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Neural plasticity after pre-linguistic injury to the arcuate and superior longitudinal fasciculi

Jason D. Yeatman[a,*] and Heidi M. Feldman[b]

[a] Department of Psychology, Stanford University, Stanford, CA, United States
[b] Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, United States

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ABSTRACT

We describe the case of girl who was born prematurely and diagnosed periventricular leukomalacia, a condition characterized by severe injury to the white matter tracts primarily surrounding the ventricles. At 12 years of age, we obtained diffusion tensor imaging (DTI) data on this child as part of a research protocol. Multiple analyses of DTI data, including tractography, showed that the left and right arcuate and superior longitudinal fasciculi were missing in the child though all other major white matter tracts were present. Standardized psychometric tests at age 12 years revealed that despite early language delays, she had average scores on expressive language, sentence repetition, and reading, functions that have been hypothesized to depend on signals carried by the arcuate fasciculus. We identified intact ventral connections between the temporal and frontal lobes through the extreme capsule fiber system and uncinate fasciculus. Preserved language and reading function after serious injury to the arcuate fasciculus highlights the plasticity of the developing brain after severe white matter injury early in life.

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1. Introduction

Cerebral white matter tracts are highly susceptible to injury from premature birth. The injuries have been attributed to the immature vascular supply to cerebral white matter, impairment in the regulation of cerebral blood flow, and vulnerability of oligodendrocyte precursors (myelin producing cells) to hypoxia, ischemia, and inflammation between 24 and 32 weeks gestation (Volpe, 2001; Back, 2006; Back et al., 2007). Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that provides quantitative measures of white matter organization and allows white matter fasciculi to be tracked *in vivo* (Basser and Pierpaoli, 1996; Mori et al., 1999; Beaulieu, 2002).

DTI analyses comparing groups of preterm children to controls have reported abnormal diffusion properties in many major cerebral white matter pathways (Nagy et al., 2003; Vangberg et al., 2006) and associations between white matter properties and behavioral outcomes (Skranes et al., 2007; Constable et al., 2008). These studies have relied primarily on voxel-based techniques in which individual brain images are normalized to match a group average. Due to

* *Corresponding author*. Department of Psychology, Stanford University, Jordan Hall, Building 420, Stanford, CA 94305, United States.
E-mail address: jyeatman@stanford.edu (J.D. Yeatman).
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variation in brain anatomy, particularly in patient populations, it may be difficult to identify which particular tracts are injured without tracking fiber pathways within individual brains (Yeatman et al., 2009; Feldman et al., 2010). Fiber-tracking based investigations of children born preterm have analyzed the cortico-spinal tract and found associations between diffusion measures and motor function (Berman et al., 2005; Adams et al., 2010). None of these studies have reported on individual variation within the preterm children, or followed the effects of particularly severe lesions on cognitive development.

In this study, we report the case of a patient who was born prematurely and diagnosed with white matter injury, near the time of birth. At 12 years of age, as part of a research protocol, we used DTI to identify specific areas of injury. We found that the patient had severe damage to the arcuate fasciculus and superior longitudinal fasciculus (SLF). This is the first case in the literature that we are aware of in which such extreme injury to these tracts occurred prior to the onset of language development. Two studies of separate groups of adolescents born preterm have found modest correlations between diffusion properties of the arcuate and phonological skills (Frye et al., 2010; Mullen et al., 2011). A case report of a child who acquired a comparably severe injury to the arcuate from radiation necrosis at age 5 years found that the patient had severe dyslexia (Rauschecker et al., 2009). Because of the large body of scientific and clinical literature that discusses the role of the arcuate fasciculus in language and reading, the goal of the study was to explore the implications of this pre-linguistic injury for language and reading functions and for patterns of neural activation during language processing in this patient.

1.1. *White matter tracts implicated in language and reading*

The arcuate fasciculus (arcuate) is a fiber tract that sweeps from the posterior temporal lobe through the parietal lobe where it parallels the SLF, until it branches laterally toward the inferior frontal and precentral gyri (Schmahmann and Pandya, 2006; Glasser and Rilling, 2008; Saur et al., 2008). Based on macaque data, the SLF has been sub-divided into three segments, all of which connect the parietal to the frontal lobe (Schmahmann and Pandya, 2006). Based on human DTI data, Catani et al. (2005) proposed an alternative segmentation procedure of perisylvian white matter that results in three segments of the arcuate fasciculus: (1) the long segment or direct pathway which connects the temporal lobe to the frontal lobe, (2) the anterior segment which connects the parietal lobe to the frontal lobe and (3) the posterior segment which connects the temporal lobe to the parietal lobe. Together the anterior and posterior segments make up the indirect pathway.

In 1874 Karl Wernicke first proposed that a lesion to temporal–frontal white matter connections would disrupt the communication between receptive language centers of the posterior temporal lobe (Wernicke's area) and expressive language centers of the inferior frontal lobe (Broca's area) (Wernicke, 1874; Lichtheim, 1885; Geschwind, 1970). Wernicke termed this "conduction aphasia" and hypothesized that this disconnection would impair speech repetition while sparing language comprehension and fluent conversational speech. The relationship between arcuate lesions and conduction aphasia was supported by early neurological case studies (Geschwind, 1965a, 1965b, 1970). Furthermore, functional magnetic resonance imaging (fMRI) studies in healthy adults suggest that signals carried along this pathway map auditory representations of speech to articulatory motor movements (Hickok and Poeppel, 2004, 2007). Recent models based on adult DTI data have proposed that signals carried along the arcuate and neighboring SLF fibers may also be essential for semantic verbalization (Catani and Ffytche, 2005; Catani et al., 2005; Catani and Mesulam, 2008; Glasser and Rilling, 2008; Rilling et al., 2008), syntactic comprehension (Friederici et al., 2006; Friederici, 2009), and skilled reading (Klingberg et al., 2000).

Another pathway, ventral to the arcuate (Parker et al., 2005), connects the superior temporal lobe to the inferior frontal lobe and is also hypothesized to be important for language comprehension (Saur et al., 2008). This ventral pathway may play a prominent role during language development (Brauer et al., 2010). The integrity of this pathway may also explain variations and recovery in behavioral profiles after arcuate damage (Glasser and Rilling, 2008).

The implications of pre-linguistic injury to the arcuate for later language or reading functioning are unknown. Lesions to left hemisphere cortical regions that are important for adult language function do not produce aphasia or the same severe deficits in children that they do in adults, though they may be associated with initial developmental delays (Feldman et al., 1992; Feldman, 1994; Bates et al., 2001; Rowe et al., 2009). Functional MRI studies have shown that this plasticity is associated with the reorganization of language functions to adjacent left hemisphere regions (Holland et al., 2007) or to right hemisphere homologs of canonical left hemisphere regions (Booth et al., 1999, 2000; Feldman, 2005). What is currently unclear is how a lesion to the white matter connection between two cortical regions would affect the organization of function.

1.2. *Objectives and hypotheses of the study*

The overall goal of this study was to relate behavioral characteristics and patterns of neural activations during language processing to the extreme white matter injury to the arcuate in this child. In terms of behavioral characteristics, we hypothesized that the patient would have relatively preserved skills in language, including sentence repetition for two reasons: (1) the previous findings of preserved function after pre-linguistic focal lesions to the left hemisphere cortex and (2) the assumption that redundancy in the neural circuitry would allow these skills to develop. However, we hypothesized that she would have weak reading skills based on the previous case report of dyslexia resulting from a childhood arcuate lesion (Rauschecker et al., 2009). In terms of patterns of neural activation during an fMRI language task, we hypothesized that the left inferior frontal gyrus, active in many different language tasks and considered a fundamental part of the language network (Friederici et al., 2003, 2006; Heim et al., 2003) would be active in this child based on the presence of pathways other than the arcuate fasciculus that have been postulated to carry information from the posterior to anterior portions of the language network in children (Brauer et al., 2010).

1.3. Case history

The patient is a 12-year-old female, born prematurely at 34 weeks gestational age by Cesarean section for decreased fetal movement and maternal hypertension. Her birth weight was 1327 g, indicating intrauterine growth retardation. She had a benign neonatal course. At 28 months of age, though ambulatory, she was diagnosed with mild spastic diplegic cerebral palsy and received treatment with physical and occupational therapy, splinting, and eventually a trial of botulinum toxin injections. She also had strabismus treated with corrective lenses. As a toddler and preschooler, she showed apparently normal receptive language development. Her expressive language, as described in the medical record, was characterized by delayed onset of verbal expression, a reduced sound inventory for age, and delayed development of expressive language skills. However, when she reached kindergarten, speech-language therapy services were discontinued because she had made excellent progress. At school, she received special education services initially in her neighborhood school and eventually in an approved private school for children with learning differences. At the time of our assessment, she was taking stimulant medications for Attention-Deficit/Hyperactivity Disorder.

An MRI scan when she was 5 years 8 months of age found left peri-atrial white matter abnormality and loss of left white matter thickness, ex-vacuo dilatation of the atrium of the left lateral ventricle. There were mild changes in the remaining periventricular white matter and a thinned corpus callosum. The findings were reported as consistent with periventricular leukomalacia. In addition, an area of abnormally increased signal in the right thalamus was considered possibly indicative of an old ischemic injury.

2. Methods

The protocol was approved by the Institutional Review Board of Stanford University. Written consent was obtained from parents and verbal assent from the participants. The study consisted of two behavioral testing sessions and two neuro-imaging sessions. The study included one patient and 12 typically developing control children between the ages of 10 and 16 years.

2.1. Behavioral assessment

The behavioral assessment consisted of the following norm-referenced standardized measures of cognitive and language abilities:

The Wechsler Abbreviated Scale of Intelligence or WASI (The Psychological Corporation, 1999), is a norm-referenced test of intellectual ability, that generates a standard score with a mean of 100 and a standard deviation of 15.

Peabody Picture Vocabulary Test, Third Edition or PPVT-III (Dunn and Dunn, 1997) is a norm-referenced test of receptive vocabulary, that generates a standard score with a mean of 100 and standard deviation of 15. Each item consists of four black-and-white drawings on a page. Participants are asked to identify which of the four illustrations best represents the stimulus word presented orally by the examiner.

Comprehensive Evaluation of Language Fundamentals-Fourth Edition or CELF-IV (Semel et al., 2005) is a norm-referenced test of expressive, receptive, and total language that generates a standard score with a mean of 100 and standard deviation of 15 for. In this study, we used the CELF-IV Receptive Language Index (CELF-IV R) to characterize the child's listening and comprehension skills and the CELF-IV Expressive Language Index (CELF-IV E) to characterize language production skills. We analyzed the sentence repetition task separately because of our interest in this particular ability after arcuate injury. This sub-scale has a mean of 10 and standard deviation of 3.

Woodcock Johnson Tests of Achievement, Third Edition (Woodcock et al., 2001) has three subtests—Word Attack, Word Identification and Passage Comprehension—that are norm-referenced tests of reading skills with a mean of 100 and a standard deviation of 15. Word Attack and Word Identification measure word and non-word reading skills. Passage Comprehension measures reading comprehension skills.

2.2. DTI acquisition and pre-processing

DTI data on the patient and 12 control subjects were acquired on a 3 T Signa Excite (GE Medical Systems, Milwaukee, WI) at Stanford University. We used a diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence (TE = 80 msec, TR = 6500 msec, FOV = 240 mm, matrix size = 128×128) to acquire 60 2 mm-thick slices in 30 different diffusion directions (b = 900). We repeated this sequence 4 times and collected 10 non-diffusion-weighted (b = 0) volumes. The data were pre-processed and analyzed using Matlab (The Mathworks, Natick, MA) and C++ based software tools: mrDiffusion and Cinch (available for download at http://white.stanford.edu/software). DTI images were corrected for eddy current distortions and registered to the T1-weighted image (Rohde et al., 2004). For each voxel in the scanned volume, a tensor model was fitted and images depicting fiber orientation (Red, Green, Blue or RGB map), fractional anisotropy (FA) and mean diffusivity were generated (Pierpaoli and Basser, 1996). RGB maps visually represent fiber principal diffusion direction: red voxels signify that fibers are oriented left/right, green voxels signify that fibers are oriented anterior/posterior and blue voxels signify that fibers are oriented superior/inferior. We visually inspected the patient's RGB map in relation to the RGB of a single age- and gender-matched control subject in order to identify areas of marked difference in fiber orientation.

2.3. Whole-brain tensor statistics

To establish in which brain regions the patient's white matter fibers were oriented outside the normal range of variation for the control group, we performed a one-sample version of the statistical eigen-vector test developed by Schwartzman et al. (2005). This test compares the orientation of the tensors in each voxel of the patient's brain to the average orientation of the tensors in the corresponding voxel for the sample of control subjects' brains. Each voxel gets summarized with a test statistic representing the probability of obtaining a tensor orientation like that of the patient's, given the measured distribution in the control population. This method has previously been used to identify regions where the white matter anatomy of a patient is severely altered compared to a control group, implying the absence of a pathway (Rauschecker et al., 2009). We used a false discovery rate correction (FDR) to correct *p*-values such that no more than 5% of significant voxels are false positives.

2.4. Fiber tract segmentation and analysis

For the visualization of fiber tract segmentation we chose a single age-, gender- and handedness-matched control subject with normal language and reading scores from the group of 12 controls, to compare to the patient. As a first step in estimating all the major white matter fascicles in the patient and control subject, we performed whole-brain tractography. Tractography estimates the trajectory of white matter fascicles by tracing a continuous path through the principal diffusion direction at each voxel in the brain (Basser et al., 2000). For each hemisphere, 8 seed points were placed at equidistant locations in all voxels where the FA value was greater than .2. Fiber tracts were estimated using a deterministic streamlines tracking algorithm (STT) with a fourth-order Runge–Kutta path integration method (Mori et al., 1999; Basser et al., 2000). For tracking purposes, a continuous tensor field was estimated using trilinear interpolation of the tensor elements. Stopping criteria for path tracing were FA $< .15$ or turning angle $> 50°$, because the reliability is low when the tensor is near-spherical or the direction of the fiber changes abruptly.

We used two different methods for fiber tract segmentation. First, we followed the segmentation procedure of Catani et al. (2005) and attempted to identify the three defined segments of the arcuate fasciculus: (1) the long segment or direct pathway which connects the temporal lobe to the frontal lobe, (2) the anterior segment which connects the parietal lobe to the frontal lobe and (3) the posterior segment which connects the temporal lobe to the parietal lobe. Second, we used the two region of interest (ROI) approach described by Wakana et al. (2007) to identify the following fiber tracts from the left and right hemisphere fiber groups: arcuate fasciculus, SLF, inferior longitudinal fasciculus (ILF), inferior frontal occipital fasciculus (IFOF), uncinate fasciculus (UF), cingulum, and sensory/motor projections. ROIs were drawn on each individual's brain based on the methods described by Wakana et al. (2007). In order to obtain a more detailed dissection of the ILF we then modified these methods and further segmented the ILF based on the methods described by Catani and Thiebaut de Schotten (2008).

To quantitatively evaluate the diffusion properties of the fiber tracts in the patient in comparison to the controls, we employed an automated full brain deterministic fiber tract segmentation procedure reported in Yeatman et al. (2011). Fibers were segmented into ILF, IFOF, UF and cortico-spinal tract in two steps. First fibers passing through 2 way-point ROIs defined in MNI space and warped to individual brains became candidates (Wakana et al., 2007). Then candidate fibers were scored based on their similarity to a fiber probability map and high scoring fibers were retained as the final fiber group (Hua et al., 2008). FA values were calculated for each fiber group by averaging the FA values across all the voxels containing fibers from that group. We created group norms by calculating the mean and variance of FA values for each fiber group in the control subjects. The patient's FA values were plotted against the mean $\pm$ 2 standard deviations for the control group.

2.5. fMRI

The fMRI task was an auditory sentence verification task consisting of auditory presentation of sentences followed by a picture (Supplemental Fig. 1). Sentences and pictures were derived from the Test For Reception of Grammar (TROG), a computerized measure of grammatical understanding (Bishop, 2003). Subjects were instructed to indicate whether the sentence and the picture matched by pressing the "true" or "false" button on a button box. A total of 72 sentences of varying syntactic difficulty were presented in random order, counterbalanced for difficulty in 3 runs of roughly 4 min each. A detailed description of the task and results for typically developing children is presented in Yeatman et al. (2010).

The purpose of the fMRI analysis was to assess whether the left inferior frontal gyrus would show activation while processing auditory language stimuli. This result would suggest the signals from auditory processing regions in the posterior temporal lobe can reach the inferior frontal gyrus in the absence of the arcuate fasciculus. SPM5 was used to analyze the data in two ways. First whole-brain voxel-wise contrast maps were used to compare activation patterns between the patient and the single matched control subject described previously. Second we defined a ROI encompassing the left inferior frontal gyrus using an automated atlas-based procedure (Maldjian et al., 2003). We quantified the extent of activation within this region for the patient, and the mean and variance in the amount of activation for control group.

2.6. Identification of alternate pathways

To evaluate all longitudinal connections to the frontal lobe that run ventral to the arcuate fasciculus (Parker et al., 2005; Friederici et al., 2006; Anwander et al., 2007; Saur et al., 2008; Friederici, 2009), we intersected the left hemisphere fiber group with a single manually defined ROI encompassing the inferior frontal gyrus, precentral gyrus and surrounding white matter. We eliminated all the fibers that did not exit this large ROI. The resulting frontal lobe fiber group was used to visualize possible preserved frontal lobe projections.

3. Results

3.1. Assessment of language and reading

The patient's scores on standardized measures of cognition, language, and reading are summarized in Table 1. Language comprehension fell within the normal range, as indicated by standard scores on the PPVT-III and CELF-IV between the 42nd and 67th percentile. Verbal repetition was normal as indexed by a sub-scale score of 11 (63rd percentile) on the Sentence Repetition subtest of the CELF-IV. Single word reading abilities and reading comprehension were also within the normal range (23rd to 75th percentile).

Despite normal scores on individually administered tests, this child was receiving intensive special education services.

Table 1 – Scores for patient on standardized measures.

Test	Score	Percentile
PPVT		
	107	67
Clinical Evaluation of Language Fundamentals Composite		
Core Language	97	42
Receptive Language	99	47
Expressive Language	96	39
Language Memory	98	44
Clinical Evaluation of Language Fundamentals Subtest		
Recalling Sentences	11	63
Concepts & Directions	9	37
Formulating Sentences	9	37
Word Classes Receptive	11	63
Word Classes Expressive	8	25
WASI		
Verbal IQ	106	65
Performance IQ	92	30
Full Scale IQ	99	47
Woodcock Johnson Tests of Achievement, Third Edition		
Word ID	96	39
Word Attack	89	23
Passage Comprehension	110	75

Hints to the nature of her functional difficulties were present in the quality of her test performance. Most notably on the vocabulary section of the WASI, where the task is to provide verbal definitions of words, the patient provided long and rambling answers with non-essential information that ultimately included the requisite information for a good score. The administration of the language tests took longer for the patient than for other subjects in the study. However, she did not show phonemic or semantic errors or substitutions. A writing sample from her school revealed age appropriate content, short sentences, and spelling errors.

3.2. *Evidence of the missing arcuate and SLF*

The first indication of the child's abnormalities was the absence of longitudinal fibers on visual inspection of the RGB map. Fig. 1 shows axial slices of the T1-weighted images and the RGB map for the patient and the control at the level of the arcuate/SLF. Axial slices through the whole brain are shown in Supplemental Fig. 2. In healthy adults and children, and in the control, the arcuate/SLF can be identified as a cluster of green voxels (fibers with anterior/posterior orientation) immediately lateral to the internal capsule (blue) (Catani et al., 2002, 2005; Catani and Thiebaut de Schotten, 2008).

To evaluate this finding further, we next employed the voxel-wise, eigen-vector analysis to confirm the loss of

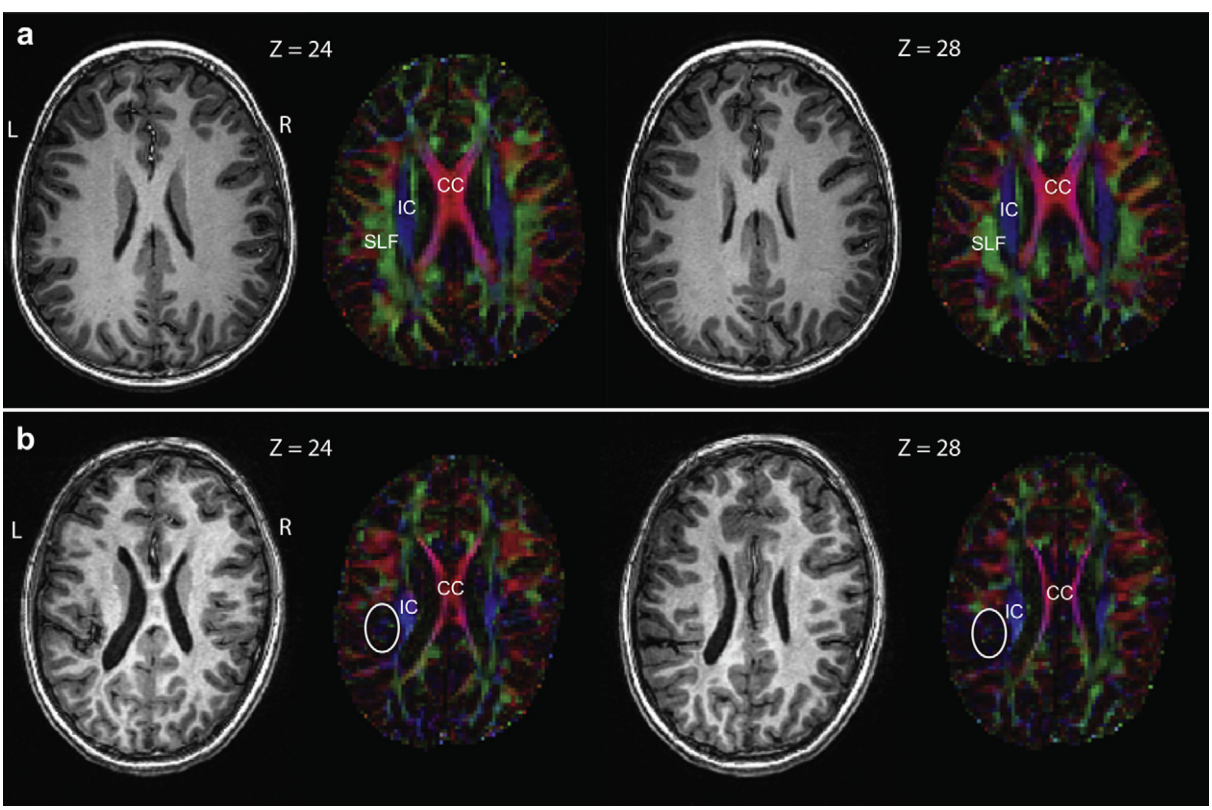

Fig. 1 – Axial slices from the control's (a) and patient's (b) T1-weighted images and corresponding RGB fiber orientation maps. The corpus callosum (CC), internal capsule (IC), and SLF/arcuate fasciculus are labeled on the control's RGB map. Absent on the patient's RGB map are the green voxels depicting regions with anterior/posterior fiber orientation, lateral to the blue voxels depicting superior/inferior fiber orientation of the IC. These missing longitudinally oriented voxels correspond to the superior longitudinal/arcuate fasciculus (open circle on patient's RGB map).

longitudinal fibers in the region of the arcuate fasciculus. Fig. 2 shows the results of this analysis. Regions of the brain where we found significant differences between the tensor orientation for the patient and the control group ($p < .05$, FDR corrected) included the periventricular white matter that typically contains the arcuate and SLF. This region can also contain fibers of the internal capsule. Voxels containing longitudinal fibers in the control group contained left–right oriented fibers in the patient, suggesting that normal long-range posterior–anterior fibers were absent or that the dominant fiber orientation had changed.

We then used tractography to confirm the absence of arcuate and SLF fibers and the presence of other major pathways (Supplemental Fig. 3). Supplemental Fig. 3a shows three-dimensional rendering of the left hemisphere fiber tracts for the control. The following tracks were all clearly visible: ILF, IFOF, UF, cingulum, motor/sensory projections, the arcuate fasciculus and the SLF for the control. Supplemental Fig. 3b shows the three-dimensional reconstructions of the left hemisphere fiber tracts for the patient. All of the studied tracts were present except the arcuate and the SLF in both the left and right hemisphere. The IFOF also appeared abnormal but could be identified.

To identify which perisylvian language pathways were present and which absent, we used the segmentation procedure of Catani et al. (2005). The results of this analysis for the patient and the control are presented as Fig. 3. In the control, we found all three segments of the arcuate fasciculus. In the patient, we found only the posterior segment coursing from the parietal lobe to posterior temporal lobe. We then tracked fibers for the patient from a ROI that typically contains the anterior and long segments. Whereas in typically developing children and adults fibers in this region are oriented longitudinally, connecting the temporal and parietal cortices to frontal cortex, in the patient all the fibers were oriented medial–lateral. We found no streamlines that coursed in a longitudinal direction.

Probabilistic fiber-tracking (Sherbondy et al., 2008) confirmed that the inability to identify the arcuate was not due to methodological limitations of deterministic fiber-tracking. For the control a single compact pathway ran posterior to anterior, dorsal to the Sylvian Fissure, along the normal path of the arcuate fasciculus. This finding is consistent with previously reported probabilistic tracking results from these regions of cortex (Saur et al., 2008). For the patient the estimated pathways were diffuse and disorganized; none followed the typical trajectory of the arcuate fasciculus (Supplemental Fig. 4).

3.3. *Abnormal diffusion properties in other fiber tracts*

The arcuate and SLF were the only fiber groups that could not be found in this patient. However, other fiber groups had

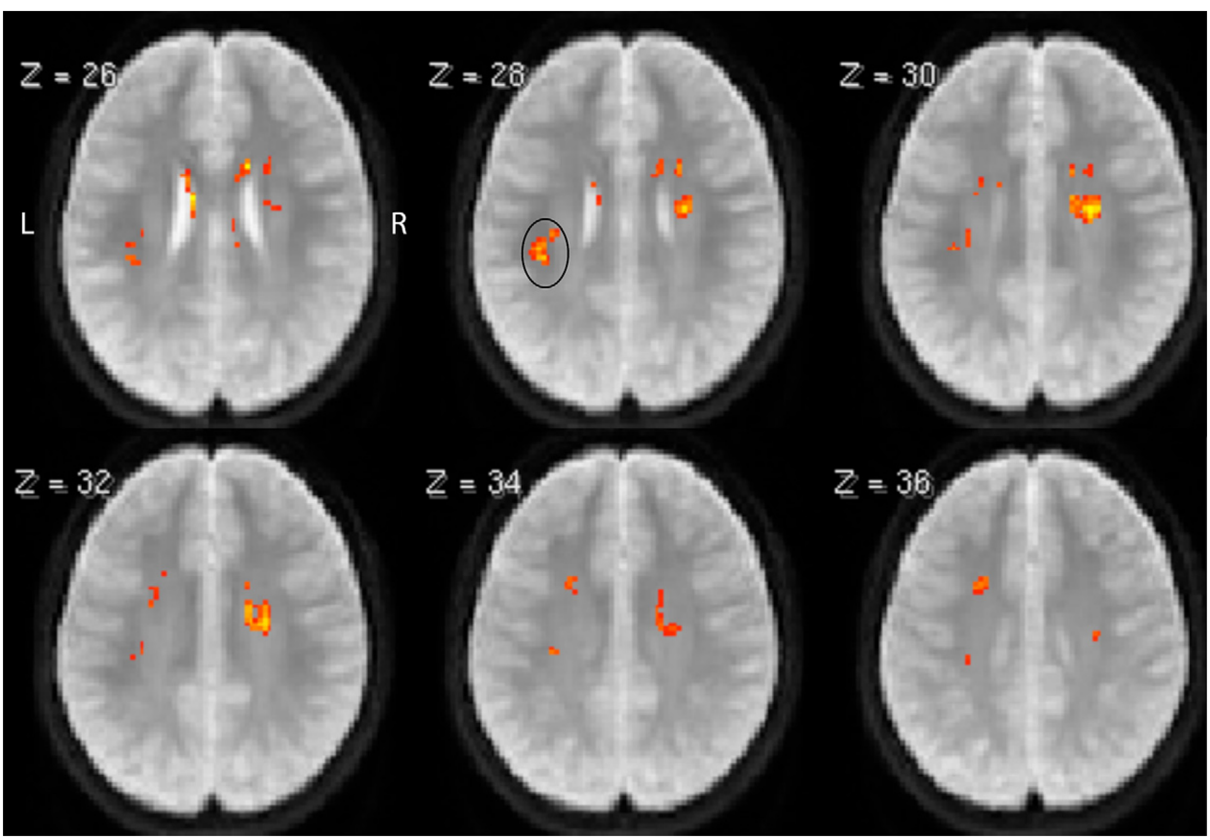

Fig. 2 – Voxels within the patient's DTI data for which the tensor orientation falls outside the 95% confidence interval of tensor orientation in the control group (FDR corrected), displayed on the mean B = 0 image for the control group. Significant differences in fiber orientation were found in periventricular white matter corresponding to the superior longitudinal/ arcuate fasciculus and also in the internal capsule. The black circle corresponds to region of the superior longitudinal/ arcuate also circled in Fig. 1.

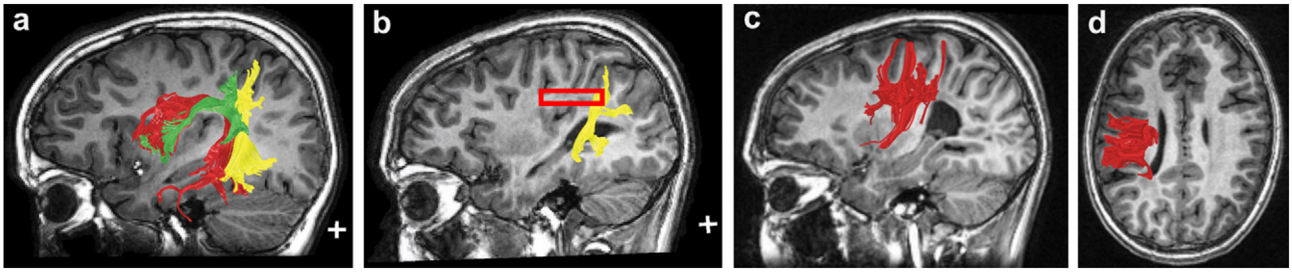

Fig. 3 – Segmentation of the arcuate fasciculus into the anterior segment (green, parietal–frontal fibers), posterior segment (yellow, temporal–parietal fibers) and long segment (red, temporal–frontal fibers), for the control subject (a) and patient (b). The anterior and long segments were absent in the patient but the posterior segment was present. Fibers tracked for the patient from a ROI that typically contains the anterior and long segments (red box in panel b) are shown in red overlaid on a sagittal (c) and axial slice (d). In typically developing children and adults fibers in this region are oriented longitudinally and connect temporal and parietal cortex to frontal cortex. In the patient all the fibers were oriented medial–lateral and there were no longitudinal connections.

reduced FA. Fig. 4 shows the patient's mean FA values for each fiber tract relative the mean values ± two standard deviations for the control group. The left and right cortico-spinal tract, IFOF and ILF all had low FA values in the patient, while the UF had normal FA values. The automated fiber tract segmentation procedure was also unable to identify the arcuate or SLF for the patient.

3.4. *fMRI activation during sentence comprehension*

fMRI results on the sentence comprehension task for the patient and control are presented in Fig. 5. Both the patient and control had significant activation in left frontal lobe (peak activation for the patient at −48, −3, 45) and the left posterior temporal lobe (peak activation for the patient at −66, −48, 6). The subject showed robust activation within the left inferior frontal gyrus ROI ($p < .05$ FDR corrected). There were 942 active voxels in this region. The control subject showed less activation in terms of the number of active voxels within the ROI. In the control group, the mean number of active voxels was 169 with a standard deviation of 145 voxels. This result suggests that despite damage to the arcuate, the inferior frontal gyrus continued to play a role in language processing.

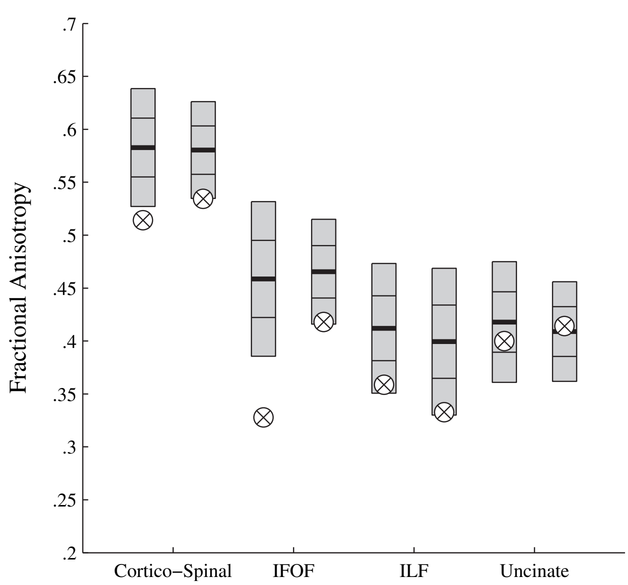

Fig. 4 – FA values for the patient compare to a sample of typically developing age-matched control children. The boxes show the mean FA value ± 2 standard deviations for each fiber group for the controls. The circles show the FA values for the patient.

3.5. *Alternative connections to the frontal lobe*

Finally, we sought to identify alternative connections that might carry signals to the frontal lobe in this patient. To determine which tracts connected to inferior frontal gyrus from other gyri beyond the immediate neighbors, we tracked fibers from a single ROI, encompassing the entire inferior frontal and precentral gyri as well as surrounding white matter. We were able to identify connections in the patient from the inferior frontal gyrus to the anterior temporal lobe and from the inferior frontal gyrus to the posterior temporal lobe (Fig. 6). We were unable to track any streamlines from the frontal lobe to the parietal lobe. The connections we identified projected through the extreme capsule, ventral to the location of the arcuate fasciculus and had frontal endpoints anterior and inferior of the pars opercularis (BA 44) where the arcuate typically ends. These tracts have been characterized in healthy adults (Saur et al., 2008) and children (Brauer et al., 2010). We were also able to identify a connection between the pars opercularis (typical arcuate endpoint) and the region where ventral temporal–frontal connections terminated (BA 45). Hence, while direct connections from the posterior temporal lobe to the pars opercularis along the arcuate fasciculus were absent, an indirect pathway between these regions remained intact (Fig. 6).

4. Discussion

In summary, we describe the case of a 12-year-old child who, based on DTI data, is missing arcuate and the SLF bilaterally. The child was initially delayed in expressive language skills. By adolescence, consistent with the hypotheses, she had normal scores on assessments of verbal IQ and expressive language, including verbal repetition. However, she provided unnecessary verbal information in some tasks and thereby

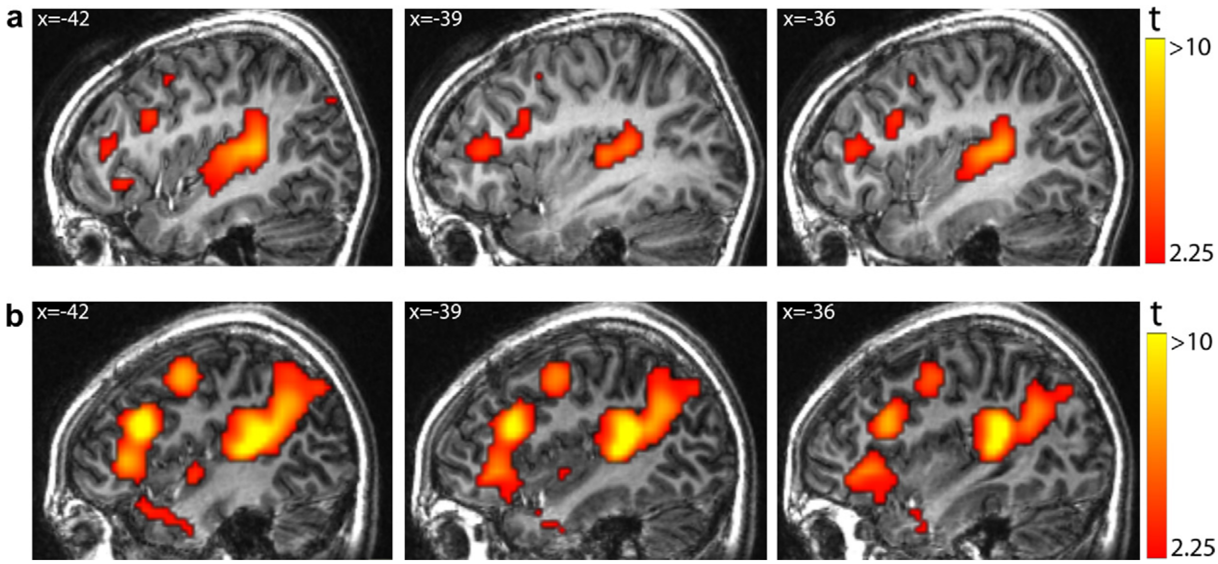

Fig. 5 – Evidence of activation in the left inferior frontal gyrus, left superior temporal gyrus and inferior parietal lobe on fMRI auditory sentence verification task. Sagittal slices showing functional activation ($p < .05$, FDR corrected) comparing sentence comprehension to baseline for the control (a) and patient (b).

took longer to complete the tasks. Our findings suggest that other routes of information flow within the language network may be possible. The possibility that the arcuate fasciculus does not play an important role in language processing would also be consistent with the data but at odds with of neuropsychological data linking the integrity of perisylvian white matter in adults to language function (Wernicke, 1874; Geschwind, 1965a, 1965b, 1970).

Contrary to our predictions, the child also had normal scores on tests of single word reading and Passage Comprehension.

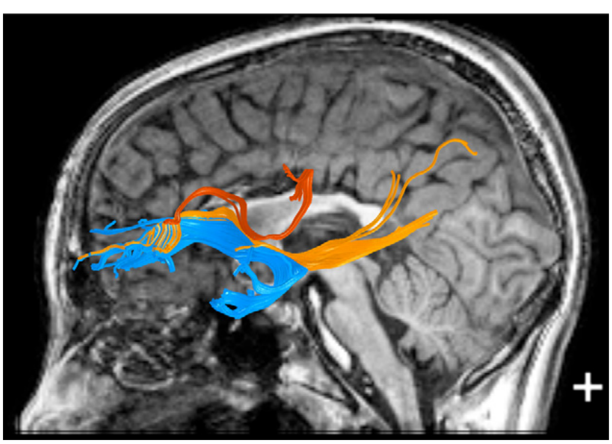

Fig. 6 – Pathways to the frontal lobe in the patient missing the arcuate fasciculus. Fibers tracked using deterministic tractography from a large ROI encompassing the inferior frontal and precentral gyri. Light blue fibers have endpoints in the anterior temporal lobe and orange fibers have endpoints in the posterior temporal lobe. Red fibers connect the anterior endpoints of the ventral connections (BA 45) to the pars opercularis (BA 44), the typical endpoint of the arcuate fasciculus. The posterior temporal lobe is connected to the pars opercularis indirectly through the orange and red fibers.

This result is in striking contrast to a case study of a child with radiation necrosis affecting this path at age 5 who subsequently failed to learn to read (Rauschecker et al., 2009). The reasons for the difference in behavioral profiles of these two patients are unclear but may be related to the ages of injury or to the patterns of injury to other pathways and brain regions.

Finally, the child activated left inferior frontal gyrus during a sentence comprehension fMRI task. The activations were similar to those of the controls. These findings suggest that this region receives signals during language processing despite the lack of direct connections along the arcuate fasciculus.

4.1. *Possible mechanisms supporting intact language function*

Redundancy in the normal white matter structures of the language network may contribute to proficient performance of the patient. Three distinct fiber systems connect temporal and frontal lobes: arcuate fasciculus, UF, and extreme capsule fiber system (Catani and Thiebaut de Schotten, 2008; Friederici, 2009; Brauer et al., 2010). One possibility is that the child, missing the arcuate fasciculus, has language information carried on ventral pathways, seen in Fig. 6. Another possibility is that short-range U-fibers connecting neighboring gyri provide an alternative route for information flow.

Many language functions seem to be supported by both specialized and redundant systems. For example, auditory language comprehension is associated with bilateral temporal activation, though each hemisphere appears to be more specialized for specific sub-components of auditory language processing (Hickok and Poeppel, 2004, 2007; Poeppel et al., 2004). Seghier et al. (2008) suggest that word reading can be accomplished with either of two different neural networks. Just and Varma (2007) assert that most cognitive functions can be performed by more than one brain area and that most brain regions perform multiple functions. In their model, the brain is organized such that particular brain regions are more efficient at processing specific tasks than other tasks, though they are able to perform many tasks. As a task becomes increasingly complex, it requires the collaboration of a larger network of regions.

The use of redundant pathways within the language system may be particularly important in development. Brauer et al. (2010) argue that the children who, like our patient, activate large areas of the inferior frontal lobe during fMRI language tasks, distribute processing across both the dorsal and ventral language pathways. Adults, who are more competent than children on the task, activate a more circumscribed area of inferior frontal lobe that corresponds specifically to the termination of the arcuate fasciculus. There data suggest that adults may rely on information flow through dorsal pathways while children rely on both dorsal and ventral pathways.

For each of the skills that are preserved in this child with severe pre-linguistic injury to the arcuate and are typically thought to depend on the arcuate fasciculus in adults, the flow of information from posterior to anterior brain regions may be served by other pathways. Given the patient's initial developmental delays and inefficient language use as an adolescent, it is possible that these alternate pathways are less advantageous for flow of language information at this age than are the arcuate and SLF. It is also noteworthy that the child had low FA in other association tracts and may have had injury to gray matter as well as to white matter. Her developmental language delay and inefficient language skills may be the cumulative effect of multiple injuries.

4.1.1. *Verbal repetition*

Because the left arcuate fasciculus provides a direct connection between Wernicke's area and Broca's area, it has been assumed that the structure is essential for verbal repetition. Neurological studies of adults with damage to left hemisphere white matter containing the arcuate often have difficulty repeating auditory information (Wernicke, 1874; Geschwind, 1965a, 1965b, 1970; Damasio and Damasio, 1980). Furthermore, DTI-based investigations of the cortical destinations of the left arcuate fasciculus in adults maintain that the anatomy of the pathway is consistent with the functional role assigned to it by neurological case studies (Catani et al., 2005; Catani and Mesulam, 2008).

Our pediatric patient had normal test scores on a sentence repetition task. This finding is consistent with results reported by Rauschecker et al., in which a child with a lesion to the left hemisphere arcuate fasciculus at age 5 years retained normal sentence repetition skills. In the patient reported here, regions typically connected by the arcuate appeared to be connected by a ventral pathway that has been characterized by previous studies (Anwander et al., 2007; Frey et al., 2008; Saur et al., 2008; Friederici, 2009).

4.1.2. *Semantic processing*

The patient's proficient receptive vocabulary skills are consistent with two proposed models of the arcuate fasciculus (Catani et al., 2005; Glasser and Rilling, 2008; Saur et al., 2008). Glasser et al. suggest that receptive vocabulary would be unaffected by arcuate damage because semantic knowledge from incoming auditory information can descend inferiorly from the superior temporal lobe to semantic stores in the middle and inferior temporal lobe via short-range cortical connections. Catani et al. (2005) argue that connections from the temporal lobe to the parietal lobe support the transmission of incoming auditory information to semantic stores in the parietal lobe. In either case, all of the requisite fibers were present in the patient.

Glasser and Rilling argue that the left arcuate fasciculus is the link between semantic stores in the middle temporal lobe and expressive language in the inferior frontal lobe, suggesting that the verbalization of semantic knowledge depends on the arcuate (Glasser and Rilling, 2008; Rilling et al., 2008). The model asserts that the arcuate supports the transmission of word meaning information stored in the middle temporal lobe to the inferior frontal lobe during spontaneous speech and language comprehension. The frontal lobe may also be important for organizing verbal information in complex language tasks, such as the ones included in the language battery (Hickok and Poeppel, 2004).

Our patient did not show substantial impairments on standardized tests of receptive or expressive language. However, she was delayed in the early phases of expressive language development and she included unnecessary information and was slow to respond on the vocabulary subtest of the verbal IQ measure. These findings could reflect that use of a different route between the middle temporal lobe and the frontal lobe requires more time for development and ultimately may be less favorable for semantic verbalizations than the arcuate would have been. At the same time, this pathway may also be important in general among children born preterm. Other studies of adolescents born preterm have found significant though modest associations between receptive semantic skills and the UF (Constable et al., 2008; Mullen et al., 2011).

4.1.3. *Reading*

Skilled reading relies on co-activation of the inferior frontal and posterior temporal lobes (Simos et al., 2006; Shaywitz and Shaywitz, 2008). Hence the arcuate fasciculus is a likely candidate pathway for explaining both neural and behavioral deficits observed in developmental dyslexia. In typically developing children, the arcuate appears to carry signals that are important for phonological processing skills, an essential component of reading (Yeatman et al., 2011). A previous case attributed a child's dyslexia to severe damage of the arcuate (Rauschecker et al., 2009). Many differences between these two cases, such as the age of injury and the degree of damage to other tracts may explain the difference in reading performance.

4.2. *Limitations*

Because this patient's data was obtained from a larger study on language in children born prematurely, we used the standard experimental protocol to characterize her specific deficits. We did not have the opportunity to administer additional measures, such as rapid naming that might have assisted in the interpretation of these data. The DTI data had 30 directions, which limited our ability to estimate multiple fiber orientations in regions of crossing fibers. This child is uncharacteristic of the general population because she had highly educated parents. She might have had superior cognitive functions had she not experienced this injury. She also received early intervention and intensive special education. The degree of compensation may be related to probable high academic potential and outstanding educational program.

4.3. Conclusions

White matter injury to the arcuate in the neonatal period does not necessarily result in severe limitations in sentence repetition, verbal comprehension, verbal expression or reading. Further studies are required to explain plasticity in the case of early white matter injury and to further investigate residual problems after severe injuries.

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Supplementary data

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