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Brain Networks Supporting Literacy Development

Iris J. Broce
Florida International University, ibroce@fiu.edu

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FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

BRAIN NETWORKS SUPPORTING LITERACY DEVELOPMENT

A dissertation submitted in partial fulfillment of
the requirements for the degree of
DOCTOR OF PHILOSOPHY
in
PSYCHOLOGY
by
Iris Broce

2016

To: Dean Michael R. Heithaus
College of Arts, Sciences and Education

This dissertation, written by Iris Broce, and entitled Brain Networks Supporting Literacy Development, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

Lorraine Bahrick

Angela Laird

Robert Lickliter

Robert Laird

Anthony Steven Dick, Major Professor

Date of Defense: November 07, 2016

The dissertation of Iris Broce is approved.

Dean Michael R. Heithaus
College of Arts, Sciences and Education

Andrés G. Gil
Vice President for Research and Economic Development
and Dean of the University Graduate School

Florida International University, 2016

DEDICATION

I dedicate this dissertation to my mother, Irinea Broce, and brothers, Christian and Miguel Broce. Their constant source of love, encouragement, and support provided me the strength and courage to succeed.

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ABSTRACT OF THE DISSERTATION

BRAIN NETWORKS SUPPORTING LITERACY DEVELOPMENT

by

Iris Broce

Florida International University, 2016

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Professor Anthony Steven Dick, Major Professor

The development of fluent reading requires coordinated development of key fiber pathways. While several fiber pathways have been implicated in reading, including the recently re-identified vertical occipital fasciculus (VOF), inferior longitudinal fasciculus (ILF), arcuate fasciculus and its 3 components, and inferior fronto-occipital fasciculus (IFOF), whether these fiber pathways support reading in young children with little to no exposure to print remains poorly understood. Consequently, over the course of three studies, the current dissertation aimed to narrow this research gap by addressing the following research questions: 1) Which fiber pathways support early literacy skill in young children 5-10 years old? 2) Are microstructural properties of these tracts predictive of age-related changes in reading across an interval of two years? 3) Do different components of the recently identified VOF differentially support reading? To answer these questions, we used diffusion-weighted imaging to measure white-matter development and to relate the microstructural properties of each fiber pathway to early literacy and literacy development. We report several novel findings that contribute to our growing understanding of the white matter connections supporting early literacy and literacy. For the first time, these studies revealed that the re-identified VOF can be reliably tracked in young children, bilaterally and is composed of three main components, which project from occipital temporal sulcus to angular, and middle and superior occipital gyri. We also found that the left AF, bilateral ILF, and particular components of the VOF play a role in early literacy and literacy development. Implications for contemporary models of reading development are discussed.

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I. INTRODUCTION

The ability to read and write, that is literacy, is a cultural invention that emerges from and is intimately tied to the human capacity for language (Dehaene 2009; Dehaene, Cohen, Morais, & Kolinsky, 2015). Before children acquire advanced literacy, they must learn several precursor skills. In alphabetic languages such as English and Spanish, these “early literacy skills” develop through experience with alphabetic instruction (Bitan & Booth, 2012; Morais, Cary, Alegria, & Bertelson, 1979; Read, Yun-Fei, Hong-Yin, & Bao-Qing, 1986). For example, early alphabetic instruction involves teaching children the rules for mapping letters of the alphabet (i.e., graphemes, or orthography) to sounds of spoken language (i.e., phonemes, or phonology), which is commonly termed grapheme-phoneme conversion. Children are also taught to assemble these sounds, letter-by-letter, to create meaningful words. This ability to manipulate individual sounds (phonemes) in words is called phonemic awareness, and constitutes a sub-category of the broader ability, phonological awareness, which describes the general recognition that words are made up of individual sound units including phonemes and syllables (Anthony & Francis, 2005). Early phonological skills include judging whether two words rhyme or identifying syllables, and blending and segmenting words into their phonological constituents. It is these skills that are linked to reading development (Anthony, Williams, McDonald, & Francis, 2007; Bryant, MacLean, Bradley, & Crossland, 1990; Byrne & Fielding-Barnsley, 1993; Lonigan, 2015). However, with experience, children rely less on phonological awareness skills to access the meaning of words (i.e., semantics) and rely more on the ability to access semantic representations directly (McNorgan, Alvarez, Bhullar, Gayda, & Booth, 2011; Schlaggar & McCandliss, 2007). Consequently, skilled readers actually develop two processing routes to literacy: 1) an indirect phonological route, mediated first by mapping visual letter representations (i.e., graphemes) to speech sound representations (i.e., phonemes) and 2) an "expert" direct lexical route, linking printed words directly to meaning (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Dejerine & Thomas, 1891; Schurz et al., 2010; Wimmer et al., 2010).

In novice readers, reliance on the indirect phonological route is considerable because they rely on grapheme-phoneme conversion and segmentation of phonological constituents of words to "sound out" most words they encounter, whereas in expert readers, reliance on the indirect phonological route is predominately recruited when reading unfamiliar words (Baddeley, Gathercole, & Papagno, 1998). Thus, in order to "sound out" an unfamiliar or novel word such as "carbageddon" both expert readers and novice readers must rely more on the indirect phonological route. In contrast, for familiar words, expert readers predominately rely on the direct lexical route in which familiar words are read as whole units without sounding out their constituent parts (e.g., armageddon). The direct route thus allows access to semantic representations without engaging phonological processes (Jobard, Crivello, & Tzourio-Mazoyer, 2003). While phonological information is often activated (Borowsky et al., 2006; McDermott, Petersen, Watson, & Ojemann, 2003), for expert readers the phonological representation is not necessary to access the meaning of words (McCandliss, Cohen, & Dehaene, 2003).

The distinction between indirect phonological and direct lexical reading routes has led several investigators to try to identify corollary brain systems that might implement the processing in each route (Vandermosten et al., 2012). Both cortical routes are proposed to begin in the early striate and extrastriate visual cortices, and the occipitotemporal cortex (Dehaene, Cohen, Morais, & Kolinsky, 2015; Dehaene McCandliss, Cohen, & Dehaene 2003). From there, the routes map onto well-known perisylvian regions involved in processing and producing oral speech and language (Dick and Small, 2015; Price 2010, 2012 shown in the top of Figure 1). The indirect route involves the posterior superior temporal gyrus and sulcus (STGp/STSp), supramarginal gyrus (SMG), and posterior inferior frontal gyrus (namely *pars opercularis*; IFGOp). The direct route involves the occipitotemporal gyrus and sulcus (OTG/OTS), including the functionally defined visual word form area (VFWA). These regions are sometimes referred to in the literature as the ventral occipitotemporal (VOT) cortex. The ventral route also includes the posterior middle temporal gyrus (MTGp), angular gyrus (AG), and anterior inferior frontal gyrus (namely *pars triangularis* and *pars orbitalis*; IFGTr and IFGOr; Booth et al., 2004, 2001; Brown et al., 2005; Cohen et al., 2000; McCandliss et al., 2003; Monzalvo & Dehaene-Lambertz, 2013; Price 2000, 2012; Pugh et al., 2001; Schlaggar et al., 2002; Shaywitz & Shaywitz, 2008; Vogel et al., 2013). These brain regions are shown in Figure 1, bottom.

Functional Cortical Organization

Indirect Phonological Route. Functional imaging studies have been invaluable in characterizing the brain regions involved in the indirect phonological route. These regions include the STSp and STGp, IFGOp, and SMG (Booth et al., 2004; Duffau, Gatignol, Denvil, Lopes, & Capelle, 2003; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Paulesu et al., 1997; Price, Moore, Humphreys, & Wise, 1997) and support processing letter-sound integration and phonological working memory. These systems are reviewed below.

Letter-sound Integration. Using the phonological route as a means for reading requires brain mechanisms responsible for integrating letter-sound combinations that are relevant to the reader's spoken language (i.e., their "phonological lexicon"). For instance, English-speaking children first learn that words can be parsed into several sounds (e.g., 'book' is comprised of '/b/, /ʊ/, /k/' phonological constituents). Parsing of speech in the auditory domain relies on key regions in the posterior superior temporal cortex (planum temporale and neighboring STSp and STGp; (van Atteveldt, Roebroeck, & Goebel, 2009; Hickok & Poeppel, 2007 for review). The posterior superior temporal cortex is also known to be involved in the cross-modal integration of visual and auditory speech information (Calvert, Campbell, & Brammer, 2000). Therefore, it is not surprising that the achievement of visual and auditory letter-sound integration involves the multisensory STG and STS (Blau et al., 2010; Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009; Blomert 2011; Van Atteveldt, Formisano, Goebel, & Blomert, 2004; van Atteveldt et al., 2009; Xiao et al., 2005). Involvement of the STG and STS in letter-sound integration is supported by research showing that these regions are active during both auditory speech processing and during reading (Borowsky et al., 2006; McDermott, Petersen, Watson, & Ojemann, 2003; Mechelli, Gorno-Tempini, & Price, 2003; Moore & Price, 1999; Price & Mechelli, 2005), but also research showing that activation in STG and STS regions are differentially activated for reading nonsense words compared to real words (Borowsky et al., 2006; Jobard et al., 2003), and for reading words compared to naming pictures (Price et al., 2006).

Furthermore, activation in the STSp and STGp in response to letter-sound correspondences is linked to reading abilities (Blau et al., 2010; Blau et al., 2009). For example, compared to unimpaired readers, both adults and children with severe reading impairments show reduced activation in the STGp/STSp for familiar letter-sound associations. These individuals with reading impairments also show reduced activation in these regions during auditory speech processing (Blau et al., 2010; Blau et al., 2009). Similarly, decreased activation in the STG and STS to congruent letter-sound correspondences in dyslexic children was associated with lower reading scores, and greater activation in the STG and STS to congruent letter-sound was associated with better reading scores (Blau et al., 2010). These findings suggest an important role for STSp/STGp in phonological processing in both the auditory and written domains.

Phonological Working Memory. The initial activation of phonological representations must be retained over short periods of time to facilitate expert reading. Maintenance of phonological representations describes phonological working memory, or the ability to maintain an active phonological representation in the absence of external perceptual (auditory or visual) stimulation. In addition to STGp/STSp, phonological working memory seems to require the recruitment of additional parietal and frontal regions, specifically the SMG and IFGOp (Cohen et al., 2004; Dietz, Jones, Gareau, Zeffiro, & Eden, 2005; Duffau et al., 2003; McDermott et al., 2003; Paulesu, Frith, & Frackowiak, 1993; Price & Mechelli, 2005; Romero, Walsh, & Papagno, 2006; Xiao et al., 2005). Phonological working memory is particularly important for applying a letter-by-letter reading strategy (Cohen et al., 2004), which is used by children at the onset of reading instruction (Church, Coalson, Lugar, Petersen, & Schlaggar, 2008), by adults when phonological demands increase (e.g., when words are longer or when they are unfamiliar; Booth et al., 2006; Church, Balota, Petersen, & Schlaggar, 2011; Price &

Mechelli, 2005; Ravizza, Delgado, Chein, Becker, & Fiez, 2004), and by people with alexia, who have impairments in reading fluency (Cohen et al., 2004). For example, compared to normal reading peers, people with alexia show a significant increase in activation in the IFGOp and SMG when reading words (Cohen et al., 2004). Moreover, the IFGOp and SMG also show greater activation to pseudowords than words (McDermott et al., 2003; Mechelli et al., 2005) and greater activation to unfamiliar than familiar words (Ischebeck et al., 2004; Xiao et al., 2005). These findings suggest that the indirect route for reading is comprised by the IFGOp, SMG, and STSp/STGp (for a meta-analysis see, Jobard et al., 2003), and these brain regions together seems to support the maintenance of phonological representations in working memory (Paulesu et al., 1993), letter-by-letter reading (Cohen et al., 2004), pseudoword reading (Borowsky et al., 2006; McDermott et al., 2003), and reading unfamiliar words (Ischebeck et al., 2004; Xiao et al., 2005).

Direct Lexical Route. In contrast to the indirect route, the direct route is implicated in whole-word reading. The brain network supporting the direct route includes several ventral brain regions, namely the OTG/OTS, MTGp, AG, and anterior IFGOr and IFGTr (Booth et al., 2001; Brown et al., 2005; Schlaggar et al., 2002; Shaywitz & Shaywitz, 2008). Through the direct route, written (orthographic) words are processed and interface with brain regions important for semantics.

Whole-word Visual Processing. Substantial research suggests that processing visual word forms as integrative perceptual objects occurs outside the primary visual regions, in the left OTG/OTS, an area commonly known as the Visual Word Form Area (VWFA; Dehaene & Cohen, 2011; McCandliss, Cohen, & Dehaene, 2003). Although not a module in the classic sense, the left occipitotemporal cortex does show sensitivity and activates preferentially to letter- and word-like visual stimuli. Further, letter- and word-like stimuli preferentially recruit the left, but not the right, occipitotemporal cortex. The occipitotemporal brain region is thus sensitive to higher-level categories (the word “cat”) and less influenced by stimulus features (such as color or texture). In other words, the region allows for perceptual invariance (Mishkin, Ungerleider, & Macko, 1983) for word stimuli and would respond if the word “cat” was written in red or in blue (Dehaene, Cohen, Sigman, & Vinckier, 2005; Mayall, Humphreys, Mechelli, Olson, & Price, 2001). Although the occipitotemporal cortex of both hemispheres processes visual stimuli in a similar categorical fashion, the left lateralization of the occipitotemporal cortex for reading is proposed to occur because of its close proximity to cortical regions and anatomical connections important for speech and language (Moore, Durisko, Perfetti, & Fiez, 2014; Yeatman, Rauschecker, & Wandell, 2013). However, this lateralization seems to require experience, as it appears after the onset of early reading instruction (Brem et al., 2010). Thus, early school age children with little to no experience reading show bilateral occipitotemporal functional activity to words, but with as little as 8 weeks of training on how to map speech sounds to alphabetic letters, these children show left-lateralized activation in occipitotemporal cortex in response to printed words.

Lateralization of the occipitotemporal cortex even occurs to stimuli that are not from Standard English alphabetic systems (Bolger, Perfetti, & Schneider, 2005; Moore et al., 2014; Szwed, Qiao, Jobert, Dehaene, & Cohen, 2014). For example, Moore et al. (2014) trained adult readers of English on either 35 Korean-fonts paired with English phonemes or 35 faces paired with the same English phonemes. After a two-week training, both Korean-fonts and face-fonts elicited greater activation in the left occipitotemporal cortex compared to the right. Given the large corpus of literature suggesting that the right occipitotemporal cortex preferentially processes faces (Golby, Gabrieli, Chiao, & Eberhardt, 2001; Kanwisher & Yovel, 2006; Kanwisher, Woods, Iacoboni, & Mazziotta, 1997), the latter study is critical in demonstrating that lateralization of the occipitotemporal cortex is associated less with visual processes per se and more with a distributed process of integrating visual information with speech and language representations (Moore et al., 2014). However, the specific way in which regions of the reading network, including OTS/OTG, IFG, MTG and AG acquire specialization for visual word processing during development remains a matter of debate. The present study aims to shed light on this matter by examining age-related and literacy dependent components influencing the lateralization of anatomical brain connectivity comprising the reading network. We plan to examine the onset of lateralization in young children who vary in their level of reading ability.

Semantic Processing. In addition to visual word processing, the ability to read words requires access to semantic representations (i.e., the lexicon). Words require access to semantic representations because in alphabetical languages, words are simply arbitrary sequences of letters (e.g., tree or arbol), which are only meaningful if the visual word form is linked to a particular concept (Binder & Desai, 2011). Thus, direct access to this concept or meaning of words is proposed to be achieved via functional connections between whole-word visual processing regions and regions involved in semantic processing (i.e., MTGp, AG, IFGOr and IFGTr; Binder & Desai, 2011; Price et al., 1997).

Several functional imaging studies show that the left MTGp is one of the most reliably activated regions during semantic processing (for a meta-analytic review, see Binder, Desai, Graves, & Conant, 2009). Patients with lesions to this region show substantial deficits in language comprehension (Chertkow, Bub, Deaudon, & Whitehead, 1997; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Noonan, Jefferies, Corbett, & Ralph, 2010). The left MTGp, more specifically, seems to be sensitive to the degree of semantic information that can be deduced from both written or spoken word information, regardless of differences in complexity (i.e., word lists versus sentences; Humphries, Binder, Medler, & Liebenthal, 2007). For example, the left MTGp shows more activation for both semantically congruent sentences and word lists compared to semantically random sentences and word lists, and shows the least activation to pseudoword sentences and words (Humphries, Binder, Medler, & Liebenthal, 2006, 2007). Furthermore, research suggests that the MTGp contribution to semantic processing changes with age (Chou et al., 2006a; Dick, Goldin-Meadow, Solodkin, & Small, 2012; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003). Thus, a large literature highlights the major role of the MTG in processing semantic information.

A large corpus of literature reliably shows involvement of the AG in semantic processing (for a meta-analysis review in adults see Binder et al., 2009) and in children (Houdé, Rossi, Lubin, & Joliot, 2010). Thus, the AG consistently shows increased activation during semantic decisions compared to perceptual decisions (e.g., matching words based on meaning versus matching symbols on the basis of perceptual features; Seghier, Fagan, & Price, 2010), to words compared to pseudowords (Binder et al., 2009), to high frequency compared to low frequency words (Graves, Desai, Humphries, Seidenberg, & Binder, 2010), to concrete compared to abstract words (Bonner, Peelle, Cook, & Grossman, 2013; Wang, Conder, Blitzer, & Shinkareva, 2010), and to more meaningful compared to less meaningful sentences and word lists (Humphries et al., 2007).

The AG has for some time been associated with orthography as well. Indeed, as early as 1891, Déjèrine identified the AG as a key structure in the reading network (Dejerine & Thomas, 1891). The AG shows consistent morphological and functional differences in individuals who learned to read as adults (late-literates) compared to illiterates (Carreiras et al., 2009), adults with good versus poor reading skill (Goldman & Manis, 2013), and dyslexic adults compared to matched controls (Hoeft et al., 2007). More recent speculation about the region's role as part of the direct route for reading has focused on the processing of orthographic visuo-spatial features in written text, and the connection of these features to the distributed semantic system (Hirnstein, Bayer, Ellison, & Hausmann, 2011; Segal & Petrides, 2013). Thus, the AG seems to be a key component of the neural system implementing reading, particularly when semantic associations are made (Price & Mechelli, 2005).

A number of functional imaging studies also implicate anterior regions of the inferior frontal lobe, particularly the IFGTr and IFGOr, in semantic selection and retrieval (Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Binder et al., 2009; Dick, Goldin-Meadow, Hasson, Skipper, & Small, 2009; Dick et al., 2012; Dick, Mok, Beharelle, Goldin-Meadow, & Small, 2014; Poldrack et al., 1999; Price 2012; Vigneau et al., 2006). For example, these regions play a critical role in selecting semantic representations among competing alternatives (Bedny, McGill, & Thompson-Schill, 2008; Hirshorn & Thompson-Schill, 2006), selecting semantically incongruent words from congruent words (Hoenig & Scheef, 2009), selecting ambiguous words from unambiguous words (Gennari, MacDonald, Postle, & Seidenberg, 2007; Zempleni, Renken, Hoeks, Hoogduin, & Stowe, 2007), and selecting context-appropriate words during semantic verbal fluency tasks (e.g., when participants are asked to generate as many words as possible for a specific semantic category, such as animals or fruits; Paulesu et al., 1997). These regions also play a role in semantic retrieval, particularly when semantic retrieval demands increase (e.g., when semantic associations between cued words and targets words decrease in strength; Wagner, Paré-Blagoev, Clark, & Poldrack, 2001; Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2012).

Moreover, the anterior IFG regions do not work in isolation, but rather work together with other semantic regions to support selection and retrieval of semantic information (Binder et al., 2009; Dick et al., 2014; Hickok & Poeppel, 2004; Whitney et al., 2012). For example, functional imaging studies often report stronger activation in both the anterior IFG and MTGp regions in tasks associated with semantic activation and meaning selection among competing semantic contexts (Devlin, Matthews, & Rushworth, 2003; Wagner et al., 2001; Ye & Zhou, 2009). In addition, stimulation of both the left IFG and MTGp using TMS disrupts semantic retrieval processes (Whitney, Kirk, O'Sullivan, Lambon Ralph, & Jefferies, 2011). Furthermore, the anterior IFG shows functional connections with the occipitotemporal cortex and AG during whole-word reading (Segal & Petrides, 2013). Thus, during reading, the anterior IFG may play an important role in collaboration with occipitotemporal cortex and AG in retrieving semantic information associated with processing orthographic visuo-spatial features of written words. Taken together, these studies suggest that the anterior IFG is part of a distributed semantic system, and may be particularly involved in selecting and retrieving word knowledge.

Development of Functional Specialization for Reading

Indirect Phonological Route Development. Developmental studies show that brain regions comprising the indirect route undergo functional specialization over development (Bitan et al., 2007; Booth et al., 2004; Koyama et al., 2010; Turkeltaub et al., 2003; Xu et al., 2001). For example, like adults, children show activation in the left temporal, parietal, and frontal regions during phonological tasks such as non-word reading, phoneme deletion and rhyming judgment (Bach et al., 2010; Booth et al., 2004; Shaywitz et al., 2002; Temple et al., 2001). However, in comparison to adults, children show reduced activation in the left IFGOp and increased activation in the left STG (Booth et al., 2004, 2001). Similarly, younger children, in comparison to older children, show reduced activation in the left IFG, reduced activation in bilateral SMG, and greater activation in the left STG and bilateral Heschl gyri, after controlling for performance on a rhyming (Bitan et al., 2007) or single word generation task (Brown et al., 2005; Schapiro et al., 2004). In addition to showing age-related differences, these regions are sensitive to experience with alphabetic scripts. For example, compared to Mandarin-speaking children (aged between 8-12-years-old), English-speaking children show greater activation in the STG, IFG, and SMG during an auditory phonological rhyming task (Brennan, Cao, Pedroarena-Leal, McNorgan, & Booth, 2013). Greater activation in the STG was also correlated with visual word processing, exclusively for English-speaking children. These findings suggest that experience learning to read in alphabetical languages shapes activation in regions implicated in letter-sound conversion and phonological processing, processes which are important for acquiring early literacy skill.

The indirect route also shows experience-dependent changes that are predictive of phonological abilities in children. For example, Bach and colleagues (2010) found that children (~8 years old) showed greater activity in left frontal regions, including the IFGOp, during a phonological awareness task (e.g., substitution of phonemes). This activity was not only predictive of better phonological awareness skill, but activity in this region also differentiated between children with normal and poor reading abilities. Normal readers showed greater left hemisphere lateralization particularly of the IFGOp, while poor readers showed greater bilateral activation of IFGOp and greater activation in superior temporal regions. Notably, given that Brem and colleagues (2010) controlled for age, greater activation of the STG in poor readers is likely associated with decreased phonological substitution abilities and less with age-related changes. Collectively, these findings show that age-related changes in literacy must be investigated while also accounting for literacy skill. The present study aims to further our understanding of the corresponding age-related and literacy-dependent changes supporting early literacy by investigating the brain systems supporting younger children, particularly because younger children (aged below 7 years) are underrepresented in the existing corpus of literature, and relating their brain architecture to later literacy skill.

Direct Lexical Route Development. The direct route also shows age-related and literacy-dependent changes. Below, I first review changes associated with visual word processing in the occipitotemporal cortex and then review changes associated with semantic processing.

Development of visual word form area (VWFA). Specialization of activation in the OTS (i.e., VWFA), important for visual word processing, is thought to occur as readers become literate (Dehaene et al., 2010). For example, adults and children show a gradient of increasing word-selectivity along the posterior-to-anterior axis of the VWFA, with the more anterior areas selective to real words and letter strings compared to other stimuli (e.g., false fonts; Brem et al., 2009; Olulade, Flowers, Napoliello, & Eden, 2013; Vinckier et al., 2007). In parallel, activity in the anterior OTS in adults, but not children, has been found predictive of reading fluency (Olulade et al., 2013), yet activation the posterior OTS seems to be predictive of reading fluency in children (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011). However, the extent to which age-related differences in occipitotemporal activation are a function of literacy-experience or age remains unclear. Some evidence shows changes in the volume of occipitotemporal functional activity evidenced until age 15 (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011). Others show increased activation in the occipitotemporal cortex compared to adults (Brem et al., 2009; Brown et al., 2005; Schlaggar et al., 2002). Conversely, some studies report the opposite, showing increased activation in the occipitotemporal cortex in adults compared to children (Booth et al., 2001). One explanation for the observed inconsistencies could be the lack of control of confounding factors associated with literacy and age. Thus, one possible way of disentangling effects associated with literacy and age is by controlling for age when investigating reading-related differences. However, the field as a whole has been remiss in tackling this problem (Schlaggar & Church, 2009). These controls will be implemented in the proposed study.

Development of Semantic Processing. Work investigating the development of the broader semantic system has focused, in reading, on the development of the MTGp, AG, and IFG in semantic processes. For example, Bitan and colleagues (2006) have explored the age-related and behavioral differences in brain networks supporting semantic processing in children 9-15 years old. Children in this study were asked whether word pairs were related in meaning (i.e., via a semantic judgment task). Consistent with the adult literature, bilateral AG showed increased activation to words with greater semantic associations, suggesting the AG might play a critical role in integrating highly related semantic features. However, compared to adults, children show reduced activation in the AG during a visual word rhyming task (Booth et al., 2004). The reduction in AG activation in children is revealed after controlling for accuracy on the semantic task, suggesting that these changes occur independent of the child’s skill in the task.

In addition to the AG, the MTG and anterior IFG (IFGOr and IFGTr) show increase activation to weaker semantic associations (e.g., word pairs unrelated in meaning) than stronger semantic associations (e.g., word pairs related in meaning), suggesting the MTG and IFG regions might play a role in facilitating semantic retrieval and selection (Chou et al., 2006a, 2006b; Schlaggar et al., 2002). In addition, independent of semantic skill, children 9-15-years-old show age-related changes in the left MTG and anterior IFG (Chou et al., 2006b; Turkeltaub et al., 2003). Taken together, these findings suggest that similar to adults, children recruit the MTG, AG, and anterior IFG during semantic processing and these regions show age-related and behavioral-related differences in the developing child.

Summary. There are two routes to literacy, an indirect and direct route (see Figure 2). The indirect route is comprised of the IFGOp, SMG, and STSp/STGp brain regions. These regions support phonological processing and are predictive of phonological awareness and nonsense word reading (i.e., decoding) in both children and adults. However, children and novice readers rely more on the indirect system than expert readers. In contrast, the direct route is comprised of the OTG/OTS, AG, MTGp, IFGTr, and IFGOr brain regions. These regions support visual word processing and semantic processing and are predictive of reading ability, including word recognition, reading speed, comprehension, and fluency. Moreover, studies report both age-related and literacy-dependent changes in both the indirect and direct routes. For example, with age and experience reading, both reading routes show a change from a bi-lateralized system to a more left lateralized system. However, studies investigating age-related differences are often confounded by reading-related differences, and studies investigating reading-related differences are often confounded by age-related differences. Therefore, part of this dissertation aims to investigate age-related and reading-related differences in the connectivity of the indirect and direct routes. We aim to extend the functional connectivity findings but investigating the structural connections of these networks, how these systems relate to behavior, and how age and literacy-related factors shape lateralization of the brain, by properly controlling for confounding factors.

White Matter Pathways Supporting Early Literacy and Literacy

A specific network of fiber pathways also supports the functional interactions among regions of these reading routes, and it is these fiber pathways that are the focus of the dissertation. The brain regions comprising the indirect route (i.e., STSp/STGp, IFGOp, and SMG) and direct route (i.e., OTS/OTG, MTG, AG, IFGOr/IFGTr) are structurally connected via specific white matter pathways that support their functional interactions. These intrahemispheric fiber pathways include the 1) arcuate fasciculus (AF), 2) inferior longitudinal fasciculus (ILF), 3) inferior fronto-occipital fasciculus (IFOF), and 4) vertical occipital fasciculus (VOF). These are illustrated in Figure 3. These pathways are also organized into indirect and direct processing routes for reading, with the AF proposed to comprise the indirect route, the ILF, IFOF proposed to comprise the direct route, and the VOF proposed to facilitate processing between the two routes. The available literature investigating their function is briefly reviewed below.

Arcuate Fasciculus (AF). The most prominent fiber pathway connecting brain regions involved in the indirect phonological route is the AF. The AF is a complex system of fronto-parieto-temporal connections. Diffusion-weighted investigations have revealed that the AF can be parsed into three separate segments (1) an anterior segment, connecting supramarginal gyrus to the inferior frontal gyrus, (2) a long segment, connecting posterior superior and middle temporal cortex to the inferior frontal gyrus and ventral premotor cortex, and (3) a posterior segment connecting posterior superior and middle temporal regions to the angular gyrus (Catani, Jones, & ffytche, 2005). Research suggests the long and posterior segments of the arcuate fasciculus support early literacy (i.e., phonological awareness) and literacy skills (i.e., whole-word reading), respectively. For example, the long segment is predictive of phonological awareness abilities in typical children (7-17 years old; Yeatman et al., 2011), kindergartners at risk for dyslexia (Saygin et al., 2013), and adults with dyslexia (Vandermosten et al., 2012). The long segment of the AF is also related to learning nonsense words (i.e., decoding; López-

Barroso et al., 2013), and the absence of it in a child aged 15 showed severe reading impairment (Rauschecker et al., 2009). Less is known about the contributions of the posterior AF segment to early literacy, although one study did report learning to read improved its structure in a group of illiterates, former illiterates who learned to read as adults, and literate adults (Thiebaut de Schotten, Cohen, Amemiya, Braga, & Dehaene, 2012). In sum, several studies show that the microstructural properties of the long and posterior segments of the arcuate fasciculus, as measured by diffusion-weighted imaging, are associated with early literacy skills such as phonological awareness.

However, the extent to which these findings extend to younger children (below 7 years of age) is understudied. Evidence suggests that the AF shows age-related change throughout childhood (Barnea-Goraly et al., 2005; Brauer, Anwander, Perani, & Friederici, 2013; Eluvathingal, Hasan, Kramer, Fletcher, & Ewing-Cobbs, 2007; Lebel & Beaulieu, 2009, 2011; Schmithorst, Wilke, Dardzinski, & Holland, 2002; Tamnes et al., 2010; Urge et al., 2014; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012; Yeatman et al., 2011). However, it is possible that associations of the microstructure of these pathways with early literacy development occur because both white matter microstructure and early literacy skill have an association with age. While this association with age has been controlled in some studies of early literacy development (Yeatman et al., 2012; Yeatman et al., 2011), others, especially for younger children, have not properly controlled for age-related differences in the microstructure of the arcuate fasciculus or in the microstructure of the white matter of the rest of the brain (e.g., see Saygin et al., 2013). Therefore, it is unclear whether the white matter of the arcuate fasciculus, or rather brain development more generally, can account for relations between the measures of white matter microstructure and early literacy. The present study aims to investigate both age-related and literacy-dependent effects associated with microstructure of the AF.

Inferior Longitudinal Fasciculus (ILF). The ILF is a long association fiber pathway connecting occipital and anterior temporal cortex. Fibers project from extrastriate areas to the middle and inferior temporal gyri, the temporal pole, parahippocampal gyrus, hippocampus, and amygdala (Catani, Jones, & Donato, 2003; Dick & Tremblay, 2012; Dick, Bernal, & Tremblay, 2013; Yeatman, Rauschecker, & Wandell, 2013). Because of its putative connectivity the tract may be important for developing literacy, but the extant evidence is inconsistent. For example, some studies suggest that the ILF plays a role in reading (Epelbaum et al., 2008; Steinbrink et al., 2008; Yeatman et al., 2012), while others do not (Saygin et al., 2013; Thiebaut de Schotten et al., 2012). Studies that have found a relation between ILF organization and literacy have focused on much older children who already have several years of experience with reading. For example, organization of the ILF predicts word and non-word reading abilities in children 7-12 years old (Yeatman et al., 2012). However, these findings have not been reported in younger children (Christodoulou et al., 2016; Saygin et al., 2013; Vandermosten et al., 2015).

Inferior Fronto-Occipital Fasciculus (IFOF). The IFOF is located medial to the ILF and projects from inferior and medial occipital lobe and in some accounts the medial parietal lobe, to the inferior frontal gyrus, the medial and orbital frontal cortex, and the frontal pole through the external capsule (Catani & Thiebaut de Schotten, 2008; Dick & Tremblay, 2012; Dick et al., 2013). Because of its connectivity there is reason to suspect that it might be involved in reading as part of the ventral direct semantic route. More specifically, the IFOF has been associated with semantic processing during auditory language processing and orthographic processing in adults, and disruption to it by electrostimulation elicits semantic disturbances (Duffau et al., 2005; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007; Moritz-Gasser, Herbet, & Duffau, 2013). In contrast to adults, Vandermosten and colleagues (2015) have found that microstructural properties of the bilateral IFOF are associated with phonological awareness in young children. Thus, a number of studies suggest that properties of the IFOF are involved in reading, but others find no relationship, specifically as it relates to adults learning new words (López-Barroso et al., 2013) and illiterate adults learning to read (Thiebaut de Schotten et al., 2012). Saygin and colleagues (2013) did not examine this pathway in their study of early literacy in pre-k and kindergarten children. Some evidence shows that the IFOF develops into adulthood (Lebel et al., 2012), and thus while there is a growing body of literature investigating whether microanatomical properties of the IFOF support reading, only initial evidence suggests it plays a role in learning to read.

Vertical Occipital Fasciculus (VOF). The VOF is known in the classical neurology literature (for a review see Yeatman et al., 2014) and has received renewed attention only recently in diffusion-weighted imaging studies of reading (Ben-Shachar, Dougherty, & Wandell, 2007; Takemura et al., 2015; Yeatman et al., 2014). The fibers of the VOF are located posterior to the AF and lateral to the ILF and the IFOF (Weiner, Yeatman, & Wandell, 2016; Yeatman et al., 2014). They project from the occipital temporal cortex and inferior temporal gyri to lateral occipital regions, particularly the transverse occipital sulcus, posterior intraparietal sulcus, middle occipital gyrus, lateral occipital sulcus, and in some cases to the angular gyrus (Takemura et al., 2015; Yeatman et al., 2013; Yeatman et al., 2014). Some suggest that the VOF may support word-reading abilities because its putative connectivity with the angular gyrus (Yeatman et al., 2013). Furthermore, in postmortem studies of patients with lesions Greenblatt (1973; 1976) reported that disruption of the fibers of the VOF by tumor or lesion is specifically associated with pure alexia. However, because it is only recently described, no diffusion-imaging studies have directly related the microstructure of the VOF to behavior. In addition, while the VOF is proposed to connect to several regions from occipital temporal cortex, we do not know which connectivity profiles support early literacy and literacy. Thus, in the present dissertation, we aim to characterize different subcomponents of the VOF and relate each component to early literacy and literacy. We also aim to address whether these pathway shows age-related changes or reading-related changes in young children.

Diffusion-weighted Imaging Techniques

Diffusion MRI is a non-invasive tool widely used to obtain information about the microstructural properties of white matter tracts *in vivo* (Basser, 1995; Basser et al., 1994; Basser & Pierpaoli, 1996). Diffusion MRI uses the diffusion process of water molecules in the brain. In white matter, the diffusion process of water typically runs parallel to axons rather than perpendicular to them. Two diffusion MRI techniques used to characterize white matter pathways are Diffusion Tensor Imaging (DTI) and High Angular Resonance Imaging (HARDI).

Diffusion Tensor Imaging (DTI). For DTI, at least 6 diffusion images with different sampling directions are needed, from which a tensor model can be fitted for anisotropic diffusion. The tensor model is described mathematically as a 3 × 3 matrix.

The diagonal components of the matrix result in the three eigenvalues and corresponding eigenvectors (i.e., x,y,z directions) at each voxel. Eigenvalues represent the magnitude of diffusion in the direction of the corresponding eigenvectors (Le Bihan & Van Zijl, 2002). Therefore, in white matter tissue, the largest eigenvalue is proposed to run along the direction of axons, and the other two eigenvalues are proposed run perpendicular to the direction of axons. Further, diffusion of water molecules along one main direction is called anisotropic diffusion, and random diffusion of water molecules (e.g., equal along all three directions) is called isotropic diffusion (Beaulieu 2002).

From the resulting eigenvalues, we can compute several indices of microstructural organization, including fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and apparent diffusion coefficient (ADC; Basser et al., 1994). Of these, the most widely reported measure is FA, which is a measure of the degree of anisotropic diffusion, with values ranging from zero (i.e., absolute isotropic diffusion) to one (i.e., absolute anisotropic diffusion). Fractional anisotropy is commonly used to quantify differences in white matter integrity (for a review, see Assaf & Pasternak, 2007). Thus, FA has been found to increase from infancy through early adulthood and found to decrease with normal aging (Lebel et al., 2012; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Fractional anisotropy is also suggested to increase with better performance on cognitive tasks, such as reading (Thiebaut de Schotten, Cohen, Amemiya, Braga, & Dehaene, 2012). From the diffusion-weighted scan, we can further calculate radial and axial diffusivity, which generally reflect myelin and axonal microstructural properties. More specifically, evidence from animal studies show that radial diffusivity values are suggested to increase with loss of myelin integrity and axial diffusivity values are suggested to increase in areas with axonal degradation (Song et al., 2005; Sun, Liang, Cross, & Song, 2008). Thus, radial diffusivity reflects diffusion processes perpendicular to the principal axis of diffusion, and axial diffusivity reflects diffusion processes along the principal axis of diffusion. In line with these findings, studies in the human show a negative relationship between radial and axial diffusivity indices with age (Kumar, Nguyen, Macey, Woo, & Harper, 2012) and also with cognitive functions such as word learning performance (López-Barroso et al., 2013).

Another diffusivity index is ADC, which reflects the magnitude of diffusion or the average diffusion within tissues. Similar to radial and axial diffusivity, studies show ADC decreases with age (Lebel & Beaulieu, 2011) and higher ADC values are related to poorer performance on cognitive tasks (e.g., reading speed) than lower ADC values (Bakhtiari, Boliek, & Cummine, 2014). Notably, the resolution of DWI is not adequate for making direct interpretations about microscopic properties of white matter, such as axonal density or myelin coherence, but rather diffusion indices reflect indirect measures of such biological microstructural properties. Moreover, DTI techniques less reliably resolve crossing, kissing, or branching fibers, which are numerous in the subcortical white matter and have been shown to bias diffusion indices (Wheeler-Kingshott & Cercignani, 2009). The HARDI methods are better at disentangling crossing fibers, but the acquisition time is much longer which makes it difficult to use in younger children (Descoteaux, Angelino, Fitzgibbons, & Deriche, 2007).

High-Angular-Resolution Diffusion Imaging (HARDI). High-angular-resolution diffusion imaging data are based on more complex mathematical models for describing and analyzing underlying white matter architecture than DTI. Whereas DTI is derived from the tensor model, where one predominant fiber direction is calculated for any given voxel, HARDI calculates the orientation distribution function (ODF) of diffusion displacement, where more than one predominate fiber direction is calculated for any given voxel (Yeh, Wedeen, & Tseng, 2010). Therefore, from the ODF, we can resolve crossing fibers and infer underlying microstructural properties. Diffusion indices for HARDI include generalized fractional anisotropy (GFA; Tuch, 2004), and quantitative anisotropy (QA; Yeh, Van Jay, & Wen-Yih, 2009). Generalized fractional anisotropy is strongly correlated with FA. Quantitative anisotropy is related to FA and GFA but are not convertible or interchangeable indices. For example, while FA and GFA are proposed to measure how fast water diffuses, QA is proposed to measure how much water diffuses (Yeh, Van Jay, & Wen-Yih, 2010). One limitation, however, to QA is that it is sensitive to the compactness of the fiber bundle, and this value varies across subjects. The limitation related to the compactness of the fiber bundle is resolved using normalized QA, which scales the maximum QA value to one (Yeh et al., 2013). The present study characterizes the fiber pathways associated with literacy skill using both DTI and HARDI techniques. The diffusion indices of interest include FA, ADC, RD, and AD for DTI data and GFA and NQA for HARDI data.

Research Aims

The current dissertation aimed to answer the following questions- Which indirect and direct perisylvian fiber pathways support early literacy and literacy development in young children? Do these fiber pathways show age-related change? Does left lateralization of these fiber pathways predict better behavioral scores? To address these questions, we composed the dissertation to include three separate studies. The first study investigated the relation between age-related differences in white matter microstructure and early literacy in young children 5-8 years old. To do this, we used diffusion-tensor imaging (DTI) to track several white matter pathways implicated in reading, including the inferior longitudinal fasciculus (ILF), vertical occipital fasciculus (VOF), arcuate fasciculus (AF) and its three sub-components, and the inferior fronto-occipital fasciculus (IFOF). The second study extended what we know about the relation between age-related differences in white matter microstructure associated with early literacy skill by investigating the relation between white matter microstructural properties and reading in a new and larger sample, over a wider age range, and across multiple times points. We had the opportunity to analyze both cross-sectional and longitudinal data in Study 2. Therefore, our results speak to both age-related differences and age-related change. For Study 2 we focused on tracts that were associated with early literacy from Study 1 and tracked them using more advanced diffusion-weighted imaging methods, specifically high-angular resolution imaging (HARDI). The HARDI method more reliably resolves crossing fibers, which are numerous in the subcortical white matter. We also broaden our age-range to include children aged 5-10 years old in our analysis of age-related change and investigated brain-behavioral relations supporting both early literacy and reading. In Study 3, we shifted our focus to the recently re-identified VOF. The present dissertation is notable in this respect in that it is the first (to our knowledge) to conduct a thorough analysis of VOF structural connectivity. Whereas in Study 1 and 2 we analyzed age-related and literacy-dependent differences of the VOF as a whole, that is by grouping occipital temporal regions as the seed region and grouping occipital and inferior parietal regions as the target region, in Study 3, we parsed the VOF into specific components and analyzed these components separately. To parse the VOF into components, we employed probabilistic tractography because this method allows for better tracing of white matter into gray matter regions. The current dissertation is also the first study to identify specific VOF components, and also investigate their age-related changes and their relation to behavior. Each of the three studies are detailed below.

II. STUDY 1

Research Question

In the present study, we investigated the age-related differences in the AF, ILF, IFOF, and VOF fiber pathways, and related their microstructural properties to behavioral measures of phonological awareness and decoding. We also investigated whether a left lateralized system predicts better early literacy skills, namely phonological awareness and decoding (i.e., the ability to read nonsense words). Given the paucity of literature on fiber pathways supporting early literacy development (which describes the precursors to literacy to which children are typically exposed to before the age of 7), we focused here on young typically developing children (5-8-years old). We also acquired measures of non-verbal ability and of auditory phonological processing to control for these measures in examining the relation between the investigated fiber pathways and early literacy skills.

We predicted that tracts of both the direct and indirect routes would be associated with early literacy skills. Specifically, several studies have reported that the AF is predictive of phonological awareness skill in typical children and in children at risk for dyslexia (Christodoulou et al., 2016; Myers et al., 2014; Vanderauwera, Vandermosten, Dell'Acqua, Wouters, & Ghesquière, 2015; Yeatman et al., 2012; Yeatman et al., 2011). In some cases, though, the association between the AF and early literacy skills is negative (Christodoulou et al., 2016; Yeatman et al., 2011). However, the direction of effects (whether microstructure of the AF is negatively or positively associated with early literacy), and the degree to which these findings extend to younger children (below 7-

years of age) is understudied. While we predict that the AF will be related to early literacy skills, we cannot make a strong prediction about the direction of effects.

In comparison to the AF, less is known about whether the ILF is related to early literacy skills such as phonological awareness. Some research suggests that the ILF is predictive of early literacy skill (Steinbrink et al., 2008; Wang et al., 2016; Yeatman et al., 2012). Other research does not (Saygin et al., 2013). Similarly, whether the IFOF plays a role in reading remains a matter of debate. While some research suggests that the IFOF is associated with literacy (Vandermosten et al., 2012b, 2015), others report no relationship between properties of the IFOF and reading, particularly in learning new words (López-Barroso et al., 2013). One problem in the existing literature is that studies do not control for confounding variables, such as age or white matter development in general, do not investigate young children, or otherwise do not investigate these pathways at all. The limited research does suggest, though, that we should discover a positive relation between ILF and IFOF microstructural properties and early literacy.

With respect the newly discovered VOF, while some authors speculate the VOF plays a role in literacy (Takemura et al., 2015; Yeatman et al., 2013), and lesion studies suggest this is the case (Greenblatt 1973, 1976), no diffusion-weighted imaging studies have directly related the VOF to behavior. Because of the VOF's putative connectivity with OTS/OTG and AG, which have been shown important for visual word processing and accessing semantic information of visuo-spatial features from word information (Dehaene et al., 2015), we predict that microstructural properties of the VOF will be related to early literacy. Finally, on the basis of findings from a previous functional imaging study suggesting left lateralization occurs at the onset of reading instruction

(Brem et al., 2010), we predicted that left lateralization of fiber pathways associated with early literacy would result in better phonological and decoding skills.

Method

Participants. Twenty typically developing children (10 females, 10 males; age range = 5-8 years, *M* age = 6.9 years, *SD* = 1.1 years) comprised the final sample. All participants were screened by phone for contraindication to MRI, were right-handed according to the Edinburgh Handedness Inventory, bilingual English/Spanish speakers with normal hearing (self-reported), had normal (or corrected to normal) vision, and were not seeking services for reading/language delay, or any other developmental disability or delay. An additional 3 children completed the diffusion-weighted scan but were not analyzed because of image artifacts indicated after the scan (one was the result of technician error; two were removed because of obvious motion artifact). An additional 11 children consented but did not complete the diffusion-weighted scan because of their refusal to assent, or to significant movement during the T1-weighted structural scan before the diffusion-weighted scan was initiated. Thus, a total of 34 children were tested to arrive at the final usable sample. Written informed consent/assent was obtained from all parents and children. All participants provided informed consent and assent, and the Western Institutional Review Board and the Florida International University Institutional Review Board approved the study.

General Procedure. Data were collected during two visits. The first included an MRI scan at Nicklaus Children’s Hospital, Miami, FL. The second visit was scheduled within two weeks of the first visit and took place at Florida International University, Miami, FL during which we administered a battery of speech, language, and early literacy measures.

Battery of Speech and Language Measures. In a session lasting about 90 minutes, the following assessments were administered to obtain a comprehensive understanding of each child's speech and early literacy ability: 1) Speech was assessed using the articulation and phonology subtests of the Diagnostic Evaluation of Articulation and Phonology (DEAP; Dodd, Hua, Crosbie, Holm, & Ozanne, 2010) and 2) early literacy was assessed using Word Attack (Test 3), Sound Awareness (Test 7), and Sound Blending (Test 8) subtests of the Woodcock-Johnson III Diagnostic Reading Battery (W-JIII; Woodcock, Mather, & Schrank, 2004). Word Attack is a measure of decoding, or the ability to read nonsense words, which requires application of the knowledge of letter-sound relations. The Sound Awareness and Sound Blending components combined provide a measure of phonological awareness (i.e., the understanding of the phonological or sound structure of words). We also measured non-verbal intelligence using the Block Design subtest of the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI – III; Wechsler, 2002) and Receptive Language (Concepts and Following Directions, Word Classes, and Sentence Structure) and Language Content Indices (Concepts and Following Directions, Word Classes, and Expressive Vocabulary) using the Clinical Evaluation of Language Fundamentals-4 (CELF-4; Semel, Wiig, & Secord, 2003). In this analysis we focus on literacy (W-JIII and related measure of DEAP phonology), and included the non-verbal intelligence measure as a covariate. Standardized scores were used in the analysis for all subtests.

Data Acquisition. Participants were scanned on a 3 Tesla Philips MRI scanner with a SENSE coil housed at Nicklaus Children's Hospital. Prior to the actual scanning session, participants underwent a simulated scan in a mock scanner to familiarize them to the MRI scanner environment. In addition, vitamin E capsules were placed on participants' fronto-temporal left forehead to verify orientation of images during post-processing. Diffusion-weighted images were collected for detecting age-related differences in white matter microstructure. Images were acquired using single-shot spin-echo echo-planar imaging sequence (15 gradient directions, *b* value = 900 s/mm2 and *b* = 0 s/mm2 (single reference scan), matrix size = 112×112, time echo [TE] = 60, time repetition [TR] = 6157, NEX = 3, FOV = 240×240 mm^2, slice thickness = 2 mm, number of axial slices = 55 (no gap), and voxel size = 0.938 mm × 0.938 mm × 2 mm). We also collected high-resolution T1-weighted anatomical images for each participant using an 8-min sagittal 3-D spoiled gradient recall (SPGR) sequence (120 axial slices, voxel size = 1.5 × .938 × .938 mm resolution). To minimize head motion, we placed cushions around the participants' head and secured a strap across their forehead. The duration of scanning time was less than 25 minutes per participant.

Diffusion Tensor Imaging Post-Processing. We used FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), DSI Studio (http://dsi-studio.labsolver.org/) and Matlab (http://www.mathworks.com) software packages for all analyses. Diffusion-weighted images were visually inspected for artifacts, including "striping" and susceptibility artifact (as noted, three children were removed at this stage). Images were denoised using the Non-Local Means Filter adapted to Rician noise distribution (NLMr; Coupe, Manjón, Robles, & Collins, 2012; Descoteaux, Wiest-Daesslé, Prima, Barillot, &

Deriche, 2008). Data were also preprocessed for eddy currents and subject motion, using affine registration to a single non-weighted diffusion reference image (*b* = 0). Using DSI Studio, we determined the tensors in each voxel using an over-determined linear equation system with least squares fitting (Jiang, van Zijl, Kim, Pearlson, & Mori, 2006). The gradient table, which is necessary to extract the diffusion tensor, was computed using an open source PARtoNRRD toolbox in Matlab (Farrell et al., 2007). The diffusion tensor was used to calculate the eigenvalues reflecting diffusion parallel and perpendicular to each of the fibers along 3 axes (x, y, z). The resulting eigenvalues were then used to compute indices of fractional anisotropy (FA), average diffusion coefficient (ADC), radial diffusivity (RD), and axial diffusivity (AD; Basser, Mattiello, & LeBihan, 1994; Hasan & Narayana, 2006). Fractional anisotropy is an index of the amount of anisotropic diffusion (i.e., diffusion parallel to the tract), normalized to take values from zero (isotropic diffusion) to one (anisotropic diffusion). Fractional anisotropy is sensitive to microstructural changes in white matter with higher FA values indicating more directional diffusion of water. Average diffusion coefficient (or mean diffusivity) is the average of the three principle eigenvalues, and represents the non-directional magnitude of diffusion. The ADC value can be decomposed into AD, measuring the parallel eigenvalue (λ_1), and RD, measuring the average of the secondary and tertiary perpendicular eigenvalues ($[\lambda_2 + \lambda_3]/2$). AD and RD quantifications are sensitive to axon integrity and myelin integrity, respectively (Beaulieu, 2009). These diffusion indices were calculated for each individual tract, bilaterally.

Fiber Tract Identification. All fiber tracking identification procedures were based on anatomical landmarks and defined on the fractional anisotropy map in DSI

Studio, with a fractional anisotropy threshold of 0.20 and fiber angles of less than 45° between connecting pixels (Catani & de Schotten, 2012). As recommended by Côté et al (2013) deterministic fiber tracking was used to track the fiber pathways. In order to maintain the anatomical integrity of the child brain, fiber tracking was conducted in the native MRI space. We manually reconstructed the following tracts: the arcuate fasciculus (AF) and its three segments, the inferior longitudinal fasciculus (ILF), the inferior fronto-occipital fasciculus (IFOF), and the vertical occipital fasciculus (VOF)**.**

Arcuate fasciculus (AF). We manually tracked the three segments of the AF. First, we tracked the whole AF using a single ROI on approximately 4 slices. The AF was defined as the green bundle of fibers running in the anterior-posterior direction located above the body of the corpus callosum and the posterior temporal stem, medial to the corona radiata, posterior to the precentral sulcus and anterior to the intraparietal sulcus (Catani & Thiebaut de Schotten, 2008; Catani, Jones, & ffytche, 2005). We also segmented the AF into three segments, namely the long (fronto-temporal), anterior (fronto-parietal) and posterior (temporo-parietal) segments. To track the long segment of the AF, we drew two ROIs on coronal slices, corresponding to the anterior and posterior boundaries, and a single ROI on an axial slice where the fronto-temporal connections project to temporal regions (Broce, Bernal, Altman, Tremblay, & Dick, 2015; Eluvathingal et al., 2007). Identical ROIs were used to track the anterior segment, with the exception that the axial ROI was loaded as a region of avoidance (ROA). To track the posterior segment, we used a five ROI approach identified on axial slices (Thiebaut de Schotten et al., 2012).

Inferior longitudinal fasciculus (ILF). We manually identified the ILF using a two-ROI approach (Catani et al., 2003). First we drew a temporal ROI on five axial slices posterior to the anterior portion of the external capsule. Second, we drew an occipital ROI on approximately 12-15 axial slices, with the parieto-occipital fissure serving as the superior border and the posterior end of the cingulum serving as the anterior border.

Inferior fronto-occipital fasciculus (IFOF). We manually identified the IFOF using a two-ROI approach (Forkel et al., 2014). We drew an occipital ROI on the white matter of the occipital lobe, posterior to the parieto-occipital sulcus and the temporooccipital notch, and a ventral ROI on the white matter of the external/extreme capsule.

Vertical occipital fasciculus (VOF). We also manually defined the VOF. The VOF was identified on the color map on approximately 4 sagittal slices as running superior–inferior, posterior to the AF and lateral to the ILF and IFOF (Pajevic & Pierpaoli, 1999; Takemura et al., 2015; Yeatman et al., 2013; see Figure 4). The ventral part of the VOF is proposed to include the fusiform, inferior occipital, or inferior temporal gyri. The dorsal part is proposed to include lateral occipital gyri and sulci and, in some accounts, angular gyrus. Investigating the fiber pathways associated with early literacy is the focus of the study. Thus, in this analysis we focused on projections from temporal (fusiform gyrus, lateral occipitotemporal sulcus, inferior temporal gyrus) to dorsal regions. To focus on projections from temporal to dorsal regions, we imported fusiform, lateral occipitotemporal sulcus, and inferior temporal ROIs provided by FreeSurfer's Desikan-Killiany parcellation available in DSI Studio (Desikan et al., 2006). These gray-matter ROIs were mapped to the participant's native space using nonlinear registration between the anisotropy map and the atlas, also included in the DSI Studio package, and were verified visually with reference to a published atlas (Duvernoy 1999). Fibers that projected to adjacent regions, including the inferior occipital gyrus, were excluded from the analysis. Thus, it would be more accurate to state that we tracked the subset of fibers of the VOF that emanate from the fusiform gyrus, lateral occipitotemporal sulcus, and inferior temporal gyrus, and connect to middle and superior occipital gyri and sulci, and posterior inferior parietal (angular gyrus) and superior parietal regions (although these parietal projections were not found in all subjects).

Analyses

Within the R statistical package (v. 3.2.4; http://www.R-project.org) we related our measures of white matter microstructure and laterality to age and to behavioral measures using robust estimates of correlation (r_{rob}; using the R function relplot; Wilcox, 2005) and robust regression (R function *rlm*; Wright & London, 2009). The American Psychological Association (APA; Wilkinson, 1999) recommends these procedures over traditional least-squares methods, which are heavily influenced by outlying values (Wilcox, 1998).

The robust correlation r_{rob} is similar to the Pearson *r,* but is less influenced by outlying values, a property that is desirable when dealing with smaller samples. Rather than removing outliers, the statistical procedure reduces their influence, and also produces a robust elliptical plot indicating outliers by placing them outside the outer ellipse of the plot (Goldberg & Iglewicz, 1992). The r_{rob} can be interpreted the same as the Pearson *r*. The robust regression also reduces the influence of outliers, in this case using a Huber loss function to apply different weights to each observation. The regression results can be interpreted in the same way as in least square regression. In fact, in cases where there are no outliers, robust methods will give identical results to least squares methods. We also improved the estimation of the reliability of the parameter estimate by using the bootstrap method (Efron 1981; 1987) to calculate the standard errors and 95% confidence intervals. Laterality was assessed using the formula (left-right)/(left + right) for each measure (Thiebaut de Schotten et al., 2011). Thus, positive values indicate left laterality.

Results

Identification of the Fiber Tracts. We were able to reliably track the bilateral ILF and right VOF in all children, the bilateral anterior, long, and posterior AF segments, and the right IFOF in 19 children, the left IFOF in 18 children, and the left VOF in 17 children**.** FA for these tracts fell within the normal range for children in this age range (Krogsrud et al., 2016; Morriss, Zimmerman, Bilaniuk, Hunter, & Haselgrove, 1999; Vandermosten et al., 2015), which serves as a validation of our tractography approach with respect to the available literature.

Age-related Differences, Sex Differences and Laterality in the Perisylvian White Matter. To characterize age-related differences of the tracts we conducted robust correlations. Table 1 summarizes the correlations for all measures. With respect to diffusion measures, significant correlations with age were revealed for FA (in left AF Long Segment; in right VOF), for AD (in right ILF and in left AF Posterior Segment), and for RD (in right VOF). For laterality indices, both Table 1 and Figure 5 (focusing on FA measures) show significant age-related differences in laterality. For the ILF and AF Long Segment, age was positively correlated with increasing left laterality (ILF FA, r_{rob}

= 0.49; $p < .05$; ILF AD, $r_{rob} = 0.65$; $p < .01$; AF Long Segment AD, $r_{rob} = 0.49$; $p < .05$). The opposite pattern was revealed for the VOF. In this case, increasing age predicted greater right laterality for the FA measure (VOF FA, $r_{rob} = -0.45$; $p < .05$) and greater left laterality for the RD measure (VOF RD, $r_{rob} = 0.57$; $p < .01$). Note that the opposing pattern for FA and RD measures is expected, given that they are inversely related (i.e., as FA increases, RD decreases).

All except one of these age effects survived when we controlled for sex, whole brain white matter microstructural properties (calculated for FA, ADC, AD, and RD), non-verbal ability (as measured by block design), and phonological ability (as measured by the DEAP phonology subtest). The exception to this is that the effect of age on right VOF FA was no longer significant. With sex included in the model, these linear models also revealed significant effects of sex in the left AF Long Segment (for Volume; $\beta = 0.48$, $p < .05$), and right AF Long Segment (for AD $\beta = -0.53$, $p < .001$, RD $\beta = 0.32$, $p < .05$). Sex differences in the development of these pathways have also been revealed in previous studies (Schmithorst 2009; Schmithorst & Holland, 2007; Schmithorst, Holland, & Dardzinski, 2008).

Relation of Perisylvian White Matter Pathways to Early Literacy Measures. To relate the white matter microstructure of the examined perisylvian fiber pathways to early literacy, we constructed robust linear models for each diffusion quantification (i.e., FA, ADC, AD, RD). Table 2 reports the effects after controlling for age in months, non-verbal ability (as measured by block design), sex, and whole brain white matter microstructural properties (calculated for FA, ADC, AD, and RD for each respective regressor of interest), and phonological ability (as measured by the DEAP phonology subtest). Although phonology and early literacy skills are related, phonological ability was included as a covariate in order to isolate literacy-specific skills of decoding and phonological awareness that require the isolation and manipulation of phonemic components in spoken and written words (Fowler, Brady, & Shankweiler, 1991; Webster & Plante, 1995; Webster, Plante, & Couvillion, 1997). We report those results in which the 95% CI did not cover zero. As Table 2 shows, the left ILF FA and AD positively predicted (and left ILF RD negatively predicted) phonological awareness. In contrast, the left and right VOF FA and AD negatively predicted phonological awareness. The left AF Posterior Segment (for AD), left AF Long Segment (for AD), right AF Posterior Segment (for ADC and AD), and right AF Anterior Segment (for AD) all negatively predicted early literacy measures. Right IFOF RD negatively predicted decoding. Finally, two laterality measures of the ILF—AD and ADC—predicted decoding.

Discussion

In this study we focused on the comprehensive network of fiber pathways supporting early literacy in typical 5-8-year-old children. The focus on very young, emerging readers is especially important given that reading intervention often occurs much later than it should, after children have already been immersed in formal schooling (Boscardin, Muthén, Francis, & Baker, 2008; Solis, Miciak, Vaughn, & Fletcher, 2014). In these young readers we report several novel findings that contribute to the growing understanding of the white matter connections supporting early literacy. Specifically, we found that a) the ventral pathway becomes increasingly important for the processing of phonological information as skills in phonological awareness and decoding are acquired, b) these skills become less associated with the dorsal AF route and with the VOF, and c) there is evidence for a shift from bilateral involvement in early literacy to a left-lateralized recruitment of brain regions involved in reading.

These findings are broadly consistent with emerging models of reading development that emphasize the importance of the left ventral occipitotemporal regions involved in phonological decoding of familiar and unfamiliar letter strings (Richlan, 2012). The findings suggest that as children acquire better phonological awareness and decoding skills, there is less reliance on the indirect phonological route (i.e., dorsal route) connectivity between temporal-parietal-inferior frontal regions via the AF, less reliance on direct connections between the ventral occipital-temporal lobe and angular gyrus via the VOF, and less reliance on the homologous tracts of the right hemisphere. Rather, there seems to be a shift to more reliance for these skills on the direct lexical-route (i.e., ventral route) involved in supporting the orthographic lexicon and fast, automatic word recognition. These findings are consistent with the idea that there is a bidirectional relation between the acquisition of literacy and reading-related phonological processing skills such as phonological awareness (Suortti & Lipponen, 2016). Thus, as children gain more exposure to text, they rely less on non-lexical form recognition systems to process words (Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003; Lonigan et al., 2009). It is also consistent with the Interactive Account of reading, proposed by Price, Devlin and colleagues (Devlin, Jamison, Gonnerman, & Matthews, 2006; Price & Devlin, 2011; Price & Mechelli, 2005a), in which, as children (and adults) learn to read, orthographic inputs come to more strongly trigger appropriate representations in phonological and semantic areas of the temporal lobes.

We reserve detailed discussion of the Study 1 findings to the General Discussion so they can be considered in the context of the other studies. However, briefly, we note that we replicate prior findings of a relation between microstructure of the AF and early literacy skill. Specifically, AD of the left AF long segment was associated with decoding, and the left AF posterior segment, and right AF anterior and posterior segment, were associated with phonological awareness. The white matter of the temporo-parietal region, which is comprised in part by fibers coursing as part of the AF, has also been associated with phonological skills in written (Klingberg et al., 2000; Thiebaut de Schotten, Cohen, Amemiya, Braga, & Dehaene, 2014) and in auditory (Han et al., 2016) language. For example, in young children increases in volume of the left dorsal white matter of the temporo-parietal region (Myers et al., 2014) and volume of the AF itself has been associated with reading skill. Relation between microstructure of the AF and our early literacy outcomes has also been found in older children (Vanderauwera et al., 2015; Vandermosten et al., 2015; Yeatman et al., 2012), for both phonological awareness and reading outcomes (Saygin et al., 2013; Wang et al., 2016). It is important to note that the association we found between these AF segments and literacy were negative. The implications of this are discussed in more detail in the General Discussion, but briefly, while a number of studies report a positive relationship, others show particularly in young children learning to read, reading ability and their developmental trajectories can significantly vary (Yeatman et al., 2011). Thus, the relation between the AF and early literacy is not necessarily straightforward, as we find again in Study 2.

With respect to the ILF, we found that several diffusion indices (namely FA, RD, and AD) of ILF microstructure were associated with phonological awareness. The direction and significance of the effects—i.e., increasing FA and AD, and decreasing RD are associated with better performance on the measures of phonological awareness—is broadly consistent with some prior work in older children (Yeatman et al., 2012; Wang et al., 2016). It does not replicate, however, the null finding reported by Saygin et al. (2013), who tested for, but did not find, a relation between ILF microstructure and phonological awareness in young children (pre-K and kindergarten aged children 4-5-years). Notably though, in conducting simple correlations between diffusion measures and the outcome measure, their analysis did not control for potential nuisance variables (e.g., age, sex, non-verbal ability and whole brain white matter values) that might hide or diminish the effects of interest. Furthermore, and potentially more importantly, in contrast to the children in our study, all of the children in that study were pre-readers. The ILF may become more important to literacy acquisition as the child acquires greater skill in reading. Like the AF, the functional significance for reading may shift over development, and the pattern we find may be specific to emerging readers. Thus, the pathway needs to be investigated in older children.

We found a similar negative association between phonological awareness and the bilateral VOF. Thus, left and right VOF FA, and left VOF AD is negatively associated with phonological awareness. While the functional role of the VOF remains unknown, it's connectivity profile suggests a potential involvement in reading development (Yeatman et al., 2014), There is empirical evidence to suggest that the VOF is an important reading pathway. For example, patients with tumors or lesions disrupting the fibers of the VOF have resulted in pure alexia (Greenblatt 1973; 1976). Our study is the first, to our knowledge, to reveal an association between the VOF and early literacy skill in young children. The data suggest that diffusion correlates of white matter microstructure of the VOF become less associated with phonological awareness as this literacy skill improves.

It is notable that the association between phonological awareness and the VOF was significant for both the left and the right VOF. The right hemisphere's contribution to reading has been investigated in a number of studies (Horowitz-Kraus, Wang, Plante, & Holland, 2014; Turkeltaub et al., 2003; Yamada et al., 2011). However, most available evidence suggests progressive disengagement of the right hemisphere as literacy development proceeds. For example, Turkeltaub et al (2003) used fMRI to show that, in children aged 6-22 years, learning to read was associated with increased left hemisphere middle temporal and inferior frontal activity accompanied by progressive decrease in activity of the right inferior temporal cortex. Additional compelling data were presented by Yamada and colleagues (2011). In that study of 5-year-old beginning readers, children who were on track in acquiring early literacy skills showed left lateralized activation in a letter-reading task, whereas children who were at-risk for reading delay (based on behavioral measures) showed bilateral activation during the task. Our data suggest some involvement of the right hemisphere in early literacy skills that may shift to left lateralization with age. Thus, in addition to the right VOF, we found significant (negative) associations with the right AF anterior and posterior segments, and an association between reduced RD and the right IFOF. But we also found that laterality of three pathways involved in early literacy, the ILF, VOF, and AF long segment, changed with age. For measures that typically increase with age (i.e., FA and AD), the ILF and AF became more left lateralized with age, while the VOF became more right lateralized. In the case of the ILF, left lateralization was also associated with decoding skill, which again suggests a shift to more recruitment of the left ventral reading pathway as children acquire early literacy skill.

III. STUDY 2

Research Question

In Study 1, we took a snapshot of the white matter pathways before neural reorganization occurs in response to acquisition of early literacy. Our data support the idea that a) the ventral pathway becomes increasingly important for the processing of phonological information as skills in phonological awareness and decoding are acquired; b) these skills become less associated with the dorsal AF route and with the VOF pathway connecting the ventral and dorsal visual streams; c) there is evidence for a shift from bilateral involvement in early literacy to a left-lateralized recruitment of brain regions involved in reading. As we noted, the findings are generally supportive of theories of literacy acquisition suggesting that as children (and adults) learn to read, orthographic inputs come to more strongly trigger appropriate representations in phonological and semantic areas of the ventral temporal lobes of the left hemisphere. However, these data should be considered with caution because of the relatively small sample, the restricted age range, and the fact that the data are from a cross-sectional design. In Study 2, we try to remedy both of these issues.

First, using a publically available data set, we are able to expand the sample size and the age range that we can explore. Reading continues to develop beyond 8-years (the maximum age in our sample in Study 1). Thus, we expand our age range in Study 2 to examine 5-10-year-olds. Second, we more than double our sample size. And finally, we consider the development of reading across three waves of data collection to examine it longitudinally.

We also improved upon the method of diffusion imaging from Study 1. In Study 1, we used a DTI model and examined age-related differences in metrics derived from this model. However, as we detail in the next sections, the DTI model is not ideal and performs poorly when fiber pathways cross or closely abut in the brain. Unfortunately, this is the *status quo* of brain connectivity—most fiber pathways in the brain are crossing or "kissing" (closely abutting) fiber pathways. In Study 2, we take advantage of a more advanced high angular resolution diffusion imaging (HARDI) method to acquire and model diffusion imaging data. The HARDI method, as we describe below, is better at resolving some of these crossing and kissing fibers in the brain. Our assumption is that we will extend our findings from Study 1 with new data, and also show more fully, using a longitudinal data set, how orthographic inputs trigger age-related changes in left ventral temporal regions supporting phonological and semantic representations necessary for expert reading.

Method

Participants. Study 2 included three annual waves of longitudinal diffusion-weighted MRI scans as well as early literacy measurements for the second wave of data and literacy measurements for the third wave of data. The initial cohort included children aged between 5-10 years old (*M*= 7.91 years, *SD*= 1.51 years, females= 26, males= 23). Demographics describing the participants across the three sample points are shown in Table 3. As part of the CMIND study, participants were screened for contraindications to MRI, were physically healthy, had a Body Mass Index within the 5th to the 95th percentile for age and gender and had no history for neurologic or psychiatric disease. All participants also scored above 85 on Full Scale IQ, were right-handed according to the

Edinburgh Handedness Inventory, native English speakers, had normal or corrected-to-normal vision and normal hearing, and maintained a least a C- average in school (children ages 6 and up). An additional 18 participants were not analyzed because of failure to complete the anatomical scan (*n*= *3)*, or did not pass image quality assessment (*n*= 15). Image quality assessment was performed following previous published methods (Yuan, 2009). A trained user of the CMIND web interface visually inspected the data. Images were assigned a quality rating that ranged from of 0 to 4, with 0 indicating good quality data and 4 indicating bad quality data. In the present study, HARDI images were included if quality was described as having no discernable motion or slice drop out (a score of 0) or some minimal motion that did not pose a threat to the integrity of the data (a score of 1). Written informed consent/assent was obtained from all parents and children. The Cincinnati Children's Hospital Medical Center IRB and Florida International University Institutional Review Board approved the study.

Behavioral Assessments. The following assessments were administered to obtain an understanding of early literacy and literacy skill: 1) Woodcock Johnson III Tests of Academic Achievement (WJ III; Woodcock, McGrew, & Mather, 2001), including the Letter Word, Passage Comprehension, and Word Attack subtests, and 2) Test of Word Reading Efficiency, Second Edition (TOWRE-2; Torgesen, Wagner, & Rashotte, 1999), Sight Word Efficiency, Phonemic Decoding Efficiency, and Total Word Efficiency subtests. The TOWRE-2 measures an individual's ability to read real words (Sight Word Efficiency) and their ability to read phonemically regular non-words (Phonemic Decoding Efficiency).

As a first check to assure the validity of the behavioral data, we assessed whether the Wave 2 scores of early literacy were correlated with Wave 3 scores of early literacy and literacy. We found that they were. Decoding skills at Wave 2 (i.e., WJ-III Word Attack standardized scores) significantly correlated with later decoding skills at Wave 3 (i.e., TOWRE-2 Phonemic Decoding Efficiency standardized scores; $r_{rob} = 0.87, p < .001$). We also found that early literacy letter-word identification ($r_{rob} = 0.69, p < .001$), passage comprehension ($r_{rob} = 0.71, p < .001$), and decoding ($r_{rob} = 0.65, p < .01$) skill at Wave 2 correlated with later reading at Wave 3 (TOWRE-2 Sight Word Reading). Figures for these analyses are presented in Figures 6-9.

MRI Scan protocols. All children were scanned at Cincinnati Children's Hospital Medical Center (CCHMC) on a 3T Philips MRI scanner, using a 32-channel SENSE head-coil. We analyzed the High Angular Resolution Diffusion Imaging (HARDI) data collected using a spin-echo single-shot EPI sequence. The following imaging parameters were used: FOV = 224 x 224 x 60 mm, 61 non-linear diffusion directions (b = 3000 s/mm^2) with seven non-diffusion-weighted images (b = 0 s/mm^2), each eight images apart, voxel size of 2 x 2 x 2 mm, acquisition matrix = 112 x 109, TR = 8112 ms, TE = 104 ms, SENSE factor = 3 (in A/P direction), total scan time = 9 min 53 sec.

High Angular Resolution Diffusion Imaging Metrics of Water Diffusion in vivo. In Study 1, we were restricted to the use of a DTI algorithm to reconstruct the fiber pathways of interest. While this metric is largely effective, and establishes reliable metrics of water diffusion in axons such as FA, AD, RD, and ADC, it is known to perform poorly under situations in which there are multiple fiber crossings in the white matter. That is, if two pathways are crossing or “kissing” (i.e., they touch closely), the DTI algorithm is unable to resolve the differences between the different fiber pathways.

Fortunately, advances in imaging methods have allowed for HARDI data acquisition of diffusion data, and with these acquisitions more advanced mathematical models of water diffusion can be implemented. These orientation diffusion distribution functions (ODFs) are designed to resolve multiple crossing fibers. Two metrics can be recovered from these diffusion models: Quantitative anisotropy (QA) and generalized fractional anisotropy (GFA).

Quantitative Anisotropy (QA). Quantitative Anisotropy is defined as the amount of anisotropic spins that diffuse along a fiber orientation, and it is given mathematically by:

$$QA = Z_0(\psi(\hat{a})\text{-}iso(\psi))$$

where ψ is the spin distribution function (SDF) estimated using the generalized q-sampling imaging, $\hat{a}$ is the orientation of the fiber of interest, and $iso(\psi)$ is the isotropic background diffusion of the SDF. The Z_0 is a scaling constant that scaled free water diffusion to 1 so that the QA value will mean the same thing across different participants (Yeh, Wedeen, & Tseng, 2010).

Figure 10 shows that QA can be defined for each peak in the SDF. Because deterministic tractography (which we use in this study) follows individual peaks across a string of voxels, we have focused on the first peak (QA_0), and we have additionally normalized the QA_0 metric so that it can be compared across different participants. This normalized QA metric, nQA, was calculated according to the generalized q-sampling imaging method from Yeh et al., (2010).

Generalized Fractional Anisotropy (GFA). Genderalized fractional anisotropy (GFA) represents an alternative indirect metric of white matter integrity that can be computed from a HARDI diffusion acquisition. It can be thought of as a higher-order generalization of FA (Descoteaux et al., 2007). The GFA metric thus begins with the ODF, and proceeds to rescale it by subtracting off the baseline term. Rescaling the ODF introduces a confound such that noise in the data, which rescales non-linearly, can appear to be anisotropic when that is not the case. The GFA corrects for this by rescaling the min-max normalized ODF with an anisotropy measure. From Tuch (2004), the GFA metric follows the same logic as the FA calculation. Thus:

$$FA = \frac{std(\lambda)}{rms(\lambda)}$$

where λ are the eigenvalues of the diffusion tensor.

GFA is given then by:

$$GFA(\psi) = \frac{std(\psi)}{\mathrm{rms}(\psi)} = \sqrt{\frac{n\sum_{i=1}^{n}(\psi(u_i)\text{-}\langle\psi\rangle)^2}{(n\text{-}1)\sum_{i=1}^{n}\psi(u_i)^2}}$$

where $\langle\psi\rangle = (\frac{1}{n}) = \sum_{i=1}^{n}\psi(u_i) = (\frac{1}{n})$ is the mean of the ODF. The output of the transformation is a scalar measure, GFA, which functions in a similar manner as FA for describing the anisotropic direction of water diffusion in the voxel. Like FA, the values range from 0 to 1.

We report GFA values only for descriptive purposes so that we can more easily relate the results to prior literature, but we note that recent empirical studies suggest that the QA measure is the better metric. In a direct comparison of FA, GFA, and QA, FA and GFA metrics led to the identification of more false fibers than QA, greater sensitivity to artefactual partial volume effects than QA, and poorer resolution of crossing fibers than QA (Yeh et al., 2013). In addition, Garyfallidis (2012) showed that the first component of QA can be used for cross-subject comparisons in a similar way to FA. Thus, we constructed the streamlines using that algorithm, and also use the nQA findings in our analysis of the relation of white matter microstructure to behavior.

HARDI Post-Processing. The image quality of the HARDI data was assessed using DTIPrep (http://www.nitrc.org/projects/dtiprep), which discards directions as a result of slice dropout artifacts, slice interlaces artifacts, and/or excessive motion. Participants with 45 directions or more were included in the study (Tournier, Calamante, & Connelly, 2009, 2013). All usable data were registered to the reference image (b=0), using a rigid body mutual information algorithm and also eddy current corrected for distortions.

Using DSI Studio, we used the generalized q-sampling imaging (GQI) model-free reconstruction method, which quantifies the density of diffusing water at different orientations (Yeh, Wedeen, & Tseng, 2010) to reconstruct the diffusion orientation distribution function (ODF), with a regularization parameter equal to 0.006 (Descoteaux et al., 2007). From this, we obtained GFA and nQA white matter indices. The calculation of GFA and nQA metrics were calculated as described in the previous section.

For fiber tract identification, we defined the fiber pathways using the same approach we described in Study 1. We used the same statistical approach as well, using robust linear models and bootstrapped confidence intervals.

Results

Identification of the Fiber Tracts. As noted above, the data consisted of three waves. For the first wave, there were a total of 49 usable scans. We were able to reliably track the bilateral ILF, VOF, AF Long Segment, AF Posterior Segment, and right AF Anterior Segment in all children and tracked the left AF Anterior Segment in 48 children. For the second and third wave of data, we reliably tracked the same tracts as in the first wave of data for all participants (second wave n = 30 children; third wave n = 19). A sub-sample of participants (n = 17) completed all three scans, and thus we were able to examine not only age-related differences (cross-sectionally), but also age-related changes (longitudinally) in the fiber pathways of interest.

Age-related Differences and Sex Differences at Wave 1. To characterize age-related differences (i.e., cross-sectional differences across participants at different ages) and sex differences of the tracts we conducted robust correlations and robust regressions. Examining simple robust correlations, we found no significant relations between age and GFA of any fiber tracts. When sex and whole brain GFA were added as predictor in the robust regression, we again found no effects, nor any effects of sex.

For the nQA measure, only the left ILF was correlated with age (r_{rob} = -0.31, p = .02). This effect held when sex and whole brain nQA were controlled ($t(45)$ = -2.52, p = .02). No significant sex effects were found for the nQA measure. There was a modest positive correlation between age and whole brain GFA (r_{rob} = 0.25, p = .08), but this was non-significant.

We also examined age-related differences in laterality (L = (L-R)/(L+R)) for each tract at Wave 1), but found no significant correlations between laterality and age at the first scan.

Age-related Changes Across Waves 1 – 3. A sub-sample of participants ($n = 17$) completed three scans, and thus we were able to examine age-related *changes* in the fiber pathways of interest. Figure 11 presents a summary of these results for the nQA measure. Similar results were found for the GFA measure. In general, we found a highly variable pattern of age-related changes in these fiber pathways, especially when they are considered along with the pattern we find for whole brain measures. When we examined the whole brain average, both GFA and nQA measures increased linearly with age, although this was only significant for the nQA measure ($\beta = 0.38$, $t(33) = 3.55$, $p = .001$). We also found linear increases in the left and right AF Long Segment (for nQA left, $\beta = 0.23$, $t(33) = 2.29$, $p = .03$; for nQA right, $\beta = 0.24$, $t(33) = 2.26$, $p = .03$), the right AF Anterior Segment (for nQA, $\beta = 0.24$, $t(33) = 2.20$, $p = .04$), and the left VOF (for GFA, $\beta = -0.19$, $t(33) = -2.01$, $p = .05$).

Early Laterality at Wave 1 Predicting Later Early Literacy and Literacy. We were interested in determining whether laterality of each fiber pathway at Wave 1 predicted early literacy (at Wave 2) and literacy (at Wave 3). For this analysis, we again calculated laterality as L = (L-R)/(L+R) for each tract at Wave 1. For early literacy, we found that greater left laterality predicted worse performance at Wave 2 for the AF Long Segment, the AF Posterior Segment, and the VOF. We found a similar pattern for Wave 3 performance, where early left laterality in all three AF segments predicted worse performance at Wave 3. Details of these results are presented in Tables 4 and 5.

Age-related changes predicting early literacy and literacy. To define age-related changes predicting early literacy and literacy, we conducted two analyses. We first examined the change scores between Waves 1 and 2 (Wave 2 – Wave 1) and related those to the Wave 2 early literacy and literacy measures (i.e., W-J III standardized scores). These relations were examined using the change scores in robust linear models to predict W-J III scores collected at Wave 2, controlling for sex, age at Wave 2, and whole brain nQA. In a second analysis, for those participants who had completed a Wave 3 assessment, we examined the change scores between Waves 2 and 3 (Wave 3 – Wave 2) and used those to predict early literacy and literacy measures collected at Wave 3 (i.e., TOWRE-2 standardized scores), controlling for sex, age at Wave 3, and whole brain nQA.

For the early literacy measures (Wave 2), we found that change scores in a number of pathways in both hemispheres positively predicted scores on the W-J III. In the left hemisphere, the AF Anterior Segment predicted Letter-Word scores, the AF Long Segment predicted Passage Comprehension, and the AF Posterior Segment predicted all three WJ-III measures (Letter Word, Passage Comprehension, and Word Attack). In the right hemisphere, the AF Anterior Segment and the AF Posterior Segment predicted Word Attack and Letter Word scores, while the ILF predicted scores on all three WJ-III measures. Details of the robust regressions are provided in Table 6.

For the literacy measures (Wave 3), we found that only the left ILF change scores predicted TOWRE-2 Sight Word Efficiency (b = 229.7 (96.7), $\beta = 0.48$, 95% CI = 38.1 to 417.3). No other significant relations between Wave 2 to 3 change scores and literacy were detected.

We also examined whether age-related changes in laterality predicted early literacy and literacy. We found no significant relations between age-related changes in laterality of any pathway and early literacy measures at Wave 2, nor did we find any relations for literacy at Wave 3.

Discussion

Using a more robust diffusion acquisition (HARDI), which is able to better resolve crossing fibers in the brain, and using a larger sample with multiple waves of data collection, Study 2 extends a number of findings from Study 1. First, we were able to track all of the fiber pathways we examined in Study 1 in almost all subjects (the exception was the IFOF, which we did not examine). When we examined age-related differences in these tracts, we found only that the left ILF nQA measure was correlated with age. Recall that in Study 1 we also found few associations with age in these pathways in 5-8-year-olds using the FA measure. We replicate that general pattern here with a larger sample. However, when we examine laterality for each tract at Wave 1, we found no significant relations between laterality and age. This does not replicate our findings from Study 1, where we found significant correlations between laterality and age for a number of fiber pathways (namely, ILF, AF Long Segment, and VOF). We note, however, that when these measures are examined longitudinally across waves, age-related *changes* in diffusion indices are revealed in a number of pathways (namely, bilateral AF and left VOF). We discuss the discrepancy between Study 1 and 2, and the advantages of examining longitudinal data, in the General Discussion.

The most interesting analyses deal with the relation between diffusion indices of these pathways and early literacy/literacy measures. With respect to behavioral measures of early literacy and literacy in general, we found that these measures are quite stable across waves. That is, the Wave 2 and Wave 3 behavioral measures were very highly correlated. We also found that both laterality indices at Wave 1, and *changes* in diffusion indices between waves, were associated with early literacy/literacy. Thus, for a number of fiber pathways (all three AF segments and the VOF), greater left laterality at Wave 1 was associated with *poorer* early literacy/literacy scores at both Wave 2 and Wave 3. The implications of this are discussed in more detail in the General Discussion, but briefly these findings are broadly in line with findings suggesting that individuals with more symmetrical pattern of connections, rather than extreme leftward lateralization, perform better at particular language related cognitive tasks (Catani et al., 2007a).

We also found that age-related *changes* in diffusion indices between Wave 1 and 2 predicted early literacy/literacy at Wave 2. These findings appeared across all W-J III measures, and in several pathways (bilateral AF in all segments, and right ILF). However, this pattern did not hold as children got older--in only one pathway (left ILF), age-related changes in diffusion indices between Wave 2 and 3 predicted TOWRE-2 Sight Word Efficiency at Wave 3.

Summary. Overall, we had the opportunity to compare our cross-sectional findings from Study 2 with our cross-sectional findings from Study 1. In particular, we found related but different age-related differences in several white matter tracts across the two studies. While we discuss these differences in more detail in the General Discussion, it is important to note that several methodological factors could be driving these differences. For example, in Study 2 we investigated a wider age-range, specifically children 5-10 years-old compared to children 5-8 years old, and we computed related but different diffusion measurements for HARDI data (e.g., Study 2: nQA and GFA) compared to DTI data (e.g., Study 1: FA, ADC, AD, RD). These diffusion parameters are sensitive to different properties of the diffusion signal and, therefore, describe different physical properties of white matter tracts, which cannot be interchangeable or convertible across methods. Thus, the age-related effects reported for Study 1 and Study 2 though related are describing different underlying microstructural properties of the tracts.

In Study 2, we also had the opportunity to assess different patterns of age-related change, that is developmental change, in the microstructural properties of several perisylvian white matter tracts and relate these measures to early literacy and literacy development. We investigated these relatons across three waves of data, which allowed us to determine whether development showed a linear or non-linear trend. Consistent with previous findings, we found that the perisylvian white matter tracts of interest predominately showed a linear developmental trajectory in young children (Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012). Other studies show a non-linear developmental trajectory in these tracts (Lebel & Beaulieu, 2011; Lebel et al., 2012). However, these studies were cross-sectional and investigate a much wider age range (e.g., 5-30-year-olds). Moreover, findings from Study 2 are broadly in line with research suggesting that patterns of white matter development differ significantly among children, and examining developmental change in diffusion measurements through longitudinal work has the advantage of providing more detailed and accurate patterns of both white matter development and reading development (Yeatman et al., 2012).

Both Study 1 and 2 substantially contributed to our growing understanding of fiber pathways supporting literacy development, but more importantly, for the first time, these studies revealed that the re-identified VOF plays a role in reading. As reviewed in earlier sections, the VOF is proposed to connect ventral occipital cortex to inferior parietal and occipital regions. However, it has been speculated that the VOF supports basic reading skill more specifically through connections from occipital temporal to angular gyrus, given that the angular gyrus is implicated in processing semantics in written language. Thus, one limitation to both Study 1 and 2 was investigating the VOF and literacy-dependent relations using grouped seed region of interests (i.e., fusiform gyrus, inferior temporal gyrus, and occipital temporal sulcus) and grouped target regions of interest (i.e., angular gyrus, intraparietal sulcus, middle and superior occipital gyri). By grouping our seed and target region of interests, it remained unclear whether the VOF more broadly contributes to literacy or whether particular connectivity patterns within VOF to particular target regions drive this brain-behavior relation. Therefore, in Study 3, we aimed to address this limitation and conduct a comprehensive analysis of the VOF by identifying different connectivity patterns between ventral occipital temporal cortex (i.e., fusiform gyrus and occipital temporal sulcus) and angular, intraparietal sulcus, and middle and superior occipital gyri.

IV. STUDY 3

Research Question

Previous research suggests the vertical occipital fasciculus projects from the occipital temporal cortex to lateral occipital regions, particularly the posterior intraparietal sulcus, middle and superior occipital gyri, and in some cases to the angular gyrus (Takemura et al., 2015; Yeatman et al., 2013; Yeatman et al., 2014). However, no studies have investigated the specific connectivity profiles from occipital-temporal to inferior parietal and occipital regions. It also remains unclear whether VOF specific cortical projections within occipital temporal regions differentially support early literacy and literacy abilities in young children. Therefore, the current study was designed to address the following research questions: 1) Does the VOF reliably project from occipital temporal cortex, namely occipital temporal sulcus and fusiform gyrus, to angular gyrus, known to be involved in processing written language? 2) Does the VOF reliably project from occipital temporal sulcus and fusiform gyrus to neighboring regions, including middle occipital, superior occipital, and intraparietal cortex? 3) Do different VOF subcomponents show different age-related changes? 4) Do different VOF subcomponents predict early literacy and literacy skill?

It was hypothesized that 1) voxels within the occipital temporal sulcus would reliably project to angular gyrus, intraparietal sulcus, middle occipital gyrus, and superior occipital gyrus; 2) voxels within the fusiform gyrus would project to the same regions but to a lesser degree than projections from the occipital temporal sulcus; 3) the VOF subcomponents will show age-related changes, and 4) of the specific VOF subcomponents, increase volume within occipital temporal sulcus and fusiform gyrus connecting to angular gyrus would result in better early literacy and literacy skill.

Method

Similar to Study 2, all data analyzed in Study 3 was obtained from National Institute of Child Health and Development (NICHD) Cincinnati MR Imaging of NeuroDevelopment (C-MIND) database, provided by the Pediatric Functional Neuroimaging Research Network at https://research.cchmc.org/c-mind/.

Participants. Study 3 included two annual waves of longitudinal diffusion-weighted MRI scans. Participants were included in the study if they had early literacy measurements from the second wave of data (year 2) and literacy measurements from the third wave of data (year 3). Demographics describing the participants across the two sample points are shown in Table 3. The procedures described below were applied to both data waves.

Anatomical Parcellation and Segmentation. We constructed surface-based models from the T1-weighted structural image of each individual using FreeSurfer (http://surfer.nmr.mgh.harvard.edu; Dale et al., 1999; Fischl et al., 1999; Fischl et al., 2002). Previous studies have successfully used FreeSurfer to create accurate surface representations for children (Dick, Bernal, & Tremblay, 2013; Tamnes et al., 2010). From FreeSurfer’s automated procedure, we obtained an anatomical parcellation and labeling of 74 cortical and subcortical sulci and gyri for each hemisphere. The anatomical parcellation scheme uses a probabilistic labeling algorithm based on the Duvernoy anatomical atlas (Cammoun et al., 2012; Desikan et al., 2006; Duvernoy 1991). All parcellations were visually verified for accuracy against a published atlas to ensure anatomical accuracy (Duvernoy, 1991). The parcellation of the brain into discrete sulci and gyri was used to extract seed and target masks to examine the connectivity of different VOF subcomponents.

Probabilistic Tracking Pre-processing Pipeline. First we aligned each participant's diffusion-weighted scan to their T1-weighted scan in FreeSurfer space. To do the alignment, we extract the b0 volume of the diffusion-weighted scan as a reference (i.e., source file), registered the source file to FreeSurfer space, and created a brain mask in source space. We registered the source file by calculating the transformational matrix from diffusion-weighted space to FreeSurfer space. We then extracted, binarized (threshold = 0.50), and dilated (voxel = 1) each participant's brain mask. From each participant's binarized FreeSurfer brain mask, we extracted our seed masks (i.e., left and right fusiform gyrus and occipital temporal sulcus) as well as our left and right cortical target masks (i.e., angular gyrus, intraparietal sulcus, middle occipital gyrus, and superior occipital gyrus). The FreeSurfer cortical parcellation labels and corresponding indices are specified in Table 7.

Using FSL BEDPOSTX (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT), we then used the quality controlled HARDI diffusion-weighted files and corresponding b-value and b-vector files to create the following outputs needed for probabilistic tractography: 1) samples and mean from the distribution on theta; 2) samples and mean from the distribution of phi; and 3) samples and mean from the distribution on anisotropic volume fraction. Together, theta and phi characterize the principal diffusion direction. Default parameters for BEDPOSTX, which are based on established methods (Behrens et al, 2007), were used to compute all samples and means from the distributions of phi, theta, and anisotropic volume fraction.

After BEDPOSTX was applied, we used FSL PROBTRACKX to recursively sample from the distribution of principal diffusion directions and create a connectivity sample at every voxel within the seed mask for each cortical target mask (intrahemispherically). Default probabilistic parameters were specified in this analysis (Behrens et al, 2007): curvature threshold = .2; number of samples = 5000; maximum number of steps= 2000; step length = 0.5. The output from PROBTRACKX was a single image in diffusion-weighted space, where all brain voxels within the seed mask had both a value of zero or one, depending on whether the target voxel was connected to the seed voxel (value of 1) or not (value of 0) and an index value corresponding to the target mask. Lastly, we extracted the volume within each seed mask proposed to connect to the target mask using AFNI 3dmaskave (https://afni.nimh.nih.gov). These volumetric measures were used to analyze brain and literacy-dependent relations.

Analyses

First, we related our measures of white matter microstructure to age and behavioral measures using robust estimates of correlation (r_{rob}; using the R function relplot; Wilcox, 2005). We also ran robust estimates of correlation to estimate the stability of the brain volume measurement from Wave 2 and 3 data. Then, we related brain volume measurements to behavior using robust regression (using the Huber loss function; Wilcox 2005). Separate analyses were conducted for each behavioral measurement (i.e., early literacy and literacy), sampled time point, hemisphere, and seed, target pair. In these analyses, gray-matter volume within the seed mask was our predictor, behavior was our outcome measure, and age and sex were included as covariates. Two seed masks were used for each hemisphere, the occipital temporal sulcus and fusiform gyrus, and four target masks were used for each hemisphere, the angular gyrus, middle occipital gyrus, superior occipital gyrus, and intraparietal sulcus. We also improved the estimation of the reliability of the parameter estimate using the bootstrap method (Efron 1981; 1987) to calculate the standard errors and 95% confidence intervals.

Results

Identification of VOF subcomponents. As noted above, the data consisted of two waves of data (i.e., waves 2 and 3). We found that fibers reliably projected from the occipital temporal sulcus to superior and middle occipital gyri and angular gyrus, bilaterally (Figure 12), and to the intraparietal gyrus but less reliably. We also found that fibers did not reliably project from fusiform gyrus to the target regions, particularly for the third wave of data. Therefore, for the remaining analysis we focus on OTS connectivity to target regions. Table 8 provides the mean (*M*) number of voxels within each seed masks connected to target mask.

Cross-sectional Analysis of Age-related Differences in the VOF subcomponents. To characterize age-related differences of the VOF subcomponents we used robust correlations. Figures 13-16 show robust elliptical plots for the volume count within each seed mask that projects to the target mask for Wave 2 and Wave 3, and Table 9 summarized the robust correlations between age and seed-target volume connectivity for Wave 2 and 3. Age was not significantly associated with any brain measures.

Relation of the VOF subcomponents to Early Literacy and Literacy. We examined the relation between VOF seed-target connectivity and early literacy and literacy skills with a series of robust linear models. Table 10 reports the effects after controlling for age in months and sex. We report only those results in which the 95% CI did not cover zero. We also calculated *p* values for each relation of interest. We found that connections projecting from the left occipital temporal sulcus predicted early literacy. More specifically, for Wave 2, we found that OTS-AG (b = 0.60 (0.27), β = 0.52, 95% CI = 0.08 to 1.13) connectivity positively predicted passage comprehension and left OTS-IPS connectivity negatively predicted passage comprehension (b = -1.21 (0.54), β = -0.50, 95% CI = -2.26 to -0.13) and decoding (b = -1.61 (0.55), β= -0.67, 95% CI = -2.68 to -0.52). For Wave 3, we found that left OTS-MOG (b = 21 (0.07), β = 0.79, 95% CI = 0.07 to 0.34) and right OTS-SOG (b = 0.19 (0.08), β = 0.82, 95% CI = 0.04 to 0.34) connectivity positively predict decoding. For our laterality measures, we found that left lateralized OTS-SOG connectivity predicted better phonemic decoding skills for Wave 3 (b = 18.34 (6.08), β = 0.60, 95% CI = 6.55 to 30.37).

Longitudinal Analysis of Age-related Changes Predicting Early Literacy and Literacy. Similar to Study 2, to define age-related changes predicting early literacy and literacy, we first examined the change scores between Wave 3 and 2 (Wave 3 – Wave 2) and related those to the Wave 3 measures of early literacy and literacy. Therefore, the relations examined used the change scores in robust linear models to predict TOWRE-2 standardized scores collected at Wave 3, controlling for sex and age at Wave 3. We found no significant relations between age-related changes in brain volume within the OTS to any target mask and literacy measures at Wave 3.

Discussion

The present study is the first, to our knowledge, to identify and describe different patterns of VOF white matter connectivity between occipital temporal cortex and inferior parietal and occipital cortex. To identify different connectivity patterns of the VOF, we used advanced probabilistic tractography, which in comparison to diffusion tensor imaging, has better success in tracing white matter connections into gray matter (Behrens et al., 2003). Broadly, findings of the present study contribute to our growing understanding of white matter connectivity, white matter development, and brain-behavioral relations supporting early literacy and literacy skill in young children.

VOF Patterns of Connectivity. Consistent with previous studies (Keser, Ucisik-Keser, & Hasan, 2016; Takemura et al., 2015; Yeatman et al., 2013; Yeatman et al., 2014), we found that the VOF connects occipital temporal cortex to inferior parietal and occipital regions. However, more specifically, we found that VOF fibers from occipital temporal sulcus project to angular gyrus, middle and superior occipital gyri, and intraparietal sulcus, bilaterally. We also found that greater brain volume within the occipital temporal sulcus projected to middle and superior occipital gyri and lesser brain volume within the occipital temporal sulcus projected to the intraparietal sulcus, across both hemispheres and waves of data. While we found no significant relations between age-related differences or age-related changes in brain volume within the OTS to any target mask, we did show that particular left and right VOF occipital temporal sulcus connectivity profiles predicted early literacy measures. Specifically, we found that at Wave 2 left VOF projections from the occipital temporal sulcus to angular gyrus positively predicted passage comprehension and to intraparietal sulcus negatively predicted both passage comprehension and non-word reading (decoding). At Wave 3, we found that projections from left VOF occipital temporal sulcus to middle occipital gyrus and left lateralization of occipital temporal sulcus to superior occipital gyrus positively predicted decoding, while projections from occipital temporal sulcus to right superior occipital gyrus negatively predicted decoding.

VOF Occipital Temporal Connectivity at Wave 2. Study 3 revealed that brain volume within the VOF occipital temporal sulcus projecting to angular gyrus supports early literacy skill, namely with passage comprehension. Broadly these findings are in line with previous neuroimaging research. For example, functional neuroimaging studies propose the occipital temporal sulcus supports whole word reading (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2011; Brem et al., 2009; Olulade et al., 2013; Vinckier et al., 2007) and the angular gyrus supports semantic processing (Bitan et al., 2006; Booth et al., 2004). Therefore, while the OTS and AG are proposed to participate in different neural computational processes, they work together to support passage comprehension, a skill that requires both reading printed words and extracting meaning from those words.

We also found a relation between brain volume within the OTS projecting to the intraparietal sulcus and both passage comprehension and non-word reading. One line of research has shown that the left IPS is functionally connected to occipital temporal regions and in particular plays an important role in verbal short-term memory and attentional processes (Majerus et al., 2006). A different line of research suggests that the left intraparietal sulcus is associated with performance on a rhyming judgment task (Bitan et al., 2007), a task which is similar to the non-word reading task in the TOWRE-2.

Collectively, results from our study and support from previous functional imaging studies suggests that left OTS-IPS connectivity support early literacy abilities.

VOF Occipital Temporal Connectivity at Wave 3. Study 3 found that white matter VOF projections from left OTS-MOG, right OTS-SOG, and left lateralization of the SOG predicted non-word reading, that is decoding. These data converge with reports from investigators using functional brain imaging (Morken, Helland, Hugdahl, & Specht, 2014; Xu et al., 2015; Shaywitz, 2004). For example, fMRI research has found both middle occipital gyrus and posterior ventral occipital temporal cortex to be functionally connected during a real word reading task (Xu et al., 2015), and that left middle occipital gyrus is significantly functionally activated in response to alphabetic processing, orthographic processing, and sentence processing (Morken, Helland, Hugdahl, & Specht, 2014). Moreover, Cornelissen and colleagues (2009) reported, in an event-related magnetoencephalography study, that the MOG responds within the first 200 ms of reading, suggesting that the MOG may play a larger role in visual-letter stimulus processing than semantic processing during reading (i.e., the 200 ms response is too early to suggest processing at the lexical level). Our study, therefore, corroborates with the extant literature by suggesting that these interactions are possibly implemented by a subcomponent of the VOF.

Lastly, we found that the right OTS-SOG and left lateralization of OTS-SOG connectivity significantly predicted decoding at Wave 3. While the right SOG has been implicated in memory function more broadly (Ventre-Dominey et al., 2005; Piekema et al., 2006; Piekema et al., 2009; Mei et al., 2010), some evidence has shown that the right SOG participates in successful encoding of words (Mei et al., 2010). In addition, at least one study has found the right SOG to be activated during a non-word reading task (Pekkola et al., 2005). Taken together, our study provides initial evidence suggesting VOF right OTS-SOG structural connectivity supports literacy function, and other research suggests that it does so by facilitating encoding of words. The left SOG, however, has been implicated as part of a common semantic system for words and pictures (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). Our results show a strong relationship between VOF left lateralization of OTS-SOG connectivity for reading non-words. Noteworthy, evidence has shown that semantic systems are not only engaged during real word reading but also during non-word reading, such as when individuals incorrectly accept a non-word (e.g., Jeap) as a member of a particular category (e.g., a vehicle; Coltheart, Patterson, & Leahy, 1994).

Summary. The present study is the first to investigate the particular VOF white matter projections from bilateral occipital temporal cortex, their corresponding age-related changes, and their relation to early literacy. We found that 1) subcomponents of the VOF occipital temporal sulcus project to several regions, including angular gyrus, middle and superior occipital gyri, and intraparietal sulcus, 2) subcomponents of the VOF fusiform gyrus also project to these regions but do so unreliably 3) VOF occipital temporal sulcus connections do not show age-related changes across the 7-12 age range, 4) VOF occipital temporal sulcus specifically predict early literacy measures, and 5) both left and right hemispheres support in early literacy function.

V. GENERAL DISCUSSION

Summary

The current dissertation aimed to answer the following questions: Which perisylvian fiber pathways support early literacy and literacy development in young children? Do these fiber pathways show age-related change? Does left lateralization of these fiber pathways predict better early literacy and literacy scores? We focused on four perisylvian fiber pathways that have been proposed to support reading, namely the arcuate fasciculus (AF) anterior, long, and posterior segments, the inferior longitudinal faciculus (ILF), the inferior fronto-occipital fasciculus (IFOF), and the vertical occipital fascuclus (VOF). In addition, we employed several different methodological and analytic techniques across three separate studies to better answer these questions.

In the first study, we investigated age-related and early literacy-dependent differences in white matter microstructure in young children 5-10-years old using diffusion tensor imaging. In the second study, we used longitudinal data to investigate age-related *changes* in white matter microstructure associated with early literacy and literacy skill. We used more advanced diffusion-weighted techniques (i.e., HARDI), which more reliably resolves crossing fibers within voxels, focused on a wider age range, added a reading measure to our early literacy measures, and analyzed three waves of data collected one year between sessions. Thus, Study 2 allowed us to not only examine age-related differences (cross-sectional sample) but also developmental differences (longitudinal sample) in white matter and reading development. Finally, for Study 3, we focused on better understanding the connectivity profile of the vertical occipital fasciculus. While in Studies 1 and 2 we explored brain-behavioral relations of the VOF as a whole, in Study 3 we parsed the VOF into subcomponents and related connectivity of these subcomponents to early literacy and literacy.

Our neurobiological parameters of interest for diffusion tensor imaging (Study 1) were fractional anisotropy (FA), apparent diffusion coefficient (ADC), radial diffusivity (RD), and axial diffusivity (AD). Diffusion parameters are sensitive to several properties of the diffusion signal. For example, with increases in myelination and axonal density, FA and AD generally increase, and ADC and RD generally decrease. Our neurobiological parameters of interest for HARDI (Study 2) were generalized fractional anisotropy (GFA) and normalized quantitative anisotropy (nQA). With increases in myelination and axonal density, both GFA and nQA generally increase. Our neurobiological parameter for Study 3 was brain volume within the occipital temporal seed region projecting to specific target regions. Lastly, for both Studies 2 and 3, we computed change scores (e.g., nQA Wave 2 – nQA Wave 1) to assess white matter development and reading development.

All behavior measures used in the present dissertation are listed and defined in Table 11. Our behavioral measures of interest were phonological awareness and decoding in Study 1, and letter-word identification, passage comprehension, decoding, and word reading in Studies 2 and 3. Letter-word identification requires children to identify letters and then read a list of words. Passage comprehension requires children to provide a missing word removed from a sentence or short paragraph. Decoding requires children to read non-words or pseudowords (e.g., jeap). Collectively, these three measures- letter-word identification, passage comprehension, and decoding- are considered basic reading skills (Woodcock, Johnson, & Mather 1990).

In this General Discussion, first I review the white matter fiber pathways supporting early literacy and literacy. I address the discrepancies between studies where necessary, and address how findings from our studies relate to the extant literature. Next, I review age-related changes associated with microstructure of literacy-related fiber pathways, followed by a review of their patterns of lateralization. I end with a discussion about theoretical implications of the current dissertation, future directions, and limitations.

White Matter Pathways Supporting Early Literacy and Literacy. Converging evidence from post-mortem, transcranial stimulation, diffusion-weighted MRI, and lesion studies suggest that the contemporary anatomical brain network supporting reading is organized along two distinct processing routes: 1) a dorsal indirect phonological route and 2) a ventral direct lexical route (for a review, see Vandermosten, Boets, Wouters, & Ghesquière, 2012). Whereas the dorsal indirect phonological route is associated with reading readiness abilities, such as processing phonological information, mapping letters to speech sounds, articulating, and naming, the ventral direct lexical route is associated with more advanced reading abilities such as mapping orthography to semantics, reading fluency, and reading accuracy (Vandermosten, Boets, Wouters, & Ghesquière, 2012). As reviewed in the Introduction, there is little consensus regarding which fiber pathways are important for successfully learning to read, particularly in the developing child. For example, in one review the AF and its three segments, ILF, and IFOF were proposed as key fiber pathways for reading, but the VOF was not, essentially because it had not yet been studied using modern imaging methods (Vandermosten, Boets, Wouters, & Ghesquière, 2012). In a different, more recent, review on reading development, the AF, ILF, and VOF were proposed as key fiber pathways for reading (Wandell & Yeatman, 2013), but the IFOF was not. Moreover, the VOF was only speculated to play a role based on its connectivity profile, but no study had related its microstructural properties to behavior. Findings from the current dissertation are in line with Wandell and colleague's (2013) account on reading development. We found that the three segments of the AF and ILF were related to early literacy and literacy skill, and we provide initial support to suggest the VOF is also related to early literacy and literacy skill. In the following section, we discuss how findings from the current dissertation relate to findings from the extant literature, particularly as these findings relate to learning to read in children.

AF Anterior Segment. The anterior segment of the AF, considered part of the dorsal phonological route, is analogous to the third subcomponent of the SLF (SLF III; Makris et al., 2005) and proposed to connected inferior frontal lobe, particularly *pars opercularis* (IFGOp) to supramarginal gyrus (SMG) and superior temporal gyrus/suclus (STG/STS).

Results from the current dissertation showed that in children 5-12 years old, age-related changes in white matter organization in left and right anterior segment predicted children’s basic reading abilities (Study 2). In addition, the right anterior segment predicted decoding (Study 2) and predicted phonological awareness in younger children, 5-10-years-old (Study 1). These results are broadly in line with neuroimaging research, which implicate regions connected by the anterior segment in the maintenance of phonological representations in working memory (Paulesu et al., 1993), letter-by-letter reading (Cohen et al., 2004), non-word reading, and word reading (Sandak et al. 2004; Posner & Raichle, 1994; Borowsky et al., 2006; McDermott et al., 2003). Findings from the current dissertation are also broadly in line with the relatively few diffusion-weighted imaging work investigating structural connectivity of the anterior segment and reading. For example, in a recent study, Travis and colleagues (2016) report that the left, but not the right, anterior segment predicts decoding and phonological awareness in 6-year-old readers compared to pre-readers. Similarly, Saygin and colleagues (2013) reported that neither the left or right anterior segment was associated with phonological awareness in 4-6-year-old pre-readers and early readers. However, both our cross-sectional sample of 5-10 year olds and a cross-sectional sample of 7-11 year olds from a previous study (Yeatman et al., 2011), examined, but did not find, a relation between left anterior segment microstructure and phonological awareness. Nonetheless, when we conducted our longitudinal analysis (Study 2), we did find that both left and right anterior segment predicted decoding and word reading. Collectively, these findings suggest that when children who are readers are compared to pre-readers, or when age-related changes in white matter microstructure are accounted for, anterior segment involvement in literacy becomes apparent. However, when children have little to no exposure to reading or when cross-sectional work among young children is conducted, anterior segment involvement in literacy is not apparent.

Moreover, contrary to the evidence discussed above, our longitudinal analysis reports involvement of the right anterior segment in early literacy. In general, relatively few studies investigate the relation between the anterior segment and reading, and some test only for left brain-behavior relations and not right brain-behavior relations (Yeatman et al., 2011). Nevertheless, some evidence suggests that microstructure of the right anterior segment (SLF III) is associated with visual short-term memory processing

(Chechlacz, Gillebert, Vangkilde, Petersen, & Humphreys, 2015) and damage to it results in visuospatial deficits (Rauschecker et al., 2009). Recent behavioral research suggests that visuospatial memory abilities in children 9-12-years-old are predictive of reading abilities (Pham & Hasson, 2014). Further, fMRI research suggests that right frontal and parietal regions, (i.e., regions potentially connected by the right anterior segment) play a role in phonological decision making (Hartwigsen et al., 2010a, 2010b). Thus, while our study provides initial support for involvement of the right anterior segment in reading, and other studies suggest that the right anterior segment may support reading through visual memory or phonological decision-making mechanisms, more generally, its involvement in reading remains poorly understood.

AF Long Segment. Substantially more research has investigated involvement of the left and right AF long segment in early literacy and literacy abilities. For example, in young children increases in the volume of the AF long segment (Saygin et al., 2013) was positively associated with phonological awareness, and of reading outcomes more generally (Wang et al., 2016). The AF long segment and early literacy and literacy relations have been found in older children as well (Vanderauwera et al., 2015; Vandermosten et al., 2015; Yeatman et al., 2012). Our findings are generally compatible with these studies and other diffusion MRI studies. For example, in Study 1, we found that AD of the left long segment was associated with decoding in young children 5-10 years old. However, the association we found between the long segment and literacy measures was negative. Although the negative AF long segment-literacy association is the opposite of what has been reported in a number of studies, not all studies show a positive association between the long segment and phonological awareness and decoding.

For example, Christodoulou and colleagues (2016) found the same negative association between AD and pseudoword reading in typical children and found no significant association for the FA measure. The negative association was interpreted by Christodoulou and colleagues as reflecting a specific pattern of white matter development in children who are just learning to read, a pattern that changes as children become expert readers. Moreover, in children 7-11-years, Yeatman and colleagues (2011) found a negative relation between phonological awareness and microstructure of the left long segment. In a follow-up longitudinal study, Yeatman and colleagues (2012) showed that for the left long segment, but not the right, younger children who are good readers have FA that declines over time, and those who are poor readers have FA that increases over time. The trend, where the left AF long segment, but not the right, predicts reading outcomes was replicated in a longitudinal study with older children 8-16 year olds (Gullick & Booth, 2015) and now in our longitudinal study (Study 2) with younger children 6-12 years old. Thus, an emerging trend featured by longitudinal work, though not the only trend, is that early on, lower FA of the AF long segment is generally associated with better reading ability.

AF Posterior Segment. Findings from Study 1 and 2 found that the left and right AF posterior segment support reading skills. These findings are in line with a recent diffusion-weighted imaging study showing that learning to read changed the microstructure properties of the left and right posterior AF segment (Thiebaut de Schotten et al., 2012). In that study, Thiebaut DeSchotten et al. found that adult illiterates had lower FA in the posterior AF segment compared to adult literates who learned to read as children and ex-illiterates who learned how to read as adults. Interestingly, FA in the posterior segment did not differ between literates and ex-literates. The authors propose these findings suggest that changes in microstructure of the AF posterior segment are malleable and can improve well into adulthood as a result of schooling.

Evidence suggesting the posterior AF segment to be critical for reading development in children is less clear than in adults. Travis and colleagues (2016) found no evidence for the AF posterior segment supporting reading in 6-year-old readers or pre-readers. Gullick and Booth (2015), in a longitudinal study of children 8-17 years old, found that across two waves of data, when analyzed cross-sectionally, the posterior segment FA trended towards a significant negative correlation across both time points. We report the same negative trend from our cross-sectional sample (Study 1). However, when Gullick et al. analyzed their data longitudinally, that is by examining change in performance between time points, they did not find a relation between the posterior AF segment and reading. In our longitudinal sample, we found that changes in microstructure of both the left and right posterior segment predicted reading outcomes. One possible explanation for the inconsistent findings between Gullick et al. and ours is that children in that sample were older (Wave 1 age-range = 8-14 years old; Wave 2 age-range = 13-17 years old) than our children (Wave 1 age range = 5-10 years old; Wave 2 age range = 8-11 years) and the gap between testing sessions was larger in their study (2-4 years) than ours (1 year). Therefore, children in our sample potentially had more varying levels of reading experience than the sample in Gullick et al., particularly at Wave 1, and learning to read potentially results in rapid change of microstructural structure within the posterior AF segment (1 year compared to 2-4 years). It is possible that we were in a better position to detect these subtle changes in the white matter of the AF related to reading.

Inferior Longitudinal Fasciculus (ILF). Study 1 found that diffusion measures (namely FA, RD, and AD) of the left ILF microstructure were correlated with phonological awareness. The direction and significance of the effects, that is increasing FA and AD, and decreasing RD, were associated with better performance on the measures of phonological awareness. In Study 2, we found that change in performance between Wave 1 and 2 predicted reading in both left and right ILF. Our work is broadly consistent with recent diffusion MRI studies. For example, in a longitudinal DWI study of 55 7-12-year-old children, Yeatman and colleagues (2012) showed that the rate of change in FA in the left ILF was predictive of phonological awareness and total reading scores. In another longitudinal study, rate of FA change of the left ILF was also found to correlate with silent word reading efficiency in 5-12-year-old pre-readers (Wang et al., 2016). Our findings are, however, inconsistent with Saygin et al. (2013), who tested for, but did not find, a relation between ILF microstructure and phonological awareness in 4-6-year-old pre-readers and early readers. Several factors could explain the inconsistent findings. For example, in conducting simple correlations between diffusion measures and the outcome measure, Saygin et al.'s analysis did not control for potential confounding variables, such as age and sex, that might influence the effects of interest. In addition, all of the children in that study were pre-readers and the children in our studies have varying levels of reading ability. Thus, it may be that microstructural organization of the ILF may be more sensitive to change as children gain reading experience.

Vertical Occipital Fasciculus (VOF). The VOF is a recently re-identified fiber pathway connecting the ventral and dorsal streams, and is dissociable from the posterior AF (using both our deterministic method, and probabilistic methods; Weiner et al., 2016).

The VOF has been speculated to play an important role in reading development on the basis of its connectivity profile from occipital temporal cortex and angular gyrus (Yeatman et al., 2014). There is empirical evidence to suggest that the VOF plays a critical role in reading. Postmortem studies of patients with lesions (Greenblatt 1973; 1976) have reported that a tumor or lesion disrupting the fibers of the VOF is specifically associated with pure alexia. However, the current dissertation is the first, to our knowledge, to establish an association between the VOF fiber pathway and reading in developing readers. More specifically, in our cross-sectional sample of young children (Study 1), we found that the left and right VOF FA, and left VOF AD was negatively associated with phonological awareness. We also found that, similar to previous work, the majority of VOF fibers projected from the lateral occipitotemporal regions (including VWFA) to the lateral superior and middle occipital extrastriate regions, and in some subjects to the posterior angular gyrus (Yeatman et al., 2013). The same VOF connectivity profile found in Study 1 was observed in Study 2, but we did not replicate the left and right VOF brain and literacy-dependent relations in Study 2. One explanation for this discrepancy is that change in VOF white matter microstructure as a consequence of reading experience could be marked by a more protracted trajectory and therefore changes cannot be detected within an annual gap between testing sessions. Another possible explanation is because we analyzed the VOF as a whole across Studies 1 and 2, changes in microstructure of the VOF differ significantly across separate occipital temporal cortex and target regions and therefore particular connections, unrelated to reading, could have significantly influenced our results.

Visual inspection of the VOF tracts across Studies 1 and 2 revealed three to four consistent subcomponents across subjects. The observation of different VOF subcomponents was the motivation for Study 3, where we conducted a comprehensive analysis of VOF connectivity. We found that fibers of the VOF reliably projected from occipital temporal sulcus to angular gyrus, middle and superior occipital gyri, and intraparietal sulcus. They also projected from the fusiform gyrus to these regions, but unreliably. In addition, we found that VOF occipital temporal sulcus connectivity was associated with early literacy and literacy measures but fusiform connectivity was not. The finding for VOF occipital temporal sulcus specificity associated with early literacy and literacy is consistent with research suggesting the visual word form, which preferentially processes words compared to other stimuli (McCandliss et al., 2003; Szwed et al., 2011) and more specifically processing visual word forms as integrative visuospatial perceptual units (Dehaene & Cohen, 2011; Dehaene, Le Clec'H, Poline, Le Bihan, & Cohen, 2002; McCandliss et al., 2003; Price & Devlin, 2011), is located within the left occipital temporal sulcus bordering the fusiform gyrus (McCandliss et al., 2003). Results from our study found that VOF projections from left OTS to left angular gyrus and left OTS to right middle occipital gyrus positively predicted reading outcomes. The VOF projections from left OTS to left intraparietal sulcus and right OTS to right superior occipital gyrus negatively predicted reading outcomes. Based on fMRI research, VOF projections to angular gyrus potentially support semantic processes involved in reading, projections to middle occipital gyrus support non-lexical visual perceptual processes involved in reading, and projections to left intraparietal sulcus and right superior occipital gyrus supports memory processes involved in reading (Bitan et al., 2007; Bitan et al., 2006; Booth et al., 2004; Morken, Helland, Hugdahl, & Specht, 2014). In sum, results from the current dissertation show that in young children, the VOF as whole plays an important role in phonological processing, and as children gain more reading experience, individual components, rather than the VOF as a whole, differentially support more advanced reading skill.

Age-related Differences in White Matter Microstructure. In Study 1 we found age-related differences in the left AF long segment, VOF, and ILF. We found a similar pattern is Study 2. The left ILF, left and right AF long segment, right AF anterior segment, and left VOF segment showed age-related changes. Thus, the present dissertation provides novel evidence that the VOF shows age-related change in young children. Our findings are also broadly in line with other research showing AF age-related differences in children (Barnea-Goraly et al., 2005; Brauer, Anwander, Perani, & Friederici, 2013; Eluvathingal, Hasan, Kramer, Fletcher, & Ewing-Cobbs, 2007; Lebel & Beaulieu, 2009, 2011; Schmithorst, Wilke, Dardzinski, & Holland, 2002; Tamnes et al., 2010; Urge r et al., 2014; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012; Yeatman et al., 2011). It is important to note that in Study 1, we found that laterality of these pathways, namely the ILF, VOF, and AF long segment changed with age as well. For measures that typically show a positive relationship with age (i.e., FA and AD), the ILF and AF became more left lateralized with age, while the VOF became more right lateralized. These patterns of lateralization are discussed further in the next section with respect to age and behavior.

Lateralization of White Matter Pathways Support Early Literacy and Literacy. Evidence suggests a left lateralized network supporting reading and language in adults (Lebel et al., 2012; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007; Vernooij et al., 2007), young children (Johnson et al., 2013; Lebel & Beaulieu, 2009), and infants (Dubois et al., 2009). Moreover, evidence suggests left lateralization occurs in response to literacy experience. For example, Turkeltaub et al (2003) used fMRI to show that, in children aged 6-22 years, learning to read was associated with increased left hemisphere middle temporal and inferior frontal activity accompanied by progressive decrease activity in the right homologue regions. In addition, Brem and colleagues (2010) showed that early school age children with little to no experience reading show bilateral occipitotemporal functional activity to words, but with as little as 8 weeks of training on how to map speech sounds to alphabetic letters, these children show leftward lateralization activation in occipitotemporal cortex in response to printed words.

Furthermore, a growing number of studies show that laterality indices in white matter microstructure are predictive of behavioral outcomes (Lebel & Beaulieu, 2009; Wang et al., 2016; Yeatman et al., 2011). As reviewed in the previous section, several indices of lateralization were observed related to age. In our cross-sectional sample, we found left lateralization of the ILF and AF long segment, and right lateralization of the VOF. However, we found only left lateralization of the ILF positively predicts better decoding skills. A different pattern emerged in our longitudinal sample (Study 2). We found that left lateralization of all three AF segments and left lateralization of the VOF negatively predicts basic reading outcomes. Therefore, increases in left lateralization in the latter study resulted in worse reading abilities. While some have found a positive correlation between AF lateralization and phonological skills vocabulary (Lebel & Beaulieu, 2009), others, in line with our Study 2, show a negative relationship. For example, one study showed that extreme leftward lateralization predicted worse cognitive functions, such as remembering words on the basis of semantic associations (Catani et al., 2007b). Consistent with extreme leftward lateralization predicting worse cognitive functions, other evidence has found that in children, the AF shows a negative leftward lateralization pattern, and this pattern is predictive of better phonological memory. Furthermore, aphasia research shows that less lateralized patterns of connectivity are predictive of better recovery from unilateral lesions, provided by compensatory mechanisms in the contralateral hemisphere (Pizzamiglio, Mammucari, & Razzano, 1985). In sum, while our cross-sectional data suggest some involvement of the right hemisphere in early literacy skills that may shift to leftward lateralization in young children, our longitudinal data suggest the opposite pattern. We show that as children gain more exposure to reading, fiber pathways supporting literacy become less leftward lateralized, thus implicating a bi-lateralized brain network for reading development.

Implications

The current dissertation has important implications for contemporary models of white matter pathways supporting reading development. For example, our work is in line with Wandell and colleague's (2013) model of white matter connectivity, implicating the AF, ILF, and VOF as key fiber pathways supporting reading development, particularly in young children who are learning to read. Our work is also in line with a growing number of studies proposing that the right hemisphere contributes uniquely to reading (Horowitz-Kraus, Wang, Plante, & Holland, 2014; Turkeltaub et al., 2003; Yamada et al., 2011). However more specifically, our findings have important implications for applying the dorsal indirect phonological and ventral direct lexical routes to reading, particularly in beginning readers. Findings from the current dissertation suggest that in young readers, basic reading measures do not map neatly onto dorsal and ventral white matter pathways. We found that both early literacy skills, such as phonological awareness, and more conventional literacy skills, such as decoding, letter-word identification, and passage comprehension recruit both dorsal and ventral routes to reading. However, more advanced literacy skills, such as reading accuracy and fluency, more specifically recruit the ventral route to reading.

Based on the dual route to reading, there are two routes for extract meaning from printed word forms, an indirect phonological route and direct lexical route. As reviewed in the Introduction, the dorsal route is classically involved in mapping orthographical information to phonological information and the ventral route is classically involved in mapping orthographical information to meaning (i.e., semantics). Phonological awareness and non-word reading tasks are considered to engage the dorsal indirect phonological route since readers sounds out each letter-sound pairing to access the meaning of words (e.g., WUN; Borowsky et al., 2006). Exception word reading and familiar word reading (e.g, *ONE*) are considered to engage the ventral direct lexical route since all letters of a word are read as a unit and that unit is linked to meaning (Borowsky et al., 2006). Novice readers typically engage the indirect phonological route to read most words they encounter since most word forms they encounter are unfamiliar. However, as word forms become more familiar, readers typically engage the direct lexical route, not only for exception words but for familiar word as well (Pugh et al. 2000; Sandak et al. 2004). Consequently, one possible reason basic reading measures do not map neatly onto dorsal and ventral white matter pathways, particularly in novice readers, is because transitioning from a novice to skilled reader requires coordinated development of both dorsal and ventral white matter pathways (Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012a). Thus, because novice readers not only use letter-sound conversion to access the meaning of words (indirect phonological route) but are simultaneously establishing novel word forms into memory (direct lexical route; Pugh et al. 2000; Sandak et al. 2004), early on both dorsal and ventral white matter pathways support early literacy and literacy skill.

Another possible reason basic reading measures do not map neatly onto dorsal and ventral white matter pathways, particularly in young readers, is because early on, children's ability to read words for meaning and non-words is influenced by phonological processing (Van Orden et al., 1988). The view that shared systems exist for mapping orthographic information to phonological information and mapping orthographic information to semantic information is not unique to findings from the current dissertation but is also supported by previous behavioral and functional imaging studies (Borowsky et al., 2006; Coltheart, Patterson, & Leahy, 1994; McDermott, Petersen, Watson, & Ojemann, 2003; Poldrack et al., 1999). For example, behavioral evidence shows that semantic systems are not only engaged during real word reading but also during non-word reading, such as when individuals incorrectly accept a non-word (e.g., jeap) as a member of a particular category (e.g., a vehicle), when they incorrectly accept a word (e.g., rows) as a category (e.g., flower), or when they incorrectly manipulate phonological representations and accept one word for another (e.g., which is a witch; Van Orden et al., 1988; Coltheart et al., 1994). Functional imaging studies supplement the behavioral studies by suggesting that functional brain networks processing dorsal phonological-orthographic based information and ventral semantic-orthographic based information overlap (Borowsky et al., 2006). Findings from the current dissertation and findings from other diffusion-weighted work (Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012b) parallel the latter finding—that is both dorsal and ventral white matter connections support both early literacy (i.e., mapping orthography to phonology) and literacy skill (i.e., orthography to semantics).

Lastly, evidence from the current dissertation also has important methodological implications for future analysis of reading development. We found that several fiber pathways show both age-related changes and literacy-dependent changes (i.e., after controlling for age). One advantage of controlling for age in studies of reading development is that we can be more confident the observed changes in white matter microstructure are specific to behavioral manipulations or outcomes of interest and less associated with variance in white matter development more generally. Put another way, by adding age to our statistical models, we can test how both age-related and literacy-dependent factors change uniquely to support reading development. Thus, future studies should make efforts to control for age in studies of reading development.

Limitations

The following limitations should be taken into account when reviewing the results of the current dissertation. Our sample size across the three studies was relatively small, though comparable to other recent diffusion-weighted studies (Broce et al., 2015; Yeatman, 2015; Gullick et al., 2015). In Study 1, we used diffusion tensor imaging, which suffers more from partial volume effects than HARDI methods. For Studies 2 and 3, behavioral data was not available across all three waves of data, further reducing our longitudinal sample size. We did not FDR correct. We did not use the same behavioral measures across all three studies, and we cannot make direct comparisons across all three studies because we used different diffusion imaging techniques and parameters.

Future Directions

The current dissertation contributes to our growing understanding of the structural brain networks support reading development in children with varying levels of reading exposure. However, future studies should aim to investigated age-related changes in brain development supporting reading in children before they have exposure to print. Doing so would paint a more detailed picture of how the brain changes in response to reading. Also, a more comprehensive battery of speech, language, and visual processing in addition to reading should be administered to better understand how brain systems develop to support reading. More fine grain measures would allow for better understanding of how different fiber pathways, and specifically how the left and right hemispheres, contribute uniquely to reading. Lastly, the current study is the first to provide initial evidence that the VOF plays a role in reading. Thus, future studies should make efforts to incorporate the VOF into their working framework of reading development.

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TABLES

Table 1

Summary of White Matter Microstructure Measures and Correlation with Age in Months for Each Tract

Measures	Hemisphere	**ILF**	**IFOF**	**AF: Anterior Segment**	**AF: Long Segment**	**AF: Posterior Segment**	**VOF**
FA	Left	0.50 (0.03) [0.08]	0.51 (0.02) [0.37]	0.46 (0.02) [0.31]	0.48 (0.03) **[0.50]***	0.47 (0.02) [-0.25]	0.41 (0.03) [0.1]
	Right	0.49 (0.03) [-0.53]	0.50 (0.03) [0.20]	0.46 (0.02) [0.22]	0.46 (0.03) [-0.04]	0.45 (0.02) [0.17]	0.41 (0.05) **[0.46]***
	Laterality	0.005 (0.03) **[0.49]***	0.01 (0.02) [0.22]	0.00 (0.02) [0.16]	0.02 (0.40) [0.44]	0.02 (0.03)* [-0.32]	0.00 (0.07) **[-0.45]***
ADC ($\lambda_1+\lambda_2+\lambda_3$)/3, 10^{-3} mm^2/s	Left	0.86 (0.03) [-0.08]	0.85 (0.03) [-0.18]	0.82 (0.02) [-0.37]	0.82 (0.02) [-0.31]	0.83 (0.02) [-0.25]	0.82 (0.02) [-0.21]
	Right	0.87 (0.04) [-0.31]	0.85 (0.02) [-0.32]	0.82 (0.02) [-0.23]	0.81 (0.03) [-0.41]	0.83 (0.02) [-0.19]	0.81 (0.03) [-0.42]
	Laterality	0.00 (0.01) [0.46]	0.00 (0.01) [0.51]	0.00 (0.01) [-0.04]	0.00 (0.01) [0.24]	0.00 (0.01) [0.01]	0.01 (0.01) [0.40]
AD (λ_1), 10^{-3} mm^2/s	Left	1.4 (0.005) [-0.02]	1.4 (0.04) [0.04]	1.2 (0.03) [-0.14]	1.3 (0.04) [-0.08]	1.3 (0.03) **[-0.62]***	1.2 (0.04) [-0.11]
	Right	1.4 (0.007) **[-0.56]****	1.4 (0.05) [-0.06]	1.2 (0.03) [-0.02]	1.3 (0.05) [-0.36]	1.3 (0.03) [-0.25]	1.2 (0.05) [0.29]
	Laterality	0.00 (0.02) **[0.65]****	0.00 (0.01) [0.35]	0.00 (0.01) [0.01]	0.01 (0.02) **[0.49]***	0.01 (0.01)** [-0.28]	0.01 (0.03) [-0.22]
RD ($\lambda_2+\lambda_3$)/2, 10^{-3} mm^2/s	Left	0.60 (0.04) [-0.05]	0.6 (0.03) [-0.21]	0.61 (0.03) [-0.36]	0.59 (0.03) [-0.44]	0.60 (0.03) [-0.02]	0.63 (0.03) [-0.21]
	Right	0.61 (0.04) [0.3]	0.6 (0.03) [-0.29]	0.60 (0.03) [-0.29]	0.59 (0.03) [-0.23]	0.60 (0.03) [-0.21]	0.63 (0.05) **[-0.52]***
	Laterality	-0.01 (0.01) [-0.22]	0.01 (0.01)* [0.01]	0.01 (0.03) [-0.14]	0.01 (0.02) [-0.33]	0.01 (0.02) [0.25]	0.01 (0.03) **[0.57]****

Note. Means, standard deviations (in parentheses), and correlations with age in months (in brackets) are presented for each measure. FA = Fractional Anisotropy. ADC = Average Diffusion Coefficient. AD = Axial Diffusivity. RD = Radial Diffusivity. Laterality is calculated as (Left – Right)/(Left + Right). Corrected and uncorrected significance tests are reported for laterality and age. ** $p < .01$ (False Discovery Rate [FDR] Corrected).□ $p < .05$ (uncorrected).

Table 2

Relation of Early Literacy Skills to Diffusion Indices Measuring Microstructure of the Perisylvian Fiber Pathways

Predictor → Outcome	B (SE)	ß	95% CI	R^2_{adj}
Fractional Anisotropy (FA)				
Left ILF → Phonological Awareness	10.0 (4.9)	0.35	0.6 to 19.7	0.43
Left VOF → Phonological Awareness	-16.0 (5.2)	-0.47	-26.0 to -5.6	0.49
Right VOF → Phonological Awareness	-10.0 (3.7)	-0.53	-17.3 to -2.9	0.30
Axial Diffusivity (AD)				
Left ILF → Phonological Awareness	9.0 (2.9)	0.46	3.1 to 14.7	0.48
Left VOF → Phonological Awareness	-18.3 (4.01)	-0.64	-26.1 to -10.4	0.47
Left AF Long Segment → Decoding	-67.8 (30.7)	-0.25	-127.2 to -70.1	0.60
Left AF Posterior Segment → Phonological Awareness	-24.6 (6.7)	-0.69	-37.6 to -11.1	0.49
Right AF Anterior Segment → Phonological Awareness	-17.4 (7.2)	-0.49	-31.2 to -3.0	0.45
Right AF Posterior Segment → Phonological Awareness	-14.3 (6.1)	-0.44	-26.1 to -19.6	0.48
Laterality ILF → Decoding	143.6 (63.3)	0.36	20.46 to 268.6	0.64
Radial Diffusivity (RD)				
Left ILF → Phonological Awareness	-8.8 (4.0)	-0.35	-16. 5 to -1.0	0.45
Right IFOF → Decoding	-122.5 (54.8)	-0.34	-227.9 to -13.2	0.57
Average Diffusion Coefficient (ADC)				
Right AF Posterior Segment → Phonological Awareness	-16.6 (6.7)	-0.40	-28.9 to -3.0	0.28
Laterality ILF → Decoding	325.5 (94.4)	0.45	139.4 to 509.3	0.60

Note. Effects reported for robust linear models after controlling for age in months, sex, DEAP phonology, whole brain microstructure quantities (FA, ADC, AD, RD, for each respective regression), and block design. Only results in which the 95% confidence interval did not cover zero are reported. ILF = Inferior Longitudinal Fasciculus. IFOF = Inferior Fronto-Occipital Fasciculus. VOF = Vertical Occipital Fasciculus. AF = Arcuate Fasciculus. DEAP = Diagnostic Evaluation of Articulation and Phonology. To reduce digits, ADC, AD, and RD values were divided by a constant (1000). Adjusted R^2 values are reported from the ordinary least squares model.

Table 3

Demographics of Participant Population

	Wave 1	Wave 2	Wave 3
Total sample size	54 (F: 30, M: 24)	30 (F: 16, M: 14)	20 (F: 13, M: 7)
Usable diffusion-weighted scans	49 (91%) F: 26 , M: 23	30 (100%) F: 16, M: 14)	19 (95%) F: 13, M: 6
Age range in years	[5.12 ; 10.90]	[8.09 ; 11.10]	[9.36 ; 12.04]
Mean age and SD in years	7.90 (1.51)	9.54 (0.84)	10.65 (0.81)

M = male, F= female, SD = standard deviation in parenthesis

Table 4

Laterality Indices at Wave 1 Predict Wave 2 Early Literacy and Literacy

Predictor → Outcome	B (SE)	ß	95% CI
<u>nQA Measure</u>			
Laterality AF Long → W-J III Letter Word	-130.4 (58.9)	-0.35	-247.0 to -16.2
Laterality AF Long → W-J III Passage Comprehension	-138.6 (41.0)	-0.41	-219.5 to -58.7
Laterality AF Posterior → W-J III Passage Comprehension	-103.4 (42.9)	-0.35	-187.8 to -19.8
Laterality VOF → W-J III Letter Word	-72.4 (23.8)	-0.48	-119.6 to -26.2

Note. Effects reported for robust linear models after controlling for age in months, sex, and whole brain nQA. AF = Arcuate Fasciculus; VOF = Vertical Occipital Fasciculus. Laterality = (Left – Right)/(Left + Right). Only results in which the 95% confidence interval did not cover zero are reported.

Table 5

Laterality Indices at Wave 1 Predict Wave 3 Early Literacy and Literacy

Predictor → Outcome	B (SE)	ß	95% CI
<u>nQA Measure</u>			
Laterality AF Anterior → TOWRE-2 Phonemic Decoding	-168.8 (49.3)	-0.58	-263.9 to -70.8
Laterality AF Anterior → TOWRE-2 Total Word Efficiency	-123.7 (47.7)	-0.48	-218.1 to -31.2
Laterality AF Long → TOWRE-2 Phonemic Decoding	-182.3 (64.9)	-0.45	-310.6 to -56.3
Laterality AF Long → TOWRE-2 Total Word Efficiency	-130.0 (60.6)	-0.37	-251.3 to -13.7
Laterality AF Posterior → TOWRE-2 Sight Word Efficiency	-140.6 (45.8)	-0.51	-230.9 to 51.3

Note. Effects reported for robust linear models after controlling for age in months, sex, and whole brain nQA. AF = Arcuate Fasciculus. Laterality = (Left – Right)/(Left + Right). Only results in which the 95% confidence interval did not cover zero are reported.

Table 6

Age-related Changes from Wave 1 to Wave 2 Predict Early Literacy and Literacy

Predictor → Outcome nQA Measure	B (SE)	ß	95% CI
Left AF anterior → W-J III Letter Word	131.60 (57.73)	0.37	16.03 to 242.32
Left AF long → W-J III Passage Comprehension	115.05 (54.45)	0.36	7.26 to 220.70
Left AF posterior → W-J III Letter Word	222.31 (72.88)	0.52	77.31 to 362.99
Left AF posterior → W-J III Passage Comprehension	142.22 (66.06)	0.37	11.36 to 270.30
Left AF posterior → W-J III Word Attack	171.35 (55.60)	0.45	61.99 to 279.95
Right AF anterior → W-J III Letter Word	199.50 (82.30)	0.44	38.29 to 360.88
Right AF anterior → W-J III Word Attack	136.79 (66.15)	0.34	6.41 to 265.70
Right ILF → W-J III Letter Word	155.86 (62.67)	0.39	32.81 to 278.46
Right ILF → W-J III Passage Comprehension	126.31 (52.94)	0.35	21.49 to 229.00
Right ILF → W-J III Word Attack	141.01 (47.25)	0.40	48.49 to 233.71
Right AF posterior → W-J III Letter Word	196.17 (74.94)	0.48	50.07 to 343.84
Right AF posterior → W-J III Word Attack	142.25 (58.89)	0.39	24.71 to 255.56

Note. Effects reported for robust linear models after controlling for age in months, sex, and whole brain nQA. ILF = Inferior Longitudinal Fasciculus; AF = Arcuate Fasciculus. Only results in which the 95% confidence interval did not cover zero are reported.

Table 7

FreeSurfer Cortical Parcellation Labels and Corresponding Indices

Left hemisphere		Right hemisphere	
Label	Indices	Label	Indices
ctx_lh_G_pariet_inf_Angular	[11125]	ctx_rh_G_pariet_inf_Angular	[12125]
ctx_lh_G_parietal_sup	[11127]	ctx_rh_G_parietal_sup	[12127]
ctx_lh_S_intrapariet_and_P_trans	[11157]	ctx_rh_S_intrapariet_and_P_trans	[12157]
ctx_lh_G_occipital_middle	[11119]	ctx_rh_G_occipital_middle	[12119]
ctx_lh_G_occipital_sup	[11120]	ctx_rh_G_occipital_sup	[12120]
ctx_lh_G_pariet_inf_Angular	[11125]	ctx_rh_G_pariet_inf_Angular	[12125]
ctx_lh_G_oc-temp_lat-fusifor	[11121]	ctx_rh_G_oc-temp_lat-fusifor	[12121]
ctx_lh_S_oc-temp_lat	[11161]	ctx_rh_S_oc-temp_lat	[12161]

These labels and indices are based on the aparc.a2009s Destrieux FreeSurfer Atlas (August 2009, Freesurfer v4.5)

Table 8

Mean (M) Number of Voxels within Occipital Temporal Seed Masks Connected to Target Mask for n Number of Participants

	OTS SEED				FUSIFORM SEED			
Targets	Year 2		Year 3		Year 2		Year 3	
	n	*M*	n	*M*	n	*M*	n	*M*
LAG	19	8	11	5.27	26	7.87	15	7.87
RAG	25	33.04	18	24.33	28	15.04	17	15.41
LIPS	13	3.46	4	4	25	4.08	15	5.2
RIPS	11	9.23	7	3.14	20	10.05	12	10.42
LMOC	23	138.7	9	139.7	30	283.4	19	300.7
RMOC	24	80.88	10	88.20	30	281.9	19	265.2
LSOC	16	51.31	15	78.07	27	27.15	17	27.44
RSOC	15	48.4	15	64.73	26	29.69	16	26.35

Table 9

Correlations Between Age and MRI Volumes

	OTS		FFA	
Targets	Year 2	Year 3	Year 2	Ye
LAG	-0.19	0.24	-0.21	-0
LMOG	0.04	0.01	0.28	0.
LSOG	0.14	-0.30	0.18	0.
RAG	-0.10	-0.44	-0.12	-0
RMOG	-0.05	0.29	-0.12	-0
RSOG	0.23	-0.11	-0.16	0.

Age was not statistically significant for any brain measure $p \leq .05$.

Table 10

Cortical Projections from Occipital Temporal Sulcus to Inferior Parietal and Occipital Lobes Predicts Early Literacy and Literacy Skill

Predictor → Outcome	B (SE)	ß	95% CI	R^2_{adj}
Volume Measures: Early Literacy				
Left OTS - Left AG → Woodcock Johnson Passage Comprehension	0.60 (0.27)	0.52	0.08 to 1.13	0.31
Left OTS - Left IPS → Woodcock Johnson Passage Comprehension	-1.21 (0.54)	-0.50	-2.26 to -0.13	0.22
Left OTS - Left IPS → Woodcock Johnson Word Attack	-1.61 (0.55)	-0.67	-2.68 to -0.52	0.33
Volume Measures: Literacy				
Left OTS - Left MOG → TOWRE-2 Phonemic Decoding Efficiency	0.21 (0.07)	0.79	0.07 to 0.34	0.34
Right OTS - Right SOG → TOWRE-2 Phonemic Decoding Efficiency	-0.14 (0.05)	-0.50	-0.23 to -0.05	0.13
Left Laterality OTS – SOG → TOWRE-2 Phonemic Decoding Efficiency	18.34 (6.08)	0.60	6.55 to 30.37	0.29

Note. Effects reported for robust linear models after controlling for age in days and sex. OTS = Occipital Temporal Sulcus; AG = Angular Gyrus; IPS = Intraparietal Sulcus; OCm = Middle Occipital Gyrus; OCs = Superior Occipital Gyrus; TOWRE-2 = Test of Word Reading Efficiency–Second Edition. Adjusted R^2 values are reported from the ordinary least squares model.

Table 11

Description of Behavioral Assessments.

Assessment		Description
DEAP	Articulation	Measures children's ability to produce individual phonemes in words, syllables, and/or in isolation
DEAP	Phonology	Measures children's use of phonological error patterns in isolated words
WPPSI – III	Block Design	Measures children's non-verbal intelligence. Children are asked to reproduce models using blocks
W-JIII	Sound Awareness	Measures children's to ability to rhyme words, and delete/substitute a syllable/phoneme from a word and express the result
W-JIII	Sounds Blending	Measures children's ability to hear single phonemes, blend the phonemes into a word, and express that word
W-JIII	Word Attack	Measures children's ability to read phonemically regular non-words
W-JIIIa	Letter Word Identification	Measures children's ability to name letters and read words aloud from a list
W-JIIIa	Passage Comprehension	Measure's children's ability to orally supply a missing word removed from s sentence or very brief paragraph
TOWRE-2	Sight Word Efficiency	Measures children's ability to read real words
TOWRE-2	Phonemic Decoding Efficiency	Measures children's ability to read phonemically regular non-words
TOWRE-2	Total Word Efficiency	The Total Word Efficiency Index is a composite score of Sight Word Efficiency and Phonemic Decoding Efficiency

Note. DEAP = Diagnostic Evaluation of Articulation and Phonology; WPPSI – III = Wechsler Preschool and Primary Scale of Intelligence Third Edition; W-JIII = Woodcock-Johnson III Diagnostic Reading Battery; W-JIIIa = Woodcock-Johnson Tests of Achievement; TOWRE-2 = Test of Word Reading Efficiency, Second Edition.

FIGURES

Figure 1. A) Lateral view of the left hemisphere showing the brain regions importan language. B) The most prominent brain regions important for literacy, marked in re order to read, the brain must link visual orthographic or written letter information w the oral language system via two routes. One route maps orthography to speech sou (phonology) through a dorsal route (blue). The other route maps directly the whole to semantic representations in the temporal lobe (green). Modified from Dick and S in press.

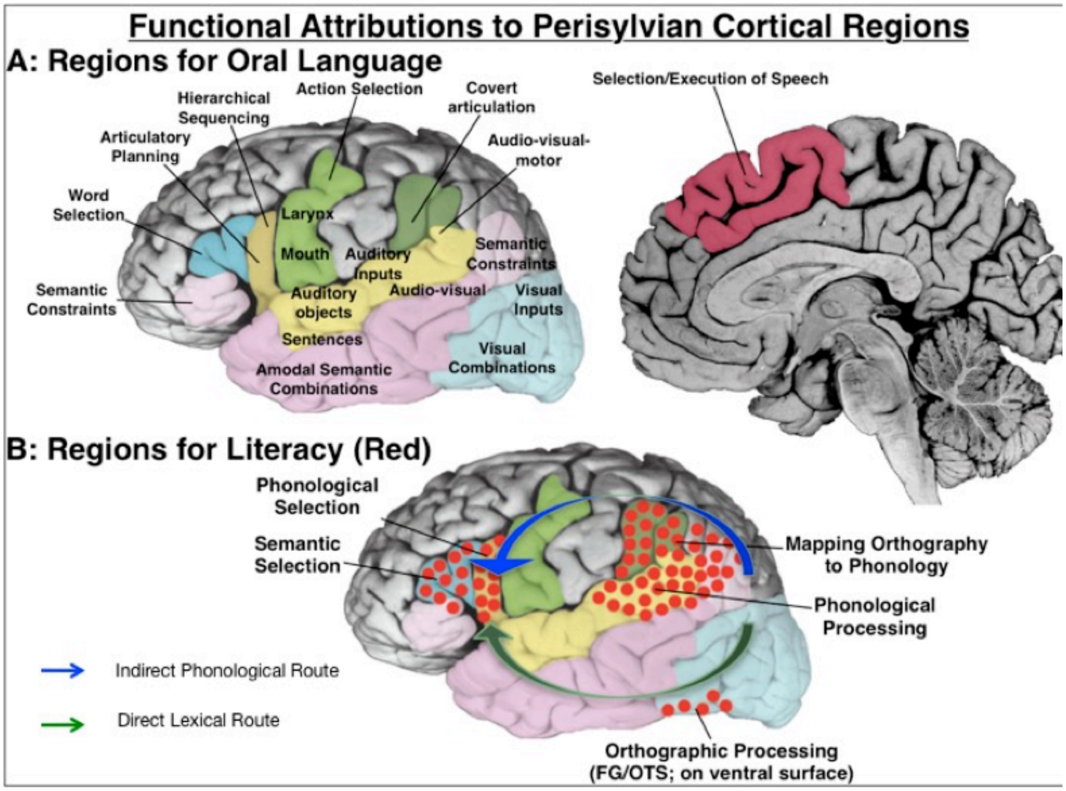


Figure 2. The brain network supporting literacy. Regions IFGOp = Inferior Frontal Gyrus, *pars opercularis*; IFGTr = Inferior Frontal Gyrus, *pars triangularis*; IFGOr = Inferior Frontal Gyrus, *pars orbitalis*; MTGp = Middle Temporal Gyrus, posterior part; STGp = Superior Temporal Gyrus, posterior part; STSp = Superior Temporal Sulcus, posterior part; AG = Angular Gyrus; SMG = Supramarginal Gyrus; IPS = Intraparietal Sulcus; LOTS = left Occipitotemporal Sulcus; ROTS = right Occipitotemporal Sulcus; V1 = Primary Visual Area; V2 = Visual Area 2; V4 = Visual Area 4. Modified figure from Dick and Small, in press.

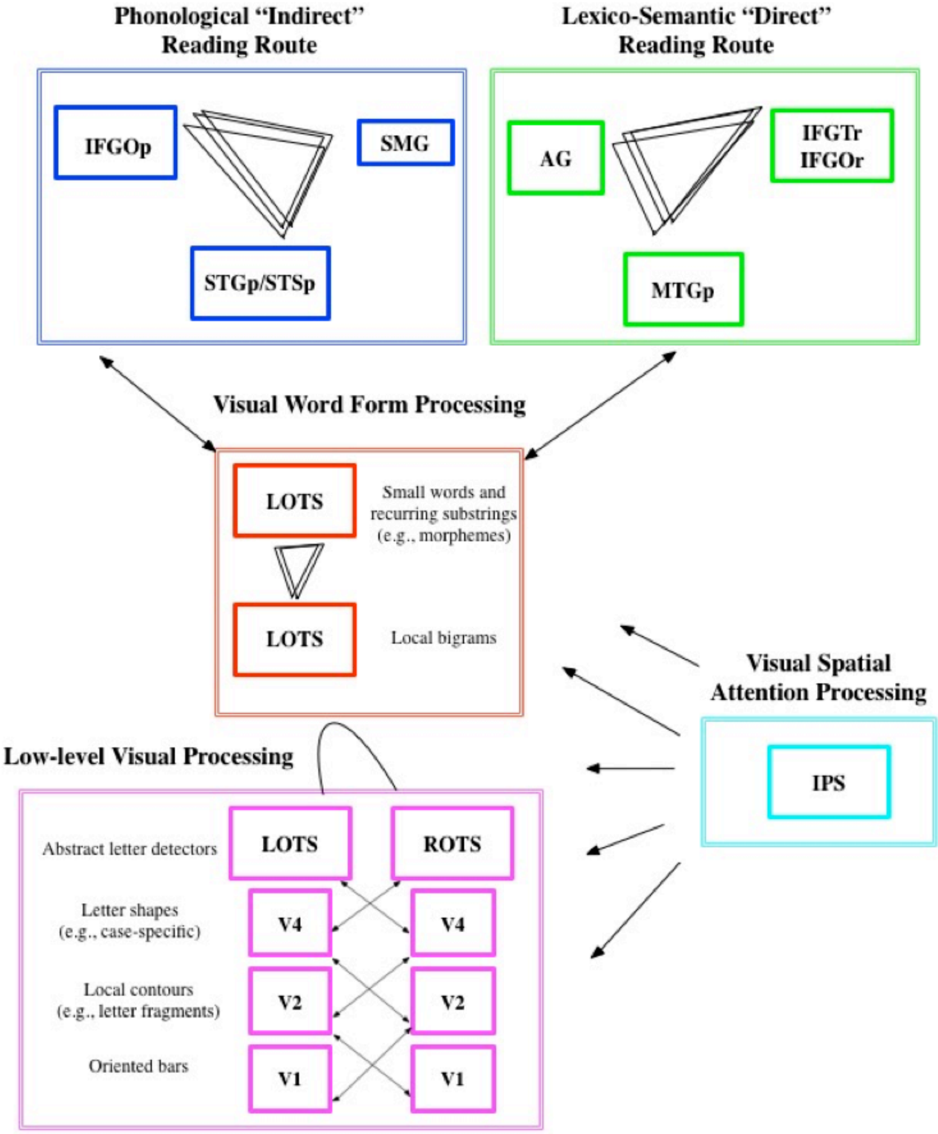


Figure 3. Medial view of the left hemisphere showing fiber pathways associated with developing literacy.

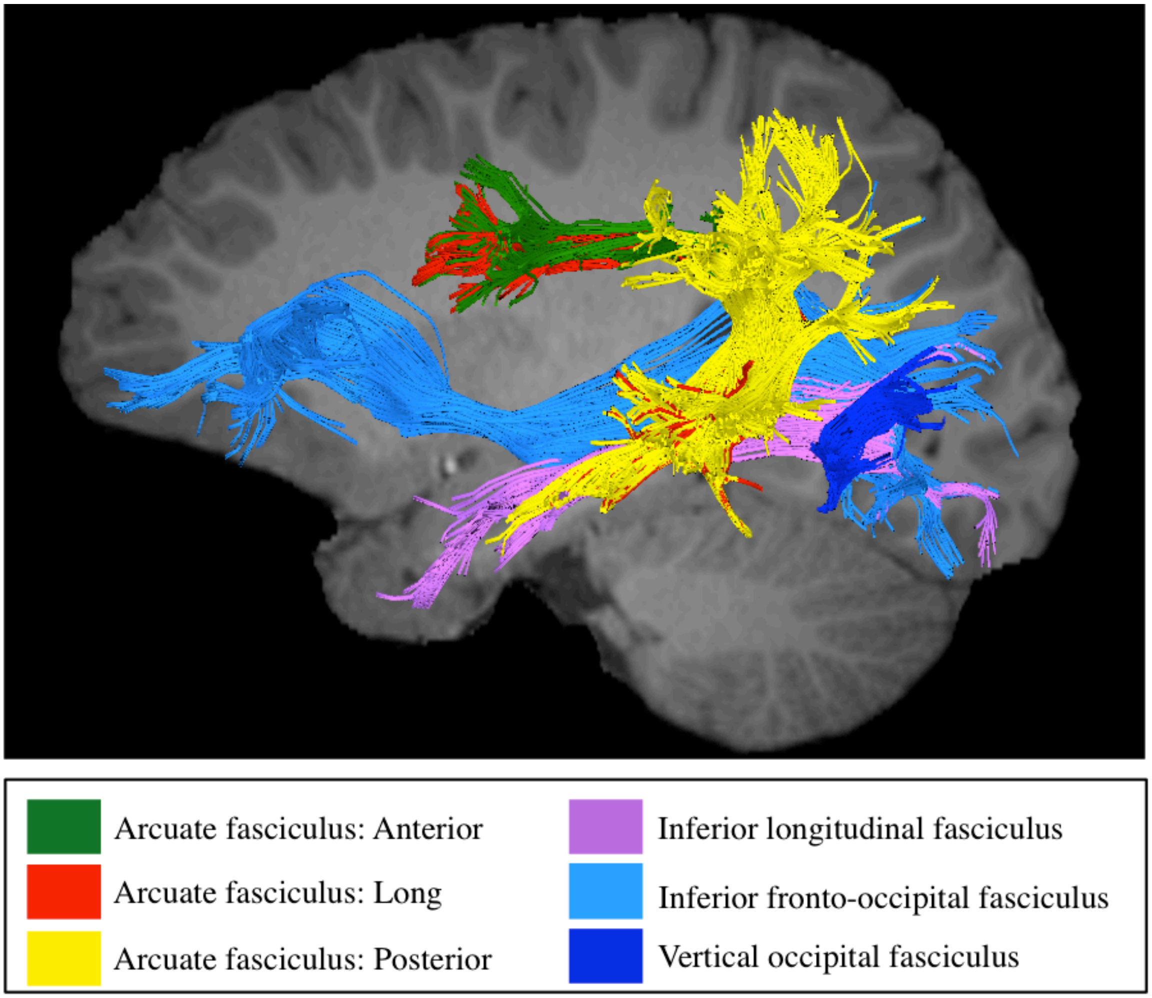


Figure 4. Region of interest (ROI) definition of the vertical occipital fasciculus (VOF) shown on the principal diffusion direction color map in representative sagittal, coronal, and axial sections of a single child's brain. The VOF is delineated in white outline and defined as posterior to the arcuate fasciculus and lateral to inferior fronto-occipital fasciculus and inferior longitudinal fasciculus.

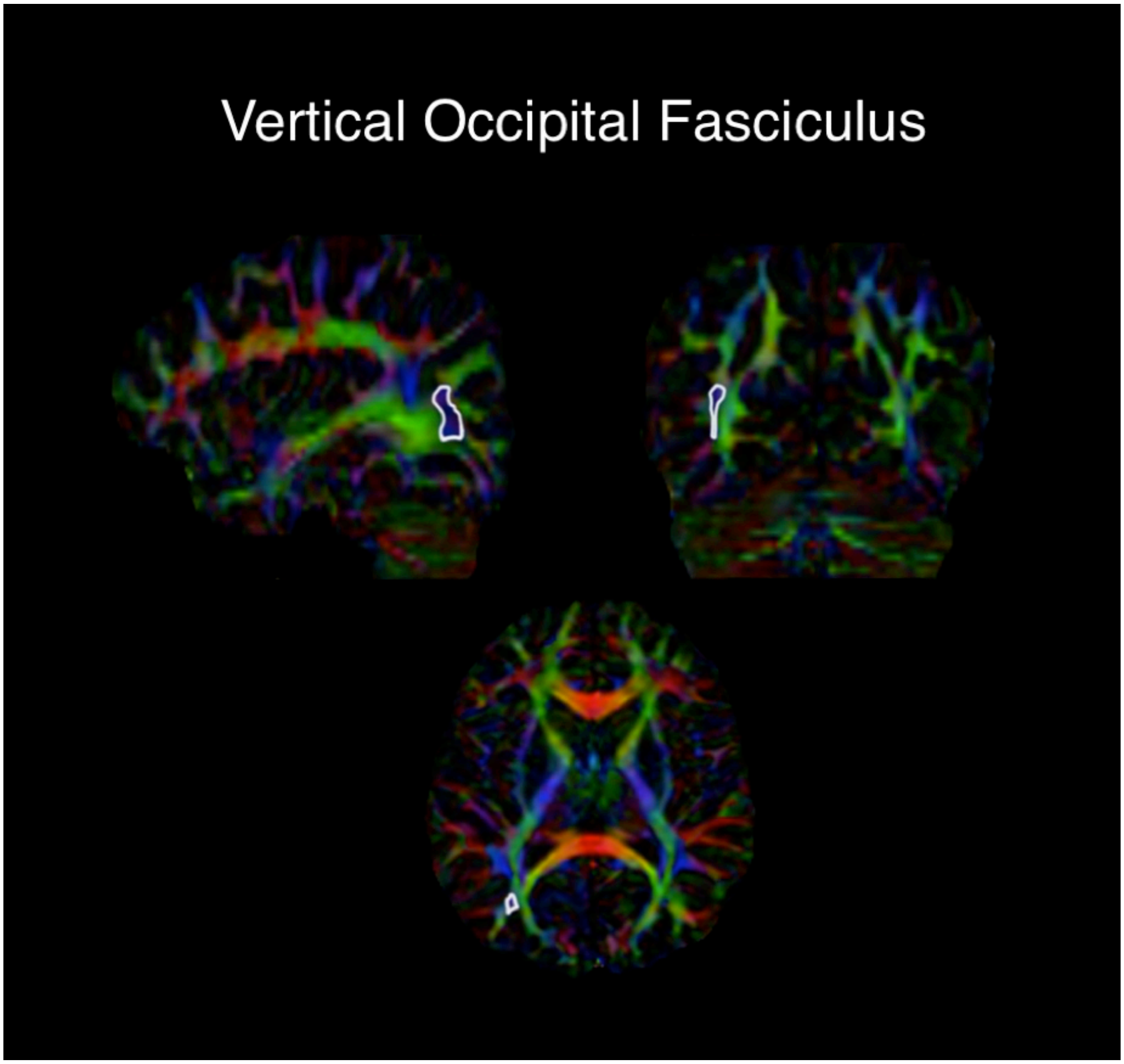


Figure 5. Age-related differences in laterality of the intrahemispheric perisylvian white matter pathways. The graphs show robust elliptical plots of the relation between age and laterality of the inferior longitudinal fasciculus (ILF), arcuate fasciculus (AF) long segment, and vertical occipital fasciculus. Robust correlation measures (r_{rob}) are provided in each graph. * p < .05. ** p < .01.

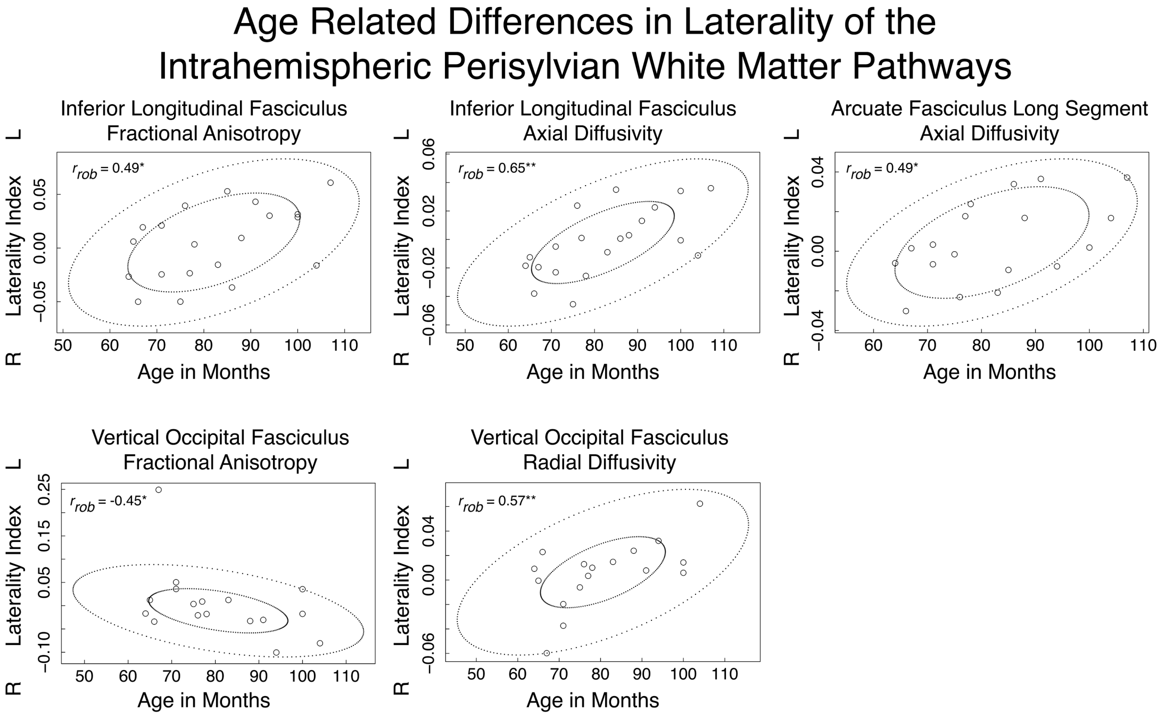


Figure 6. Decoding skills at Wave 2 significantly correlate with decoding skills at Wave 3, $p < .001$.

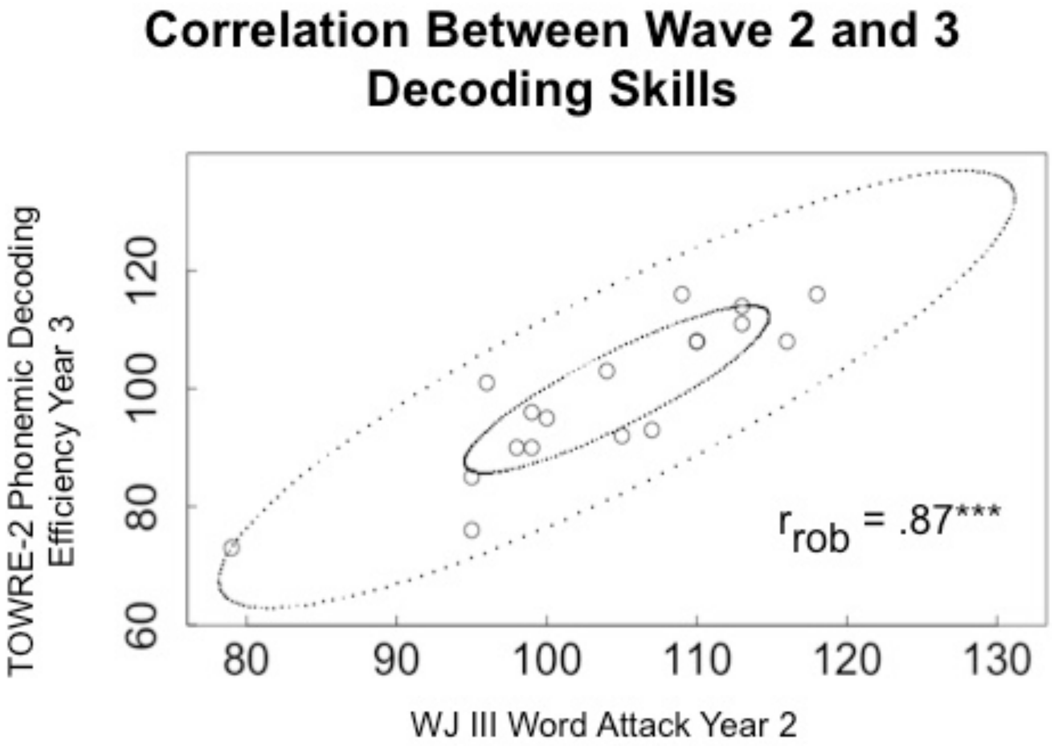


Figure 7. Letter-word identification at Wave 2 significantly correlate with later reading skill at Wave 3, *p* < .001.

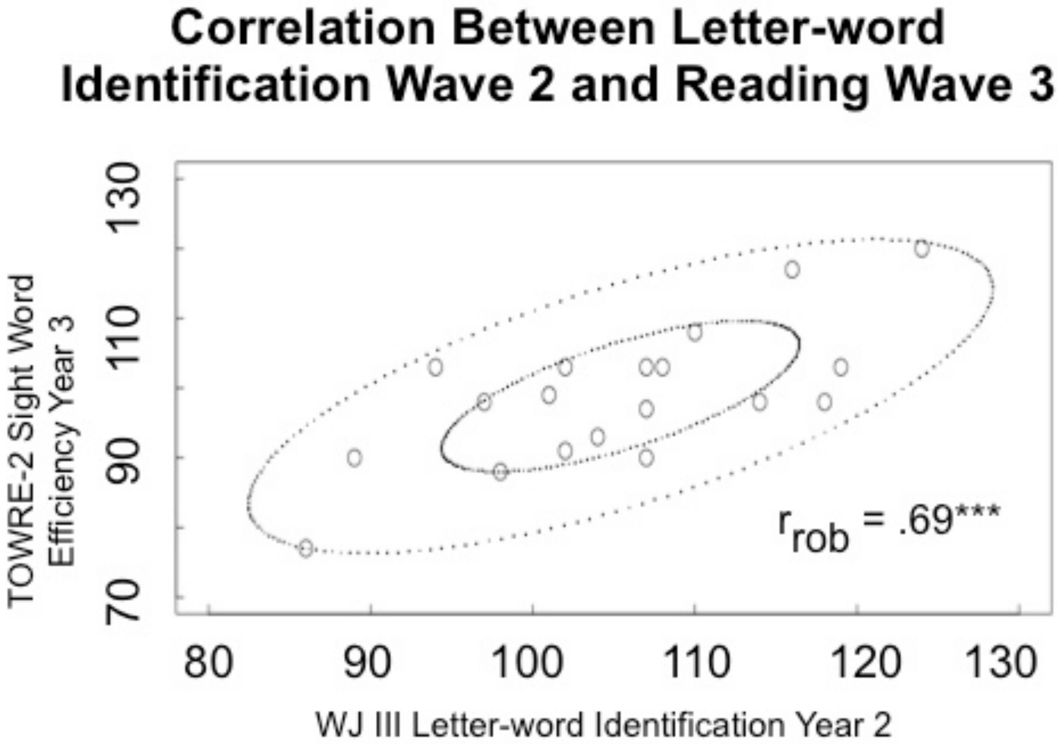


Figure 8. Passage Comprehension at Wave 2 significantly correlate with later reading skill at Wave 3, $p < .001$.

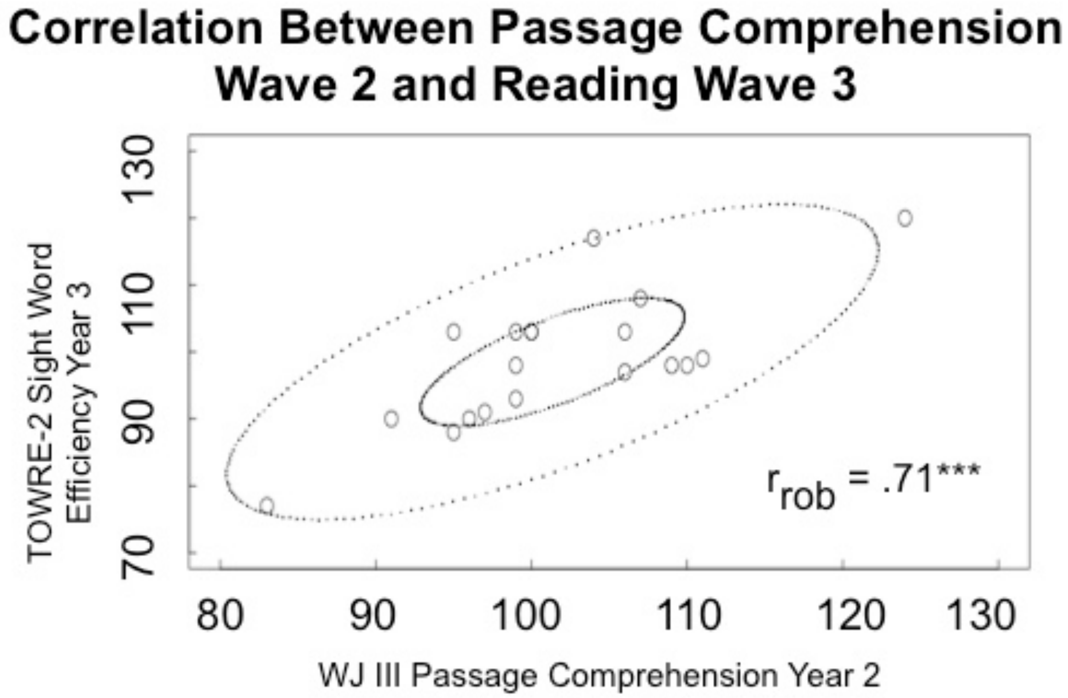


Figure 9. Decoding skills at Wave 2 significantly correlate with later reading skill at Wave 3, $p < .01$.

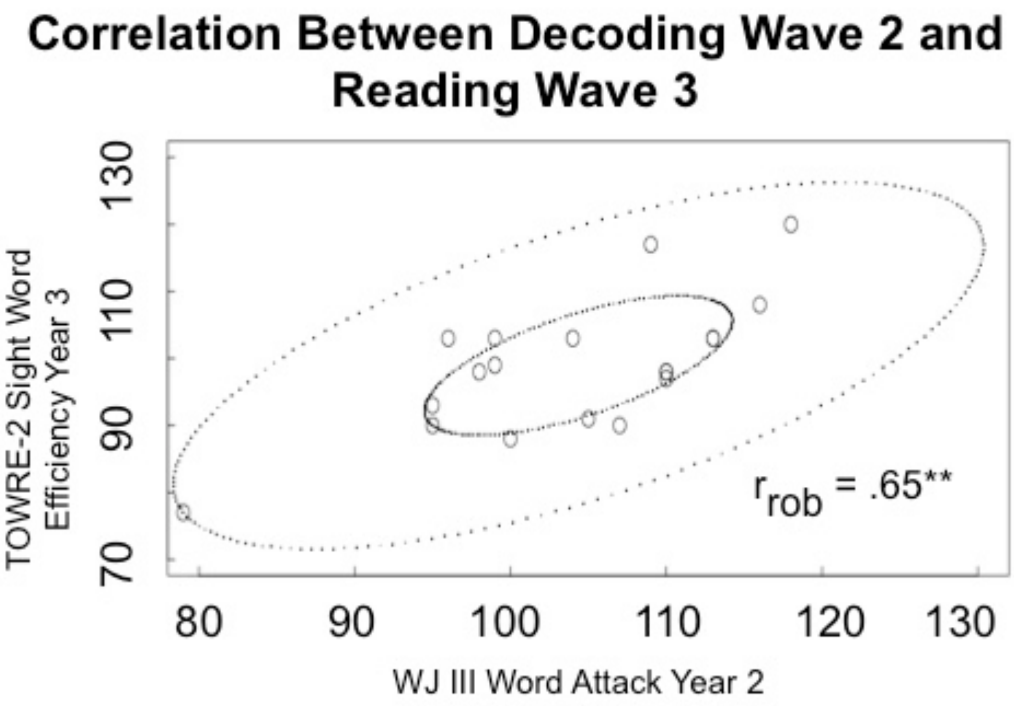


Figure 10. Left: A hypothetical model of the quantitative anisotropy (QA) calculation from the spin distribution function (SDF). The outline represents the SDF calculated by generalized *q*-sampling imaging. The center sphere is the isotropic diffusion estimated by its minimum value. A separate QA is defined for each peak orientation (reprinted from Garyfallidis, 2012). Right: ODF in voxels of the centrum semiovale reconstructed using generalized *q*-sampling imaging (reprinted from Yeh et al., 2010).

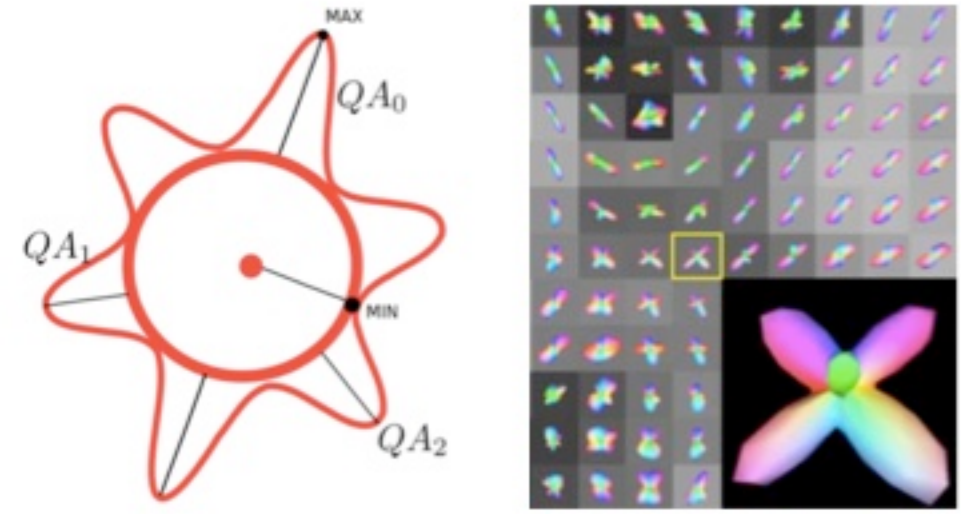


Figure 11. Summary of age-related changes across waves 1 - 3.

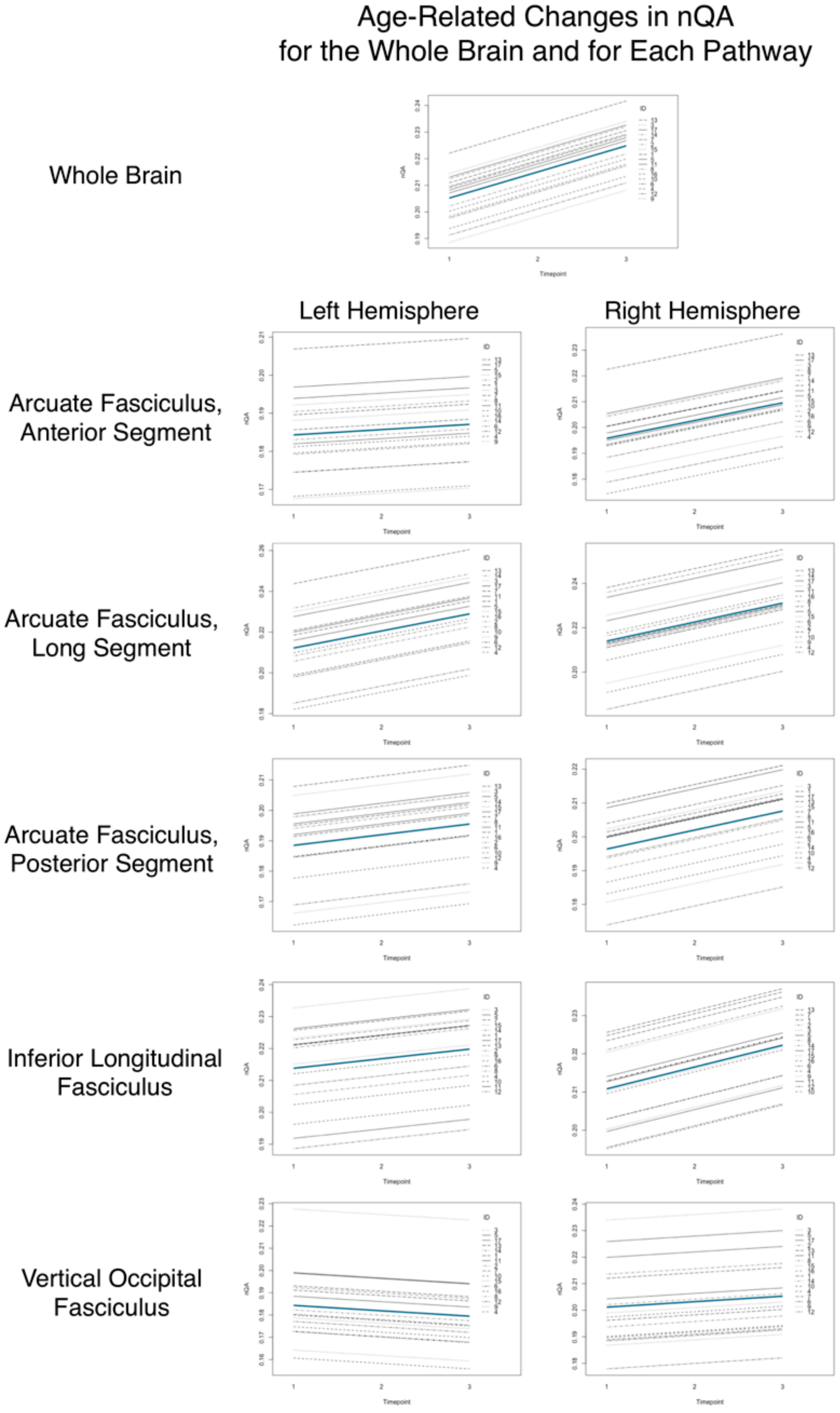


Figure 12. Volume within occipital temporal sulcus connecting to angular gyrus (orange), middle occipital gyrus (green), and superior occipital gyrus (yellow) for two participants.

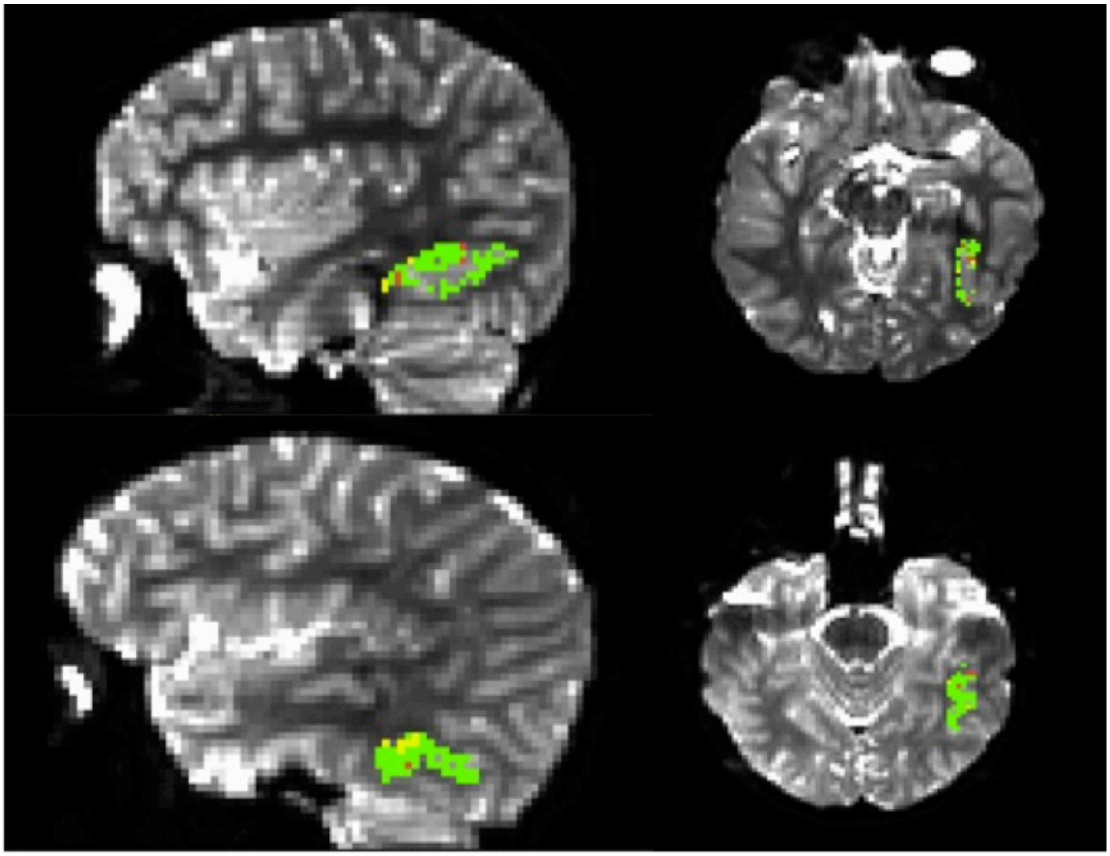


Figure 13. Year 2 Age-related Differences in Brain Volume within Occipital Temporal Sulcus

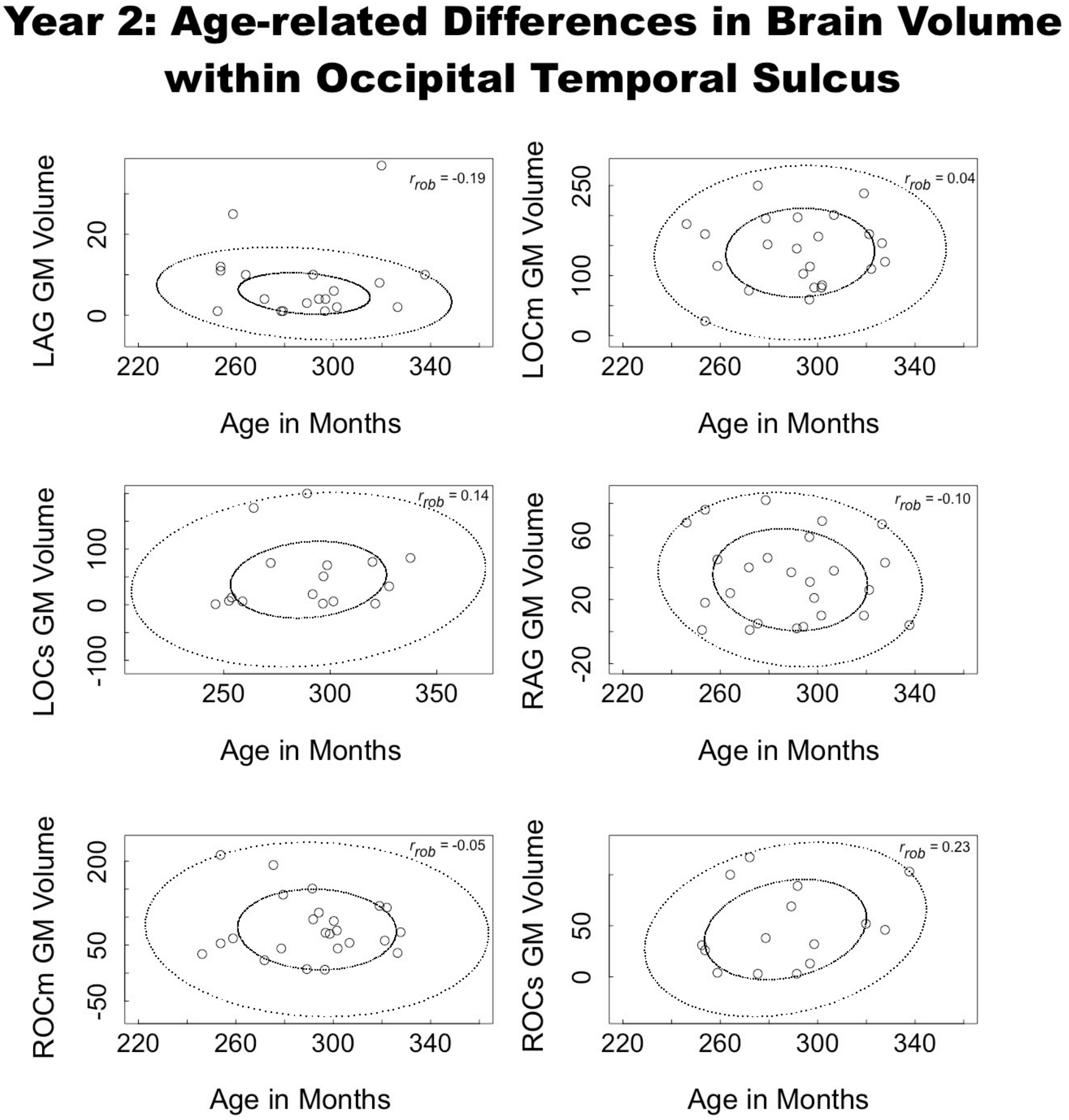


Figure 14. Year 2 Age-related Differences in Brain Volume within Fusiform Gyrus

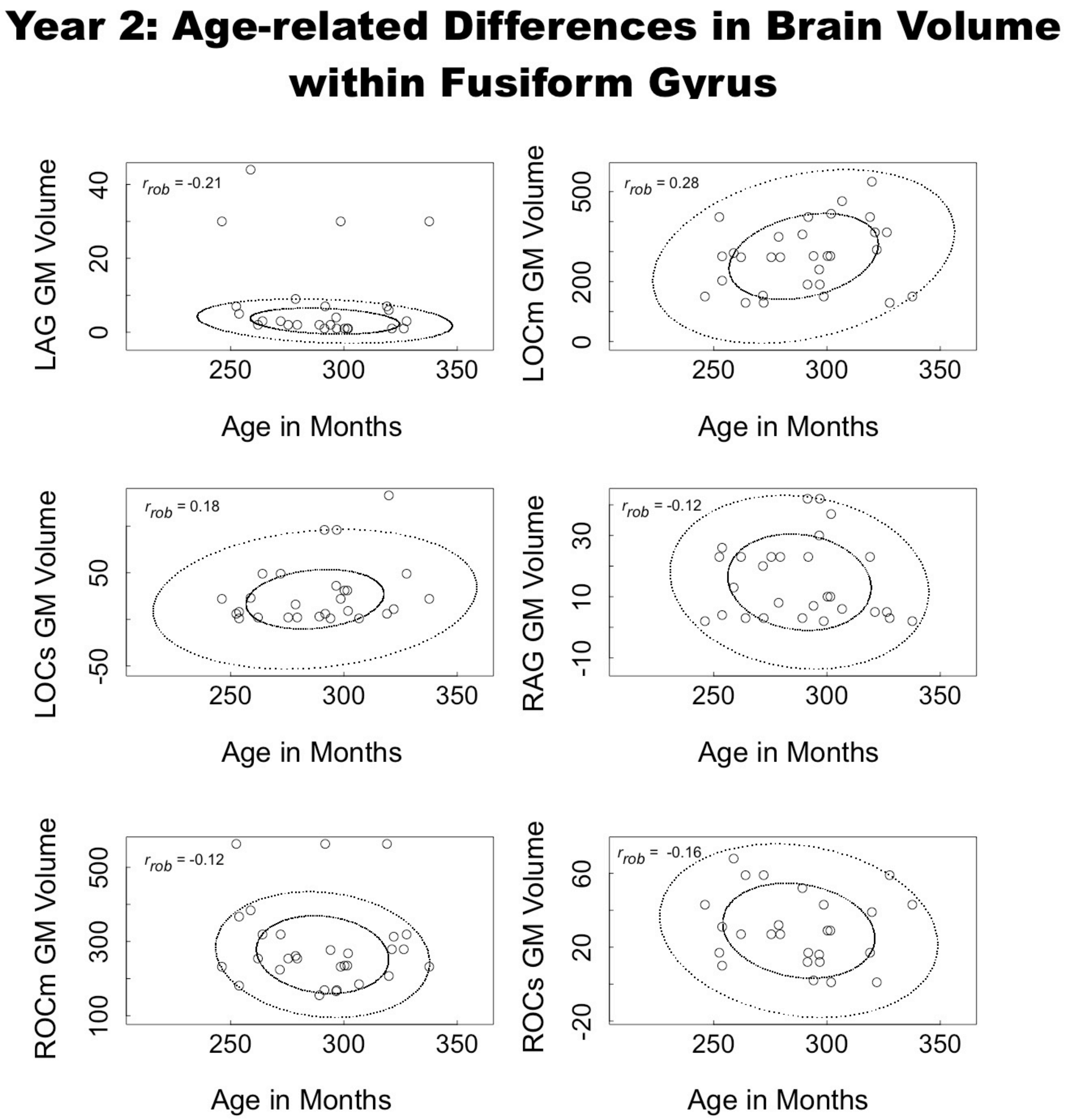


Figure 15. Year 3 Age-related Differences in Brain Volume within Occipital Temporal Sulcus

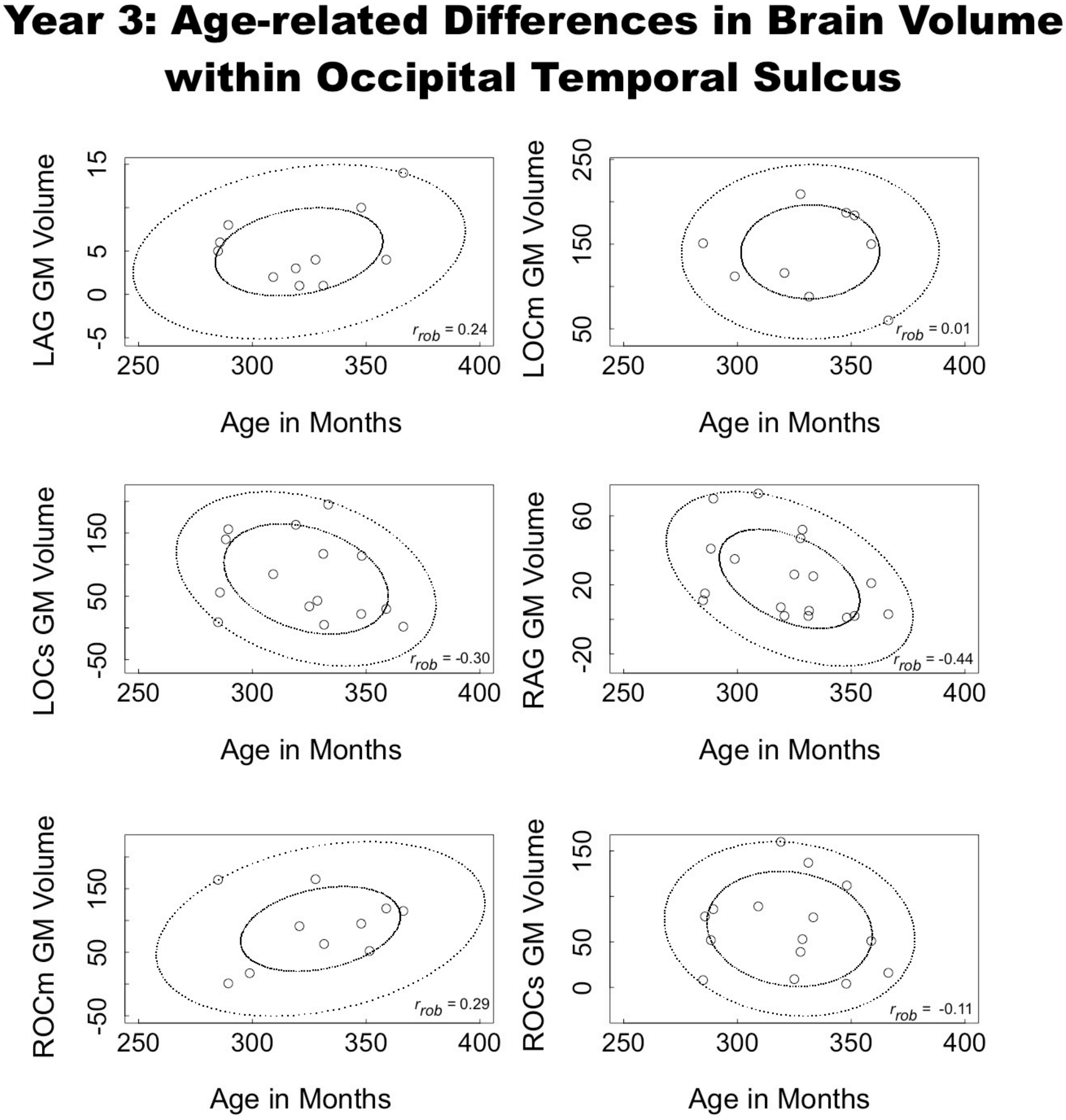
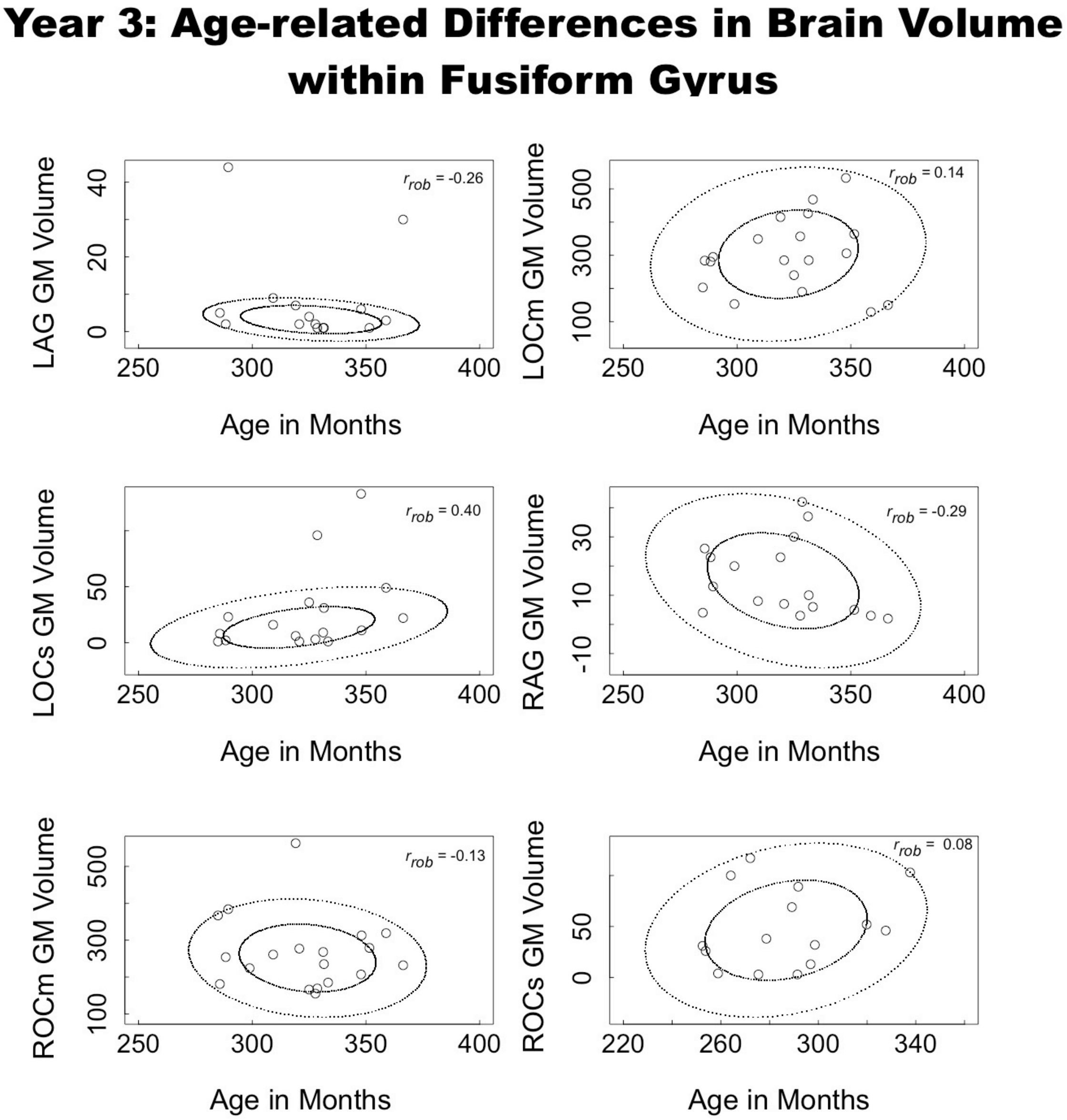

Year 3: Age-related Differences in Brain Volume within Occipital Temporal Sulcus

Figure 16. Year 3 Age-related Differences in Brain Volume within Fusiform Gyrus



VITA

IRIS BROCE

2006-2011	B.A., Psychology San Diego State University, San Diego, CA.
2011-2013	M.S., Psychology Florida International University, Miami, FL.
2011-2016	Doctoral Candidate, Psychology Florida International University, Miami, FL.

PUBLICATIONS AND PRESENTATIONS

Broce, I., Bernal, B., Altman· N., Bradley, C., Baez, N., Cabrera, L., Hernandez, G., … Dick, A.S. (under review). Fiber pathways supporting early literacy. *Neuropsychologia.*

Broce, I.J, Mattfeld, A., Bernal, B., Altman· N., Bradley, C., Baez, N., … A., Dick, A.S. (2016). Fiber pathways important for early literacy. Poster presented at the Neurobiology of Language Conference, London, England.

Garic, D., Broce, I.J., and Dick, A.S. (2016). Development of the Frontal Aslant Tract (FAT) and its relation to executive function in typical children. Poster presented at the Neurobiology of Language Conference, London, England.

Torres, D., Noguera, D., Broce, I.J., and Dick, A.S. (2016). Relation of Inferior Fronto-Occipital Fasciculus Microstructure to Language in Children. Poster presented at Florida Undergraduate Research Conference (FURC), Miami, FL.

Noguera, D., Torres, D., Broce, I.J., and Dick, A.S. (2016). Inferior Longitudinal Fasciculus and Early Literacy Skill in Young Children. Poster presented at the Florida International University Undergraduate Research Symposium, Miami, FL.

Long, H. B., Panara, K., Molina, L., Williams, M., Buglo, E., Broce, I., … & Uddin, L. (2016). Sex differences in white matter tracts of the human anterior commissure: A diffusion magnetic resonance imaging study. Poster presented at the University of Miami Undergraduate Research Symposium, Miami, FL.

Broce, I., Bernal, B., Altman, N., Tremblay, P., & Dick, A. S. (2015). Fiber tracking of the frontal aslant tract and subcomponents of the arcuate fasciculus in 5-8-year-olds. *Brain and Language, 149,* 66-76.

Dick, A. S., & Broce, I. (2015). The neurobiology of gesture and its development. In G. Hickok and S. L. Small (Eds.) *Neurobiology of language* (pp. 389-398). San Diego, CA: Elsevier.

Broce, I.J, Baez, N., Cabrera, L., Hernandez, G., Dick, A.S. (2015). Fiber pathways supporting early literacy in young children. Poster to be presented at the Neurobiology of Language Conference, Chicago, Illinois.

Baez, N., Broce, I.J., Onunkwo, A., Hernandez, G., Dick., A.S. (2015) The Subcallosal Fasciculus of Muratoff in Young Children Poster presented at Florida Undergraduate Research Conference (FURC) Miami, Florida.

Broce, I.J, Iribarne, I., Moraczewski, D., Sheffield, M., Bernal, B., Altman, N., Dick., A.S. (2014) Frontal aslant fiber tract in the developing brain: A Diffusion Tensor Imaging (DTI) study. Poster presented at Cognitive Neuroscience Society in Boston, Massachusetts.

Deferia, A., Broce, I.J., Dick, A.S. (2014) Neurobiology of narrative-level sentence Comprehension. Poster presented at the Fourth Annual Florida Undergraduate Research Conference in Miami, FL.

Broce, I.J, Dick, A.S. (2014). Fiber pathways for language in the developing brain: A Diffusion Tensor Imaging (DTI) study. Invited talk at the Florida International University Center for Children and Families Colloquium, Miami, FL.

Carmenate, Y., Dick, A.S., Broce, I.J. (2013) Cerebellar contributions to language recovery following pre- or perinatal brain damage. Poster presented at SRI Mini Symposium at Florida International University, Miami FL.

Dick, A.S., Bradley, C., Broce, I.J, Bernal, B., Junco, B., Maharaj, A., & Altman, N. (2012). Individual and developmental differences in audiovisual speech perception: An eye-tracking and fMRI study. Invited talk at the the Conference for the Society for the Neurobiology of Language, San Sebastian, Spain.

Broce, I.J, Dick, A.S., Tremblay, P., Hasson, U., Andric, M., Small, S.L. (2012) The neurobiology of sentence comprehension in a narrative context. Poster presented at Neurobiology of Langauge Conference in San Sebastian, Spain.

Friend, M., Pace, A.E., Broce, I.J. (2011) Action, Interrupted: Sensitivity to Event Structure Extends to Novel Complex Events. Poster presented at SRCD Biennial Meeting in Montreal, Quebec, Canada.

Broce, I.J., Pace, A.E., Friend, M. (2011) Action, Interrupted: Sensitivity to Event Structure Extends to Novel Complex Events. Poster presented at SDSU Student Research Symposium.