Fiber tracking of the frontal aslant tract and subcomponents of the arcuate fasciculus in 5–8-year-olds: Relation to speech and language function

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Abstract

Long association cortical fiber pathways support developing networks for speech and language, but we do not have a clear understanding of how they develop in early childhood. Using diffusion-weighted imaging (DWI) we tracked the frontal aslant tract (FAT), arcuate fasciculus (AF), and AF segments (anterior, long, posterior) in 19 typical 5–8-year-olds, an age range in which significant improvement in speech and language function occurs. While the microstructural properties of the FAT and the right AF did not show age-related differences over the age range we investigated, the left AF evidenced increasing fractional anisotropy with age. Microstructural properties of the AF in both hemispheres, however, predicted receptive and expressive language. Length of the left FAT also predicted receptive language, which provides initial suggestion that this pathway is important for language development. These findings have implications for models of language development and for models of the neurobiology of language more broadly.

Introduction

Two fundamental problems facing researchers exploring the neurobiology of speech and language and its development are the establishment of a comprehensive map of the fiber pathways comprising the network's structural connectivity, and the establishment of the functional relevance of the various fiber pathways to specific linguistic domains. Indeed, understanding connectivity of the speech/language network can provide critical insights into function. Before the advent of diffusion-weighted imaging (DWI), studying human brain connectivity was challenging because it required exploration of either lesioned tissue or postmortem tissue (Catani & Thiebaut de Schotten, 2012). These challenges have been overcome to some degree with DWI, which allows the mapping of fiber pathway connectivity *in* vivo, and has even allowed the tracking of new pathways (Brauer, Anwander, Perani, & Friederici, 2013; Dick, Bernal, & Tremblay, 2014; Dick & Tremblay, 2012; Gierhan, 2013). However, despite considerable progress, there is still much to be learned about the fiber pathways supporting speech and language development. This is particularly the case for the

period of early childhood, as this age-range is typically under-represented in empirical studies of fiber pathway development. This under-representation occurs despite the fact the age range between 5- and 8-years is a time of rapid change in several complementary areas of speech and language development: phonological processing, articulation, receptive language, and expressive language. For example, between 5- and 8-years, children improve articulation and phonological skill. About 50% of 5-year-olds still show phonological error patterns (gliding, cluster reduction, stopping, and fronting), which are seen less frequently in 7–8-year-olds (Dodd, Holm, Hua, & Crosbie, 2003; Dodd, Hua, Crosbie, Holm, & Ozanne, 2010). Children also show improvement in higher-level receptive and expressive language over this age range (Chomsky, 1969; F. Dick, Wulfeck, Krupa-Kwiatkowski, & Bates, 2004; Kendeou, Van den Broek, White, & Lynch, 2009). Thus, while there is extensive development at the behavioral level, less is known about the underlying white matter supporting speech and language development in 5-to-8-year-olds.

In fact, there is no work investigating the development of an intriguing new pathway identified by DWI, the frontal aslant tract (FAT; Catani et al., 2012, 2013; Ford, McGregor, Case, Crosson, & White, 2010; Kinoshita et al., 2014; Klein et al., 2007; Kronfeld-Duenias, Amir, Ezrati-Vinacour, Civier, & Ben-Shachar, 2014; Oishi et al., 2008; Vassal, Boutet, Lemaire, & Nuti, 2014; Vergani et al., 2014). The pathway's putative connectivity linking the posterior inferior frontal gyrus, *pars opercularis* (IFGOp) and the pre-supplementary/supplementary motor area (pre-SMA and SMA), two regions known for their roles in speech and language function, suggests that the tract could play an important part in the development of these domains. Some brain-behavior correlations support this contention. For example, Catani et al. (2013) reported, in a sample of people with primary progressive aphasia (PPA), that microstructure of the FAT is associated with verbal fluency performance. Vassal et al. (2014), using intraoperative electrostimulation and DWI, showed that stimulation of the FAT induced speech arrest, with normalization of speech occurring when stimulation stopped. In addition to replicating the electrostimulation findings by Vassel et al., Kinoshita et al. (2014) reported that resection of the FAT was associated with transient speech initiation

disorders. Finally, microstructure of the FAT is associated with fluency deficits in adults who stutter (Kronfeld-Dueniaset al., 2014). The emerging evidence thus suggests that the FAT may play a role in speech and possibly in its development. However, the FAT has never been characterized in children, andits functional relevance to speech and language is still under investigation. The first aim of the present study is to characterize thispathway in young children and explore its potential relevance tospeech and language function.

Another pathway that is important to understanding the development of speech and language is the arcuate fasciculus (AF; historically called the superior longitudinal fasciculus/arcuate fasciculus; SLF/AF). In contrast to the FAT, there is a substantial literature on the AF, an important fiber pathway that forms the substrate of the dorsal speech/language pathway connecting the frontal, inferior parietal, and temporal regions (Dick et al., 2014;Hickok & Poeppel, 2007) involved in auditory-motor mapping (Saur et al., 2008), processing speech (Maldonado, Moritz-Gasser, & Duffau, 2011), and syntax (Friederici, Bahlmann, Heim, Schubotz, & Anwander, 2006; Wilson et al., 2011). One issue with studying the pathway in children is the sometimes-inconsistent anatomical definition and nomenclature, and the fact that historically the arcuate component was not dissociated from other components of the SLF (Brauer et al., 2013; Fernández-Miranda et al., 2014; Glasser & Rilling, 2008; Makris et al., 2005). Despite the inconsistency in definition, the most widely-cited model in the literature on development of the pathway is that of Catani and colleagues (Catani & Thiebaut de Schotten, 2012; Catani, Jones, & ffytche, 2005; Thiebaut de Schotten et al., 2011). In this model, the focus is on the perisylvian connectivity of three subcomponents of the AF: (1) the anterior component, analogous to the third subcomponent of the SLF (SLF III; Makris et al., 2005), proposed toconnect the supramarginal gyrus to the inferior frontal gyrus, (2)the long segment, proposed to connect the posterior superior andmiddle temporal cortex to the inferior frontal gyrus and ventral premotor cortex, and (3) the posterior segment, proposed to connect the posterior superior and middle temporal regions to the angular gyrus. Many studies have shown asymmetries in the AFin typical adults (Barrick, Lawes, Mackay, & Clark, 2007; Catani

et al., 2007; Fernández-Miranda et al., 2014; Glasser & Rilling, 2008; Nucifora, 2005; Parker et al., 2005; Powell et al., 2006; Thiebaut de Schotten et al., 2011; Upadhyay, Hallock, Ducros, Kim, & Ronen, 2008; Vernooij et al., 2007), with differences in the lateralization profile of each of the three AF segments.

Similar studies have been conducted in typical children with a focus on understanding age-related differences and developing laterality of the AF (Barnea-Goraly et al., 2005; Brauer, Anwander, & Friederici, 2011; Brauer et al., 2013; Eluvathingal, Hasan, Kramer,Fletcher, & Ewing-Cobbs, 2007; Giorgio et al., 2008; Lebel & Beaulieu, 2009; Lebel & Beaulieu, 2011; Oishi, Faria, Yoshida,Chang, & Mori, 2013; Schmithorst, Wilke, Dardzinski, & Holland, 2002; Tamnes et al., 2010; Tiwari et al., 2011; Urger et al., 2014; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012; Yeatman et al., 2011). The findings of age-related differences of the pathway are mixed. For example, Schmithorst et al. (2002) found increased anisotropy with age over the left hemisphere AF from 5- to 18-years, but this was not replicated in a different sample of 6–17-year-olds (Eluvathingal et al., 2007). To explain the lack of findings of maturation of FA, Eluvathingal et al. suggested thatthe AF likely undergoes ‘‘substantial maturation before the age of6 years to support basic proficiency in speech.. .’’ (p. 2765).However, when the different segments of the AF were examined, and when different measures were used (namely radial and axial diffusivity measures expected to decline with age), Eluvathingalet al. did report significant negative correlations with age. These patterns were found in all three segments bilaterally. This suggestssome potential for maturation of these pathways during early childhood, which would fit with the age-related differences in speech and language that occur at the behavioral level.

The findings for age-related differences in laterality are also mixed. In a study of 5- to 17-year-olds, Urger et al. (2014) reported no significant laterality of their defined SLF and AF tracts, a findingthat is consistent with Tiwari et al. (2011). Eluvathingal et al. (2007) reported left laterality of the long segment, and right laterality of the posterior segment, but they reported no evidence for differences in lateralization associated with age. Similarly, in a large sample ranging in age from 5 to 30 years, Lebel and Beaulieu (2009) reported that the majority of participants showed left lateralization of the AF

(assessed with FA and number of streamlines), which was uncorrelated with age. Thus, they suggested that ‘‘arcuate fasciculus lateralization is present in early childhood’’ (p. 3568). However, their sample had very little representation of children in the early childhood years (less than 5% of the sample was comprised of children 5- to 8-years of age). Consequently, it is difficult to make a strong statement, based on the available data, about the development of laterality of the AF in this younger age range.

Only a handful of these studies have related development of the AF to behavioral measures of speech and language. Measures of the tract microstructure and laterality have been related to general verbal IQ or vocabulary measures (Lebel & Beaulieu, 2009; Peters et al., 2012; Schmithorst, Wilke, Dardzinski, & Holland, 2005; Urger et al., 2014), and to speech processing in noise (Schmithorst, Holland, & Plante, 2011). For example, after controlling for age and sex, Urger et al. (2014) reported an association between left (but not right) AF microstructure and expressive (but not receptive) language. Similarly, Lebel and Beaulieu (2009) reported an association between left lateralization and phonology and vocabulary. These studies are important, and evidence an association between AF white matter microstructure and speech and language function, but the limited representation of young children in the samples does not allow for a detailed understanding of the development of these fiber pathways in early childhood.

In order to expand our current understanding of the development of these pathways in younger children, we used DWI in 19 5–8-year-olds to assess specific age-related differences in the microstructure properties of the FAT and AF white matter tracts, and relate these properties to behavioral measures of speech and language. First, we predicted that we would be able to track the FAT in young children, and we further predicted that, given the known age-related differences in speech and language function over this age range, the FAT would show age-related differences. The predictions regarding age-related differences for the AF were more exploratory for this age range—some studies show asymmetric age-related differences across hemispheres (Schmithorst et al., 2002), while other studies do not (Eluvathingal et al., 2007; Urger et al., 2014). Finally, given the putative linguistic functions of the perisylvian regions that are supported by the FAT and AF white matter

connections, we expected that subcomponents of the AF and FAT would predict specific speech language functions.

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 obvious motion artifact). An additional 11 children were 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. Written informed consent/assent was obtained from all parents and children. 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, during which we administered a battery of speech and language measures.

Battery of speech and language measures

In a session lasting about 90 min, the following assessments were administered to obtain a comprehensive understanding of each child's speech and language ability: (1) the Diagnostic

Evaluation of Articulation and Phonology (DEAP; Dodd et al., 2010), including articulation and phonology subtests; (2) the Clinical Evaluation of Language Fundamentals-4 (CELF-4; Semel, Wiig, & Secord, 2003), with subtests to establish the Receptive Language (Concepts and Following Directions, Word Classes, and Sentence Structure) and Language Content Indices (Concepts and Following Directions, Word Classes, and Expressive Vocabulary); and (3) to measure non-verbal intelligence, the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI – III; Wechsler, 2002) Block Design subtest. Additional behavioral measures were collected but are not reported here. Standardized scores were used in the analysis forall subtests.

Data acquisition

Participants were scanned on a 3 Tesla Philips MRI scanner witha SENSE coil housed at Nicklaus Children's Hospital. Prior to the actual scanning session, participants underwent a simulated scanin 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/mm^2 and b = 0 s/mm^2 (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 mm × .938 mm × .938 mm resolution). Placing cushions around the head and securing a strap across the forehead minimized head motion. The duration of scanning time was less than 25 min 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; Coupé, 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, following the same implementation method as DTI Studio (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 indices of fractional anisotropy (FA), average diffusion coefficient (ADC), radial diffusivity (RD), and axial diffusivity (AD) (Basser, Mattiello, & LeBihan, 1994; Hasan & Narayana, 2006). FA 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). FA is sensitive to microstructural changes in white matter with higher FA values indicating more directional diffusion of water. ADC (or mean diffusivity) is the average of the three principle eigenvalues, and represents the non-directional magnitude of diffusion. This 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. We also quantified the volume, number of streamlines, and tract length, for each of the identified fiber pathways.

Fiber tract identification

All fiber tracking identification procedures were based on anatomical landmarks and defined on the FA map in DSI Studio, with a FA threshold of 0.15 and fiber angles of less than 40° between connecting pixels. In order to maintain the anatomical integrity of the child brain, fiber tracking was conducted in the native MRI space. To facilitate reproducibility in future studies, detailed ROI definitions are included in Supplemental Materials.

We manually identified the FAT in each individual using a two region of interest (ROI) approach to replicate recent studies (Catani et al., 2012; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). To determine whether the majority of fibers track to the SMA or to the pre-SMA, we manually identified two segments of the FAT. The first component consisted of connections between the IFGOp and the SMA. The second component consisted of connections between the IFGOp and pre-SMA. Both SMA and pre-SMA were defined as the area in the medial frontal cortex in the superior frontal gyrus lying dorsal to the cingulate sulcus. The SMA was defined as rostral to the primary motor cortex and caudal to the vertical commissure anterior (VCA) line (Picard & Strick, 1996). The pre-SMA was defined as rostral to the VCA line and caudal to the virtual line passing through the genu of the corpus callosum (Kim et al., 2010; Picard & Strick, 1996).

We also manually identified the whole AF and three AF segments. First, we tracked the whole AF using a single ROI on 4 slices. The AF was defined as the 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 et al., 2005). This definition, common in published atlases (Oishi, Faria, Zijl, & Mori, 2011), often includes additional fibers not identified in more recent parcellations of the AF, which identify three main segments. We also tracked these three AF segments, namely the anterior (fronto-parietal), long (fronto-temporal), 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 (Eluvathingal et al., 2007). Identical ROIs were used to track the anterior segment, with the exception that the axial ROIwas loaded as a region of avoidance (ROA). To track the posteriorsegment, we used a five ROI approach identified on axial slices (Thiebaut de Schotten et al., 2012).

Data analysis

Within the *R* statistical package (v. 2.15.1; http://www.R-pro- ject.org) we related our measures of white matter microstructureand laterality to age and behavioral measures using robust estimates of correlation (r_{rob}; using the *R* function *relplot*; Wilcox, 2012) 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 outsidethe outer ellipse of the plot (Goldberg & Iglewicz, 1992). The r_{rob} can be interpreted the same as the Pearson *r*. The robust regressionalso reduces the influence of outliers, in this case using a Huberloss function to apply different weights to each observation. The regression results can be interpreted in the same way as in least squares 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 to calculate the standard errors, 95%, and 99% confidence intervals (Efron, 1987).

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. One-sample *t*-tests against zero (indicating no laterality) assessed reliability of the effect. Independent samples *t*-tests assessed sex differences. Dueto the large number of comparisons, False Discovery Rate (FDR;Benjamini &

Hochberg, 1995) correction ($p < .05$) was applied to the correlation, regression, and laterality analyses.

Results

Identification of the FAT and AF tracts

We were able to reliably track the left and right AF and the anterior, long, and posterior AF segments in all children. Both FA and ADC values for this tract fell within the normal range for children (Morriss, Zimmerman, Bilaniuk, Hunter, & Haselgrove, 1999), which serves as a validation of our tractography results. An important finding of this study was that we were able to track both the left and right FAT in 17 out of 19 children. Fig. 1 and Table 1 provide the tracts and summary statistics, including laterality indices and correlations with age. In one child we were able to track the left FAT, but not the right FAT. In a different child we found the opposite pattern. However, it is notable that in both cases the tracts appeared when the step size was adjusted to a more liberal level of 2 mm. Thus, the lack of identification should not be taken to indicate an absence of the tract, but may indicate an artifact in the data, reduced myelination of the tract, or Type II statistical error. The tractography also provided more specific information about the connectivity of the FAT. The predominance of connections projected from the IFGOp to the pre-SMA. Only a subset of children (7 for the left hemisphere; 11 for the right hemisphere) also showed projections from the IFGOp to the anatomically defined SMA. Because of this, the summary results and analysis of age and task-related associations focus on the pre-SMA component of the FAT.

Age-related differences and laterality in the FAT and AF

To characterize age-related differences of the FAT and AF we conducted robust correlations. Fig. 2 shows robust elliptical plots for the FA measure, and Table 1 summarizes the correlations for all other measures. For the FAT, there was very little evidence for age-related differences over the age range we investigated. Only the right FAT axial diffusivity measure showed a negative relationship to age, but

this did not survive the multiple comparison correction. For the FA measures, neither the left nor the right FAT showed age-related differences, with effect sizes near zero (r_{rob} = .16; p > .05 for left; r_{rob} = .02; p > .05 for right).

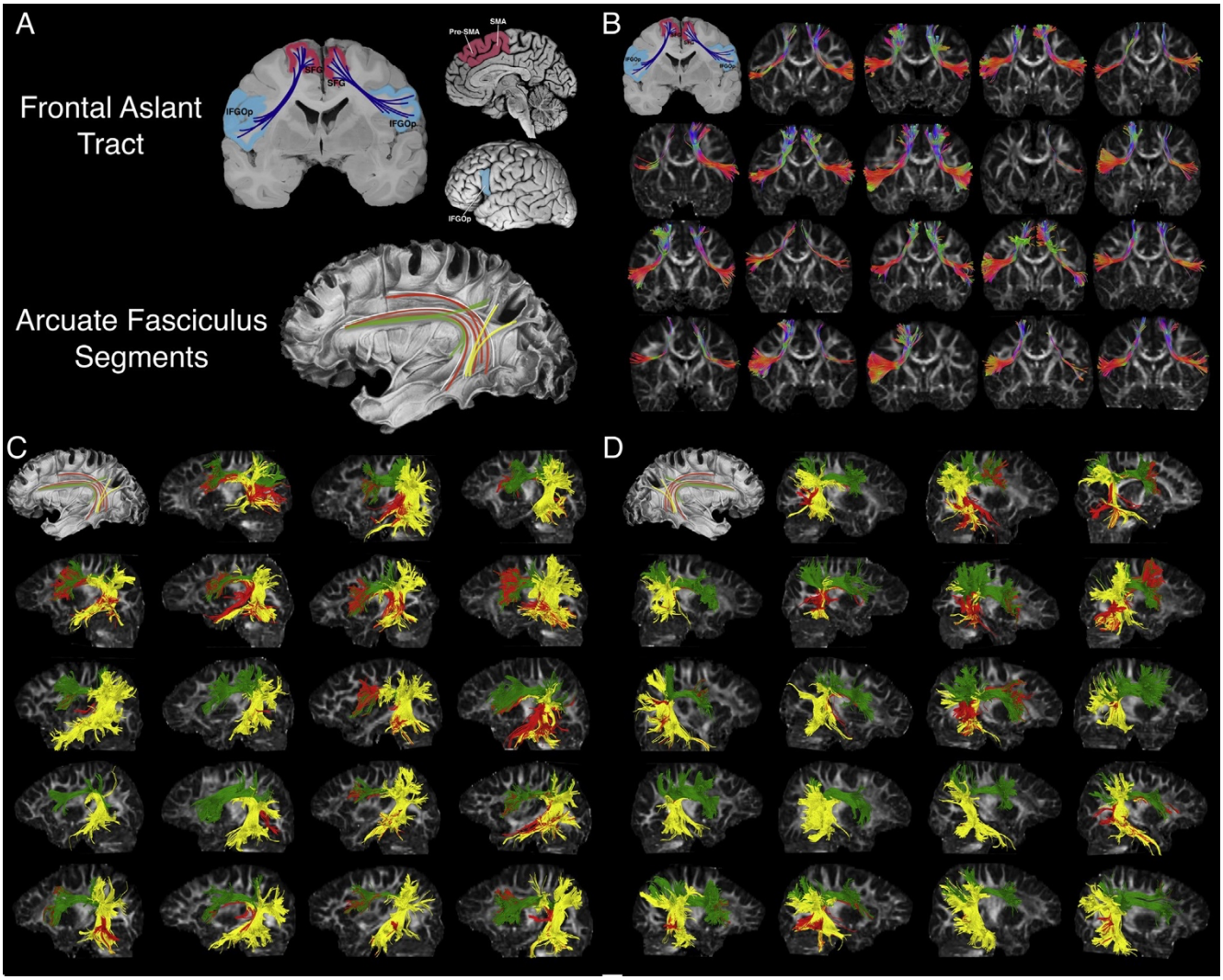

Fig. 1. (A) The putative frontal aslant tract (FAT) and arcuate fasciculus (AF) segments (green = anterior; red = long; yellow = posterior), superimposed on an anatomical reference. Reprinted with permission from Dick, A. S., Bernal, B., & Tremblay, P. (2014). The language connectome: New pathways, new concepts. *The Neuroscientist*, *20*, 453–467. (B) FAT pathways tracked for all 19 children, in coronal view. In one subject (row two, column 4) we could not track the right FAT. In another (row four, column 3)we could not track the left FAT. (C and D) AF segments tracked for all 19 children, in left (C) and right (D) hemispheres.

Table 1

Summary of white matter microstructure measures and correlation with age in months for each tract.

Measures	Hemisphere	Frontal aslant	Arcuate fasciculus (AF)	AF: anterior segment	AF:long segment	AF: posterior segment
FA	Left	0.41 (0.02) [0.16]	0.45 (0.02) **[0.88***]**	0.46 (0.02) [0.31]	0.48 (0.03) **[0.53†]**	0.47 (0.02) [-0.25]
	Right	0.40 (0.02) [0.02]	0.45 (0.02) [0.15]	0.46 (0.02) [0.22]	0.46 (0.03) [-0.04]	0.45 (0.02) [0.17]
	Laterality	0.01 (0.03) [0.06]	0.01 (0.02) **[0.47†]**	0.00 (0.02) [0.16]	**0.02 (0.40)*** [0.44]	**0.02 (0.03)*** [-0.32]
ADC ($\lambda_1 + \lambda_2 + \lambda_3$)/ 3, 10^{-3} mm^2/s	Left	0.84 (0.02) [-0.08]	0.82 (0.02) [-0.42]	0.82 (0.02) [-0.37]	0.82 (0.02) [-0.35]	0.83 (0.02) [-0.25]
	Right	0.84 (0.02) [0.03]	0.82 (0.02) [-0.21]	0.82 (0.02) [-0.23]	0.81 (0.03) [-0.41]	0.83 (0.02) [-0.19]
	Laterality	**-0.01 (0.01)***** [-0.15]	0.00 (0.01) [-0.28]	0.00 (0.01) [-0.04]	0.00 (0.01) [0.24]	0.00 (0.01) [0.01]
AD (λ_1), 10^{-3} mm^2/s	Left	1.2 (0.03) [-0.06]	1.2 (0.03) [-0.02]	1.2 (0.03) [-0.14]	1.3 (0.04) [0.15]	1.3 (0.03) **[-0.62†]**
	Right	1.2 (0.03) **[-0.45]**	1.2 (0.03) [-0.05]	1.2 (0.03) [-0.02]	1.3 (0.05) [-0.36]	1.3 (0.03) [-0.25]
	Laterality	0.00 (0.01) [0.01]	0.00 (0.01) [0.16]	0.00 (0.01) [0.01]	0.01 (0.02) **[0.49†]**	**0.01 (0.01)***** [-0.28]
RD ($\lambda_2 + \lambda_3$)/2, 10^{-3} mm^2/s	Left	0.64 (0.02) [-0.08]	0.61 (0.03) **[-0.60†]**	0.61 (0.03) [-0.36]	0.59 (0.03) **[-0.57†]**	0.60 (0.03) [-0.02]
	Right	0.64 (0.03) [0.03]	0.61 (0.03) [-0.24]	0.60 (0.03) [-0.29]	0.59 (0.03) [-0.23]	0.60 (0.03) [-0.21]
	Laterality	-0.01 (0.01) [-0.07]	**0.01 (0.01)† [-0.45†]**	0.01 (0.03) [-0.14]	0.01 (0.02) [-0.33]	0.01 (0.02) [0.25]
Streamlines	Left	204.9 (246.8) [-0.22]	3170.1 (1045.4) [0.14]	911.5 (444.5) [-0.26]	517.1 (383.2) [0.36]	1516.8 (814.5) [-0.44]
	Right	357.3 (314.4) [-0.39]	3115.9 (1256.7) [0.03]	1280.8 (654.2) [0.32]	415.6 (527.2) [-0.09]	897.6 (447.3) [-0.34]
	Laterality	-0.17 (0.54) [0.21]	0.02 (0.15) [0.19]	-0.15 (0.36) [-0.35]	**0.28 (0.54)** [0.25]	**0.24 (0.30)**** [-0.10]
Length (mm)	Left	69.3 (5.0) [-0.30]	59.7 (7.9) **[0.48†]**	56.8 (9.2) [-0.23]	85.6 (10.0) [0.10]	58.4 (6.7) [-0.32]
	Right	68.8 (5.5) [0.12]	62.8 (8.6) [0.28]	64.5 (7.2) [0.27]	75.6 (14.7) [-0.04]	54.0 (7.0) [-0.20]
	Laterality	0.00 (0.04) [-0.41]	-0.03 (0.06) [0.33]	**-0.07 (0.09)**** [-0.12]	**0.06 (0.09)*** [0.14]	**0.04 (0.07)†** [-0.05]
Volume (mm^3)	Left	2434.4 (1827.7) [-0.26]	19626.4 (5554.3) [0.14]	6991.9 (2328.2) [-0.12]	5869.7(3357.9) [0.36]	10381.5 (3987.8) [-0.39]
	Right	3580.7 (2096.2) [-0.28]	18824.3 (5431.6) [0.02]	9143.8 (3187.5) [0.35]	4070.6 (3597.3) [-0.03]	7484.76 (2638.4) [-0.29]
	Laterality	**-0.99 (0.008)***** [0.27]	0.02 (0.14) [0.14]	**-0.13 (0.23)†** [-0.31]	**0.06 (0.09)*** [0.20]	**0.16 (0.21)**** [-0.12]

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, and these are marked in bold.

* $p < .05$ (False Discovery Rate [FDR] Corrected).

** $p < .01$ (FDR corrected).

*** $p < .001$ (FDR corrected).

† $p < .05$ (uncorrected).

In contrast, the left AF did show age-related differences in white matter microstructure, measured by FA values ($r_{rob} = .88$; $p < .001$), but the right AF did not ($r_{rob} = .15$; $p > .05$, Fig. 2). The difference between the correlations was significant (Williams' test for difference between correlated correlations, $t(18) = 9.37$, $p < .001$). For the AF and associated segments, the strongest age effects were found for the FA measure, although a similar pattern of results was found for other measures (see Table 1; note while FA tends to increase with age, ADC, AD, and RD tend to decrease). The age effects in the whole AF appeared to be driven by the long segment, and (to a lesser extent) the posterior segment. No associations with age were found for the anterior segment. Compared to the FAT, the AF also showed on average higher FA and AD, and lower RD and ADC values for both hemispheres (for

left hemisphere FA: $t(17) = 9.5, p < .001$; left hemisphere ADC: $t(17) = -3.9, p < .001$; left hemisphere AD: $t(17) = 2.6, p < .018$; left hemisphere RD: $t(17) = -6.7, p < .001$); right hemisphere FA: $t(17) = 9.6, p < .001$; right hemisphere ADC: $t(17) = -5.4, p < .001$; right hemisphere AD: $t(17) = 2.41, p < .028$; right hemisphere RD: $t(17) = -7.7, p < .001$). No reliable sex differences were found for any of the ten identified tracts (independent samples *t*-test, lowest $p = 0.19$, uncorrected; note that sex was balanced in this sample).

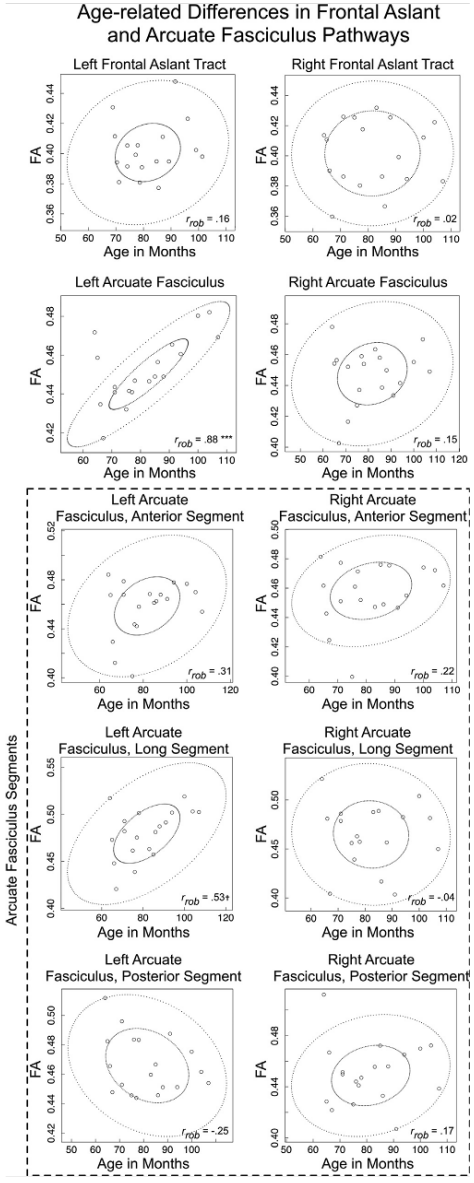

Fig. 2. Age-related differences in fractional anisotropy (FA) are shown for each tract in each hemisphere. The frontal aslant tract (FAT) shows little age-related differences in either hemisphere. In contrast, FA increases monotonically with age in the left arcuate fasciculus (AF). $^{***}p < .001$ (False Discovery Rate corrected). $^{\dagger}p < .05$, uncorrected.

Two measures (ADC and volume) evidenced right lateralization in the FAT. In addition, FAT AD was negatively associated with age, but not to a corrected level of significance. For the full AF, no measures evidenced significant laterality. However, anterior segment length was right lateralized, long segment length and volume were left lateralized, and posterior segment FA, AD, number of streamlines, and volume were left lateralized. No significant associations with age survived the statistical correction for multiple comparison correction, although several uncorrected associations were revealed. These included positive associations with AF FA and long segment AD, and a negative association with AF RD.

Relation of the FAT and AF to speech and language

To relate the FAT and AF white matter microstructure to speech and language, we constructed robust linear models for each white matter quantification (i.e., FA, ADC, AD, RD, number of streamlines, length, and volume). Table 2 reports the effects after controlling for age in months, non-verbal IQ, sex, and whole brain white matter microstructural properties (calculated for FA, ADC, AD, RD, number streamlines, length, and volume for each respective regressor of interest). Due to the large number of regressions, we report those results in which the 99% CI did not cover zero (results for 95% CIs are reported in Supplementary Table 1). We calculated *p* values for the effect of interest, and report both uncorrected and FDR corrected results. As Table 1 shows, left FAT FA and length predicted CELF Language Content Index and CELF Receptive Language Index, respectively, although the former did not survive the statistical correction. Microstructure of the bilateral AF and associated segments were significant predictors CELF Language Content and Receptive Language. The number of streamlines in the right anterior AF and left posterior AF predicted the DEAP phonology index, but this did not survive the statistical correction. In the Discussion, we focus on results that survived the statistical correction.

Table 2

Relation of articulation, phonology, receptive, and expressive language to microstructure of the frontal aslant tract (FAT), arcuate fasciculus (AF) tract, and anterior, long, and posterior AF segments.

Predictor → Outcome	B (SE)	B	99% CI	R^2_{adj}
Fractional Anisotropy (FA)				
Left FAT → CELF Language Content	355.72 (124.49)	0.58	42.01 to 677.02	0.52
Left AF → CELF Receptive Language	547.04 (130.21)	0.81	215.30 to 881.92*	0.51
Left AF → CELF Language Content	484.39 (123.29)	0.65	177.41 to 792.15*	0.64
Right AF → CELF Receptive Language	396.37 (120.09)	0.63	99.57 to 702.17	0.29
Left Anterior AF → CELF Receptive Language	418.40 (91.19)	0.82	186.32 to 646.03*	0.50
Left Anterior AF → CELF Language Content	332.76 (81.81)	0.59	116.27 to 548.04*	0.67
Left Long AF → CELF Receptive Language	260.89 (80.93)	0.61	55.48 to 470.25	0.38
Left Long AF → CELF Language Content	252.09 (67.31)	0.53	83.96 to 423.91*	0.62
Right Long AF → CELF Receptive Language	282.44 (76.99)	0.81	84.77 to 481.39*	0.43
Average Diffusion Coefficient (ADC)				
Left AF → CELF Receptive Language	-265.61 (90.21)	-0.55	-501.64 to -38.76	0.24
Left AF → CELF Language Content	-227.33 (80.97)	-0.43	-437.18 to -20.03	0.54
Right AF → CELF Receptive Language	-253.78 (90.80)	-0.52	-488.75 to -20.96	0.21
Right Posterior AF → CELF Receptive Language	-288.90 (88.73)	-0.50	-464.95 to -117.12	0.28
Right Posterior AF → CELF Language Content	-209.86 (82.00)	-0.40	-422.37 to -1.17	0.49
Radial Diffusivity (RD)				
Left AF → CELF Receptive Language	-325.72 (88.95)	-0.74	-553.41 to -101.57*	0.41
Left AF → CELF Language Content	-295.63 (74.53)	-0.60	-488.58 to -102.63*	0.62
Right AF → CELF Receptive Language	401.86 (79.90)	-0.91	-612.19 to 197.80*	0.46
Right AF → CELF Language Content	-295.42 (82.50)	-0.61	-516.06 to -88.43*	0.53
Left Anterior AF → CELF Receptive Language	321.06 (75.00)	-0.77	-512.27 to -129.62*	0.50
Left Anterior AF → CELF Language Content	-272.47 (67.12)	-0.59	-445.27 to -99.10*	0.62
Right Anterior AF → CELF Receptive Language	-373.04 (75.56)	-0.75	-522.94 to -226.76	0.49
Right Anterior AF → CELF Language Content	-241.24 (79.02)	-0.53	-447.90 to -40.90*	0.53
Left Long AF → CELF Receptive Language	-281.58 (73.40)	-0.74	-474.35 to -91.42*	0.39
Left Long AF → CELF Language Content	-230.21 (68.82)	-0.55	-409.51 to -54.95*	0.59
Right Long AF → CELF Receptive Language	-285.55 (55.12)	-0.86	-429.19 to 147.59*	0.57
Left Posterior AF → CELF Language Content	-226.38 (73.52)	-0.47	-417.07 to -38.33	0.55
Right Posterior AF → CELF Receptive Language	-329.08 (87.54)	-0.82	-549.43 to -106.23*	0.30
Streamlines				
Right Anterior AF → DEAP Phonology	0.004 (0.001)	0.60	0.0009 to 0.008	0.03
Left Posterior AF → DEAP Phonology	-0.007 (0.002)	-0.63	-0.01 to -0.0003	0.12
Length				
Left FAT → CELF Receptive Language	1.77 (0.44)	0.78	0.65 to 2.89*	0.41

Note. Effects reported for robust linear models after controlling for age in months, sex, whole brain microstructure quantities (FA, ADC, AD, RD, streamlines, and length, for each respective regression), and block design. Only results in which the 99% confidence interval did not cover zero are reported. Both uncorrected and False Discovery Rate (FDR) corrected results are reported. FDR corrected *p* values were calculated and are denoted by * next to the CI. AF = Arcuate fasciculus. FAT = Frontal aslant tract. CELF = Clinical Evaluation of Language Fundamentals. 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.

Discussion

Despite considerable examination of the development of speech and language at the level of behavior, we still know little about how the fiber pathways supporting speech and language develop in early childhood. The present study contributes significantly to this understanding by tracking two major fiber pathways in 5–8-year-old children, the AF and its associated segments of the dorsal stream, and a novel fiber pathway, the FAT. We also characterized age-related differences and laterality of these pathways, and related the microstructure of the pathways to speech and language outcomes. Regarding age-related differences, while weexpected to find age-related differences in the FAT, we found instead that microstructural properties of the FAT remained remarkably consistent over the age range we investigated. We also found evidence for right laterality of the FAT (as measured by ADCand volume). In contrast to the FAT, we found age-related differences in the AF and its segments, although this was driven almost exclusively by changes on the left, but not right, hemisphere. Microstructural properties of the AF in both hemispheres, though, predicted receptive and expressive language, even after controlling for a number of confounding factors (i.e., age, sex, nonverbal ability, and whole brain white matter microstructure). This provides further support for the involvement of these bilateral pathways in supporting developing speech. Length of the left FAT also predicted receptive language, which provides initial suggestionthat this pathway is important for developing language. These findings have implications for models of language development and for models of the neurobiology of language more broadly, and we discuss these implications in detail below.

Frontal aslant tract (FAT) microstructure and development

The FAT is a newly described fiber tract that does not appear in earlier studies of white matter, but has been recently identified in adults (Catani et al., 2012, 2013; Ford et al., 2010; Kinoshita et al., 2014; Klein et al., 2007; Kronfeld-Duenias et al., 2014; Oishi et al., 2008; Vassal et al., 2014; Vergani et al., 2014). The present study isthe first, which we know of, to characterize the FAT in children. Our data suggest that it is a robust bilateral tract. However, the connectivity of the tract has been

somewhat unclear in the literature, with adult studies claiming connectivity from the posterior inferior frontal gyrus to the pre-SMA, the SMA, and anterior cingulate (Catani et al., 2012, 2013; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012; Vergani et al., 2014). We found that, in children, the predominance of fibers from the IFGOp project to the pre-SMA, with some fibers projecting to the SMA in some children. Projections to the anterior cingulate were minimal. Thus, we believe the tract is primarily involved in supporting a functional connection between IFGOp and pre-SMA. This precise characterization is important because it provides evidence of the tract's possible functional relevance to speech and language. Unlike SMA, the pre-SMA is not directly connected to M1 or to the spinal cord, but is densely connected to the prefrontal cortex (Luppino, Matelli, Camarda, & Rizzolatti, 1993). Thus, the pre-SMA is proposed to be more involved in motor preparation for speech, including action selection, while the SMA is proposed to be involved in action execution (Nachev, Kennard, & Husain, 2008; Tremblay & Gracco, 2006, 2009; Tremblay & Small, 2011). The IFGOp, on the other hand, may play a role in selection (phonological or semantic selection) during speech and language comprehension, and in word retrieval and articulation during speech production (see Price, 2010, 2012 for reviews).

The predominance of IFGOp connections to pre-SMA thus suggests that the tract should have a role in action selection for, or initiation of, speech, and may possibly be interpreted as an ''action selection loop'' for speech. This functionality is consistent with the relation between verbal fluency deficits and FAT microstructure (Catani et al., 2013), with speech arrest noted during electrostimulation of the FAT (Kinoshita et al., 2014; Vassal et al., 2014), with the association to fluency deficits in adults who stutter (Kronfeld-Duenias et al., 2014), and with the association between damage to mesial frontal areas and transcortical motor aphasia (Freedman, Alexander, & Naeser, 1984). In our study, only a modest relation was found between FAT microstructure and behavior.

Microstructure of the FAT predicted expressive (for FA measures) and receptive language (for tract length), but only the latter survived the multiple comparison correction. We did not find an

association to measures of phonology and articulation. For the phonology and articulation measures, a restricted range is a potential limitation— most children performed well on the DEAP, with more than 50% of children scoring above 100 (range 75–110) in the standard scores. Thus, we might expect to find stronger relations between FAT white matter development and speech measures in younger children, or in children with speech-sound disorders or other specific language impairment. It is also possible that the measures we used may not have been sufficiently sensitive to the function of the tract. To better characterize the function of the pathway, future studies of this pathway should include a sensitive measure of fluency, and of semantic/lexical or phonological selection.

In addition to characterizing the connectivity of and possible function of the FAT in children, we investigated age-related differences. We found no strong evidence for age-related differences in the microstructure of the FAT over the 5–8-year age range. The tract also showed some evidence of right laterality (as measured by ADC and volume), which is the opposite of the pattern found in right-handed adults, who show a general left-laterality of the FAT volume (Catani et al., 2012). While we did not find evidence for significant association with age and change in laterality, in the measure of tract volume there was a trend toward increasing left laterality with age ($r_{rob} = 0.27$). This may suggest that left laterality emerges over a longer developmental timeline. Because this is a ‘‘snap-shot’’ of the tract’s development we do not know if the FAT shows age-related change in younger or older children. Indeed, the lack of age-related differences is surprising given the known protracted development of the white matter of the frontal lobe (Giedd et al., 2015). This suggests further investigations of age-related differences in the FAT are warranted, and will require a wider age-range to fully characterize the pathway.

Arcuate fasciculus (AF) microstructure and development

We were able to characterize the AF and the anterior, long, and posterior segments bilaterally in all children, and to establish patterns of age-related differences in the white matter microstructure of these tracts. In general, for the anterior and long segments, the laterality of the tract is consistent

with the patterns reported in adults (Thiebaut de Schotten et al., 2011) and in children (Eluvathingal et al., 2007). Thus, we found that the anterior segment was right lateralized, and the long segment was left lateralized. For the posterior segment, in contrast to Thiebaut de Schotten et al. (2011), who reported no evidence for laterality of this segment, we found significant left laterality across a number of measures. In their study of 6–17-year-olds, Eluvathingal et al. (2007) also found laterality of this segment, but in this case there was a rightward asymmetry. Taken together, these findings suggest that the posterior segment may show greater individual variability across samples, possibly in the case of the present study due to the sociodemographic background, to the sex ratio, or to the focused age range of the sample.

It is also notable that our findings regarding laterality were qualified by age-related differences in the development of the left and right fiber pathways. Specifically, we found that the left, but not the right, AF showed age-related increases in FA (with a very large effect for the left AF, $r_{rob} = 0.88$). This replicates and extends some prior work, but not others. For example, in an early investigation of this pathway, Schmithorst et al. (2002) reported significant positive correlation of FA with age (over 5–18 years) in the left AF, but not the right. In contrast, Eluvathingal et al. (2007) reported the opposite result; increasing age was correlated with increasing FA in the fronto-parietal (anterior) segment of the right, but not left, AF. Other studies report no significant relation between age and laterality of the AF (Lebel & Beaulieu, 2009; Tiwari et al., 2011; Urger et al., 2014).

A number of factors may explain these discrepant findings regarding age-related differences. One issue concerns the specific measure of laterality, which may mask or make less prominent age-related change *within* each pathway. Thus, while we did find a correlation between age and laterality of the AF as measured by FA, the effect size was more moderate, and did not survive a statistical correction for multiple comparisons. The discrepant findings in the literature might also be explained by different anatomical definitions of the AF pathways across studies. Indeed, FA changes associated with age have been more apparent when the tract segments are addressed separately (Eluvathingal et al., 2007). Finally, the discrepant findings might be explained by sig-

nificant individual differences in pathway development across children. This latter explanation is intriguing and has some empir- ical support. In a recent longitudinal study Yeatman et al. (2012) identified significant individual variability in the developmental trajectories of the left AF, with some children showing increases in FA, and others showing decreases, between the ages of seven and eleven years. The longitudinal approach used by Yeatman and colleagues is likely needed to establish a robust trajectory of the AF, which would go a long way toward adjudicating between the differing characterizations of the tract's development.

Despite the differences across the hemispheres in the correlation of FA with age, white matter microstructure of *bilateral* AF pathways predicted improved performance on receptive and expressive language measures on the CELF. The strongest effects were found across multiple measures for the full AF tract, and for the anterior and long segments. For the posterior segment, only RD of the right posterior AF significantly predicted CELF receptive language. Effect sizes for both hemispheres were moderate to large, with standardized betas between 0.53 and 0.91 (for FDR corrected effects). These findings are consistent with the proposed connectivity of the AF, which represents the dorsal stream within contemporary models of speech and language processing, and which is proposed to connect the inferior frontal, inferior parietal, and posterior temporal regions of the perisylvian language zone (Brauer et al., 2013; Dick et al., 2014; Dick & Tremblay, 2012; Gierhan, 2013). The findings are also consistent with prior investigations relating the development of the AF with general verbal IQ or vocabulary measures (Lebel & Beaulieu, 2009; Peters et al., 2012; Schmithorst et al., 2005). But beyond that, they reinforce the contri- bution of the right hemisphere to higher-level language, which is often ignored (Hickok & Poeppel, 2007), but which is consistently implicated in functional imaging studies (Ferstl, Neumann, Bogler, & Yves von Cramon, 2008; Lindell, 2006). In fact, it is sometimes the case that studies of fiber pathway development for language report detailed findings only for the left AF (e.g., Yeatman et al., 2012). Our results suggest that attention should be paid to both hemispheres, at least as it applies to higher-level receptive and expressive language function early in development. However, functional imaging

research suggests that a further left-lateralization oflanguage may occur after the age of 8 (Brauer & Friederici, 2007; Friederici, Brauer, & Lohmann, 2011; Holland et al., 2007; Szaflarski, Holland, Schmithorst, & Byars, 2006), and so these findings may be specific to the age range under study.

Conclusions and importance of findings for a model of the neurobiology of language development

Broadly, the work presented here complements and extends the dorsal–ventral stream model for language. Here, we tracked the FAT for the first time in young children, clarified its connectivity between the IFGOp and pre-SMA, established some evidence for right lateralization of the tract in early childhood, and showed that there is potential functional relevance for language. However, we found no evidence that the FAT shows age-related differences over this age range. It could certainly show age-related differences beyond eight years, a possibility that is made more plausible bythe fact that FA of the tract is on average significantly lower than that of the AF. But the fact that we found essentially no differencesover a three-year period would suggest that later development would be rather abrupt. An alternative plausible explanation is that the FAT is already mature by early childhood, although this possibility would require investigation in a younger age group than we examine here. For the AF, a tract that remains a central focus in thestudy of speech and language development, we show that FA of the left hemisphere increases during early childhood. However, microstructural properties of the bilateral AF and its segments predict receptive and expressive language outcomes. The findings we report here thus also extend prior work by emphasizing the potential importance of the contribution of the non-language dominant right hemisphere to language early in development (Brauer & Friederici, 2007; Friederici et al., 2011; Holland et al., 2007; Szaflarski et al., 2006).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandl.2015.06. 006.

References

Barnea-Goraly, N., Menon, V., Eckert, M., Tamm, L., Bammer, R., Karchemskiy, A., et al. (2005). White matter development during childhood and adolescence. A cross-sectional diffusion tensor imaging study. *Cerebral Cortex, 15*(12), 1848–1854.

Barrick, T. R., Lawes, I. N., Mackay, C. E., & Clark, C. A. (2007). White matter pathway asymmetry underlies functional lateralization. *Cerebral Cortex, 17*(3), 591–598. http://dx.doi.org/10.1093/cercor/bhk004.

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). Estimation of the effective self- diffusion tensor from the NMR spin echo. *Journal of Magnetic Resonance Series B, 103*(3), 247–254.

Beaulieu, C. (2009). The biological basis of diffusion anisotropy. In H. Johansen-Berg & T. E. J. Behrens (Eds.), *Diffusion MRI: From quantitative measurement to in-vivo neuroanatomy* (pp. 105–126). UK: Academic Press London.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B (Statistical Methodology), 57*(1), 289–300.

Brauer, J., Anwander, A., & Friederici, A. D. (2011). Neuroanatomical prerequisites for language functions in the maturing brain. *Cerebral Cortex, 21*(2), 459–466.

Brauer, J., Anwander, A., Perani, D., & Friederici, A. D. (2013). Dorsal and ventral pathways in language development. *Brain and Language, 127*(2), 289–295. http://dx.doi.org/10.1016/j.bandl.2013.03.001.

Brauer, J., & Friederici, A. D. (2007). Functional neural networks of semantic and syntactic processes in the developing brain. *Journal of Cognitive Neuroscience, 19*(10), 1609–1623.

Catani, M., Allin, M. P., Husain, M., Pugliese, L., Mesulam, M. M., Murray, R. M., et al. (2007). Symmetries in human brain language pathways correlate with verbal recall. *Proceedings of the National Academy of Sciences of the United States of America, 104*(43), 17163–17168. http://dx.doi.org/10.1073/pnas.0702116104.

Catani, M., & Thiebaut de Schotten, M. (2012). *Atlas of human brain connections*. New York:

Oxford University Press.

Catani, M., DellAcqua, F., Vergani, F., Malik, F., Hodge, H., Roy, P., et al. (2012). Short frontal lobe connections of the human brain. *Cortex; A Journal Devoted to the Study of the Nervous System and Behavior, 48*(2), 273–291.

Catani, M., Jones, D. K., & ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology, 57*, 8–16.

Catani, M., Mesulam, M. M., Jakobsen, E., Malik, F., Martersteck, A., Wieneke, C., et al. (2013). A novel frontal pathway underlies verbal fluency in primary progressive aphasia. *Brain: A Journal of Neurology, 136*(Pt 8), 2619–2628. doi:10.1093/brain/ awt163.

Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex, 44*(8), 1105–1132. http://dx.doi.org/10.1016/j.cortex.2008.05.004.

Chomsky, C. (1969). *The acquisition of syntax in children from 5 to 10*. Cambridge, Mass.: M.I.T. Press.

Coupé, P., Manjón, J., Robles, M., & Collins, L. (2012). Adaptive multiresolution non- local means filter for 3D MR image denoising. *IET Image Processing, 6*(5), 558–568.

Descoteaux, M., Wiest-Daesslé, N., Prima, S., Barillot, C., & Deriche, R. (2008). Impact of Rician adapted non-local means filtering on HARDI. *Medical Image Computing and Computer-Assisted Intervention, 11*(Pt 2), 122–130.

Dick, A. S., Bernal, B., & Tremblay, P. (2014). The language connectome: New pathways, new concepts. *The Neuroscientist, 20*, 453–467.

Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: Consensus and controversy in the connectional anatomy of language. *Brain: A Journal of Neurology, 135*, 3529–3550.

Dick, F., Wulfeck, B., Krupa-Kwiatkowski, M., & Bates, E. (2004). The development of complex sentence interpretation in typically developing children compared with children with specific language impairments or early unilateral focal lesions. *Developmental Science, 7*(3), 360–

377.

Dodd, B., Holm, A., Hua, Z., & Crosbie, S. (2003). Phonological development: A normative study of british english-speaking children. *Clinical Linguistics and Phonetics, 17*(8), 617–643.

Dodd, B. J., Hua, Z., Crosbie, S., Holm, A., & Ozanne, A. (2010). *Diagnostic evaluation of articulation and phonology*. Psychological Corporation.

Efron, B. (1987). Better bootstrap confidence intervals. *Journal of the American Statistical Association, 82*, 171–185.

Eluvathingal, T. J., Hasan, K. M., Kramer, L., Fletcher, J. M., & Ewing-Cobbs, L. (2007). Quantitative diffusion tensor tractography of association and projection fibers in normally developing children and adolescents. *Cerebral Cortex (New York, N.Y.: 1991), 17*(12), 2760–2768. doi:10.1093/cercor/bhm003.

Farrell, J. A., Landman, B. A., Jones, C. K., Smith, S. A., Prince, J. L., van Zijl, P., et al. (2007). Effects of signal-to-noise ratio on the accuracy and reproducibility of diffusion tensor imaging–derived fractional anisotropy, mean diffusivity, and principal eigenvector measurements at 1.5 T. *Journal of Magnetic Resonance Imaging, 26*(3), 756–767.

Fernández-Miranda, J. C., Wang, Y., Pathak, S., Stefaneau, L., Verstynen, T., & Yeh, F. C. (2014). Asymmetry, connectivity, and segmentation of the arcuate fascicle in the human brain. *Brain Structure and Function*. http://dx.doi.org/10.1007/ s00429-014-0751-7.

Ferstl, E. C., Neumann, J., Bogler, C., & Yves von Cramon, D. (2008). The extended language network: A meta-analysis of neuroimaging studies on text comprehension. *Human Brain Mapping, 29*, 581–593.

Ford, A., McGregor, K. M., Case, K., Crosson, B., & White, K. D. (2010). Structural connectivity of broca's area and medial frontal cortex. *NeuroImage, 52*(4), 1230–1237.

Freedman, M., Alexander, M. P., & Naeser, M. A. (1984). Anatomic basis of transcortical motor aphasia. *Neurology, 34*(4), 409–417.

Friederici, A. D., Bahlmann, J., Heim, S., Schubotz, R. I., & Anwander, A. (2006). The brain differentiates human and non-human grammars: Functional localization and structural

connectivity. *Proceedings of the National Academy of Sciences of the United States of America, 103*(7), 2458–2463. http://dx.doi.org/10.1073/ pnas.0509389103.

Friederici, A. D., Brauer, J., & Lohmann, G. (2011). Maturation of the language network: From inter- to intrahemispheric connectivities. *PLoS ONE, 6*(6), e20726. http://dx.doi.org/10.1371/journal.pone.0020726.

Giedd, J. N., Raznahan, A., Alexander-Bloch, A., Schmitt, E., Gogtay, N., & Rapoport, J. L. (2015). Child psychiatry branch of the national institute of mental health longitudinal structural magnetic resonance imaging study of human brain development. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 40*(1), 43–49. http://dx.doi.org/10.1038/ npp.2014.236.

Gierhan, S. M. (2013). Connections for auditory language in the human brain. *Brain and Language, 127*(2), 205–221. http://dx.doi.org/10.1016/j.bandl.2012.11.002.

Giorgio, A., Watkins, K. E., Douaud, G., James, A. C., James, S., De Stefano, N., et al. (2008). Changes in white matter microstructure during adolescence. *NeuroImage, 39*(1), 52–61.

Glasser, M. F., & Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cerebral Cortex, 18*, 2471–2482.

Goldberg, K. M., & Iglewicz, B. (1992). Bivariate extensions of the boxplot. *Technometrics*, 307–320.

Hasan, K. M., & Narayana, P. A. (2006). Retrospective measurement of the diffusion tensor eigenvalues from diffusion anisotropy and mean diffusivity in DTI. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine/Society of Magnetic Resonance in Medicine, 56*(1), 130–137. http://dx.doi.org/10.1002/mrm.20935.

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience, 8*(5), 393–402.

Holland, S. K., Vannest, J., Mecoli, M., Jacola, L. M., Tillema, J.-M., Karunanayaka, P. R., et al.

(2007). Functional MRI of language lateralization during development in children. *International Journal of Audiology, 46*(9), 533–551.

Jiang, H., van Zijl, P. C., Kim, J., Pearlson, G. D., & Mori, S. (2006). DtiStudio: Resource program for diffusion tensor computation and fiber bundle tracking. *Computer Methods and Programs in Biomedicine, 81*(2), 106–116. http://dx.doi.org/ 10.1016/j.cmpb.2005.08.004.

Kendeou, P., Van den Broek, P., White, M. J., & Lynch, J. S. (2009). Predicting reading comprehension in early elementary school: The independent contributions of oral language and decoding skills. *Journal of Educational Psychology, 101*(4), 765.

Kim, J. H., Lee, J. M., Jo, H. J., Kim, S. H., Lee, J. H., Kim, S. T., et al. (2010). Defining functional SMA and pre-SMA subregions in human MFC using resting state fmri: Functional connectivity-based parcellation method. *NeuroImage, 49*(3), 2375–2386. http://dx.doi.org/10.1016/j.neuroimage.2009.10.016.

Kinoshita, M., de Champfleur, N. M., Deverdun, J., Moritz-Gasser, S., Herbet, G., & Duffau, H. (2014). Role of fronto-striatal tract and frontal aslant tract in movement and speech: An axonal mapping study. *Brain Structure and Function*. http://dx.doi.org/10.1007/s00429-014-0863-0.

Klein, J. C., Behrens, T. E., Robson, M. D., Mackay, C. E., Higham, D. J., & Johansen- Berg, H. (2007). Connectivity-based parcellation of human cortex using diffusion MRI: Establishing reproducibility, validity and observer independence in BA 44/45 and SMA/pre-sma. *NeuroImage, 34*(1), 204–211. http://dx.doi.org/10.1016/j.neuroimage.2006.08.022.

Kronfeld-Duenias, V., Amir, O., Ezrati-Vinacour, R., Civier, O., & Ben-Shachar, M. (2014). The frontal aslant tract underlies speech fluency in persistent developmental stuttering. *Brain Structure and Function*. http://dx.doi.org/ 10.1007/s00429-014-0912-8.

Lebel, C., & Beaulieu, C. (2009). Lateralization of the arcuate fasciculus from childhood to adulthood and its relation to cognitive abilities in children. *Human Brain Mapping, 30*(11), 3563–3573.

Lebel, C., & Beaulieu, C. (2011). Longitudinal development of human brain wiring continues from childhood into adulthood. *The Journal of Neuroscience. The Official Journal of the Society for Neuroscience, 31*(30), 10937–10947. http://dx.doi.org/10.1523/JNEUROSCI.5302-10.2011.

Lindell, A. K. (2006). In your right mind: Right hemisphere contributions to language processing and production. *Neuropsychology Review, 16*(3), 131–148. http://dx.doi.org/10.1007/s11065-006-9011-9.

Luppino, G., Matelli, M., Camarda, R., & Rizzolatti, G. (1993). Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *Journal of Comparative Neurology, 338*(1), 114–140. http://dx.doi.org/ 10.1002/cne.903380109.

Makris, N., Kennedy, D., McInerney, S., Sorensen, A. G., Wang, R., Caviness, V., et al. (2005). Segmentation of subcomponents within the superior longitudinal fascicle in humans: A quantitative, in vivo, DT-MRI study. *Cerebral Cortex, 15*, 854–869.

Maldonado, I. L., Moritz-Gasser, S., & Duffau, H. (2011). Does the left superior longitudinal fascicle subserve language semantics? A brain electrostimulation study. *Brain Structure and Function, 216*(3), 263–274. http://dx.doi.org/10.1007/ s00429-011-0309-x.

Morriss, M. C., Zimmerman, R. A., Bilaniuk, L. T., Hunter, J. V., & Haselgrove, J. C. (1999). Changes in brain water diffusion during childhood. *Neuroradiology, 41*(12), 929–934.

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience, 9*(11), 856–869.

Nucifora, P. G. P. (2005). Leftward asymmetry in relative fiber density of the arcuate fasciculus. *NeuroReport, 16*, 791–794.

Oishi, K., Faria, A. V., Yoshida, S., Chang, L., & Mori, S. (2013). Quantitative evaluation of brain development using anatomical MRI and diffusion tensor imaging. *International Journal of Developmental Neuroscience. The Official Journal of the International Society for Developmental Neuroscience, 31*(7), 512–524. http://

dx.doi.org/10.1016/j.ijdevneu.2013.06.004.

Oishi, K., Faria, A. V., Zijl, P. C. M., & Mori, S. (2011). *MRI atlas of human white matter*. New York: Academic Press.

Oishi, K., Zilles, K., Amunts, K., Faria, A., Jiang, H., Li, X., et al. (2008). Human brain white matter atlas: Identification and assignment of common anatomical structures in superficial white matter. *NeuroImage, 43*(3), 447–457. http://dx.doi.org/10.1016/j.neuroimage.2008.07.009.

Parker, G. J., Luzzi, S., Alexander, D. C., Wheeler-Kingshott, C. A., Ciccarelli, O., & Lambon Ralph, M. A. (2005). Lateralization of ventral and dorsal auditory- language pathways in the human brain. *NeuroImage, 24*(3), 656–666. http://dx.doi.org/10.1016/j.neuroimage.2004.08.047.

Peters, B. D., Szeszko, P. R., Radua, J., Ikuta, T., Gruner, P., DeRosse, P., et al. (2012). White matter development in adolescence. Diffusion tensor imaging and meta- analytic results. *Schizophrenia Bulletin, 38*(6), 1308–1317. http://dx.doi.org/ 10.1093/schbul/sbs054.

Picard, N., & Strick, P. L. (1996). Motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex (New York, N.Y.:, 1991 6*(3), 342–353.

Powell, H. W., Parker, G. J., Alexander, D. C., Symms, M. R., Boulby, P. A., Wheeler-Kingshott, C. A., et al. (2006). Hemispheric asymmetries in language-related pathways: A combined functional MRI and tractography study. *NeuroImage, 32*(1), 388–399. http://dx.doi.org/10.1016/j.neuroimage.2006.03.011.

Price, C. J. (2010). The anatomy of language: A review of 100 fmri studies published in 2009. *Annals of the New York Academy of Sciences, 1191*(1), 62–88.

Price, C. J. (2012). A review and synthesis of the first 20years of PET and fmri studies of heard speech, spoken language and reading. *NeuroImage, 62*(2), 816–847. http://dx.doi.org/10.1016/j.neuroimage.2012.04.062.

Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., et al. (2008).

Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences of the USA, 105*(46), 18035–18040.

Schmithorst, V. J., Holland, S. K., & Plante, E. (2011). Diffusion tensor imaging reveals white matter microstructure correlations with auditory processing ability. *Ear and Hearing, 32*(2), 156–167. http://dx.doi.org/10.1097/ AUD.0b013e3181f7a481.

Schmithorst, V. J., Wilke, M., Dardzinski, B. J., & Holland, S. K. (2002). Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence. A cross-sectional diffusion-tensor MR imaging study. *Radiology, 222*, 212–218.

Schmithorst, V. J., Wilke, M., Dardzinski, B. J., & Holland, S. K. (2005). Cognitive functions correlate with white matter architecture in a normal pediatric population: A diffusion tensor MRI study. *Human Brain Mapping, 26*(2), 139–147.

Semel, E., Wiig, E. H., & Secord, W. A. (2003). *Clinical evaluation of language fundamentals-4 (CELF-4)*. San Antonio, TX: The Psychological Corporation.

Szaflarski, J. P., Holland, S. K., Schmithorst, V. J., & Byars, A. W. (2006). FMRI study of language lateralization in children and adults. *Human Brain Mapping, 27*(3), 202–212.

Tamnes, C. K., Østby, Y., Walhovd, K. B., Westlye, L. T., Due-Tønnessen, P., & Fjell, A. M. (2010). Intellectual abilities and white matter microstructure in development: A diffusion tensor imaging study. *Human Brain Mapping, 31*(10), 1609–1625.

Thiebaut de Schotten, M., Dell'Acqua, F., Valabregue, R., & Catani, M. (2012). Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex; A Journal Devoted to the Study of the Nervous System and Behavior, 48*(1), 82–96. http://dx.doi.org/10.1016/j.cortex.2011.10.001.

Thiebaut de Schotten, M., Ffytche, D. H., Bizzi, A., Dell'Acqua, F., Allin, M., Walshe, M., et al. (2011). Atlasing location, asymmetry and inter-subject variability of white matter tracts in the human brain with MR diffusion tractography. *NeuroImage, 54*(1), 49–59. http://dx.doi.org/10.1016/j.neuroimage.2010.07.055.

Tiwari, V. N., Jeong, J. W., Asano, E., Rothermel, R., Juhasz, C., & Chugani, H. T. (2011). A sensitive diffusion tensor imaging quantification method to detect language laterality in children: Correlation with the Wada test. *Journal of Child Neurology, 26*(12), 1516–1521. http://dx.doi.org/10.1177/0883073811409225.

Tremblay, P., & Gracco, V. L. (2006). Contribution of the frontal lobe to externally and internally specified verbal responses: FMRI evidence. *NeuroImage, 33*(3), 947–957. http://dx.doi.org/10.1016/j.neuroimage.2006.07.041.

Tremblay, P., & Gracco, V. L. (2009). Contribution of the pre-SMA to the production of words and non-speech oral motor gestures, as revealed by repetitive transcranial magnetic stimulation (rtms). *Brain Research, 1268*, 112–124. http://dx.doi.org/10.1016/j.brainres.2009.02.076.

Tremblay, P., & Small, S. L. (2011). On the context-dependent nature of the contribution of the ventral premotor cortex to speech perception. *NeuroImage, 57*(4), 1561–1571. http://dx.doi.org/10.1016/j.neuroimage.2011.05.067.

Upadhyay, J., Hallock, K., Ducros, M., Kim, D.-S., & Ronen, I. (2008). Diffusion tensor spectroscopy and imaging of the arcuate fasciculus. *NeuroImage, 39*(1), 1–9.

Urger, S. E., De Bellis, M. D., Hooper, S. R., Woolley, D. P., Chen, S. D., & Provenzale, J. (2014). The superior longitudinal fasciculus in typically developing children and adolescents: Diffusion tensor imaging and neuropsychological correlates. *Journal of Child Neurology*. http://dx.doi.org/10.1177/0883073813520503.

Vassal, F., Boutet, C., Lemaire, J.-J., & Nuti, C. (2014). New insights into the functional significance of the frontal aslant tract-an anatomo-functional study using intraoperative electrical stimulations combined with diffusion tensor imaging- based fiber tracking. *British Journal of Neurosurgery*, 1–3. http://dx.doi.org/ 10.3109/02688697.2014.889810.

Vergani, F., Lacerda, L., Martino, J., Attems, J., Morris, C., Mitchell, P., et al. (2014). White matter connections of the supplementary motor area in humans. *Journal of Neurology,*

Neurosurgery, and Psychiatry. http://dx.doi.org/10.1136/jnnp- 2013-307492.

Vernooij, M. W., Smits, M., Wielopolski, P. A., Houston, G. C., Krestin, G. P., & van der Lugt, A. (2007). Fiber density asymmetry of the arcuate fasciculus in relation to functional hemispheric language lateralization in both right-and left-handed healthy subjects: A combined fmri and DTI study. *NeuroImage, 35*(3), 1064–1076.

Wechsler, D. (2002). *WPPSI-III manual: Wechsler preschool and primary scale of intelligence-iii*. New York: Psychological Corp.

Wilcox, R. R. (1998). How many discoveries have been lost by ignoring modern statistical methods? *American Psychologist, 53*(3), 300.

Wilcox, R. R. (2012). *Introduction to robust estimation and hypothesis testing* (3rd ed.). Waltham, MA: Academic Press.

Wilkinson, L. (1999). Statistical methods in psychology journals: Guidelines and explanations. *American Psychologist, 54*(8), 594 (Retrieved from Google Scholar).

Wilson, S. M., Galantucci, S., Tartaglia, M. C., Rising, K., Patterson, D. K., Henry, M. L., et al. (2011). Syntactic processing depends on dorsal language tracts. *Neuron, 72*(2), 397–403. http://dx.doi.org/10.1016/j.neuron.2011.09.014.

Wright, D. B., & London, K. (2009). *Modern regression techniques using R: A practical guide*. London: Sage Publications Ltd.

Yeatman, J. D., Dougherty, R. F., Ben-Shachar, M., & Wandell, B. A. (2012). Development of white matter and reading skills. *Proceedings of the National Academy of Sciences of the United States of America, 109*(44), E3045–E3053. http://dx.doi.org/10.1073/pnas.1206792109.

Yeatman, J. D., Dougherty, R. F., Rykhlevskaia, E., Sherbondy, A. J., Deutsch, G. K., Wandell, B. A., et al. (2011). Anatomical properties of the arcuate fasciculus predict phonological and reading skills in children. *Journal of Cognitive Neuroscience, 23*(11), 3304–3317. http://dx.doi.org/10.1162/jocn_a_00061.