Brain Imaging and Behavior (2019) 13:973–984
https://doi.org/10.1007/s11682-018-9903-3

ORIGINAL RESEARCH

The mis-wired language network in children with developmental language disorder: insights from DTI tractography

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Published online: 22 June 2018

Abstract

This study aims to detect the neural substrate underlying the language impairment in children with developmental language disorder (DLD) using diffusion tensor imaging (DTI) tractography. Deterministic DTI tractography was performed in a group of right-handed children with DLD ($N = 17$; mean age 10;07 ± 2;01 years) and a typically developing control group matched for age, gender and handedness ($N = 22$; mean age 11;00 ± 1;11 years) to bilaterally identify the superior longitudinal fascicle, arcuate fascicle, anterior lateral segment and posterior lateral segment (also called dorsal language network) and the middle and inferior longitudinal fascicle, extreme capsule fiber system and uncinate fascicle (also called ventral language network). Language skills were assessed using an extensive, standardized test battery. Differences in language performance, white matter organization and structural lateralization of the language network were statistically analyzed. Children with DLD showed a higher overall volume and higher ADC values for the left-hemispheric language related WM tracts. In addition, in children with DLD, the majority (88%; 7/8) of the studied language related WM tracts did not show a significant left or right lateralization pattern. These structural alterations might underlie the language impairment in children with DLD.

Keywords Developmental language disorder · Structural connectivity · DTI · Language network · Dorsal stream · Ventral stream

Introduction

Developmental language disorder (DLD) represents one of the most common childhood learning disabilities, with a prevalence of approximately 6% of preschool children (Tomblin et al. 1997). DLD is characterized by difficulties with producing and understanding oral language. These difficulties cannot be attributed to sensorimotor, intellectual or other developmental impairments, especially autism spectrum disorder, and are not related to obvious brain lesions or socio-affective deprivation (Reilly et al. 2014). Also, terminology to define this language impairment has varied over many years and terms as developmental dysphasia (Parisse and Maillart 2009), DLD (Bishop et al. 2016; Rapin and Dunn 2003) and specific language impairment (D. V Bishop 1992) are often used interchangeably (De Guibert et al. 2011). Until now, the etiology of DLD remains largely unknown. However, there is growing evidence that a complex interaction between several genes and environmental risk factors may affect the anatomo-functional organization of language processing in the brain (Bishop 2006; Fisher et al. 2003; Rice et al. 2009; Simpson et al. 2015). Studies investigating the neurobiology of language suggest that large parts of the left and right perisylvian cortex, in collaboration with a distributed cortico-subcortical network, are involved in language processing (Dick et al. 2013; Krishnan et al. 2016; Mayes et al. 2015). Growing evidence supports the dual stream "dorsal-ventral" model for language processing (Dick et al. 2013). According to this model, cortical language regions are connected by multiple subcortical dorsal and ventral white matter (WM) tracts. Dorsal tracts include the superior longitudinal fascicle (SLF) and several branches of this SLF, whereas ventral tracts include the extreme capsule fiber system (ECFS), uncinate fascicle (UF), inferior longitudinal fascicle (ILF) and middle longitudinal fascicle (MdLF). The development of advanced

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quantitative magnetic resonance imaging (MRI) techniques such as voxel-based morphometry (Badcock et al. 2012; De Fossé et al. 2004; Girbau et al. 2014; Soriano-Mas et al. 2009), functional MRI (Weismer et al. 2005) and diffusion tensor imaging (DTI) (Verhoeven et al. 2012; Vydrova et al. 2015) have confirmed microscopic anomalies in brain structure and function in language related regions in children with DLD. DTI is a non-invasive method to investigate WM bundles underlying the language network in vivo. Until now, only few studies have investigated structural connectivity properties of the language network in DLD, using DTI (Morgan et al. 2018; Roberts et al. 2014; Verhoeven et al. 2012; Vydrova et al. 2015).

Driven by a potential link between structural connectivity and language performance in DLD, the present study investigated the WM organization of the dorsal and ventral language network in a group of children with DLD and a group of typically developing children, matched for age, gender and handedness. In a final step we aimed to relate the structural connectivity measures of the language network to the language function of children with DLD.

Methods

Participants

Seventeen school-aged children with DLD (mean age 10;07 ± 2;01 years; 11 males and 6 females) and 22 typically developing controls (mean age 11;00 ± 1;11 years; 15 males and 7 females) were included. Both groups were matched for age, gender and handedness. All participants were right-handed native Dutch speakers with normal hearing and had a normal intelligence with a performance or full scale intelligence quotient (IQ) above 80.

Patients with DLD were recruited through the Multidisciplinary University Centre for Speech, Language Pathology and Audiology (MUCLA), University Hospital Leuven and diagnosed by a multidisciplinary team based on neuropediatric, neuropsychological and language examinations according to the DSM-IV criteria. However, to ensure the persistent character of their language problems, all children followed at least 1 year intensive speech language therapy after DLD diagnosis and had to perform below 1.25 SD on at least 1 language component: phonology, lexicon, semantics, morphology, syntax and pragmatics in an expressive or receptive way. The age at DLD diagnosis ranged from 5;02 to 12;10 years (mean age: 8;02 ± 1;09 years). Almost half of the children (8/17; 47%) had confirmed co-morbid disorders, of which dyslexia (5/17; 29%) was the most prevalent. Table 1 presents an overview of the patient characteristics.

Typically developing children were actively recruited. None of them had a history of neurological or psychiatric conditions or a current medical, developmental or psychiatric diagnosis. They did not report any language problems. The parents of the healthy volunteers completed the Social Communication Questionnaire (Rutter et al. 2003) and Social Responsiveness Scale (Constantino and Gruber 2005) questionnaires to exclude the presence of substantial ASD symptoms.

This study protocol was approved by the Ethical board of the University Hospitals Leuven, Belgium. Parents and children were informed about the experiment; informed consent was obtained from all parents/guardians according to the Declaration of Helsinki, with additional assent from all participating children.

Neuropsychological and language assessment

Neuropsychological assessment included achievement of the full Dutch Wechsler Intelligence Scale for Children, Third Edition (Kort et al. 2005). Language skills of our study population were assessed with the Dutch version of the Clinical Evaluation of Language Fundamentals (CELF-4NL) (Kort et al. 2008). To assess language performance of all language domains (e.g. semantics, phonology, morphology, syntax, pragmatics) in an expressive and receptive way, the following subtests of the CELF-4NL were used: Concepts and Following Directions (CFD), Word Structure (WS), Recalling Sentences (RS), Formulating Sentences (FS), Word Classes-Expressive (WC-E), Word Classes-Receptive (WC-R), Sentence Comprehension (SC), Expressive Vocabulary (EV), Word Definitions (WD), Understanding Spoken Paragraphs (USP), Sentence Assembly (SA), Semantic Relationships (SR), Number Repetition Forward (NR-F), Number Repetition Backward (NR-B), Word Associations (WA) and Phonological Awareness (PA). After administrating this CELF-4NL battery, five indices were derived: the Core Language Score (CLS), a measure of general language ability that quantifies a child's overall language performance, and four other specific language indices. First, the Receptive Language Index (RLI) provides a measure of auditory comprehension and listening skills. Second, the Expressive Language Index (ELI) gives an indication of the ability to express oneself verbally. Third, the Language Content Index (LCI) is a measure of various aspects of semantic development, including vocabulary, word definitions, comprehension of directions and spoken paragraphs and comprehension of associations and relationships between words. Finally, the Language Structure Index (LSI) measures skills related to the interpretation and production of structural aspects of language, including word structure and formulating and recalling sentences (Semel et al. 1998). The Peabody Picture Vocabulary Test (PPVT-III-NL) (Dunn and Dunn

Table 1 Patient characteristics of DLD group

ID	Sex	Age at testing (years)	Age at diagnosis (years)	Familial DD	Co-morbidities	Education type	Impaired index scores	Impaired subtest scores
1	M	15;02	7;06	No	None	Integrated	4/5	7/12
2	M	11;00	10;08	No	None	Regular	4/5	7/13
3	M	13;10	10;06	No	Dyslexia	Regular	3/5	5/12
4	F	13;03	12;10	Suspected (brother)	Dyscalculia	Regular	5/5	10/13
5	M	8;11	8;05	No	None	Regular	5/5	8/11
6	F	10;11	7;10	No	None	Special	5/5	10/14
7	F	8;07	8;01	No	Functional hearing loss	Regular	2/5	6/12
8	M	10;11	10;05	No	Dyslexia	Regular + additional support and guidance	4/5	8/13
9	F	8;09	6;06	No	None	Special	5/5	8/12
10	M	9;10	10;01	No	Dyslexia	NA	0/5	3/13
11	M	10;02	7;01	Yes	Dyslexia	NA	4/5	10/13
12	M	9;07	6;10	No	Dyslexia	Integrated	5/5	8/14
13	F	8;01	7;02	No	Suspicion of dyscalculia	Integrated	5/5	8/12
14	M	8;09	5;11	No	ASD	Integrated	5/5	10/13
15	M	8;05	5;02	No	None	Regular	2/5	4/12
16	M	12;06	6;01	No	None	Integrated	5/5	11/13
17	F	10;10	10;04	No	None	Special	5/5	9/12

ID patient identification, *M* Male, *F* Female, *ASD* autism spectrum disorder, *NA* not available, *NA** not available (due to incomplete language test assessment); Integrated (education) the child attends a regular school but receives guidance from a special school counselor

2005) was used to assess receptive vocabulary. Handedness was assessed with the Dutch version of the Oldfield Handedness Questionnaire (Oldfield 1971) in all participants. IQ scores and language skills were evaluated on the day of scanning or in a time interval of less than 1 month prior to scanning. The total duration of testing was on average 3 h.

Magnetic resonance image acquisition

All acquisitions were performed on the same 3 T whole-body scanner (Philips, Best, The Netherlands) using a 32-channel head coil. Anatomical imaging consisted of a high resolution structural volume acquired using a coronal 3D turbo field echo T1 weighted images sequence with the following parameters: 182 contiguous coronal slices covering the whole brain and brainstem, slice thickness = 1.2 mm, repetition time (TR) = 9.6 ms, echo time (TE) = 4.6 ms, field-of-view (FOV) = 250 X 250 mm^2, matrix size = 256 X 256, in plane pixel size = 0.98 X 1.20 mm^2, and acquisition time = 6 min 26 s.

DTI data were acquired using an optimized single-shot-spin-echo, echo planar imaging sequence with the following parameters (Leemans and Jones 2009): 58 contiguous sagittal slices, slice thickness = 2.5 mm, TR = 7.6 s, TE = 65 ms, FOV = 200 X 240 mm^2, matrix size = 80 X 94, in plane pixel size = 2.5 X 2.5 mm^2, acquisition time = 10 min 32 s. Diffusion gradients were applied in 60 non-collinear directions (b = 1300 s/mm^2) and one non-diffusion weighted image was acquired.

These techniques are highly sensitive to motion artifacts and require a considerable amount of time for image acquisition. Therefore, a successful acquisition of these images can be very challenging in young children. To reduce motion artifacts and to improve the comfort of the child, a new approach, called the space training protocol, was designed. This space protocol aims to make the MRI scanning session a pleasant experience for children by immersing them in a story about a cosmonautic adventure. Furthermore, this protocol was designed to achieve a successful acquisition in a time and resource efficient manner, without lengthy preparation procedures or repeated visits to the hospital.

Diffusion tensor imaging analysis

Preprocessing

Raw diffusion MR data were transferred to an offline workstation. All the images were first visually inspected for the presence of apparent artefacts. MRI data were pre- and postprocessed using ExploreDTI (Leemans et al. 2009). Motion and eddy current correction of the diffusion-weighted images was performed. During this preprocessing step, the b-matrix was corrected for the rotational component of participant motion to ensure that deviations in the diffusion weighting originating from this rotations would be taken into account (Leemans and Jones 2009). Based on visual inspection of the acquired native data, and visual inspection of the data-quality-summary report as implemented in ExploreDTI, those children with apparent motion artefacts (signal drop outs, smearing etc.) were excluded.

Subsequently, the diffusion tensors (DT) were estimated using nonlinear least squares fitting. Whole-brain fiber tractography was calculated for each DTI data set using a uniform 2 mm seed point resolution and the following thresholds: fractional anisotropy (FA) termination threshold of 0.2, angle threshold of 30°, and a minimal fiber tract length threshold of 50 mm.

Fiber tracking: Region of interest definition

Deterministic fiber tractography was used to identify bilateral the ECFS, UF, ILF and MdLF (referred to as the ventral pathway); and the SLF and its three subcomponents (referred to as the dorsal pathway) (Fig. 1). We defined regions of interest (ROI's) for tractography in the native diffusion space on the FA and color coded maps. These ROI's were defined manually on coronal and axial slices based on a priori knowledge of the anatomy of the tracts. The ROI's were drawn according to the ROI definition protocols of (Catani et al. 2002) for the SLF, (Wakana et al. 2007) for the ECFS, UF and ILF and (Makris et al. 2013) for the MdLF. When necessary, NOT ROI's were placed in order to exclude fibers from neighbouring tracts.

Fiber tracking: Tract partitioning

The methodology for subdividing the SLF in 3 different components is less established than the tractography of the entire tracts, which are easily identified in the FA and color coded maps (Catani et al. 2005). Delineation of the full SLF by visual exploration allows the detection of the cortical terminations of each individual segment (Fig. 1). Between these 3 landmarks, a SEED ROI and an AND ROI were drawn to detect the longitudinal, posterior and anterior segment (Fig. 1).

Statistical analysis

All statistical analyses were performed using SPSS software version 23 (SPSS Inc.).

First, test-age equivalent standard scores of language skills were compared between patients with DLD and typically developing children using an unpaired t-test for normally distributed data. The Mann-Whitney U test was used for non-normally distributed data. Statistical significance was set to $P < 0.008$ to account for Bonferroni correction and the number of tests performed ($N = 6$). Because the typically developing group performed above average on language performance, a one sample t-test was performed to compare the age corrected core language index and other language index scores between

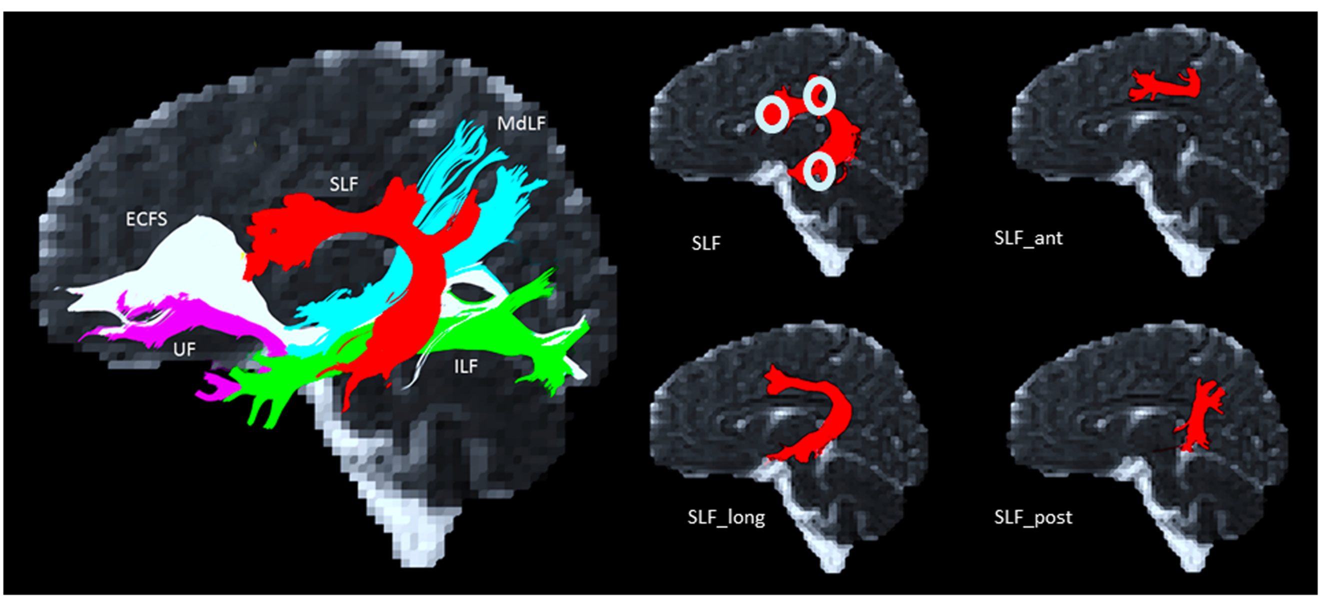

Fig. 1 Deterministic fiber tractography of the dorsal and ventral language network. Reconstruction of the left dorsal and ventral language network: superior longitudinal fascicle (SLF); extreme capsule fiber system (ECFS); inferior longitudinal fascicle (ILF); middle longitudinal fascicle (MdLF); uncinate fascicle (UF). Subdivision of the SLF: longitudinal SLF (SLF_long), posterior SLF (SLF_post) and anterior segment of the SLF (SLF_ant)

the group of children with DLD and the mean normal values ($H_0 = 100$) as provided by the CELF-4NL and PPVT-III-NL norms. *P* values below 0.05 were considered significant.

Second, tract volume (VOL), mean FA and apparent diffusion coefficient (ADC) values were obtained from each participant's language related WM tracts. Differences in tract VOL, FA and ADC between both groups were tested using multivariate analyses of variances (MANOVA's) for the left-hemispheric and right-hemispheric tracts separately. A series of analyses of variances (ANOVA's) was used to detect differences between both groups for DTI metrics of the SLF segments. To detect inter-hemispheric differences in FA, a laterality index (LI_{FA}) was calculated according to the following formula (for example for the FA of the SLF): $(FA_{SLF\ left} - FA_{SLF\ right}) / (FA_{SLF\ left} + FA_{SLF\ right})$. LI_{FA} values close to "0" indicate no lateralization of FA for the studied WM tract. A participant with a positive LI_{FA} is relatively left lateralized for the studied WM tract, while a negative LI_{FA} reflects relative right-hemispheric FA lateralization (Vandermosten et al. 2013). Statistical significance of the degree of lateralization was determined using a one-sample t-test for each tract ($H_0 = 0$). Differences in LI_{FA} between both study groups were tested using multivariate analyses of variances (MANOVA's). A series of analyses of variances (ANOVA's) was used to detect differences in LI_{FA} between both groups for the SLF segments. Bonferroni correction was applied to account for multiple comparisons.

Third, to explore the relationship between structural connectivity metrics (VOL, FA & ADC) of left- and right-hemispheric language related WM tracts and test-age equivalent standard scores of language performance, semi-partial correlations were assessed for each study group with age included as control variables for the DTI metrics. Bonferroni correction for multiple comparisons was performed using the threshold for corrected *P* value set at 0.05, divided by the number of language subdomains with significant group differences (compared to the mean normative values ($H_0 = 100$)).

Results

Language

Children with DLD obtained mean scores significantly lower ($P < 0.001$) than the normative value for the PPVT-III-NL as well as all CELF-4NL index scores and subtests. Among the index scores, ELI and LSI showed the lowest mean standard scores, whereas RLI showed the highest mean standard score. The mean core language index in the DLD group was 75.4 (SD 10.6). This was significantly lower ($P < 0.001$) compared to typically developing control children (mean standard score 113.3, SD 9.6). Compared to the mean normative values, children with DLD scored significantly lower on all language index scores as well as the PPVT-III-NL (Table 2).

DTI metrics

First, a main effect of group was observed for VOL of left-hemispheric WM tracts ($P = 0.020$) indicating that patients with DLD present with overall higher tract VOL values of the left-hemispheric WM tracts compared to typically developing children. Post hoc, a higher VOL of the UF ($P = 0.001$) and anterior part of the SLF ($P = 0.002$) was found in the DLD group. For left-hemispheric ADC values, a main effect of group ($P = 0.030$) was found, suggesting higher ADC values of the left-hemispheric WM tracts in the DLD group compared to typically developing children. No significant post hoc differences were found. For FA of the left-hemispheric WM tracts, a trend ($P = 0.064$) was observed towards overall higher FA values in typically developing controls compared to patients with DLD. Univariate analyses corrected for multiple comparisons revealed that patients with DLD showed decreased FA values in the left ILF ($P = 0.005$) and MdLF ($P = 0.019$) (Fig. 2).

Second, for the right-hemispheric tracts, no overall differences in tract VOL, ADC and FA values were found between

Table 2 Language test scores of children with DLD and typically developing control children

Domain	DLD		CO	
	Mean ± SD	P compared to norm (P_{50})	Mean ± SD	P compared to norm (CO group)
CLS	75.4 ± 10.6	< 0.001	113.3 ± 9.6	< 0.001
RLI	81.2 ± 13.0	< 0.001[a]	113.4 ± 10.0	< 0.001[a]
ELI	73.8 ± 10.2	< 0.001[a]	112.3 ± 10.0	< 0.001[a]
LCI	79.5 ± 9.7	< 0.001[a]	114.0 ± 9.1	< 0.001[a]
LSI	73.9 ± 10.0	< 0.001[a]	112.7 ± 9.6	< 0.001[a]
PPVT-III-NL	86.6 ± 8.9	< 0.001[a]	110.5 ± 10.1	< 0.001[a]

CLS core language score, *RLI* receptive language index, *ELI* expressive language index, *LCI* language content index, *LSI* language structure index, *PPVT-III-NL* Peabody Picture Vocabulary Test – 3rd edition, Dutch version; *P* P value, *SD* standard deviation, *a* Wilcoxon signed ranks test / Mann-Whitney U test was used

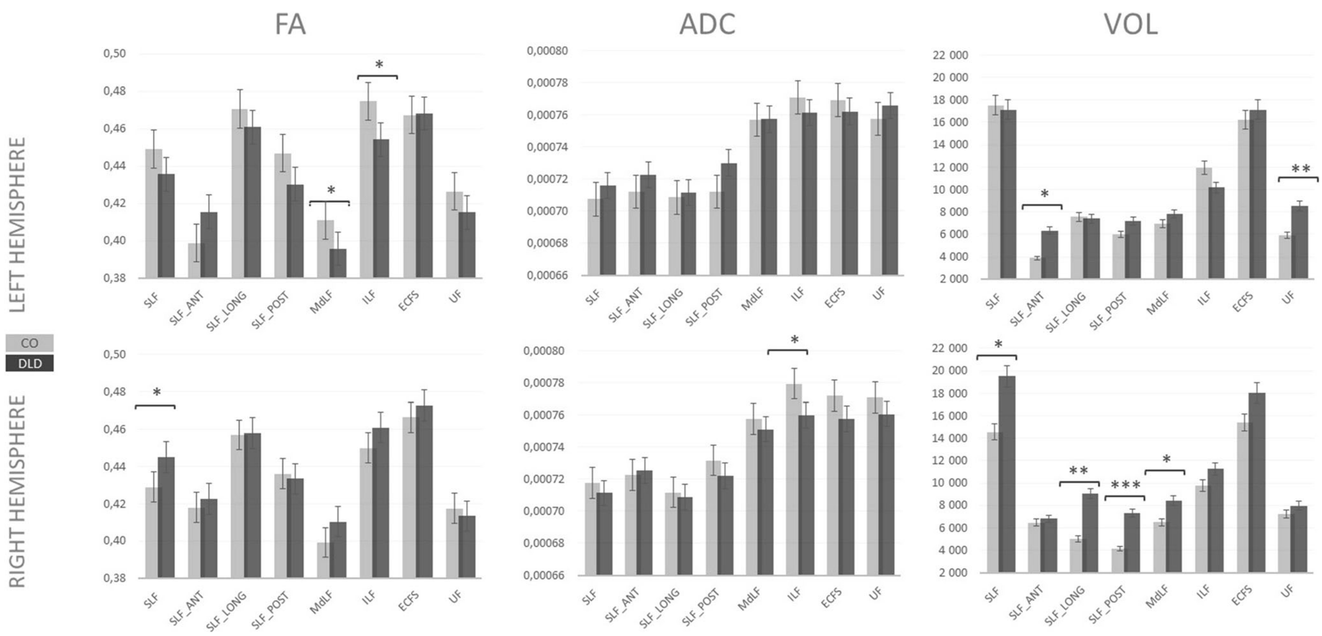

Fig. 2 Bar charts representing the between-group differences in fractional anisotropy, apparent diffusion coefficient and tract volume of the studied language related white matter tracts. The bar chart illustrates for each group and both hemispheres the standard deviation (error bars) and means of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values as well as tract volume (VOL) calculated after deterministic fiber tractography of the studied language related white matter tracts. Asterisks indicate significant between-group differences (* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$) as a result of a series of analyses of variances (ANOVA's)

patients with DLD and controls. However, assessment of the individual tracts showed several significant group differences. A higher VOL of the SLF ($P = 0.012$), MdLF ($P = 0.014$), longitudinal (P = 0.001) and posterior ($P < 0.001$) part of the SLF was detected in children with DLD compared to typically developing children. Also, lower ADC values of the ILF ($P = 0.044$) and a higher FA of the SLF ($P = 0.049$) were detected in children with DLD. Inspection of Fig. 2 demonstrates a pattern towards increased right-hemispheric FA values in patients with DLD relative to controls across the SLF, SLF_ant, MdLF, ILF and ECFS. A trend towards lower ADC values was observed in children with DLD relative to controls across the SLF, SLF_long, SLF_post and all ventral language related WM tracts. Finally, a trend towards a higher tract VOL was observed for all dorsal and ventral WM tracts in patients with DLD.

Table 3 Inter-hemispheric FA differences of the studied language related white matter tracts for children with DLD and typically developing children

Tracts	LI_{FA} CO				LI_{FA} DLD			
	Mean	SD	95% CI	P	Mean	SD	95% CI	P
SLF	0.023	0.031	0.009; 0.037	0.002*	−0.011	0.031	−0.027; 0.005	n.s.
SLF_ant	−0.026	0.038	−0.044; −0.009	0.006*	−0.011	0.031	−0.027; 0.006	n.s.
SLF_ long	0.014	0.022	0.003; 0.026	0.020*	0.006	0.031	−0.015; 0.026	n.s.
SLF_post	0.016	0.031	−0.001; 0.033	0.063	−0.003	0.048	−0.028; 0.021	n.s.
ECFS	0.001	0.016	−0.006; 0.008	n.s.	−0.005	0.019	−0.014; 0.005	n.s.
ILF	0.027	0.020	0.018; 0.036	<0.001*	−0.007	0.028	−0.022; 0.007	n.s.
MdLF	0.014	0.021	0.005; 0.024	0.005*	−0.018	0.035	−0.036; 0.000	0.047*
UF	0.010	0.016	0.003; 0.018	0.008*	0.002	0.015	−0.005; 0.010	n.s.

Overview of the results on the single t-tests to detect whether the lateralization index of the fractional anisotropy (LI_{FA}) of the studied white matter tracts differ significantly from zero, indicating FA asymmetry. Asterisks indicate significant differences from zero; SD = standard deviation; *CI* Confidence Interval, *P* P value, *SLF* superior longitudinal fascicle, *SLF-long* longitudinal SLF, *SLF-ant* anterior SLF, *SLF-post* posterior SLF, *ECFS* extreme capsule fiber system, *ILF* inferior longitudinal fascicle, *MdLF* middle longitudinal fascicle, *UF* uncinate fascicle, *n.s.* not significant

Third, the group of typically developing children showed a significant left-hemispheric lateralization of FA for all language related WM tracts, except for the posterior part of the SLF and the ECFS. A significant right-hemispheric lateralization was found for the anterior part of the SLF ($P = 0.006$). A trend has been documented suggesting a left-hemispheric lateralization for the posterior part of the SLF ($P = 0.063$). In contrast, in the group of children with DLD, none of the studied dorsal and ventral language related WM tracts showed a significant left or right lateralization pattern, except for the MdLF ($P = 0.047$; $LI = -0.018$). Results are presented in Table 3. Also, a main effect of group was found for LI_{FA} ($P < 0.001$) indicating that typically developing children have overall more positive LI_{FA} values compared to children with DLD. Assessment of the individual tracts showed significantly more positive LI_{FA} values for the SLF ($P = 0.002$), MdLF ($P = 0.001$) and ILF ($P < 0.001$) in typically developing children. Percentage histograms comparing the distribution of LI_{FA} values of the dorsal and ventral language network between DLD patients and typically developing children are presented in Figs. 3 and 4.

Correlation between DTI metrics and language

Bonferroni correction for multiple comparisons was set with the corrected P value at <0.008 (= 0.05/6) for the 6 language scores (CLS, RLI, ELI, LCI, LSI and PPVT-III-NL) included in the correlation analyses. In the DLD group, no significant correlations were found. In the typically developing group, a Bonferroni corrected correlation was found between the PPVT and FA of the right ECFS ($R = 0.581$; $P = 0.006$) and between the RLI and ADC of the right MdLF ($R = -0.624$; $P = 0.003$).

Discussion

Although advanced neuroimaging may have an expanding role in the investigation of neurodevelopmental language disorders, DTI studies of DLD are scarce and results from structural and functional imaging studies are often inconsistent. Based on a comparison with typically developing children, we studied a group of 17 children with DLD and focused on

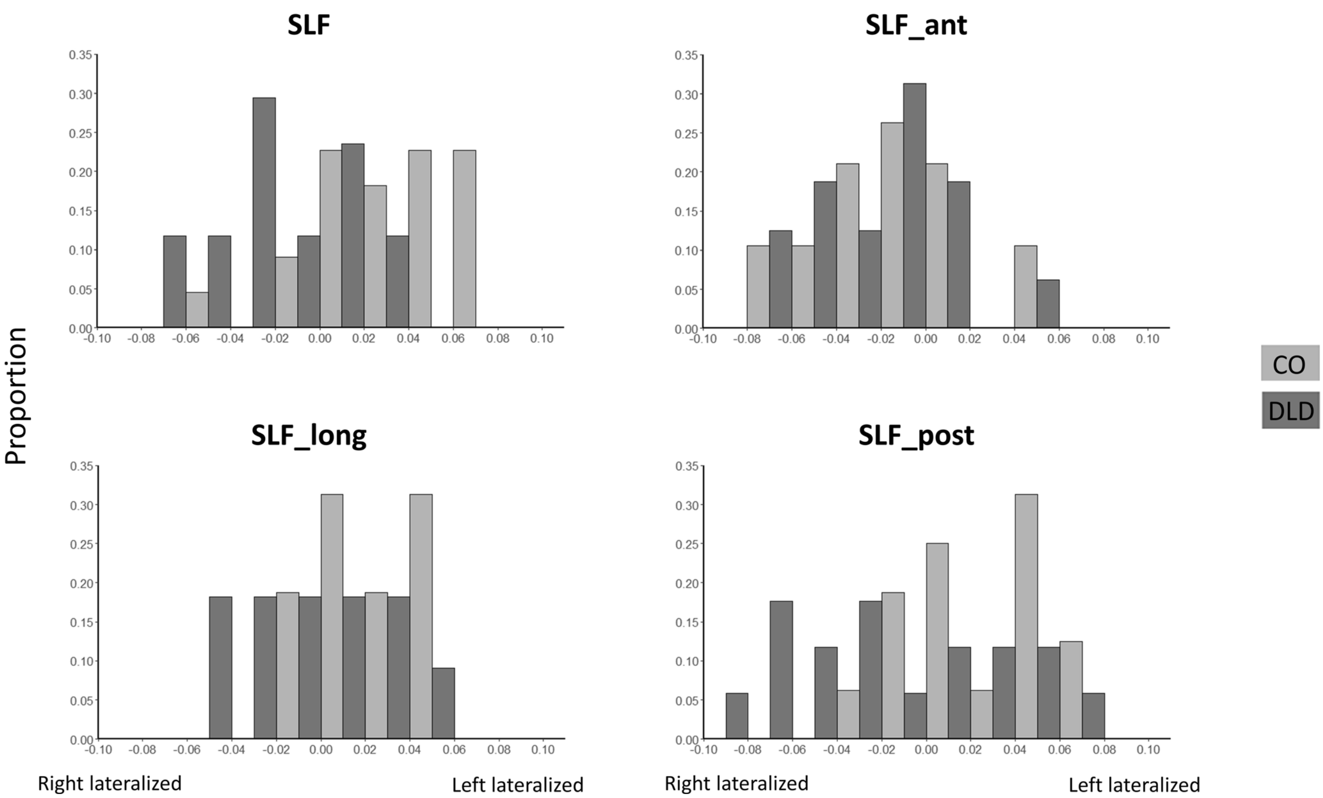

Fig. 3 Percentage histograms comparing the distribution of LI_{FA} values of the dorsal language network between DLD patients and typically developing children. Comparison of lateralization index of FA (LI_{FA}) of the dorsal language network (superior longitudinal fascicle (SLF); longitudinal SLF (SLF-long); anterior SLF (SLF-ant); posterior SLF (SLF-post)) for patients with developmental language disorder (DLD) versus age and gender matched healthy control subjects (CO). LI_{FA} values close to "0" indicate no lateralization of FA for the studied WM tract. A positive LI_{FA} indicates a relatively left lateralized WM tract, while a negative LI_{FA} reflects relative right FA lateralization

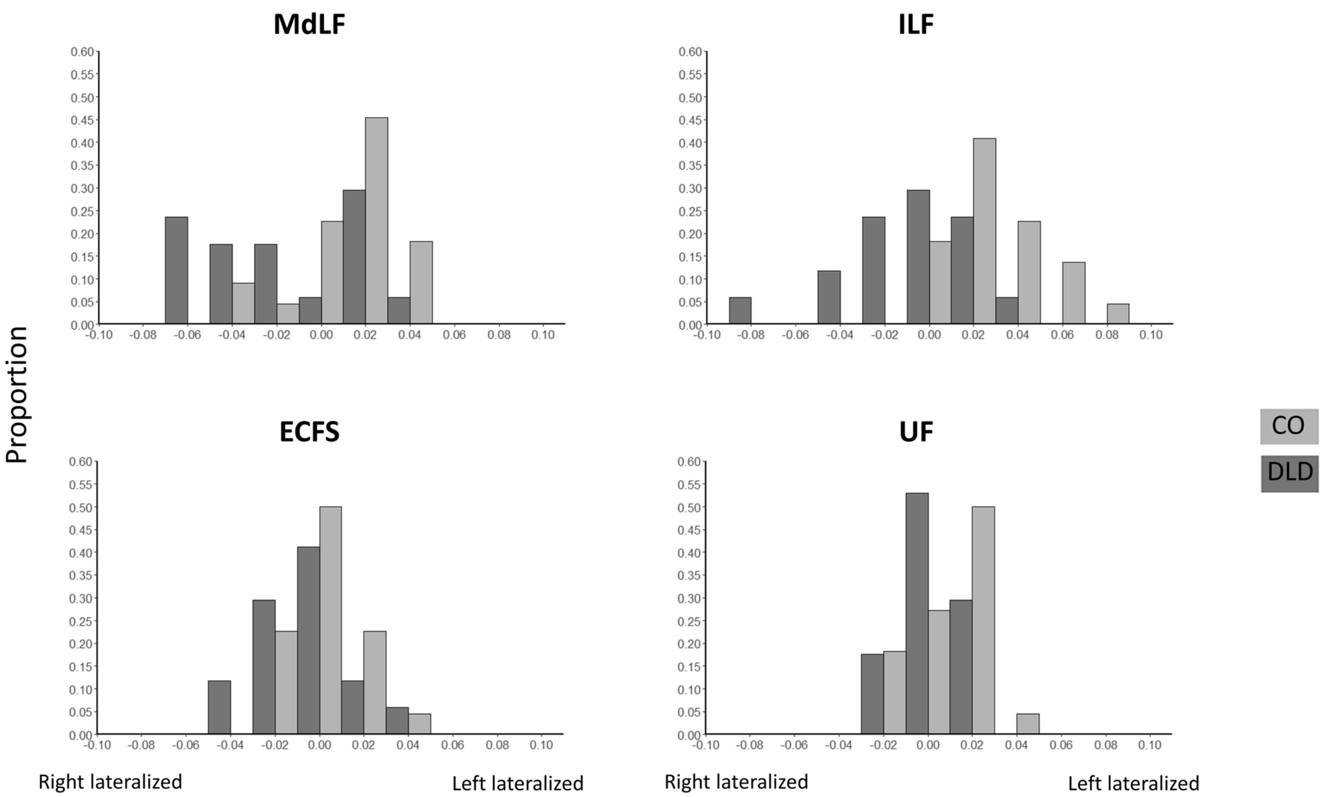

Fig. 4 Percentage histograms comparing the distribution of LI_{FA} values of the ventral language network between DLD patients and typically developing children. Comparison of lateralization index of FA (LI_{FA}) of the ventral language network (extreme capsule fiber system (ECFS); inferior longitudinal fascicle (ILF); middle longitudinal fascicle (MdLF); uncinate fascicle (UF)) for patients with developmental language disorder (DLD) versus age and gender matched healthy control subjects (CO). LI_{FA} values close to "0" indicate no lateralization of FA for the studied WM tract. A positive LI_{FA} indicates a relatively left lateralized WM tract, while a negative LI_{FA} reflects relative right FA lateralization

both dorsal and ventral language related WM tracts to find structural alterations of these WM pathways. The main alterations found to be associated with DLD included 1) an overall increased VOL and ADC values of left-hemispheric language related WM tracts relative to healthy controls and 2) a different lateralization pattern of the studied language related WM tracts.

First, diffuse alterations of the WM macro- and microstructure were found in left-hemispheric dorsal and ventral language related WM fiber tracts in children with DLD, as demonstrated by an increased VOL and increased ADC values of all investigated tracts respectively. Furthermore, a trend ($P = 0.064$) was observed towards overall lower FA values in children with DLD compared to typically developing children. These findings point towards an abnormal development of the left-hemispheric WM pathways within the ventral and dorsal language streams in children with DLD compared to their typically developing peers. Structural maturation of the brain is characterized by an increased myelination of WM fibers, which is reflected by increased FA values from infancy until adulthood (Barnea-Goraly et al. 2005; Brauer et al. 2011; Eluvathingal et al. 2007; Lebel and Beaulieu 2011; Mukherjee et al. 2002; Schmithorst et al. 2002). Increased FA values are commonly associated with decreased mean ADC values, a parameter reflecting water content and density. Previous DTI studies in patients with DLD demonstrated reduced FA values of the SLF, the main association WM tract of the dorsal language network (Verhoeven et al. 2012). Also, Roberts et al. reported elevated ADC values of the left arcuate fascicle, the longitudinal part of the SLF, in children with DLD (Roberts et al. 2014). Additionally, Vydrova was the first to investigate dorsal as well as ventral language related WM tracts (Vydrova et al. 2015). They confirmed previous findings indicating deficient connectivity of the arcuate fascicle and as a novel finding, demonstrated abnormal development of the IFOF, UF and ILF as part of the ventral system in patients with DLD. Our results are in line with previous results and add to the knowledge of the microstructural neural correlates of language dysfunction, specifically in children with DLD.

In contrast, a trend towards a higher FA of the left anterior part of the SLF and almost all right-hemispheric WM tracts (except the UF and posterior part of the SLF) was found in the studied cohort of DLD patients. This overconnectivity of the anterior part of the SLF might reflect an intra-hemispheric compensatory mechanism for structural language deficits in children with DLD. Such a left-hemispheric compensation mechanism was also found by Duffau and colleagues using functional MRI (Duffau et al. 2001). However, compensation mechanisms could also be inter-hemispheric. This activation of right-hemispheric regions is well-known after left acquired brain lesions associated with aphasia (Crinion and Leff 2007). Also, right-hemispheric compensatory activation has been commonly reported in a large variety of childhood speech and language deficits, including dyslexia (Hoeft et al. 2011) and stuttering (Kell et al. 2009; Preibisch et al. 2003) and could result from compensation of aberrant brain functioning in the left contralateral hemisphere. The results of our study support evidence for these intra- as well as inter-hemispheric compensation mechanisms in children with DLD.

Second, a more right-hemispheric lateralization pattern was found for all studied language related WM tracts in children with DLD. Our results support the hypothesis of an atypical language lateralization for developmental language disorders. Using advanced structural and functional neuroimaging techniques, a left-hemispheric dominance for language processing has been well established in humans. DTI studies in healthy adults showed a larger volume (Glasser and Rilling 2008; Parker et al. 2005; Powell et al. 2006), a higher fiber density (Vernooij et al. 2007) and a higher FA (Büchel et al. 2004; Parker et al. 2005; Powell et al. 2006) of the arcuate fascicle in the left hemisphere compared to the right one. A similar pattern of left-hemispheric language lateralization of the arcuate fascicle was demonstrated in children (Lebel and Beaulieu 2009). The results of our study correspond with those of Lebel et al. (Lebel and Beaulieu 2009) and add evidence of a clear left-lateralization of the ILF, MdLF and UF, as part of the ventral language stream, in typically developing right-handed school-aged children. However, an atypical lateralization in itself is not abnormal. Atypical functional lateralization has been reported in 5% of right-handed and up to 80% of left-handed healthy children (Szaflarski et al. 2002; Szaflarski et al. 2012). Moreover, a decreased leftward lateralization of language processing was also reported in clinical conditions including speech delay (Bernal and Altman 2003), stuttering (Brown et al. 2005), autism spectrum disorder (Kleinhans et al. 2008; Knaus et al. 2010) and dyslexia (Heim et al. 2003; Maisog et al. 2008). Our study adds to the growing body of evidence that a well-defined form of DLD affecting structural aspects of language is associated with atypical structural lateralization of core language WM tracts. It remains however to be determined whether this is a specific biomarker of typical DLD. As suggested by (Whitehouse and Bishop 2008), a common underlying mechanism might cause both the atypical cerebral lateralization and the language impairment.

A well-known issue with developmental language disorders is its clinical heterogeneity and recruitment of large homogenous cohorts of DLD patients is very challenging, even at a specialized referral centre for speech, language pathology and audiology (MUCLA). This heterogeneity may be a crucial source of inconsistent results in the current literature. Although we focused mainly on resistant structural rule-like deficits (i.e. mainly phonology and morphosyntax), the specificity of our findings requires further investigation and more precisely characterized patients in larger scale studies are needed to understand the potential clinical and pathophysiological correlates of DTI abnormalities. Future large scale studies need to investigate whether distinct subtypes of DLD are associated with distinct brain anomalies. Also DTI has limitations: DTI tractography only provides indirect indices of tissue properties and therefore uncertainty exists about the correspondence between tractography measures and underlying biological factors (number of streamlines, degree of myelination…) (Catani et al. 2007). Furthermore, partial volume effects and complex multiple fiber orientations within a single voxel detract from the accuracy of DTI based fiber tracking (Vos et al. 2011; Wedeen et al. 2008). Such challenges are being addressed by other techniques such as Q-ball and Q-space imaging, constrained spherical deconvolution which hold promise for future work (Jeurissen et al. 2011; Tournier et al. 2008). Although these recently developed techniques might provide more accurate and unambiguous results, the more complex data processing, long imaging times and strong demands on the magnetic field gradient hardware still impede practical application in a clinical setting. We are aware that DTI tractography may not reflect the functional dominance of the investigated tracts. However, our primary goal was to investigate structural abnormalities of brain development in children with DLD. Future studies using functional MRI are needed to further unravel the structure-function relationships in DLD.

Conclusion

In summary, this study demonstrates several macro- and microstructural alterations of language related WM tracts, and a lack of a left-hemispheric lateralization of the language network in the DLD group. These alterations might underlie the language impairment in children with DLD.

Acknowledgments The authors are grateful to our participants and healthy volunteers who made this research possible.

Compliance with ethical standards

Conflict of interest None.

Ethical approval This study protocol was approved by the Ethical board of the University Hospitals Leuven, Belgium.

Informed consent Parents and children were informed about the experiment; informed consent was obtained from all parents/guardians according to the Declaration of Helsinki, with additional assent from all participating children.

Abbreviations ADC, apparent diffusion coefficient; ANOVA, Analyses of variance; ASD, autism spectrum disorder; CAS, childhood apraxia of speech; CELF-4NL, Clinical Evaluation of Language Fundamentals – 4th edition, Dutch version; CFD, Concepts and Following Directions; CLS, Core Language Score; CO, control; DT, diffusion tensors; DLD, developmental language disorder; DTI, diffusion tensor imaging; ECFS, extreme capsule fiber system; ELI, Expressive Language Index; EV, Expressive Vocabulary; FA, fractional anisotropy; FS, Formulating Sentences; FOV, field-of-view; ILF, inferior longitudinal fascicle; IQ, intelligence quotient; LCI, Language Content Index; LI, laterality index; LSI, Language Structure Index; MANOVA, multivariate analyses of variance; MdLF, middle longitudinal fascicle; MRI, magnetic resonance imaging; MUCLA, Multidisciplinary University Centre for Speech, Language Pathology and Audiology; NR-B, Number Repetition Backward; NR-F, Number Repetition Forward; PA, Phonological Awareness; PPVT-III-NL, Peabody Picture Vocabulary Test – 3rd edition, Dutch version; RLI, Receptive Language Index; ROI, region of interest; RS, Recalling Sentences; SA, Sentence Assembly; SD, standard deviation; SC, Sentence Comprehension; SR, Semantic Relationships; SLF, superior longitudinal fascicle; T, Tesla; TR, repetition time; TE, echo time; UF, uncinate fascicle; USP, Understanding Spoken Paragraphs; VOL, volume; WA, Word Associations; WC-E, Word Classes-Expressive; WC-R, Word Classes-Receptive; WD, Word Definitions; WM, white matter; WS, Word Structure

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