3-24-2014

Fiber Pathways for Language in the Developing Brain: A Diffusion Tensor Imaging (DTI) Study

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FIBER PATHWAYS FOR LANGUAGE IN THE DEVELOPING BRAIN: A

DIFFUSION TENSOR IMAGING (DTI) STUDY

A thesis submitted in partial fulfillment of

the requirements for the degree of

MASTER OF SCIENCE

in

PSYCHOLOGY

by

Iris Broce

2014

To: Dean Kenneth G. Furton
     College of Arts and Sciences

This thesis, written by Iris Broce, and entitled Fiber Pathways for Language in the Developing Brain: A Diffusion Tensor Imaging (DTI) Study, having been approved in respect to style and intellectual content, is referred to you for judgment.

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

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Date of Defense: March 24, 2014

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Florida International University, 2014

ACKNOWLEDGMENTS

ABSTRACT OF THE THESIS

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Professor Anthony Dick, Major Professor

The present study characterized two fiber pathways important for language, the superior longitudinal fasciculus/arcuate fasciculus (SLF/AF) and the frontal aslant tract (FAT), and related these tracts to speech, language, and literacy skill in children five to eight years old. We used Diffusion Tensor Imaging (DTI) to characterize the fiber pathways and administered several language assessments. The FAT was identified for the first time in children. Results showed no age-related change in integrity of the FAT, but did show age-related change in the left (but not right) SLF/AF. Moreover, only the integrity of the right FAT was related to phonology but not audiovisual speech perception, articulation, language, or literacy. Both the left and right SLF/AF related to language measures, specifically receptive and expressive language, and language content. These findings are important for understanding the neurobiology of language in the developing brain, and can be incorporated within contemporary dorsal-ventral-motor models for language.

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CHAPTER I

INTRODUCTION

Although great strides have been made in understanding brain development over the last century, the relation between brain development and behavior is an active field of inquiry. Particularly, with the advent of the magnetic resonance imaging (MRI) technique of diffusion-weighted imaging, scientific research has shifted to studying white matter development, which is the development of connections between neurons in the brain and central nervous system. Using diffusion weighted imaging, white matter development can be investigated in typically developing children and related to behavior. Specifically, different white matter pathways can be identified, tracked, characterized, and quantified in terms of their structural integrity, and these metrics can be related to a number of behavioral outcome measures. In the present study we focus on identifying a new fiber pathway—the frontal aslant tract (FAT)—for the first time in young children. We then relate the putative language pathway and another pathway of the dorsal speech stream, the superior longitudinal fasciculus/arcuate fasciculus (SLF/AF), to speech, language, and literacy outcomes. The findings we report contribute to a growing understanding of brain development and its relation to behavior.

CHAPTER II

LITERATURE REVIEW

Investigating White Matter Development *in vivo*

Neurons are the major components of information processing and storage in the human brain. However, they have different parts and each part contributes uniquely to neural transmission. For example, in addition to the neural cell body or soma, parts of the neuron such as dendrites or even the cell body itself, are specifically designed to facilitate the receipt of information to the neuron from other neurons (Lenroot & Giedd, 2006). In most cases neurons also have a single axon that emanates from the neural cell body (Lenroot & Giedd, 2006). The axon is primarily involved in transmission of information away from the neuron to other neurons. In the nervous system, these axons form tightly organized cords, much like an electrical wiring system, called white matter tracts (Lenroot & Giedd, 2006). Through this organization, they connect different areas of the brain, sometimes several centimeters apart. Also like an electrical wiring system, most central nervous system axons are insulated. In the brain, a substance made mostly of lipids called myelin accomplishes this insulation. Myelin serves a number of functions, which contribute to a substantial increase in the efficiency and speed of neural transmission of information (Lenroot & Giedd, 2006). Because it is a lipid substance, myelin also gives the brain's white matter its light appearance.

It has been known for more than a century that over the course of development, different parts of the brain myelinate at different rates (Flechsig, 1896), which means they acquire the full myelin sheath at different times depending on what part of the brain the axon is projecting from and to. However, historically these studies required

postmortem examination of fetal, infant, or child brain tissue, which is prohibitive for most researchers interested in brain development. New technology call diffusion-weighted imaging, or diffusion tensor magnetic resonance imaging (DTI-MRI), invented in 1994 (Basser, Mattiello, & LeBihan, 1994), now allows the examination of the development of white matter in vivo.

Diffusion Tensor Imaging takes advantage of differences in water diffusion in axons of high versus low structural integrity. The diffusion process follows Brownian motion--that is, the random thermal motion of molecules in biological tissues. Much like a plumbing pipe, diffusion in axons, especially myelinated axons of the white matter, is anisotropic (or, directional), with water molecules moving faster along the length of an axon than perpendicular to it (Mori & Zhang, 2006). The advances of DTI make it possible to quantify individual differences in white matter integrity (fractional anisotropy; FA) and the degree of diffusion of water molecules through different tissues (apparent diffusion coefficient; ADC). For these measures, FA takes on values of 0 (i.e., when diffusion is completely isotropic) to 1 (i.e., when diffusion is anisotropic). The ADC values range from $0.60 - 1.05 \times 10^{-3}$ mm^2/s, and have an identifiable range of values in typically developing brains of $0.84 +/- 0.11 \times 10^{-3}$ mm^2/s (Sener, 2001). However, these values are age and region specific, which means different white matter tracts mature at different rates over development. The ADC values in deep white matter for infants 3-4 months of age are higher (M = $1.11 +/- 1.20 \times 10^{-5}$ mm^2/s) compared to adults (Morriss, Zimmerman, Bilaniuk, Hunter, & Haselgrove, 1999), but ADC values decrease (at a slower rate after 4 months), reaching adult values by around 36 months (Morriss et al., 1999; Schneider, Ilyasov, Hennig, & Martin, 2004).

Using DTI, visualization of white matter tracts in three-dimensional space can be achieved using methods that follow the path of greatest diffusion along the x, y, z axis (Basser et al., 1994). For example, the method of tract tracing used in this study follows the value of FA from pixel to pixel to trace out fiber tracts. Advances in DTI have enriched our understanding about how particular fiber pathways connect regions to support speech, language and literacy in adults (Bernal & Altman, 2010; Catani, Jones, & ffytche, 2005; Glasser & Rilling, 2008; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). However, in part because the methodology is relatively new, little is known about the development of these pathways, and their corresponding function in young children remains understudied.

White Matter Development

The organization and integrity of white matter tracts follows a protracted developmental timeline. It begins in the fetal period and continues into adulthood, but there are also regional differences in the timing of development (Kasprian et al., 2008; Lebel et al., 2012; Zhai, Lin, Wilber, Gerig, & Gilmore, 2003). Research suggests that maturation of fiber tracts during the first 2 years of life in normal developing infants is characterized by three stages 1) rapid change during the first 12 months, 2) slow modifications during the second year, and 3) slower development after 24 months (Geng et al., 2012; Hermoye et al., 2006; Schneider et al., 2004). In addition to this characteristic temporal order, fiber tracts develop in region-specific ways (Dubois et al., 2008; Paus et al., 2001; Zhai et al., 2003). Flechsig (1896) showed that white matter development in infants begins first in "projection" pathways of the primary sensory and motor regions. Moreover, several "association" fiber pathways, which connect secondary

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regions of the cortex, are identifiable at birth. These include the superior longitudinal fasciculus, cingulum, corpus callosum, inferior fronto-occipital, and inferior frontal occipital fasciculus (Dubois et al., 2008; Geng et al., 2012; Hermoye et al., 2006). A number of these pathways show reduced white matter integrity at birth. For example, FA values are highest in deep white matter structures (e.g., corpus callosum) and lowest in frontal-temporal connections (e.g., the superior longitudinal fasciculus and inferior longitudinal fascicles; Dubois et al., 2008; Hermoye et al., 2006; Schneider et al., 2004). These pathways also show prolonged developmental trajectories, with frontal-temporal and frontal-parietal connections showing extended age-related change (Barnea-Goraly et al., 2005; Lebel et al., 2012).

After infancy, age-related changes in white matter development continue through childhood and into early adulthood (Nagy, Westerberg, & Klingberg, 2004; Paus et al., 1999; Reiss, Abrams, Singer, Ross, & Denckla, 1996), but again maturation is regionally specific, with some fiber pathways developing to maturity later than others (Barnea-Goraly et al., 2005; McGraw, Liang, & Provenzale, 2002; Wilke, Krägeloh-Mann, & Holland, 2007). For example, of the association tracts, the inferior longitudinal and fronto-occipital fasciculi are the first to mature, while the superior longitudinal fasciculus/arcuate fasciculus (SLF/AF) and the uncinate fasciculi are the last (Lebel et al., 2012). Optimal white matter development has many advantages. For example, increases in myelination and axonal thickness concomitant with improved organization of white matter tracts result in increased efficiency and speed of neural transmission (Aboitiz, Scheibel, Fisher, & Zaidel, 1992; Schmithorst, Wilke, Dardzinski, & Holland, 2005). Secondly, several studies have related these changes to behavioral changes in children.

For example, age-related changes in white matter integrity have been associated with visual information processing efficiency (Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006), working memory capacity (Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Nagy et al., 2004), and overall intelligence (IQ; Schmithorst et al., 2005). Researchers have also explored speech, language, and literacy correlates of white matter development. For example, age-related changes in white matter integrity have been associated with auditory processing ability (Schmithorst, Holland, & Plante, 2011), phonological awareness skill (Yeatman et al., 2011), reading speed (Nagy et al., 2004), and accuracy reading words and pseudowords (Qiu, Tan, Zhou, & Khong, 2008; Yeatman et al., 2011). However, maturation should not be considered as the sole contributor to enhanced performance. For example, several studies found that white matter integrity significantly predicted working memory capacity (Klingberg et al., 1999) or phonological awareness (Yeatman et al., 2011), even after controlling for age. Therefore, the evidence suggests that other factors aside from maturation (e.g., experience) account for observed brain/behavior relations.

While these studies have significantly contributed to our understanding of white matter development in relation to behavioral changes, they have typically been studied in older children. They have also failed to develop a comprehensive picture of how the known perisylvian language pathways develop and contribute to a broader language profile—that is, a profile that establishes the child's skill in multisensory speech processing, phonological and articulatory ability, receptive and expressive language ability, and literacy. Therefore, the present study aims to establish a better understanding of how perisylvian language pathways relate to speech, language, and literacy. In the next

section we review which fiber pathways are thought to anchor the perisylvian language network in the human brain.

Contemporary Model of the Neurobiology of Language

Our investigation is framed within a contemporary model for the neurobiology of language, which is a dual stream model analogous to the model for visual processing (Dick & Tremblay, 2012; Dick, Bernal, & Tremblay, 2013; Hickok & Poeppel, 2007; Poeppel, Emmorey, Hickok, & Pylkkänen, 2012). The dual stream model examines dorsal and ventral processing streams. The dorsal stream involves interactions between frontal, parietal, and temporal brain regions and has been implicated in mapping auditory speech sounds to articulatory (motor) representations and also in processing complex syntactic structures. The most prominent pathway proposed to connect these regions is the superior longitudinal fasciculus/arcuate fasciculus (SLF/AF). In comparison, the ventral stream has been implicated in mapping auditory speech sounds to meaning and also in processing less complex syntactic structure. The most prominent pathways within the ventral stream are the uncinate fasciculus (UF), the extreme capsule (EmC), the middle longitudinal fasciculus (MdLF), the inferior longitudinal fasciculus (ILF), and the inferior fronto-occipital fasciculus (IFOF). A third set of fiber pathways comprising the motor stream establish the connections necessary for speech production, and include the cortico-bulbar system, the cortico-striatal loops, and the cortico-cerebellar system. A newly discovered association pathway of the cortex, the frontal aslant tract (FAT), has been proposed as an important pathway in the motor stream. See *Figure 1* below.

Long-Association Fiber Pathways of the Perisylvian Cortex

To Pre-SMA and SMA

- 🟢 Superior longitudinal/arcuate fasciculus
- 🔵 Extreme capsule fiber system
- 🟠 Inferior longitudinal fasciculus
- 🟦 Inferior fronto-occipital fasciculus
- 🟡 Middle longitudinal fasciculus
- 🔴 Uncinate fasciculus
- 🟣 Frontal aslant tract
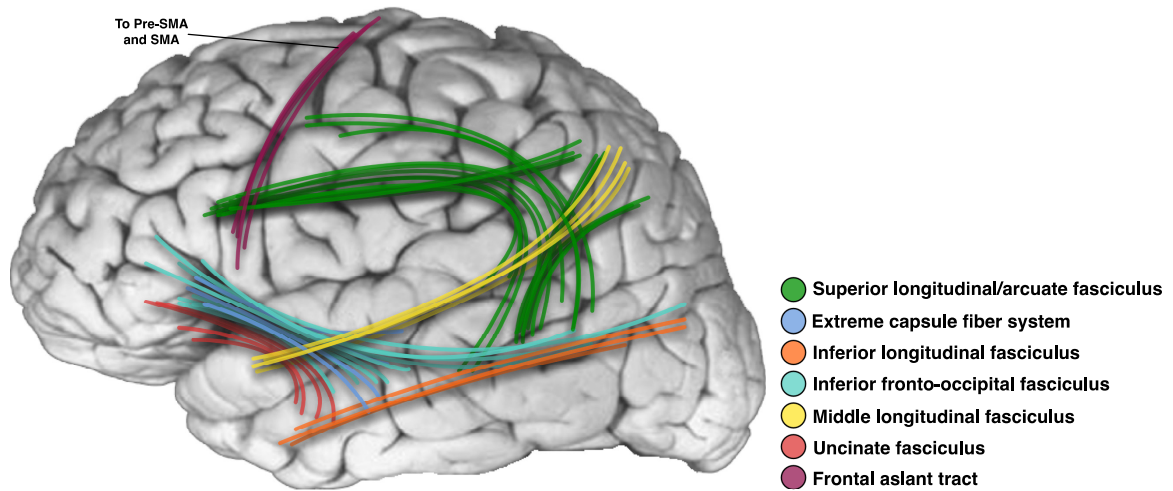
Figure 1. Lateral view of the left hemisphere showing the most prominent fiber pathways for language. The current study focuses on two: the SLF/AF in green and the FAT in purple. Reprinted from Dick and Small, in press.

Fiber Pathways for Speech, Language, and Literacy

From the set of fiber pathways that serve the processing of language, from early speech perception to semantic processing to narrative-level understanding, the present study focuses on two main pathways that are most associated with developing speech, language, and literacy abilities. The first is the well-known SLF/AF pathway that anchors the dorsal stream and is thought to be involved in phonological processing, receptive and expressive language processing, and literacy. The second pathway is the newly described Frontal Aslant Tract (FAT) of the motor speech stream (see *Figures 2* and *3*). Below we briefly review what is known about the putative functions and development of these two pathways with respect to speech, language, and literacy.
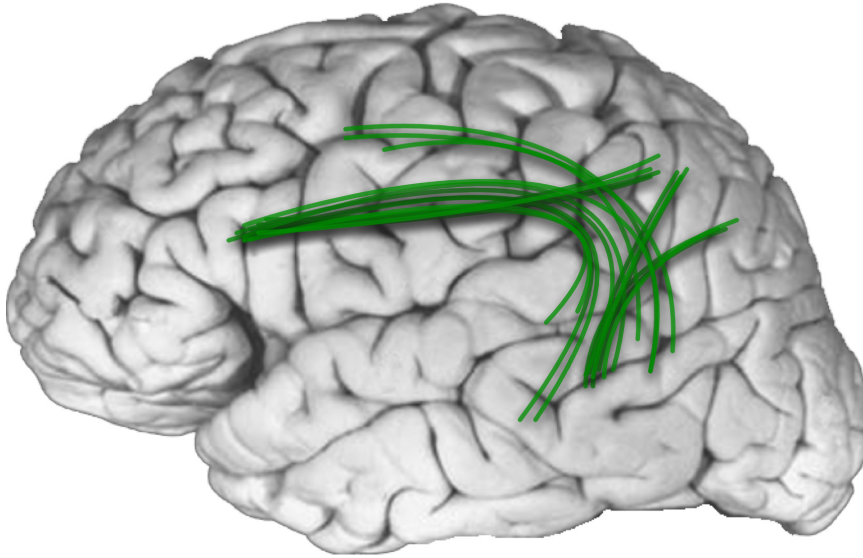
Figure 2. Connections of the SLF/AF in lateral view.
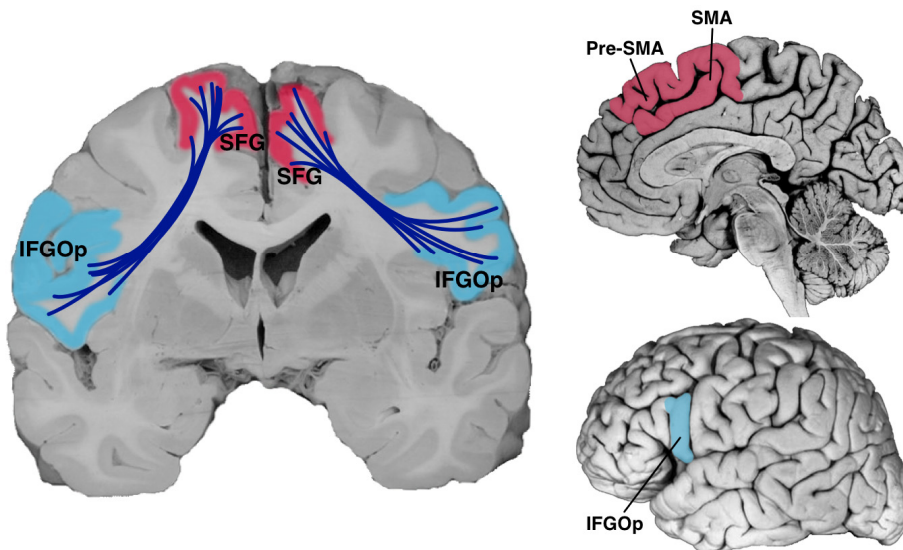
Figure 3. Connections of the frontal aslant tract (FAT) in coronal section, with outline of the inferior frontal and superior frontal origins and terminations in the medial and lateral sagittal views. IFGOp = inferior frontal gyrus, pars opercularis; SFG = superior frontal gyrus; SMA = supplementary motor area; Pre-SMA = pre-supplementary motor area.

Behavioral and Neural Components of Speech, Language, and Literacy

Behavioral Components of Speech. It is often underappreciated that speech development occurs in a multisensory context. Infants develop in a multisensory environment, and early speech perception experiences are often accompanied by visual speech information. A very large corpus of research suggests that multisensory stimulation provides tangible benefits to the developing child (Bahrick, Lickliter, & Flom, 2004; Blomert & Froyen, 2010; Erdener & Burnham, 2013; Gogate & Bahrick, 1998; Gogate, Bahrick, & Watson, 2000; Lachs, Pisoni, & Iler Kirk, 2001; Magnan & Ecalle, 2006; Magnan, Ecalle, Veuillet, & Collet, 2004; Nath, Fava, & Beauchamp, 2011; Ross et al., 2011; Sekiyama & Burnham, 2004). For example, amodal information, which refers to information shared across multiple sense modalities (i.e., temporal synchrony, rhythm, tempo), seems to have the effect of directing attention to what is important in the environment, and enhancing salient features of actions and objects (Bahrick et al., 2004; Calvert, Campbell, & Brammer, 2000). Broadly, the detection of temporal synchrony seems to be an important skill in producing meaningful, unified percepts (Bahrick & Lickliter, 2004). For example, during synchronous AV speech stimulation, visual input from a speaker's mouth and lips has the effect of speeding up and enhancing auditory neural processing, indexed by shorter latencies and larger amplitudes compared to unisensory auditory stimulation (van Wassenhove, Grant, & Poeppel, 2005). These results in turn may have the affect of facilitating categorical learning of speech information.

Early detection and identification of synchronous AV speech information seems to facilitate the perception and learning of more complex speech skills. The impact of

visual speech influence on speech perception seems to emerge early, around 4-months of age (Bahrick, 2010; Kuhl & Meltzoff, 1982). By 4-months, infants successfully match congruent speech information (i.e., visual /a/, auditory /a/) versus incongruent (i.e., visual /i/, auditory /a/) speech information (Kuhl & Meltzoff, 1982). In the same study, Kuhl and Meltzoff (1982) also found that infants spontaneously produced sounds that resembled those of the female actress articulating the vowels, with respect to intonation, contours, and overall durations. These findings suggest that infants may be making use of the visual articulatory information from the speaker's lips and mouth and auditory information from the sound of the speaker's voice to produce the sounds themselves. Findings from Kuhl and Meltzoff (1982) are consistent with the intersensory redundancy hypothesis, which suggests that the overlap of amodal properties (e.g., temporal synchrony, rhythm, or intensity) guides what we attend to, perceive, learn and remember (Bahrick 2010). Therefore, congruent and synchronous AV speech (e.g., congruent audiovisual /ba/) may help recruit attention (Bahrick 2010), speed up neural processing (van Wassenhove, Grant, & Poeppel, 2005), and help with learning properties across a third domain (e.g., articulatory /ba/). These data suggest that early sensitivity to multisensory AV speech information, such as the detection of synchrony and other linguistic properties of speech, may serve as a strong foundation, a bootstrapping effect, for later, more sophisticated speech and literacy skill in childhood and adulthood.

The influence of multisensory audiovisual speech on auditory speech perception continues to show age-related change well into middle childhood and adulthood, but there seems to be rapid development in the period between 5- and 8-years. For example, there are age-related differences in the degree to which visual speech information

enhances the perception of auditory speech, such that children benefit significantly less from observing visual information than adults (Desjardins, Rogers, & Werker, 1997; Massaro, Thompson, Barron, & Laren, 1986; McGurk & MacDonald, 1976; Sekiyama & Burnham, 2008). In fact, younger children (5-years-old) seem to take less advantage of visual speech information than older children (8-years-old) (Van Linden & Vroomen, 2008). It has been suggested that preschool children (age 5) have less experience producing speech compared to older children, and as a result do not benefit from AV speech to the same degree (Desjardins et al., 1997; Van Linden & Vroomen, 2008). Therefore, the degree of experience with multimodal speech matters, and the research suggests that the multimodal speech perception system is one that takes years to develop into full maturity, but that also shows significant development between 5- and 8-years.

Neural Components of Speech. Several brain regions have been implicated in AV speech, predominately the inferior frontal/ventral premotor, inferior parietal, and posterior temporal regions, and these regions have been proposed to be connected by the SLF/AF (Bernal & Altman, 2010; Catani et al., 2005; Dick & Tremblay, 2012; Martino et al., 2013; Thiebaut de Schotten et al., 2012). Two processing streams, namely the auditory-visual and auditory-motor pathways, ground functional interactions among this frontal-parietal-temporal network. The first, the sensory-sensory (auditory-visual) pathway is anchored by the posterior superior temporal sulcus (STSp), and connects visual domains (especially MT/V5), primary auditory cortex, STSp, and inferior frontal regions (Arnal, Morillon, Kell, & Giraud, 2009; Calvert, 1997). Evidence in older children (Nath & Beauchamp, 2012; Nath et al., 2011) and adults (Arnal et al., 2009; Barrós-Loscertales et al., 2013; Calvert, 1997) suggest that auditory and visual

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information are integrated into perceptual units in the STSp. For example, the amplification of the activation in STSp has been associated with perceiving McGurk fusions. McGurk fusions occur when perceivers are presented with incongruent visual and auditory stimuli (e.g., visual /da/, auditory /ba/), and as a consequence report hearing a syllable that is different from the original stimuli (e.g., ga).

The second, the "sensory-motor" stream has been suggested to be involved in mapping the perceptual units of sound (i.e., phonological information) in the auditory modality to articulatory representations involved in producing those sounds (Callan, Jones, Callan, & Akahane-Yamada, 2004; Skipper, van Wassenhove, Nusbaum, & Small, 2007). This stream is anchored by the inferior supramarginal gyrus/planum temporale (iSMG/PTe), and connects inferior frontal gyrus, premotor cortex, anterior insula, and in some reports precentral and somatosensory brain regions to the posterior planum temporal (Spt), and focal regions of the STG and STS (Buchsbaum, Hickok, & Humphries, 2001; Callan et al., 2004; Dronkers, 1996; Hickok & Poeppel, 2000; Wilson, 2004).

The auditory-motor network has been primarily implicated in planning and executing speech movements (e,g., speech production). However, several lines of neuroscience research suggest that motor regions play a crucial role in AV speech perception as well, namely through functional interactions between auditory, motor, and somatosensory brain regions (Callan et al., 2004; Skipper, Nusbaum, & Small, 2005; Skipper et al., 2007; Watkins, Strafella, & Paus, 2003) and with the iSMG/PTe as an important structure facilitating integration (Griffiths & Warren, 2002; Karbe, Herholz, Weber-Luxenburger, Ghaemi, & Heiss, 1998; Okada & Hickok, 2009). The FAT tract in

particular may contribute to audiovisual processing by facilitating interactions between speech-motor regions of the supplementary motor areas and the inferior frontal gyrus. However, to date this has not been investigated.

In summary, two processing streams seem to be involved in auditory and audiovisual speech perception, namely the auditory-visual and auditory-motor pathways and these pathways are connected by the SLF/AF. While the SLF/AF has been proposed to connect the described speech network, we do not know if there are structural differences in the SLF/AF related to speech in the developing child's brain, and in particular there is no evidence linking the development of these fiber pathways to age-related changes in audiovisual speech perception. It is also notable that no studies have identified the FAT in children of any age, nor attempted to relate the integrity of this tract to developing speech. Given its putative involvement in speech production, the FAT may also contribute to speech perception, especially in children who are continuing to develop articulatory and phonological skill.

Behavioral Components of Language. Language is a complex cognitive task that requires processing multiple levels of information, such as word-level processing, sentence processing, and discourse processing. Development of language proceeds across these levels. Thus, infants can learn to discriminate speech sounds by 4-6 months, and by 6-8 months, infants begin to babble, or produce sounds that are within their native inventory of phonemes (Bates, Benigni, Bretherton, Camaioni, & Volterra, 1979; Lewedag, Oller, & Lynch, 1994; Masataka, 2001). Comprehension at the word level emerges around 8-10 months (Bates, Benigni, Bretherton, Camaioni, & Volterra, 1979), and production of words occurs a few months later at 11-13 months (Bates & Dick, 2002;

Shore, Bates, Bretherton, Beeghly, & OConnell, 1990). With age, more complex skills

emerge. For example, at 18-20 months, infants begin to combine words together (Bauer

& Thal, 1990), and by 24 months, the combinations of words follow the appropriate

grammatical structure of their native language (Bauer, Wenner, Dropik, & Wewerka,

2000). While the developing child begins to produce meaningful and grammatically

correct utterances by 24 months, we must acknowledge that there are individual

differences in toddlers' receptive and expressive language, meaning their ability to

understand and produce language, and this is predictive of children's later receptive and

expressive language in early school years.

Neural Components of Language. The neural network for expressive and

receptive language includes the fronto-temporo-parital neural network reviewed for

speech perception and production, including the inferior frontal/ventral premotor, inferior

parietal, and posterior temporal regions. However, processing beyond phonological-level

information, at the semantic and syntactic level, includes more extensive perisylvian

language cortical regions including the occipito-temporal and middle and inferior

temporal regions (Catani & Mesulam, 2008; Dick, Solodkin, & Small, 2010; Glasser &

Rilling, 2008; Hickok & Poeppel, 2004). Some additional projections to the SLF/AF have

been associated with higher-level language processing. For example, neuroimaging

evidence in addition to evidence from adults with stroke has found that damage to the

SLF is related to deficits in repetition of speech, while the AF components seems to be

important for comprehension of speech (Breier, Hasan, Zhang, Men, & Papanicolaou,

2008). Only one study has related the FAT to behavioral measures of language (Catani et

al., 2013). Catani and colleagues characterized the FAT in adults with Primary

Progressive Aphasia and found that white matter integrity of the FAT was associated with the expressive language measure of verbal fluency (Catani et al., 2013). As already mentioned, no study of the FAT has been conducted in children, but given the association with expressive language in adults with aphasia, we might expect the FAT to support developing expressive language in children.

      Behavioral Components of Literacy. Literacy is developing at the same time as language and the ability to read requires children to develop several skills. First, the child must know the phonological structure (i.e., the units of sounds) of a given language regardless of language dominance. In alphabetic languages, such as English or Spanish, children must also learn to map letters to speech sounds (i.e. phonemes), and then assemble these sounds serially, letter-by-letter to create meaningful words (Durgunouglu, Nagy, & Hancin-Bhatt, 1993; Liberman & Shankweiler, 1987; Read, Yun-Fei, Hong-Yin, & Bao-Qing, 1986). The ability to recognize and manipulate the sound structure of spoken words is called phonological awareness (Mattingly, 1972), and has been found to be the most significant predictor in later reading and vocabulary skill in school-aged kindergarten children (Lundberg, Olofsson, & Wall, 1980). In fact, these effects are also detected over an extended developmental timeline; so much so that early phonological awareness predicts literacy outcomes from kindergarten through the fourth grade and remain remarkably stable (Wagner et al., 1997). Therefore, children, especially young children, may profit from phonological training even before beginning to read, and further may profit from a continuation of phonologically mediated training through the elementary school grades. These results have important implications not only for preschool instruction, but also for developing literacy and teaching programs geared

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toward adults and individuals with reading disabilities. Importantly a number of gains in literacy are occurring in the 5-8-year age range we target in the present study.

Neural Components of Literacy. A growing body of literature has investigated the structural connectivity supporting literacy in children and found that fibers traveling anterior to posterior in the temporal and parietal cortex are associated with reading (Klingberg et al., 2000). These fibers, which travel as part of the SLF/AF, have been proposed to connect inferior frontal/ventral premotor, supramarginal gyrus and angular gyrus in the parietal lobe, occipital temporal areas, and posterior temporal cortical regions (Shaywitz & Shaywitz, 2008), and they play a critical role in phonological awareness (e.g., rhyming tasks) and reading (Beaulieu et al., 2005; Shalom & Poeppel, 2008; Temple et al., 2003).

White matter integrity of the SLF/AF in the temporal-parietal region of the left hemisphere has been significantly related with reading scores in reading-impaired children and adults and typically developing children (Klingberg et al., 2000; Nagy et al., 2004; Thiebaut de Schotten, Cohen, Amemiya, Braga, & Dehaene, 2012). One case study reported that a 5-year-old acquired severe dyslexia after damage to the arcuate fasciculus (Rauschecker et al., 2009). Taken together, the aforementioned evidence suggests that the inferior frontal-parietal-temporal network, connected by the perisylvian SLF/AF is important for reading. In contrast, the FAT has not been associated with literacy, and there is little reason to suspect that it might be, as it does not provide connectivity to temporal and parietal regions most important for reading.

CHAPTER III

HYPOTHESES AND PREDICTIONS

As our review shows, there is a growing literature investigating developing fiber

pathways and the relation of these to speech, language, and literacy. However, the vast

majority of these studies have investigated older children (e.g., older than 8 years). This

is often done for practical reasons, as it is difficult to scan younger children because of

issues with MRI image artifacts as a result of movement during the scan. As our literature

review suggests, though, this focus on older children misses the considerable

development in speech, language, and literacy occurring in younger age ranges,

particularly from 5-8-years. Although these behavioral-level trends are well established,

almost no work has investigated the developing fiber pathways that contribute to this

development.

To fill the considerable knowledge gap, the present study aims to characterize the

specific age-related changes in SLF/AF and the FAT white matter microstructure and

relate white matter microstructure of both pathways to speech, language, and literacy

abilities. The most prominent fiber pathway identified with language and literacy is the

SLF/AF. The SLF/AF has been investigated in children, but these children are much

older than we investigate here (typically 8-11-years old), and there is often little

investigation of the relation to specific behavioral measures of language, or if behavioral

measures are used, they are gross language measures (e.g., verbal IQ). The FAT is newly

described in adults, but has never been shown in children. Therefore, the aims of the

present study are to: 1) identify the FAT in young children who are still developing

speech, language, and literacy, 2) relate the FAT to speech, language, and literacy, 3)

characterize the SLF/AF, and 4) relate the SLF/AF to speech, language, and literacy. The measures of speech, language and literacy skill that we investigate include performance on AV speech perception task, and performance on a battery of tests assessing phonology, articulation, receptive and expressive language, and phonological awareness.

We predict that, after controlling for age, whole brain white matter integrity, non-verbal IQ, and sex, higher white matter integrity (higher FA values; lower ADC values) of the SLF/AF and FAT will be related to better speech, language and literacy skills. The exception to this is that we did not expect a relation between FAT white matter integrity and literacy. The latter hypothesis is supported by our review of the neural components of literacy, which predominately include connections among inferior frontal/ventral premotor, supramarginal gyrus and angular gyrus in the parietal lobe, occipital temporal areas, and posterior temporal cortical regions (Shaywitz & Shaywitz, 2008). While the FAT has been proposed to connect supplementary motor and pre-supplemetary motor areas with the inferior frontal gyrus, it does not make connections to inferior parietal and occipitotemporal regions involved in literacy. Therefore, we do not expect a relation between the FAT white matter integrity and literacy.

CHAPTER IV

METHOD

Participants

Nineteen children (9 females, 10 males; age range = 5-8 years, M age = 6.8 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), and

had normal (or corrected to normal) vision. An additional 3 children completed the

diffusion weighted scan but were not analyzed because of image artifacts indicated after

the scan (one was due to an error of the technician; two were removed due to motion

artifact). An additional 11 children were consented but did not complete the diffusion

weighted scan because of their refusal to assent, or because of significant movement

during the T1-weighted structural scan before the diffusion-weighted scan was initiated.

Written informed consent/assent was obtained from all parents and children for whom we

have usable data. The Western Institutional Review Board and the Florida International

University Institutional Review Board approved the study.

Procedure

Data were collected during two visits. The first visit took place at Miami

Children's Hospital, Miami, FL and consisted of three sessions: 1) a pre-test session

audiovisual speech categorization task (~8 min) to determine individual's categorical

speech perception, 2) a scanning session (~25 min), and 3) a post-test session (~4 min) to

determine visual influence of speech. The second visit was scheduled within two weeks

of the first visit and took place at Florida International University. During this visit (~90

min), we administered a battery of language tests measuring phonology, articulation, receptive and expressive language, and reading abilities.

Stimuli for the Audiovisual Speech Task. Six adults (3 females) were recorded speaking syllables (/ba/, /da/, /pa/, /ka/) with a digital video camera under two conditions (Visual Speech [VS] and Masked Speech [MS]). In the MS condition, speakers wore a surgical mask to hide lip and mouth speech-related movements. In the VS condition, speakers did not wear a surgical mask. Two additional speakers (1 female) were recorded saying these same syllables with a remote microphone. The consonant-vowel (/ba/, /da/, /pa/, /ka/) utterances were selected because the place of articulation of the consonant varied along a single factor. The same vowels were selected because the formant structure has been shown to provide superior signal/noise ratio relative to the MRI scanner during functional runs (Miller & D'Esposito, 2005).

From these audio recordings, two naturalistic 7-step continua (ba ←→ da; pa ←→ ka) were developed using Praat software. The start of each vowel /a/ was clipped to isolate the consonant. Then the vowel from one recording was affixed to each consonant. Affixing the vowel from one recording to each consonant ensured that identical vowels were heard across all constants. Then we used "Pitch Synchronous Overlap and Add" to modify the pitch and duration of each sound, and interpolated between these two modified sounds to develop the continua. By combining the audio clips from the continua with the video clips from the six speakers, we created the audiovisual clips. For both VS and MS conditions, the consonantal burst of the auditory file was aligned to the consonantal burst of auditory portion of the video file. All clips were edited to last 1.6 seconds.

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Pre-and-post-test categorical syllable perception. The categorical syllable perception task included pre-and post-test sessions. The purpose of the pre-test was to identify each individual's speech categorical boundary. To do this, we used the MS stimuli to create a second factor, Ambiguity. We used the MS to avoid visual influences from the lips and mouth, and therefore better capture their auditory syllable perception. Along the seven step pa ←→ ka or /ba/ ←→ da speech continua, the first and last steps were designed as unambiguous. Steps in between the first and last were considered ambiguous because as you move along the pa ←→ ka continuum, the /pa/ starts to sound more like a /ka/. However, while some participants may hear the /pa/ sound change to a /ka/ sound at the third step of the continuum, others might hear it change at the fourth and fifth step. The two ambiguous sounds along the continuum in which the participant shifts from one category (e.g., /pa/) to a different category (e.g., /ka/) defined their speech categorical boundary. Therefore, to determine the pre-test categorical boundary, participants were presented with MS stimuli. Each step along the continuum was presented 3 times in a pseudo-randomized sequence for a total of 48 trials across the two continua (~8 mins). Children were asked to watch the video clip and repeat out loud the sound they heard. Their responses determined which step along the 7 step continua (e.g., /ba/ ←→ /da/), the child shifted from one speech category (e.g., /ba/) to a different speech category (e.g., /da/), without the influence of speech-related lip and mouth movements. The two ambiguous sounds at the category boundary along with two unambiguous sounds (the ends of the continua) were presented to each participant during the post-test session.

The purpose of the post-test session was to calculate the degree to which visual information from the lips and mouth influenced participant's categorical speech perception. For the post-test, children were presented with the VS and MS stimuli using only the ambiguous and endpoints of the continuum (48 stimuli total, ~ 8mins). Therefore, each participant heard different sounds depending on how they categorized them in the pre-test. Once more, children were asked to watch the video clip and repeat out loud the sound they heard. For each stimulus, the difference in steps along the continuum across the VS and MS condition serves as a measure of AV integration.

Assessments. The following assessments were administered to obtain a complete understanding of each child's speech and language ability: the Diagnostic Evaluation of Articulation and Phonology (DEAP; Dodd, Zhu, Crosbie, Holm, & Ozanne, 2002), including articulation, and phonology subtests, the Clinical Evaluation of Language Fundamentals-4 (CELF-4; Semel, Wiig, & Secord, 2003), including receptive language (REC), expressive vocabulary (EXP), concept and directions, word class, and sentence structure subtests, the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI – III; Wechsler, 2002) Block Design subtest, and the Word Attack (Test 3), Sound Awareness (Test 7), and Sound Blending (Test 8) subtests of the Woodcock-Johnson III Diagnostic Reading Battery (WJ III DRB; Schrank & Mather, 2006). For this analysis, we used the DEAP for measuring phonology and articulation, the CELF for measuring receptive and expressive language, and the WJ-III for measuring literacy. We also used the block design subtest of the WPPSI-III to control for non-verbal IQ. Standardized scores were used in the analysis for all subtests.

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Data Acquisition. Participants were scanned on a 3 Tesla Philips MRI scanner with SENSE coil housed at Miami 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 individual differences in white matter architecture. 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 (reference scan), matrix size = 112×112, time echo [TE] = 60, time repetition [TR] = 6157, NEX = 3, FOV = 240×240 mm2, slice thickness = 2 mm, number of axial slices = 55 (no gap), and voxel size = 0.938 mm x 0.938 mm x 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). Head motion was minimized by placing cushions around the head and securing a strap across the forehead. The duration of scanning time was approximately 25 min per subject, not including setup time.

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 denoised using the Non-Local Means Filter adapted to Rician noise distribution (NLMr; Coupé, Manjón, Robles, & Collins, 2011). The filter restores the intensity of voxels by computing a weighted average of all voxel intensities in the

image, producing better quality fractional anisotropy maps (Descoteaux, Wiest-Daesslé, Prima, Barillot, & Deriche, 2008; Wiest-Daesslé, Prima, Coupé, Morrissey, & Barillot, 2008). Data were preprocessed also for eddy currents and subject motion, using affine registration to a non-weighted diffusion reference image (b =0). Non-brain tissue was removed using FSL's automated brain extraction tool (BET). 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 be used to compute FA and ADC values (Basser et al., 1994).

We verified that the orientation and directions of tensors were correct using the fractional anisotropy red-green-blue (RGB) color map across all axes. We used well-defined fiber pathways for this verification, and inspected whether the cingulum was oriented along the anterior-posterior axis (labeled green) in the sagittal plane, whether the cortico-spinal tract (CST) was oriented along the superior-posterior axis (blue) in the coronal plane, and finally whether the corpus callosum was oriented along the medial-lateral axis (red) in the axial plane.

Fiber Tract Identification. All fiber tracking procedures were performed in DSI Studio with a fractional anisotropy threshold of 0.15 and fiber angles of less than 40° between connecting pixels. These thresholds are standard thresholds used by a prominent published atlas of white matter tracts (Oishi et al., 2008).

Manual Fiber Tract Identification. We manually identified the SLF/AF for each individual using a one region of interest (ROI) approach. The SLF/AF region of interest was guided by fiber orientation maps and defined on the fractional anisotropy map computed from the averaged DT-MRI volume: red for medial-lateral, green for anterior-posterior, and blue for superior-inferior. We manually defined an ROI that encompassed all green voxels lateral to the internal capsule (Catani et al., 2005). The SLF/AF ROI was defined liberally, making sure to include all possible SLF/AF voxels and allowing voxels from neighboring tracts as well.

We also manually identified the FAT. We used a two-ROI approach (Catani et al., 2012; Thiebaut de Schotten et al., 2012). The first ROI was drawn in the posterior part of Broca's territory (i.e., precentral cortex, BA 6, *pars opercularis*, BA 44). The second ROI was drawn in the SMA and pre-SMA in the superior frontal gyrus (BA 8 and 6; Lawes et al., 2008; Oishi et al., 2008). All fibers passing through these ROIs were reconstructed in three dimensions and visualized using streamtubes. The streamtube method is used because it represents structures with primarily linear diffusion, that is the diffusion tensor along one direction in a 3D field (one eigenvalue) is much larger than the other two and therefore corresponds to linear anisotropy diffusion (Zhang, Demiralp, & Laidlaw, 2003). White-matter tracts tend to produce tensors with linear anisotropy (Coremans, Luypaert, Verhelle, Stadnik, & Osteaux, 1994).

Data Analysis

Use of Robust Statistics. We related our calculations of FA and ADC measures of white matter integrity to age and behavioral outcome measures using robust estimates of correlation (r_{rob}) and robust regression (using the Huber loss function). We used robust

procedures because they are less influenced by outliers and increase the precision of

parameter estimates when there are outliers (Wilcox, 2012; Wright & London, 2009). We

also calculated 95% confidence intervals using bootstrap methods for estimating the

parameters (Efron, 1992; Efron & Tibshirani, 1986). We used the R statistical package

(v. 2.15.1; http://www.R-project.org) to conduct these analyses.

CHAPTER V

RESULTS

The goal of the analysis was two-fold. First, we identified and characterized age-related changes of white matter integrity in two fiber tracts important for language, the frontal aslant tract (FAT) and the superior longitudinal fasciculus/arcuate fasciculus (SLF/AF). Second, we related these changes to developing speech, language, and literacy.

Identification of the FAT and SLF/AF Tracts

We were able to track both the left (M FA = 0.40, SD = .02; M ADC = 0.84 +/- 0.02 x 10^{-3} mm^2/s) and right (M FA values = 0.40, SD = .02; M ADC = 0.84 +/- 0.02 x 10^{-3} mm^2/s) FAT in 17 out of 19 children. See *Figure 4* on the next page. In one child we were not able to track the left FAT, but we were able to track the right FAT; in a different child we were not able to track the right FAT, but we were able to track the left FAT. However, it is notable that both of these FAT tracts appeared when the step size was adjusted to a more liberal level (of 2 mm). See *Figure 5* on the next page. Thus, the lack of identification should not be taken to indicate an absence of the tract, but may indicate an artifact in the data, noise in the data, reduced myelination of the tract, or Type II statistical error.

We were also able to reliably track the left (M FA = 0.45, SD = .02; M ADC = 0.82 +/- 0.02 x 10^{-3} mm^2/s) and right (M FA = 0.44, SD = .02; M ADC = 0.82 +/- 0.02 x 10^{-3} mm^2/s) SLF/AF in all children (see *Figure 6*). Both FA and ADC values for this tract fell within the normal range for children (Morriss et al., 1999; Sener, 2001).
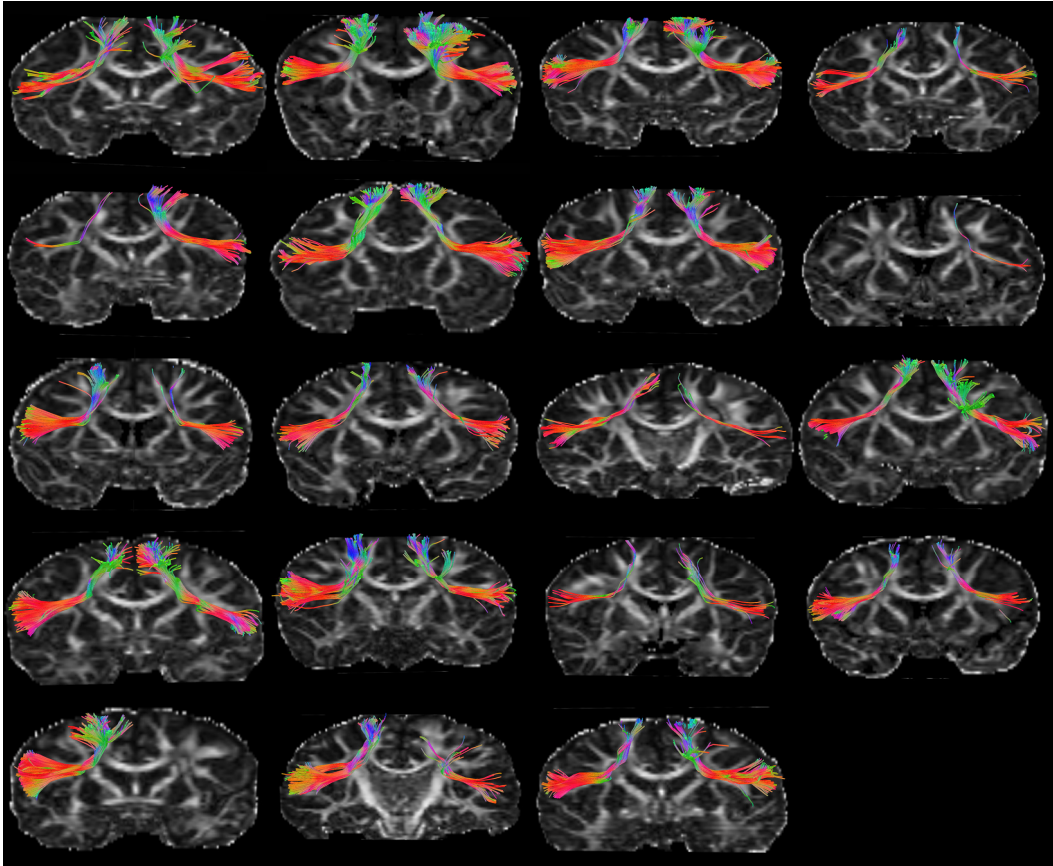
Figure 4. Connections of the Frontal Aslant Tract (FAT) in 19 children. Note: This mosaic is displayed in radiological orientation. Therefore, the right side of the image represents the left cerebral hemisphere.
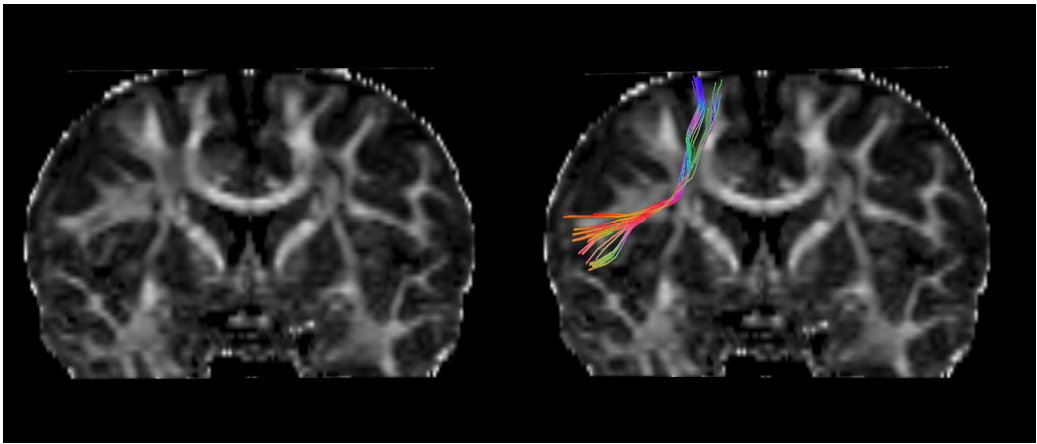
Figure 5. Left: FAT of one child was not identified in the right hemisphere under more stringent step size (of 1 mm). Right: FAT appeared when the step size was adjusted to a more liberal level (of 2 mm). Note: Figures are displayed in radiological orientation.
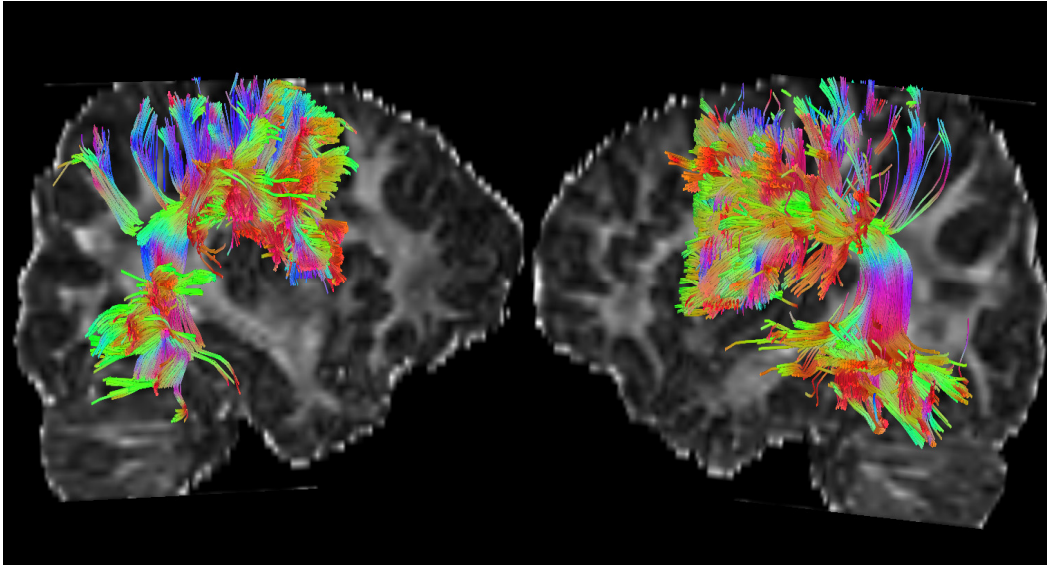
Figure 6. Left and right connections of the SLF/AF in one child.

Age-related Change in the FAT and SLF/AF

To characterize age-related changes of the FAT and SLF/AF we ran robust correlations. *Figures 7* and *8* show robust elliptical plots (relplots; (Goldberg & Iglewicz, 1992). Neither the left nor the right FAT showed age-related changes in white matter integrity, measured by FA values (*Figure 7*) and by ADC values (*Figure 8*). In contrast, the left SLF/AF did show age-related changes in white matter integrity, measured by FA values (r_{rob} = .88; p < .001), but the right SLF/AF did not (*Figure 7*). Neither tract showed significant age-related change in ADC (*Figure 8*).
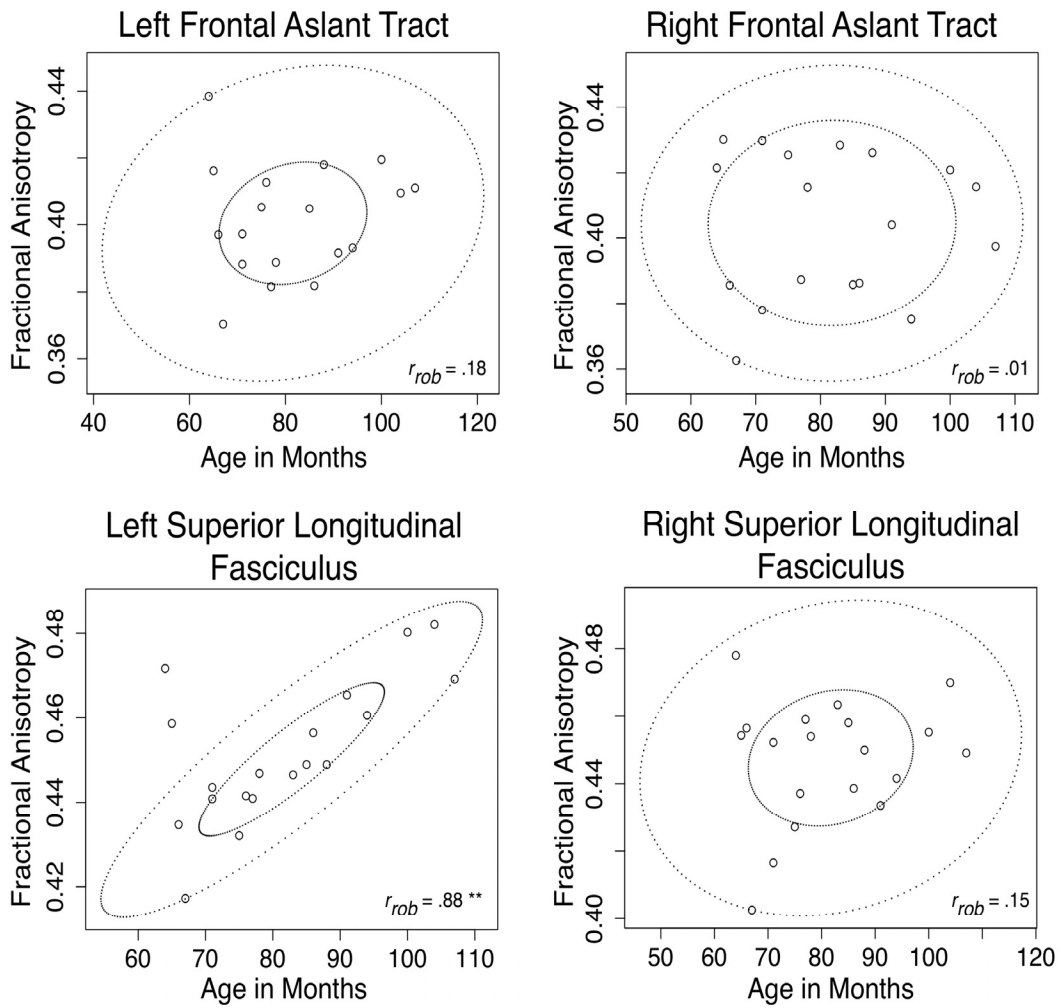
Figure 7. Top: Age-related changes in fractional anisotropy in the left and right Frontal Aslant Tract. Bottom: Age-related changes in fractional anisotropy in the left and right Superior Longitudinal Fasciculus/Arcuate Fasciculus.
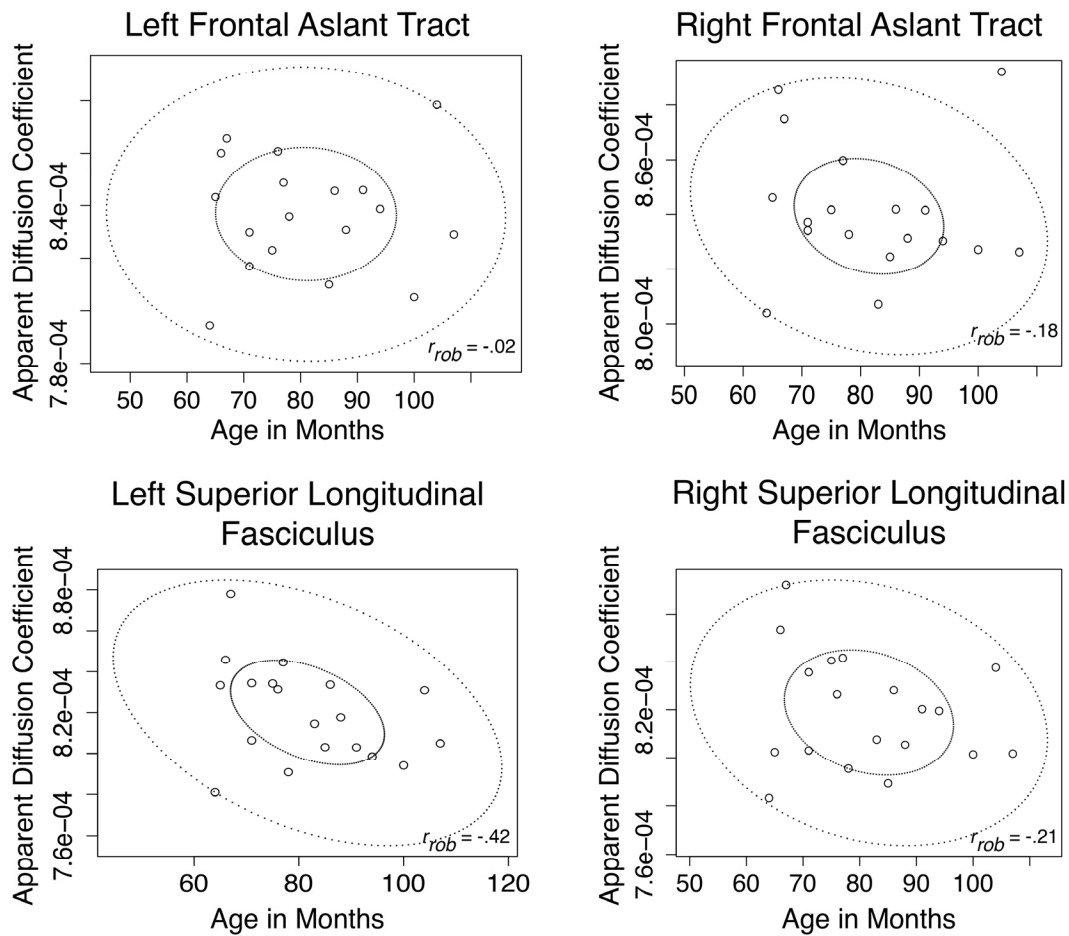
Figure 8. Top: Age-related changes in apparent diffusion coefficient in the left and right Frontal Aslant Tract. Bottom: Age-related changes in apparent diffusion coefficient in the left and right Superior Longitudinal Fasciculus/Arcuate Fasciculus.

Relation of the FAT and SLF/AF to Speech, Language, and Literacy

To relate the FAT and SLF/AF white matter integrity to speech, language, and literacy we conducted robust linear models. For these models we bootstrapped the residuals (10,000 iterations) to obtain the 95% confidence intervals. The effects are reported after controlling for age in months, non-verbal IQ, sex, and whole brain FA in

the model. The adjusted R^2 values are reported from the ordinary least squares model; these are not available for robust models, and should be interpreted with caution. In *Table 1 on the next page,* only those findings in which the bootstrapped confidence intervals do not cover zero are reported. Results indicate that the right FAT was negatively related to phonology. Therefore, increased white matter integrity of the right FAT as measured by FA values, was associated with lower phonological scores. Moreover, we failed to find evidence that the FAT white matter integrity (as measured by FA and ADC) was related to our measures of AV speech perception, articulation, language, or literacy. In contrast, we found that both the left and right SLF/AF were related to language, specifically receptive language, expressive vocabulary, and language content, as measured by the CELF

Frontal Aslant Tract (FAT) and Superior longitudinal fasciculus/arcuate fasciculus integrity predicts receptive and expressive language and phonology

Predictor → Outcome	B (SE)	ß	95% CI	R^2_{adj}
Fractional Anisotropy (FA) Measures				
Right FAT → Phonology	-186.3 (88.8)	-0.46	-360.2 to -12.0	0.16
Left SLF/AF → CELF Receptive Language	547.0 (131.5)	0.66	287.1 to 802.7	0.51
Left SLF/AF → CELF Language Content	484.4 (120.4)	0.60	247.5 to 719.6	0.64
Right SLF/AF → CELF Receptive Language	396.4 (118.2)	0.52	168.9 to 632.4	0.30
Right SLF/AF → CELF Language Content	265.2 (113.3)	0.36	43.4 to 487.7	0.46
Right SLF/AF → CELF Expressive Vocabulary	66.9 (31.4)	0.42	5.3 to 128.6	0.12
Apparent Diffusion Coefficient (ADC) Measures				
Left SLF/AF → CELF Receptive Language	-26.6 (9.1)	-0.45	-45.0 to -9.2	0.24
Left SLF/AF → CELF Language Content	-22.7 (8.0)	-0.40	-39.0 to -7.4	0.54
Left SLF/AF → CELF Expressive Vocabulary	-6.3 (2.3)	-0.52	-10.8 to -1.7	0.10
Right SLF/AF → CELF Receptive Language	-25.4 (9.1)	-0.43	-43.2 to -7.5	0.21
Right SLF/AF → CELF Language Content	-18.3 (8.2)	-0.32	-34.6 to -2.3	0.46

Note. Effects reported for robust linear models after controlling for age in months, sex, and whole brain FA (for FA predictors) or whole brain ADC (for ADC predictors), and block design. FAT = Frontal Aslant Tract; SLF/AF = Superior longitudinal fasciculus/arcuate fasciculus. CELF = Clinical Evaluation of Language Fundamentals. To reduce digits, ADC values were divided by a constant. Adjusted R^2 values are reported from the ordinary least squares model.

CHAPTER VI

DISCUSSION

The work presented here showed that different white matter pathways can be identified, tracked, characterized, and quantified in terms of their structural integrity, and these metrics can be related to a number of behavioral outcome measures. In the present study we identified a new fiber pathway—the frontal aslant tract (FAT)—for the first time in young children. In addition to the FAT, we also characterized the superior longitudinal fasciculus/arcuate fasciculus (SLF/AF), another pathway of the dorsal speech stream, and related the two tracts to speech, language, and literacy outcomes. The findings in the current study contribute to a growing understanding of brain development and its relation to behavior.

Frontal Aslant Tract (FAT)

The FAT is a newly described fiber tract that has been recently identified in adults (Catani et al., 2012; Ford, McGregor, Case, Crosson, & White, 2010; Lawes et al., 2008; Oishi et al., 2008). However, this is the first study to identify the FAT in children. We were able to identify the FAT bilaterally in almost all children. Advances in our understanding of FAT connectivity is important because of its putative involvement in speech production, speech perception, language, and literacy, especially in children who are continuing to develop these skills.

The FAT has been suggested to make connections from the superior frontal gyrus (Lawes et al., 2008), the posterior SMA (Oishi et al., 2008), and the pre-SMA (Ford et al., 2010) to the inferior frontal gyrus (Catani et al., 2013). It has been suggested to play a role in speech production (Catani et al., 2013; Dick et al., 2013) and found to be related

to verbal fluency in patients with primary progressive aphasia (Catani et al., 2013). Several fMRI studies suggest that motor regions are activated during speech perception tasks (Skipper et al., 2005; Skipper et al., 2007; Tremblay & Small, 2011; Wilson, 2004; Wilson & Iacoboni, 2006). The shared neural activation maps between speech perception and production suggest a close relationship between sensory and motor domains that may be important for communicating information about the acoustic speech sounds (e.g., /ba/) and how to produce these sounds (Tremblay & Small, 2011). The primary finding of this study was that the FAT indeed provides a direct connection between the posterior SMA (Oishi et al., 2008), and the pre-SMA (Ford et al., 2010) to the inferior frontal gyrus (Catani et al., 2013). However, the FAT did not show age-related change. Absence of age-related change in the FAT may reflect that the tract is rather mature by 5-8 years old. Furthermore, it may be that age-related changes could be observed at younger ages, for example, when infants are learning to babble.

In addition, we expected the FAT to play a critical role in speech and language, especially in children who are currently developing these skills. In the present study, we found a significant negative relationship between white matter integrity of the right FAT and phonology. This finding was unexpected. If any relationship existed, we expected both the left and right FAT to be positively related to phonology. However, the relation between FAT integrity and phonology may be better understood by further delineating different connections within the pathway. That is, evidence suggests that the pre-SMA and SMA are anatomically and functionally distinct, with the pre-SMA a prefrontal region and the SMA a non-primary motor region (Luppino, Matelli, Camarda, & Rizzolatti, 1994; Picard & Strick, 1996; Tremblay & Gracco, 2010). Therefore, isolating

pre-SMA and SMA might better capture interactions between white matter integrity and speech and language. In addition, fMRI studies have suggested the pre-SMA as playing a critical role in more complex/cognitive motor control (Kim et al., 2010), such as the selection of words and oral motor responses (Tremblay & Gracco, 2010). Simultaneous activity in the pre-SMA and IFG has been reported as critical in the selection process of spoken word generation (e.g., compared to reading aloud; Tremblay & Gracco, 2006). In comparison, the SMA has been implicated in making connections with the spinal cord and important in action generation (Tremblay & Gracco, 2006). The aforementioned evidence suggests the possibility that there are two functionally distinct tracts, similar to the SLF/AF (discussed below), and the fiber tracts from the pre-SMA may be correlated with online selection and generation of speech, compared with the SMA in repetition of speech. Broadly, isolating contributions of the pre-SMA and SMA may more accurately characterize the relationship between the FAT and speech, language, and literacy.

In addition to the negative relationship between the right FAT and phonology, we also failed to find a significant relationship between the left and right FAT and AV speech perception, articulation, language, and literacy. While the non-significant relationship of the FAT and literacy was expected, we did expect a relationship between FAT integrity and articulation. In this case, it may be that the FAT is mature by the age range we tested, and shows little age-related change. Our behavioral measures of articulation suggest that typical developing children do not vary much in their ability produce speech sounds—most children performed well on the DEAP, with a range between 75 and 110, and the majority of children scoring above 105 (n=15), a score of 110 indicating ceiling performance. Thus, one way of looking at this is that the

behavioral and brain data are congruent and show relative maturity at this age. However, this result should be interpreted with caution because of the ceiling effects in the behavioral measures. Moreover, children in the present study are typically developing. Therefore, we might observe a different brain/behavior relation in children who have speech disorders (Sener, 2001). Future studies that investigate a younger age cohort, or children with speech pathologies, may reveal a fundamental relationship between this pathway and articulation.

Superior Longitudinal Fasciculus/Arcuate Fasciculus (SLF/AF)

The present study also characterized the SLF/AF bilaterally in all children. The SLF/AF has been well studied in both adults and children. Previous work with older children (7-11 years old) suggests that left AF fibers show age-related changes (Yeatman et al., 2011). Schmithorst and colleagues (2002) also report significant positive correlation of FA with age (5-18 years old) in the left arcuate fasciculus, but not the right. The lateralization of change in FA is similar to what we reported here. The present work also focuses on a narrow age range (5-8 years) because during this age range children are developing speech, language, and literacy skill. We expanded on these finding by focusing on contributions from both the left and right hemisphere and showing that the left and right hemispheres show a different developmental trend, with the left SLF/AF showing a significant increase in FA with age.

The current study found asymmetric trajectories of brain development in the SLF/AF. We found age-related changes in white matter integrity in left SLF/AF but not the right. The SLF/AF connects frontal, temporal, and parietal lobes (Hickok & Poeppel, 2007), which are important for processing speech, language, and literacy (Paus et al.,

1999; Beaulieu et al., 2005; Klingberg et al., 2000). In addition, while both hemispheres are implicated in language processing, evidence suggests that more generally, language processing is strongly left dominant (Hickok & Poeppel, 2007). Therefore, age-related changes in the left SLF/AF but not the right may reflect asymmetrical re-organization of the SLF/AF fiber pathway to be more coherent during language development. Of note, the work presented here also suggests that maturation of the SLF/AF is not the sole predictor of language. For example, despite that age-related changes in white matter integrity were specific to the left SLF/AF, we found that white matter integrity in both the left and right SLF/AF predicted receptive language, expressive vocabulary, and language content. These results were robust even after controlling for age, sex, non-verbal IQ, and whole brain white matter integrity.

Moreover, we found a non-significant relationship between white matter integrity of the SLF/AF and speech and literacy. Other studies have provided evidence for white matter integrity in the SLF/AF for reading (Klingberg et al., 2000), phonological awareness (Yeatman et al., 2011), and speech (Catani et al., 2005). However, aside from Yeatman and colleagues (2011), the aforementioned studies were conducted in adults. The distinct findings may also be related to evidence suggesting that different components of the SLF/AF contribute uniquely to speech (Catani et al., 2005), and literacy (Thiebaut de Schotten et al., 2012). Therefore, the next step should be to characterize the different components of the SLF/AF, for the same reasons proposed for the FAT, and relate them to speech and literacy.

Importance of Findings for a Model of the Neurobiology of Language

More broadly, the work presented here complements the dorsal-ventral-motor model for language. In the introduction, we proposed the SLF/AF and the FAT as important for language. We characterized the SLF/AF in the developing brain and found that both the left and right SLF/AF predicted receptive language, expressive vocabulary, language content, but not speech and literacy. In retrospect, this makes sense because our measures of receptive and expressive language are based on the child's listening and auditory comprehension abilities and their ability to name illustrations of people, objects, and actions, respectively. Successfully doing this task requires the entire SLF/AF tract and both hemispheres.

The primary finding was that both the left and right SLF/AF predicted language, specifically receptive and expressive language, and language content. While both the left and right SLF/AF predicted receptive language and language content, the left SLF/AF as predictors accounted for more variance in the model compared with the right SLF/AF predictors with respect to receptive language and language content. The finding is consistent with models of language, which suggest that language is processed bilaterally, although not identically (Hickok & Poeppel, 2004; Ivry, 1998; Poeppel, 2003; Zatorre, Meyer, Gjedde, & Evans, 1996). That is, while the two hemispheres contribute to language processing, each hemisphere performs different computations on the incoming speech signal (Hickok, 2009). Thus, our findings suggest that the left and right SLF/AF are important for language, but their contributions are not identical.

We also found that the left SLF/AF and the right SLF/AF predicted expressive vocabulary, measured by the CELF. The expressive vocabulary subtest evaluates the

student's ability to name illustrations of people, objects, and actions (referential naming). Both the left and right hemispheres are implicated in phonological processing and involve both motor/premotor cortices (Hickok & Poeppel, 2007). Therefore, this finding is consistent with the idea that language is a bilateral process in the normal brain.

In addition, evidence from patients with neurological deficits reveals similar reports with respect to bilateral contributions to language processing. For example, auditory comprehension at the lexical level in the right hemisphere is spared in split-brain patients and patients undergoing the Wada test (Barde, Baynes, Gage, & Hickok, 2000; McGlone, 1984). It is noteworthy, however, that findings from the present study do not negate that in typical right-handed individuals the left hemisphere is a prominent contributor to language function. Rather, the findings support the right hemisphere, more specifically the right SLF/AF, in language processing. In addition, while this study does not inform us about how different components of the SLF/AF participate in comprehension and articulation, it does reveal that the SLF/AF as a whole is important for language.

Lastly, the dorsal-ventral-motor model for language processing suggests a motor component. The FAT was suggested to make connection from typically motor regions to the IFG (Catani et al., 2013; Dick et al., 2013). Although the present study found no age-related change or a functional specialization of the FAT with respect to speech, language, and literacy, this does not mean that the FAT does not serve an important function for language. In fact, as mentioned earlier, others have found the FAT important for language production (Catani et al., 2013). Incorporating the FAT as part of the dorsal-ventral-motor model for language is essential not only in understanding language, but also in

other domains, for example, during neurosurgery, where avoiding fibers that are important for language and motor function are essential. Therefore, in addition to mapping prominent fiber tracts such as the SLF/AF and others from the ventral stream, as specified in the introduction, the FAT should also be considered.

Summary

In the present study, we were able to track the FAT for the first time in children. While the FAT did not show age-related change, the left SLF/AF did show age-related change, but the right SLF/AF did not. White matter integrity of the right FAT predicted phonology but did not predict performance on AV speech, articulation, language, and literacy. White matter integrity in the left and right SLF/AF predicted language, specifically receptive language, expressive vocabulary, and language content. Neither the left or right SLF/AF predicted speech or literacy. We propose understanding the relationship between the FAT and SLF/AF and speech and literacy requires isolating components from each that are implicated in speech and literacy.

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