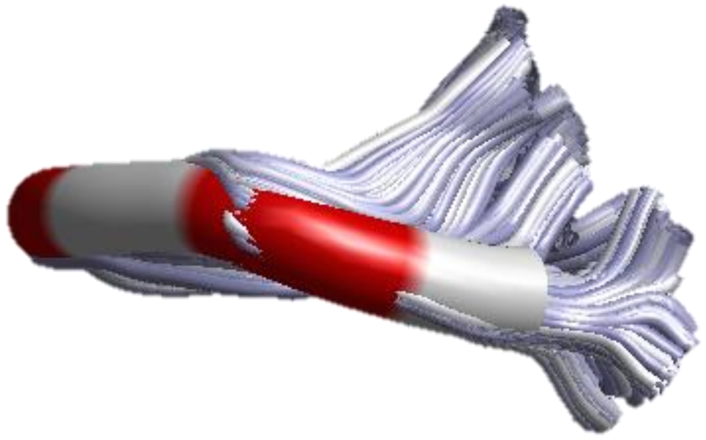
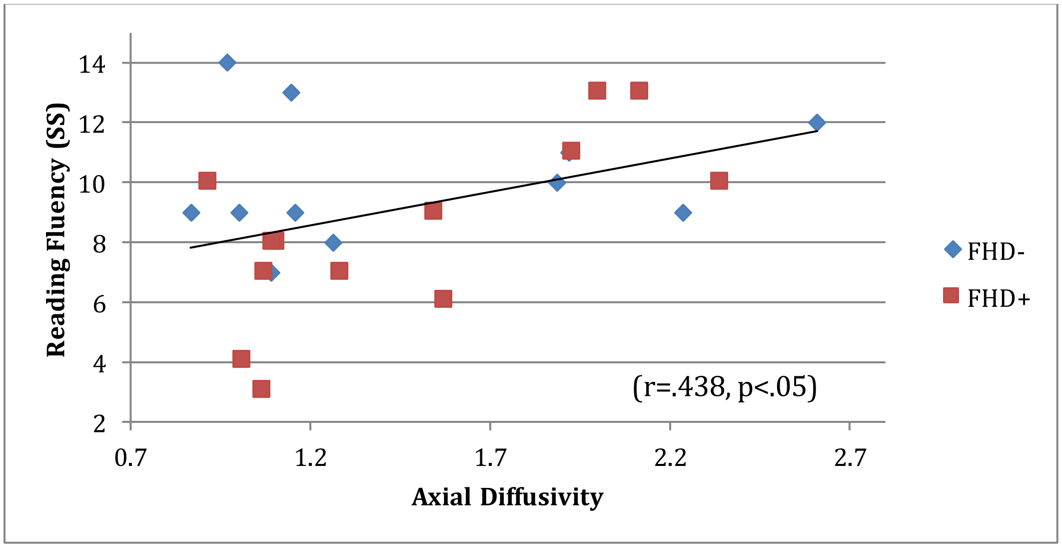


Figure 3.2. Preschoolers with a familial risk of DD (FHD+) display greater AD of the splenium of the CC compared to preschoolers without a familial risk of DD (FHD-). Regions of the splenium of the CC that significantly differed (p<.05, corrected) in AD between children with and without a risk of DD are displayed in red.



Brain-behavior results. AD of the splenium of the CC was positively correlated with GORT-5 reading fluency standard score across children with and without a familial risk of DD (r=.438, p<.05, uncorrected) (Figure 3.3). FA and RD of the splenium of the CC were not correlated with GORT-5 reading fluency standard scores across children with and without a familial risk of DD.

Figure 3.3. AD of the splenium of the CC assessed in preschool is positively correlated with reading fluency in children assessed at school-age (i.e., about 7.5 years old). Children with a familial risk of DD (FHD+) are displayed in red and children without a familial risk of DD (FHD-) are displayed in blue. Gray Oral Reading Test Reading Fluency subtest standard scores are displayed.



Regression results. Since a correlation was observed between a) AD of the splenium of the CC and b) GORT-5 reading fluency across children with and without a familial risk of DD, a series of regression analyses were run. Backward linear multiple regression was employed with the predictor variables: family history, age, sex, SES, nonverbal intelligence, and AD of the splenium of the CC, and the criterion variable of GORT-5 reading fluency standard score. The model that included the predictor variables AD of the splenium of the CC (*t*=4.038, p=.001, beta=.684), nonverbal intelligence (*t*=3.347, p=.003, beta=.558), and

SES (t=.2.613, p=.017, beta=.408) accounted for 53.4% of the variance in reading fluency (power=.97). The predictor variables family history (*t*=-.451, p=.657), age (*t*=-.413, p=.684), and sex (*t*=-.623, p=.540) were excluded from the model.

Backward stepwise (likelihood ratio) logistic regression was employed to determine whether the predictors: family history, age, SES, nonverbal intelligence, WRMT letter identification, WRMT word identification, CTOPP blending, CTOPP nonword repetition, and AD of the splenium of the CC correctly classify fluent and dysfluent school-age readers.

The final model consisted of AD of the splenium of the CC, CTOPP nonword repetition, and WRMT letter identification had 91.7% accuracy (sensitivity: 88.9%; specificity: 93.3%) (Nagelkerke R Square: .831) in discerning fluent and dysfluent readers. The addition of age, family history, sex, SES, nonverbal intelligence, CTOPP blending, and WRMT word identification did not significantly improve the model, and thus, were excluded. A previous model consisting of the behavioral predictors CTOPP nonword repetition and WRMT letter identification had 83.3% accuracy (sensitivity: 77.8%; specificity: 86.7%) (Nagelkerke R Square: .585) in discerning fluent and dysfluent readers. A model consisting solely of the brain measure AD of the splenium of the CC had 70.8% accuracy (sensitivity: 55.6% and specificity: 70.8%) (Nagelkerke R Square: .277) in discerning fluent and dysfluent readers.

Discussion

The aims of the current study were to determine whether preschoolers with and without a familial risk of DD differ in white matter connectivity of the splenium of the CC, and to assess whether diffusivity measures of the splenium of the CC in preschool were associated with school-age reading fluency in children with and without a familial risk of DD. Results indicated that preschool children with a familial risk of DD displayed greater FA and AD of the splenium of the CC than children without a familial risk of DD. This replicates Frye et al. 2008 finding that adults with DD display greater FA and AD of the splenium of the CC than their typically developing peers. To our knowledge this is the first study to observe such white matter differences within the splenium of the CC in preschoolers at-risk of DD.

FA is a summary measure of AD and RD. Animal studies have shown that AD is associated with increased axonal degeneration and/or increased fiber complexity (i.e., an axon which is interrupted by increased numbers of crossing fibers) (Song et al., 2005; Harsan et al., 2007; Frye et al., 2011).

Since preschoolers with a familial risk of DD displayed higher AD values than the children without a familial risk of DD, this could mean that they have reduced fiber complexity than children without a familial risk of DD. Preschoolers with a familial risk of DD display increased fiber complexity than children without a familial risk of DD, which may enable greater recruitment of the right hemisphere as a compensatory mechanism. Unfortunately, the underlying biological properties of these diffusivity measures are still under debate (Wheeler-Kingshott & Cercignaani, 2009).

In terms of prediction of reading fluency, AD of the splenium of the CC in preschoolers was positively correlated with school-age reading fluency across groups irrespective of familial risk of DD. Moreover, linear multiple regression analyses revealed that AD of the splenium of the CC, nonverbal intelligence, and SES assessed in preschool accounted for 53.4% of the variance in school-age reading fluency. Previously AD of the splenium was reported to be positively correlated with phonological awareness skills in adults (Frye et al., 2008). Furthermore, prior work also observed a positive correlation between CC microstructure and hemispheric language lateralization (Westerhausen et al., 2006).

A number of prior studies have observed brain-behavior associations with SES and reading (Eckert et al., 2001; Noble et al., 2006; Hackman et al., 2009; Raizada et al., 2008; Monzalvo et al, 2012; Noble et al., 2012; Noble et al., 2015). In fact, it is estimated that SES accounts for 10 percent of the variance in reading abilities (Petersen & Penington, 2015). Studies have reported positive associations between phonological awareness abilities and left fusiform activity in lower SES children, but not their higher SES counterparts (Noble et al., 2006; Hackman et al., 2009). Studies have also reported a positive association between SES and hemispheric specialization in the left inferior frontal gyrus (Raizada et al., 2008; Hackman et al., 2009). One recent study observed that ten-year-olds with DD displayed reduced brain activity in the visual system to both words and faces and in speech regions when presented with language than typically developing peers (Monzalvo et al., 2012). Interestingly, they found that having a lower SES amplified these neural activation differences between children with and without a diagnosis of DD. In other words, low SES worsened performance. Recently Noble and colleagues (2015) also observed that surface area of a number of brain areas implicated in language and reading was positively correlated with SES assessed via parental education.

A recent Italian longitudinal study (Luoni et al., 2015). examined the effect of being on the low end of the SES scale. They investigated fifth grade children who started testing at first grade, on a confrontation naming task (i.e., the Boston Naming Task). In a sample of 126 children, they observed that confrontation naming was positively correlated with nonverbal intelligence during grades 1, 2, 3, 4, and 5. Furthermore, SES calculated at the end of each grade had a significant effect in grades 1 through 4. Confrontation naming also correlated with reading fluency from year to year. This is in line with the current study's results which observed AD of the splenium of the CC, nonverbal intelligence, and SES accounted for over 53% of the variance in reading fluency assessed two years later.

Logistic regression was also employed to assess whether family history, age, sex, SES, nonverbal intelligence, letter identification, word identification, blending, nonword repetition, and AD of the splenium of the CC assessed in preschool differentiate fluent and dysfluent readers at school-age. The final model including the predictor variables AD of the splenium of the CC nonword repetition and letter identification had over 91% accuracy in classifying fluent and dysfluent school-age readers suggesting that combining brain and behavioral measures is most efficacious in predicting reading fluency than models consisting of only behavioral or brain measures.

Letter identification and nonword repetition have previously been shown to predict reading and reading-related skills. Children with a familial risk of DD who go on to develop DD are slower to acquire letter knowledge than their peers who ultimately do not receive a DD diagnosis (Snowling & Lervag, 2016). A longitudinal study in Finnish children observed that letter identification skills assessed at the beginning of kindergarten was found to be the best predictor of fourth grade reading comprehension and fluency (Leppanen et al., 2008). The authors suggest that early orthographic knowledge contributes directly to early decoding skills as well as later reading fluency and comprehension. A subsequent longitudinal study observed than letter identification, nonword repetition, and rapid automatized naming at the beginning of kindergarten predicted word reading accuracy and fluency at the end of first grade (Catts et al., 2015). Nonword repetition has also been shown to correlate with concurrent reading decoding and spelling deficits in children with language impairment (Baird et al., 2011).

The current study also has limitations. The first limitation being the relatively small sample of children with and without a familial risk of DD with follow-up reading fluency data. The sample size may not have had sufficient power to identify group differences between children with and without a familial risk of DD. Another limitation is that the current study has imaging data from only one-time point. Future studies are needed with multiple imaging time points such that the developmental trajectories of reading fluency in children with and without a familial risk of DD may be elucidated. Furthermore, future studies are needed to determine whether atypicalities of the splenium are specific to DD or whether they may be predictive of neurodevelopmental disorders in general. One final limitation is that AFQ software only tracks the anterior and posterior regions of the CC, and thus, one cannot speculate about groups differences in central regions of the CC, such as the body. Prior research has suggested that individuals with DD may differ from controls in the body of the CC Fine et al., 2007; Dougherty et al., 2007; Hasan et al., 2012). Future studies are needed to determine whether the body of the CC is associated with reading and reading-related skills in infants and preschoolers.

In summary, the current investigation has established that preschoolers with a familial risk of DD display increased FA and AD of the splenium of the CC compared to preschoolers without a familial risk of DD. This mirrors prior research in adults and adolescents with DD (Frye et al., 2008; Hasan et al., 2012). Additionally, AD of the splenium of the CC along with nonverbal intelligence and SES accounted for over 53% of the variance in school-age reading fluency. Furthermore, a model consisting of AD of the splenium of the CC, nonword repetition and letter identification had over 91% accuracy in classifying fluent and dysfluent school-age readers.

Conclusion

Learning to read is critical for an individual's future success, yet a significant proportion of children struggle while learning to read and are ultimately diagnosed with DD. Typically, children do not receive a diagnosis of DD until second or third grade, even though research suggests that early intervention is the gold standard of care (Torgesen et al., 2001; Torgesen & Hudson, 2006; Vaughn et al., 2010). The goal of this dissertation is to identify whether infants and preschoolers at familial risk of DD differ in measures of white matter microstructure prior to learning to read. A second goal of this dissertation is to determine the optimal set of predictors of subsequent reading skills.

Experiment 1 reported that infants at familial risk of DD differ in terms of white matter microstructure from infants without a familial risk of DD. Specifically, at-risk infants displayed reduced FA and increased RD of the left AF and reduced FA and reduced AD of the splenium of the CC compared to infants without a risk of DD. Experiment 1 also observed a positive correlation between FA of the left AF assessed in infancy and vocabulary skills measured at age four, and a negative correlation between RD of the left AF assessed in infancy and vocabulary skills measured at age four. Furthermore, a positive correlation was observed between AD of the splenium of the CC assessed in infancy and print knowledge measured at age four. Backward stepwise regression analyses revealed that RD of the left AF measured in infancy accounted for over 26% of the variance in vocabulary skills in four-year-olds, and AD of the splenium of the

CC accounted for 46% of the variance in print knowledge in four-year-olds. Interestingly, neither model was significantly improved by incorporating age, sex, family history, or SES.

Experiment 2 demonstrated that white matter microstructure was positively correlated with neural activity during a phonological processing task. Preschoolers with a familial risk of DD displayed reduced neural activity during a phonological processing task in bilateral occitpitotemporal, left temporoparietal, and cerebellar regions. This replicates prior findings by Raschle et al. 2012. An ROI analysis revealed that preschoolers with and without a familial risk of DD displayed positive correlations between FA of the left AF and brain activity in the left medial temporal gyrus and left lingual gyrus during an fMRI alliteration task. Preschoolers with and without a familial risk of DD also displayed positive correlations between FA of the splenium of the CC and brain activity in the left medial temporal gyrus and left lingual gyrus during an fMRI alliteration task.

Experiment 3 established that preschoolers with a familial risk of DD display increased FA and AD of the splenium of the CC compared to peers without a familial risk of DD. This replicates Frye et al., 2008 finding in adults and is the first study to find such a pattern in preschoolers. Furthermore, AD of the splenium of the CC was positively correlated with reading fluency. In fact, backward stepwise regression demonstrated that AD of the splenium of the CC, nonverbal intelligence, and SES account for over 53% of the variance in school-age reading fluency assessed two years later. In a subsequent analysis where children were classified as fluent or dysfluent school-age readers, AD of the splenium of the CC, nonword repetition, and letter identification skills successfully discerned fluent and dysfluent readers with over 91% accuracy.

A model consisting of DWI measures of the splenium and psychometrics correctly discerned fluent and dysfluent readers with over 91% accuracy. EEG predictions may lack specificity, the ability of a measure to correctly identify individuals without a disease, and as a result are susceptible to a significant percentage of false positives resulting in the over-diagnosis of DD in at-risk children. For example, a recent study utilizing EEG to diagnosis children with ADHD reported a specificity of only 57% (Sangal & Sangal, 2014). EEG studies may also lack sensitivity, the ability of a measure to correctly identify individuals with a disease, which may result in a number of children not receiving a warranted diagnosis. For instance, van Zujien and colleagues (2013) observed the absence of a mismatch negativity response was predictive of deficits in reading fluency in only 39% (10 of 26) of infants who later were later classified as non-fluent readers meaning 16 infants would wrongly be diagnosed. Furthermore, it has been argued that the mismatch negativity component is inconsistent across studies in infants and children (Bishop, 2007). The final model in Experiment 3 consisting of AD of the splenium, WRMT letter identification, and CTOPP nonword repetition had 88.9% specificity and 93.3% sensitivity in discerning fluent and dysfluent readers two-years later. This model would result in the allocation of services to children with greater fiscal responsibility than the aforementioned EEG studies.

Interestingly, it was observed that infants with a familial risk of DD displayed reduced FA and AD of the splenium of the CC than infants without a familial risk of DD whereas preschoolers with a familial risk of DD displayed greater FA and AD than their peers without a familial risk of DD. Although these findings seem paradoxical, the trajectory of CC connectivity may very well be different in young infants and older children. A recent study tracked the development of the left AF and left inferior longitudinal fasciculus over a three-year period in children 7-12 (Yeatmen et al., 2012). Children with above-average reading skills initially had low FA in the aforementioned tracts that increased over the three-year period. In contrast, children with below-average reading skills, FA of these tracts diminished over time. The findings in this dissertation mirror the findings observed for children with above-average reading skills in children without a familial risk of DD. Children with a familial risk of DD may display an increase in white matter microstructure as a means of compensation, recruiting right hemisphere homologues to accomplish reading and reading-related tasks. This demonstrates the importance of longitudinal studies with multiple imaging time points beginning in infancy to better understand the development of reading skills.

The main method utilized in this dissertation is AFQ. AFQ assesses FA, AD, and RD at multiple regions along a tract rather than providing a summary average measure of the aforementioned diffusivity measures. This is advantageous since summarizing an entire tract with a single diffusion parameter may lose critical information, whereas examining diffusion measures at multiple points along a tract provides a more comprehensive characterization of white matter tracts (Basser et al., 1994; Wang et al., 2016). This is particularly important during early childhood when there are rapid changes in brain development due to myelination and pruning.

A limitation of the AFQ software is that it does not tract the entire CC. AFQ provides measures of the forceps major, which joins homologous regions of the occipital lobe via the splenium, and the forceps minor, which joins homologous regions of the anterior frontal lobe via the genu of the CC (Yeatmen et al., 2012). Since ample prior research implicated the splenium in DD, the splenium was the focus of this dissertation (Frye et al., 2008; Odegard et al., 2009; Hasan et al., 2012; Vandermosten et al., 2012). However, there is evidence that the body of the CC may also be implicated in DD (Fine et al., 2007; Dougherty et al., 2007; Hasan et al., 2012). Future studies are needed to determine whether the body of the CC is associated with reading and reading-related skills in infants and preschoolers.

Future longitudinal studies are needed with multiple imaging time points to track the developmental trajectories of the neural basis of reading in typically developing and at-risk infants and children. These studies will inform researchers whether predictors in infancy have stable predictive power throughout the school years. Further investigation is needed to determine whether brain and behavioral predictors of reading development can result in the recognition and diagnosis of children with DD at an earlier age when treatment is most efficacious.

In conclusion, this dissertation has shown that white matter microstructure is associated with subsequent reading skills. Furthermore, it was shown that neural activity during phonological processing is associated with measures of white matter microstructure.

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EDUCATION

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BA	Boston University, Psychology with Distinction Thesis: The Acquisition of an Artificial Lexicon via Alphabetic and Whole-Word Training in Typical and Poor Readers	May 2011 GPA 4.0
BS	Boston University, Human Physiology	May 2011 GPA 3.3

HONORS & AWARDS

Teaching Fellowship Boston University	September 2015, 2012, 2011
Unrestricted Travel Grant Boston University	July 2015, 2014
Nelson Butters Award for Best Poster Massachusetts Neuropsychological Society	May 2015
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Graduate Research Assistant Scholarship September 2014, 2013
Boston University

Teaching Fellow of the Year, Psychology May 2013
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RESEARCH EXPERIENCE

Research Associate, Boston Children's Hospital May 2013 to Present
Advisor: Nadine Gaab, PhD
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- Conduct dyslexia and autism research with children and infants
- Perform structural and functional brain analyses
- Execute statistical analyses
- Run behavioral and functional neuroimaging sessions

Unpaid Internship, Boston Children's Hospital September 2010 to May 2013
Advisor: Nadine Gaab, PhD

- Conducted dyslexia research with children
- Analyzed fMRI data via SPM
- Executed VBM analyses via SPM and FSL
- Performed statistical analyses via SPSS
- Tested participants and performed psychometric assessments

Unpaid Internship, Boston University September 2009 to May 2012
Advisor: Jacqueline Liederman, PhD

- Conducted dyslexia research focusing on novel word learning in adults
- Created a paradigm for novel word learning
- Designed visual and auditory stimuli for the experiment
- Tested participants and performed psychometric assessments
- Analyzed, scored, and coded data

PUBLICATIONS, PRESENTATIONS, & ABSTRACTS

Figuccio, M. J. & Gaab, N. (2016). *Music abilities predict language and reading skills in young readers: A longitudinal study.* Manuscript in preparation.

Figuccio, M. J., Wang, Y., & Gaab, N. (2016). *Infant white matter microstructure predicts pre- reading skills in preschoolers with and without a familial risk of developmental dyslexia.* Manuscript in preparation.

Figuccio, M. J., Wang, Y., & Gaab, N. (2016). *Preschool white matter microstructure predicts reading comprehension and fluency in school-age children with and without a familial risk of developmental dyslexia.* Manuscript in preparation.

Shetreet,E., **Figuccio, M. J.**, Chierchia, G., & Gaab, N. (2015). *SOME and NOT EVERY: Children's understanding of scalar implicatures*. Manuscript in preparation.

Figuccio, M. J. (2016). School-age reading fluency and comprehension are predicted by white matter connectivity in preschool. In **M. J. Figuccio** (Chair), *Brain and behavioral longitudinal studies of reading: a search for protective factors.* Symposium conducted at the 23rd Society for the Scientific Study of Reading Meeting, Porto July 2016.

Figuccio, M. J., Wang, Y., & Gaab, N. (2016). Infant white matter microstructure predicts preschool pre-reading skills in children with and without a familial risk of developmental dyslexia. In M. Vandermosten (Chair), *Neurobiology of dyslexia: cause or consequence?* Symposium conducted at the 23rd Society for the Scientific Study of Reading Meeting, Porto July 2016.

Figuccio, M. J., Yu, X., Wang, Y., & Gaab, N. (2016). Activation during phonological processing is associated with white matter microstructure in preschoolers with and without a familial risk of developmental dyslexia. Poster presented at the 23rd Annual Cognitive Neuroscience Society Meeting, New York, April 2016.

Figuccio, M. J., Wang, Y., Langer, N., Peysakhovich, B., Becker, B., Sliva, D., & Gaab, N. (2015). White matter connectivity in infancy predicts preschool pre-reading skills in infants with a familial risk of developmental dyslexia. Talk presented at the 7th International Summer School on Literacy Research, Egmond aan Zee, August 2015.

Figuccio, M. J., Wang, Y., Langer, N., Peysakhovich, B., Becker, B., Sliva, D., & Gaab, N. (2015). Examining atypical structural connectivity in infants at risk for dyslexia and its relationship to language skills in infancy and preschool. Poster presented at the 22nd Society for the Scientific Study of Reading Meeting, Big Island, July 2015.

Figuccio, M. J., Adrade, P., Adrade, O., & Gaab, N. (2015). Musical perceptual abilities predict reading and writing skills in young readers: A longitudinal study. Poster presented at the Massachusetts Neuropsychological Society Annual Science Symposium, Boston, May 2015.

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