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Altered hemispheric lateralization of white matter pathways in developmental dyslexia: Evidence from spherical deconvolution tractography

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ABSTRACT

This study examines the structural integrity and the hemispheric lateralization patterns of four major association fiber pathways in a group of French dyslexic children and age-matched controls (from 9 to 14 years), using high angular diffusion imaging combined with spherical deconvolution tractography. Compared with age-matched controls, dyslexic children show increased hindrance-modulated oriented anisotropy (HMOA) in the right superior longitudinal fasciculus (SLF). They also show a reduced leftward asymmetry of the inferior fronto-occipital fasciculus (IFOF) and an increased rightward asymmetry of the second branch of the SLF (SLF II). The lateralization pattern of IFOF and SLF II also accounts for individual differences in dyslexic children's reading abilities. These data provide evidence for an abnormal lateralization of occipito-frontal and parieto-frontal pathways in developmental dyslexia.

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1. Introduction

Developmental dyslexia is a learning disability affecting the acquisition of fluent reading skills despite normal intelligence and schooling (Lyon, Shaywitz, & Shaywitz, 2003), with prevalence estimated around 3–7% of the population (Lindgren, Derenzi, & Richman, 1985). It is increasingly acknowledged to be a genetically influenced disorder with a neurological basis, which in turn engenders cognitive deficits affecting reading acquisition (Butterworth & Kovas, 2013; Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012). Nevertheless, a full understanding of the pathophysiology of developmental dyslexia and of its links with cognitive deficits and possible genetic factors remains an important challenge (Giraud & Ramus, 2013).

Developmental dyslexia is often characterized as a disconnection syndrome, implicating weaker functional connections between reading-related cortical regions, notably left inferior frontal cortex, ventral occipito-temporal cortex and the temporo-parietal junction (Boets et al., 2013; Horwitz, Rumsey, & Donohue, 1998; Paulesu et al., 1996; Pugh et al., 2000). A recent meta-analysis of PET and fMRI activation studies of dyslexia has further suggested that dyslexia might be related to multiple dysfunctional systems in the left hemisphere reflected by i) reduced involvement in distributed left hemispheric regions across inferior frontal, premotor, supramarginal and occipito-temporal cortices, which might be associated with reading and the visual-to-phonology processes, and ii) less engagement in a more dorsal fronto-parietal network (left parietal and premotor cortices), which could be associated with motor or visuo-spatial perception/attention (Paulesu, Danelli, & Berlingeri, 2014). These results are partly supported by diffusion tensor imaging (DTI) studies showing reduced white matter connectivity in some portions of temporo-parietal and frontal white matter pathways (Deutsch et al., 2005; Klingberg et al., 2000; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010; Vandermosten, Boets, Poelmans, et al., 2012; for a review see Vandermosten, Boets, Wouters, & Ghesquiere, 2012).

However, standard DTI models used in previous studies showed limitations in fiber-crossing regions, spuriously yielding reduced fractional anisotropy (FA) where highly directional fibers may cross, and leading tractography algorithms astray (Vanderauwera, Vandermosten, Dell'Acqua, Wouters, & Ghesquière, 2015; Wandell & Yeatman, 2013). For instance, it is not clear whether reduced FA reported in dyslexic individuals in the fronto-parietal region reflects a reduced connectivity or myelination, or an increase of fiber orientations, as several bundles cross in that region. Another limitation of standard tractography algorithms is that they typically do not allow distinguishing between neighboring tracts such as the arcuate and the superior longitudinal fasciculi. Thus previous studies on dyslexia have attributed some FA differences to the arcuate fasciculus (AF), sometimes solely on the basis of probabilistic atlases (Carter et al., 2009; Deutsch et al., 2005; Klingberg et al., 2000; Niogi and McCandliss, 2006; Odegard, Farris, Ring, McColl, & Black, 2009; Steinbrink et al., 2008), sometimes on the basis of an actual reconstruction of the AF (Saygin et al., 2013; Vandermosten, Boets, Poelmans, et al., 2012; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012, Yeatman et al., 2011), but without concurrent consideration of the superior longitudinal fasciculus (SLF). This is important as these pathways connect different cerebral regions and their involvement in dyslexia may have different interpretations.

Developmental dyslexia has also been associated with atypical cerebral asymmetry, as suggested by clinical studies (Orton, 1937; Witelson, 1977), functional imaging (Lehongre, Morillon, Giraud, & Ramus, 2013; Lehongre, Ramus, Villiermet, Schwartz, & Giraud, 2011; Richlan, Kronbichler, & Wimmer, 2011) and anatomical dissection and imaging of specific cortical regions (Altarelli et al., 2014; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985). Plausibly, a deviant hemispheric lateralization of cortical regions should be associated with similarly deviant lateralization of white matter pathways. Surprisingly, this hypothesis has only been tested for the AF in dyslexic adults (Vandermosten, Poelmans, Sunaert, Ghesquiere, & Wouters, 2013). Whether other white matter pathways such as the ventral pathways [i.e., the inferior fronto-occipital fasciculus (IFOF) and the inferior longitudinal fasciculus (ILF)] that are shown to be relevant to reading skills (e.g., Vandermosten, Boets, Poelmans, et al., 2012; Yeatman et al., 2012) also involve abnormal asymmetric patterns in dyslexia requires further testing.

In the present study, we attempt to systematically investigate the connectivity and lateralization patterns of major pathways related to reading and dyslexia (the arcuate fasciculus: AF, the superior longitudinal fasciculus: SLF, the inferior fronto-occipital fasciculus: IFOF and the inferior longitudinal fasciculus: ILF) (Rimrodt et al., 2010; Saygin et al., 2013; Vandermosten, Boets, Wouters, et al., 2012; Yeatman et al., 2011; Yeatman et al., 2012), by using optimized diffusion sequence parameters and tractography algorithms that overcome the limitations of standard DTI. Our goals were twofold: i) to evaluate whether the group differences that were found between dyslexic and normal readers in white matter pathways using standard DTI algorithms can be replicated with advanced tractography methods, and ii) to further examine whether dyslexic children show any deviation of hemispheric lateralization patterns compared with their age-matched controls.

2. Materials and methods

2.1. Participants

Thirty-two dyslexic and 32 typically developing children participated in this study. Children's age ranged from 109 to 169 months (9–14 years). All children were native French speakers with normal vision and hearing abilities. Dyslexic children were referred by a clinic for reading and language disabilities. No child was diagnosed with a history of brain damage, psychiatric, or any other cognitive disorder. For inclusion, dyslexic children had to present a delay greater than 18 months on text reading age [based on accuracy and speed of the Alouette test (Lefavrais, 1967)] while control children had to be no more than 12 months behind. Two dyslexic children were removed from the tractography analysis due to

Table 1 – Demographical data, behavioral scores, and brain measurements.

	Control children		Dyslexic children		Test statistics
	N	Mean (SD)	N	Mean (SD)	
Subject characteristics					
Gender (male/female)	31	18/13	26	13/13	χ^2 (1) = .371, p = .543
Handedness (left/right)	31	2/29	26	3/23	χ^2 (1) = .457, p = .499
Age (months)	31	137.90 (16.33)	26	139.27 (15.77)	t (55) = −.320, p = .751
Maternal education	31	2.65 (1.38)	26	3.08 (1.80)	t (55) = −1.029, p = .308
Paternal education	31	2.52 (1.61)	26	3.62 (1.92)	t (55) = −2.352, p = .022
Non-verbal IQ	31	110.29 (17.09)	26	106.00 (15.69)	t (55) = .980, p = .332
Verbal IQ	31	123.84 (18.70)	26	107.88 (18.22)	t (55) = 3.246, p = .002
Reading age (months)	31	145.94 (18.65)	26	87.27 (11.43)	t (55) = 13.979, p < .0001
Behavioral tests					
Word reading accuracy (/20)	31	18.65 (1.64)	25	10.52 (4.33)	t (54) = 9.650, p < .0001
Word reading time (sec)	31	15.30 (4.00)	25	65.68 (39.45)	t (54) = −7.082, p < .0001
Pseudoword reading accuracy (/20)	31	17.45 (1.73)	25	11.36 (3.37)	t (54) = 8.759, p < .0001
Pseudoword reading time (sec)	31	22.00 (5.37)	25	57.80 (34.81)	t (54) = −5.656, p < .0001
Text reading accuracy (%)	31	96.41 (2.02)	24	77.81 (17.78)	t (53) = 5.791, p < .0001
Text reading speed (nb of correct words/3 min)	31	397.88 (67.52)	24	112.73 (80.55)	t (53) = 14.277, p < .0001
Spelling (%)	31	82.75 (13.77)	26	37.94 (20.18)	t (55) = 9.922, p < .0001
RAN digits (sec)	31	21.33 (3.19)	26	32.60 (7.62)	t (55) = −7.493, p < .0001
RAN objects (sec)	31	35.86 (6.92)	26	51.23 (9.52)	t (55) = −7.043, p < .0001
Phoneme deletion (/24)	31	22.97 (1.38)	26	17.89 (4.77)	t (55) = 5.667, p < .0001
Spoonerism (/12)	31	7.83 (2.56)	24	2.29 (2.73)	t (52) = 7.679, p < .0001
Digit span (WISC scaled score)	31	10.87 (2.68)	26	6.58 (2.18)	t (55) = 6.554, p < .0001
Brain measurements					
Whole-brain HMOA	31	.1057 (.004)	26	.1056 (.005)	t (55) = .051, p = .959
Head motion parameter	31	4.2392 (1.378)	26	4.9358 (2.413)	t (55) = −1.365, p = .178

incorrect scanning parameters during data collection. One dyslexic child and one control child were also removed due to incomplete diffusion data. Three dyslexic children with overall WISC nonverbal IQ standard scores lower than 80 were not included into the statistical analysis (Wechsler, 2005). For the remaining 26 dyslexic and 31 control children, age, sex, handedness, and nonverbal IQ were matched (see subject characteristics in Table 1). The study was approved by the ethics committee of Bicêtre Hospital and informed consent was obtained from all children and their parents. Analyses of grey matter volume, cortical thickness and planum temporale asymmetry of an overlapping set of participants have been published previously (Altarelli et al., 2013, 2014; Jednoróg et al., 2015). Control participants were also included in a previous analysis of the effects of socioeconomic status on brain anatomy (Jednorog et al., 2012).

2.2. *Behavioral measures*

A battery of behavioral tests was administered to determine participants' intellectual, verbal and reading abilities. Children's intellectual abilities were estimated using the WISC blocks, matrices, similarities and comprehension subtests (Wechsler, 2005). Reading ability was estimated by the Alouette test (Lefavrais, 1967), a meaningless text that assesses both reading accuracy and speed, and by a word and nonword reading fluency test Odedys (Jacquier-Roux, Valdois, & Zorman, 2005). Orthographic skill was assessed by a word spelling-to-dictation test (Martinet & Valdois, 1999). Phonological skills were tested by a phoneme deletion task (Sprenger-Charolles, Béchennec, Colé, & Kipffer-Piquard, 2005), a spoonerism test (Bosse & Valdois, 2009), the WISC digit span subtest assessing verbal working memory (Wechsler, 2005), and rapid automatized naming (RAN) tasks for digits and objects (Plaza & Robert-Jahier, 2006). Parental education was recorded as the highest diploma obtained, coded on a 1–6 scale.[1] Handedness was based on children's writing hand. Behavioral data are shown in Table 1.

For the purpose of correlation analyses with brain measures, we defined five composite measures by averaging z-scores as follows: reading accuracy (READACC) was computed from word, pseudoword, and text reading accuracy; reading fluency (READFUL) from word and pseudoword reading time and text reading speed; RAN from digit and object RAN; phonological processing abilities (PHONO) from phoneme deletion, spoonerisms, and digit span; spelling (SPELL) simply was the z-score of the word spelling test. Signs were adjusted such that positive z-scores represented above-average performance. An alternative, data-driven approach using principal component analysis is reported in Supplement S1.1.

2.3. *Image acquisition and tractography analysis*

All children underwent an MRI exam in a 3T MRI system (Tim Trio, Siemens Medical Systems, Erlangen, Germany), equipped with a whole body gradient (40 m T/m, 200 T/m/sec) and a 32-channel head coil. A diffusion-weighted (DW) spin-echo single-shot EPI sequence was used, with parallel imaging (GRAPPA reduction factor 2), partial Fourier sampling (factor 6/8) and bipolar diffusion gradients to reduce geometric

[1] From 1: postgraduate diploma to 6: neither high school diploma nor professional certificate. This is the official scale from the French national statistics agency (INSEE).

distortions. The whole brain was imaged with an isotropic spatial resolution of 1.7 mm^3 (matrix size = 128 × 128, field of view = 218 mm), and 70 interleaved axial slices. Diffusion gradients were applied along 60 orientations, uniformly distributed, with a diffusion weighting of b = 1400 sec/mm^2 (repetition time = 14,000 msec, echo time = 91 msec). In order to make this protocol tolerable for children, three optimal subsequences were acquired with 20, 21, and 19 DW volumes (Dubois, Poupon, Lethimonnier, & Le Bihan, 2006), in which gradient orientations were as uniformly distributed as possible in space. Additionally three images were acquired with no diffusion gradient applied (b = 0). Each sequence took about 6 min, resulting in a total acquisition time of 18 min.

Raw DW data from the three sequences were first concatenated into a single data file. The images were then simultaneously registered and corrected for subject motion and geometrical distortions using ExploreDTI (http://www.exploredti.com, see Leemans & Jones, 2009). Multiple orientations in voxels containing different populations of crossing fibers were estimated using a damped Richardson-Lucy algorithm for spherical deconvolution (SD) (Dell'Acqua et al., 2010). Algorithm parameters were chosen following Thiebaut de Schotten et al. (2011).

Whole brain tractography was performed by selecting every brain voxel with at least one fiber orientation as a seed voxel. From these voxels, and for each fiber orientation, streamlines were propagated using Euler integration with a step size of 1 mm (as described in Dell'Acqua, Simmons, Williams, & Catani, 2013). When entering a region with crossing white matter bundles, the algorithm followed the orientation vector of least curvature (as described in Schmahmann et al., 2007). Streamlines were halted when a voxel without fiber orientation was reached or when the curvature between two steps exceeded a threshold of 60°. Spherical deconvolution, fiber orientation vector estimations and tractography were performed using in-house software developed with MATLAB v7.8 (The Mathworks, Natick, MA).

For each participant, tract dissections were performed in the native space using TrackVis (http://www.trackvis.org, see Wedeen et al., 2008), which allows for the identification of the tracts, visualization in 3 dimensions, and quantitative analyses on each tract. A region-of-interest (ROI) approach was used to extract the tracts of interest, and the protocol for defining the ROIs for each fiber tract was based on previous tractography studies: IFOF (Catani & Thiebaut de Schotten, 2008), ILF (Catani & Thiebaut de Schotten, 2008), the three segments of SLF (SLF I: dorsal, SLF II: middle, SLF III: ventral; Thiebaut de Schotten et al., 2011), and the three segments of AF (long fronto-temporal, posterior temporo-parietal, and anterior fronto-parietal segments; Catani, Jones, & ffytche, 2005). Note that the anterior fronto-parietal segment of the AF represents a subportion of the SLF III restricted to language areas.

In order to automate some steps of tract dissection and limit inter-subject variability related to the operator expertise, ROIs were defined on the MNI152 template provided with the FMRIB Software Library package (FSL, http://www.fmrib.ox.ac.uk/fsl/). For each subject, a contrast map for white matter similar to FA but independent from fiber crossing, named a convergence map (CS maps; Dell'Acqua et al., 2006), was calculated using the Richardson-Lucy Spherical Deconvolution Algorithm. The convergence map of each subject then was registered to the MNI152 template using Advanced Normalization Tools (ANTs, http://www.picsl.upenn.edu/ANTS/), which combine affine with diffeomorphic deformations (Avants, Epstein, Grossman, & Gee, 2008; Klein et al., 2009). The inverse deformation was then applied to the ROIs defined on the MNI152 template in order to bring them to the native space of every participant.

Individual dissections of the tracts were then visually inspected in each participant's native brain space and corrected by two anatomists (JZ and MTS). Hindrance-modulated oriented anisotropy (i.e., HMOA; Dell'Acqua et al., 2013) was extracted for each dissected pathway and was used as a compact measure of fiber density and connectivity characterizing the diffusion properties along each tract orientation. HMOA has the advantage of being specific to the orientation of each tract, hence more accurate than DTI fractional anisotropy (FA), which decreases where fibers cross due to local partial volume effect (Dell'Acqua et al., 2013; Dubois et al., 2014). HMOA averaged across each entire tract was taken as the main variable of interest. A mean whole-brain HMOA measure was also extracted for each participant, to be used as a covariate in order to distinguish tract-specific from more global inter-individual differences in HMOA, related for instance to children's age.

2.4. Statistical analysis

Statistical analysis was performed using SPSS software (SPSS 18, Chicago, IL). Group differences in subject characteristics and behavioral measures were tested through independent-sample t-tests or chi-square tests. Regarding the microstructure of white matter pathways, general linear models with repeated measures were run separately for IFOF, ILF, SLF, and AF, with the mean HMOA measure of each pathway as dependent variable, group (dyslexic *vs* control) and sex (male *vs* female) as between-subject variables, and hemisphere (left *vs* right) as a within-subject variable. For the AF and the SLF, segment was also entered into the model as a second within-subject variable, since each of them includes three different segments. Age, parental education, whole-brain HMOA, and head motion parameter[2] were entered into the model as covariates.[3] Results were corrected for multiple comparisons

[2] The absolute values of z scores of six head motion parameters (3 directions of translations and 3 directions of rotations) were averaged to obtain a composite score for head motion parameter.

[3] Age, sex and socioeconomic status (SES) have been shown to affect multiple brain measures (e.g., Jednorog et al., 2012; Lenroot et al., 2007; Wallace et al., 2006), so we consider it a safe approach to systematically include them as covariates in all analyses, even if they do not differ between groups. Similarly, given that individuals vary in global brain measures, and that local brain measures are correlated with global measures of the same nature, we follow the general approach of always including the corresponding global measure (here, whole-brain HMOA) as a covariate in the analysis of local measures (here, individual tract HMOA), in order to avoid confusing local with global effects (Altarelli et al., 2013; Jednorog et al., 2012). Head motion parameter has been shown to significantly influence group effects and may produce spurious group differences (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2013), so we also included it as a covariate into our models.

of tracts using the False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995). Significant interactions involving group were further investigated by separate between-subject analyses for each region (hemisphere or segment) FDR-corrected for multiple testing of hemisphere or segment, with the same between-subject factors and covariates. In the Results section, we therefore report uncorrected *p*-values and we compare them to the FDR-corrected alpha threshold, noted q^*. An additional, more global multivariate analysis is reported in Supplement S2.

Lateralization differences indicated in the previous analysis by group by hemisphere interactions were further confirmed by analyses of the HMOA lateralization index [HMOA LI = (right HMOA − left HMOA)/(right HMOA + left HMOA); A negative LI score indicates that HMOA of the tract is left lateralized while a positive LI score reflects right HMOA lateralization and LI value close to zero means no lateralization]. Regarding group differences in HMOA LIs, general linear models were employed with HMOA LI as dependent variable, group (dyslexic *vs* control) and sex (male *vs* female) as between-subject variables, and age, parental education, and head motion parameter as covariates. Lateralization patterns of HMOA LIs in each group were examined using one-sample *t*-tests comparing HMOA LI with zero for controls and dyslexics separately. When such lateralization differences were evident, tests of within-group partial Pearson correlations between the LIs and behavioral measures (READACC, READFUL, RAN, PHONO, and SPELL) were then conducted within patient and control groups separately, controlling for sex, age, parental education, and head motion parameter. Results were FDR-corrected for multiple tests. Significant results relevant to lateralization were confirmed after excluding left-handed children. Since some behavioral measures were not normally distributed (Supplementary Table S6), results reported as significant with Pearson correlations were confirmed using the nonparametric Spearman rank correlation coefficient with same covariates as partial Pearson correlations (Spearman, 1904). To account for possible effects from outliers, skipped-correlations with multiple comparison correction were further conducted using an open source Matlab toolbox (Pernet, Wilcox, & Rousselet, 2013). An additional correlation analysis between LIs and components from principal component analysis is reported in Supplement S1.2.

3. Results

3.1. Demographics and behavioral results

Descriptive statistics for demographics and behavioral measures for the two groups are shown in Table 1. There was no group difference for age, sex, handedness, and non-verbal IQ. The two groups were also matched in maternal educational level. However, dyslexic children had higher paternal educational level than control children. As expected, dyslexic children performed worse than controls on all measures of literacy and phonological skills, as well as on verbal IQ.

3.2. Group differences in white matter pathways

Whole-brain HMOA and head motion parameter did not show any difference between the two groups, as shown in Table 1. Examples of the left hemisphere pathways in one representative participant are illustrated in Fig. 1. Fig. 1 also presents mean HMOA and the lateralization index (LI) of HMOA for each of the investigated pathways and their sub-segments in both groups.

Statistical analyses revealed an effect of hemisphere by group interaction [$F_{(1, 49)} = 5.950$, $p = .018 <$ FDR-corrected $q^* = .025$, $\eta_p^2 = .108$] in IFOF. A trend toward higher HMOA on the right hemisphere in dyslexic children than the controls [$F_{(1, 49)} = 4.012$, $p = .051$, Cohen's d = .5446] was found. A hemisphere by group interaction effect across the entire SLF was also detected [$F_{(1, 49)} = 6.211$, $p = .016 <$ FDR-corrected $q^* = .025$, $\eta_p^2 = .113$]. Although the triple hemisphere by segment by group interaction was not significant, examination of each segment suggests that this effect is driven by SLF II [$F_{(1, 49)} = 6.816$, $p = .012 <$ FDR-corrected $q^* = .017$, $\eta_p^2 = .122$]. We will therefore focus on SLF II for lateralization analyses. Follow-up within-hemisphere analyses revealed a significant group effect for the right SLF as a whole with dyslexic children having a higher HMOA than controls [$F_{(1, 49)} = 7.241$, $p = .010 <$ FDR-corrected $q^* = .025$, Cohen's d = .7316]. Further statistical analyses for group differences in LIs of IFOF and SLF II confirmed hemisphere by group interaction effects and showed that the dyslexic group was significantly less left-lateralized than the control group in IFOF [$F_{(1, 50)} = 5.706$, $p = .042$, Cohen's d = .6364; LI of dyslexics: $t = -1.778$, $p = .088$; LI of controls: $t = -5.837$, $p < .0001$] and significantly more right-lateralized than the control group in SLF II [$F_{(1, 50)} = 6.464$, $p = .014$, Cohen's d = .6748; LI of dyslexics: $t = 3.426$, $p = .002$; LI of controls: $t = -.722$, $p = .476$]. No other significant results for group effects or interaction effects between group and other variables were found. Details for non-significant group effects and group by hemisphere interaction effects of each pathway and all post-hoc analyses as well as lateralization tests may be found in Supplementary Tables S7, Table S8 and Table S9.

3.3. Correlations between lateralization of white matter pathways and behavioral measures

Following the observation of hemisphere by group interactions in IFOF and SLF II, confirmed by group differences in the lateralization index (LI), we further tested correlations between the LIs of these two tracts and five behavioral measures, separately for each group. Partial Pearson correlation tests showed that correlations hold mainly within the dyslexic group (Table 2). In the dyslexic group, two correlations survived FDR-correction ($p <$ FDR-corrected $q^* = .005$): the more right-lateralized the IFOF, the worse the reading accuracy ($r = -.599$, $p = .0016$, $R^2 = .3585$) and spelling accuracy ($r = -.586$, $p = .0017$, $R^2 = .3435$). Similarly a trend toward a correlation between the LI of SLF II and reading accuracy ($r = -.363$, $p = .0744$, $R^2 = .1318$) was observed in the dyslexic group. The correlations emerging in the control group were negative trends between the LI of SLF II and spelling accuracy ($r = -.386$, $p = .0319$, $R^2 = .1491$) as well as reading accuracy ($r = -.311$, $p = .0884$, $R^2 = .0967$). However, no correlation

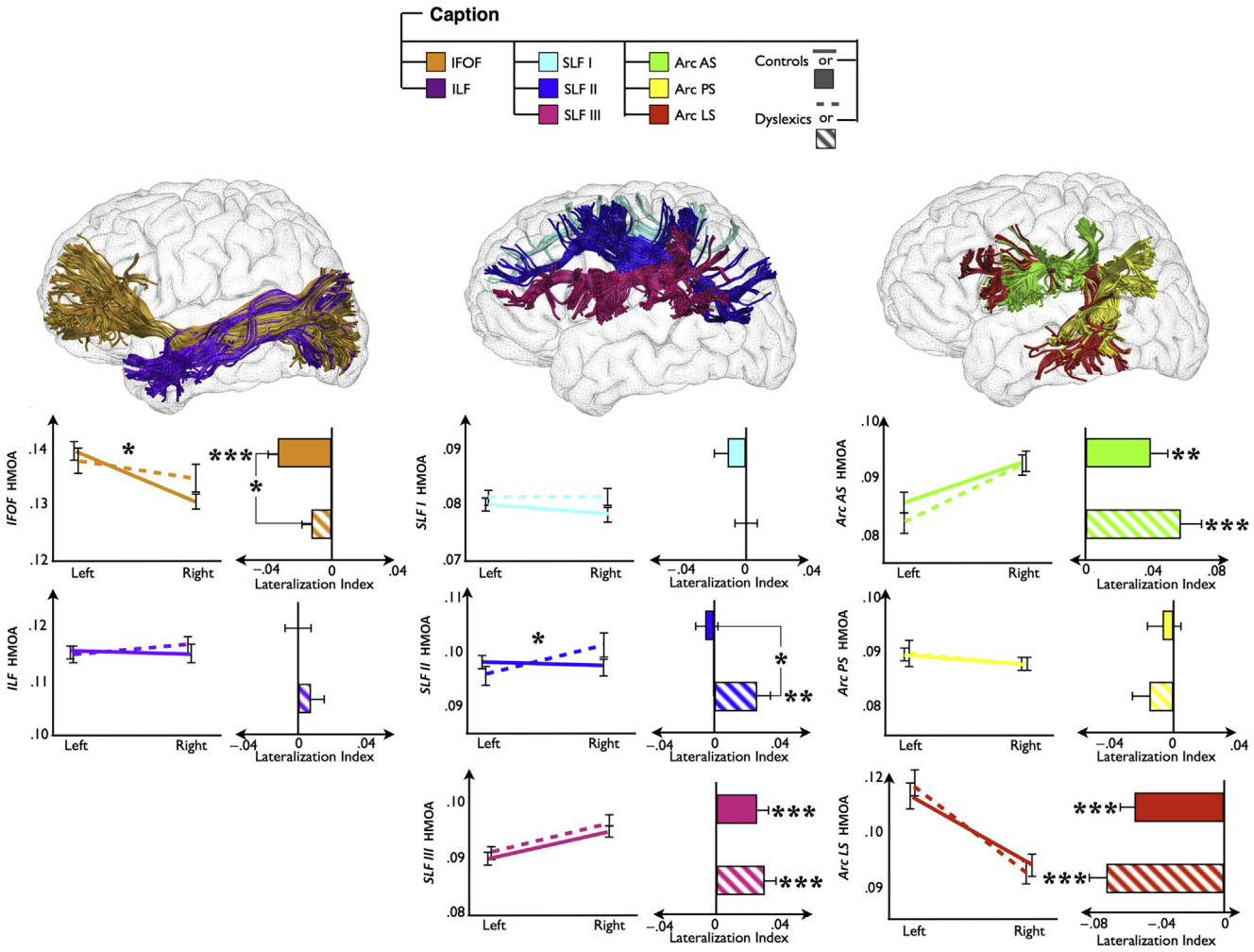

Fig. 1 – Illustration of association fiber tracts of interest: the inferior fronto-occipital fasciculus (IFOF), the inferior longitudinal fasciculus (ILF), the three segments of the superior longitudinal fasciculus (SLF I, SLF II, SLF III), and the three segments of the arcuate fasciculus (Arc AS, Arc PS, and Arc LS) from a single representative participant (upper panel). Average measurements of raw mean hindrance-modulated oriented anisotropy (HMOA) and lateralization index [LI = (right−left)/(right + left)] of HMOA for each of the investigated fiber tracts in dyslexic and control groups (lower panel). A negative LI score indicates that HMOA of the tract is left lateralized while a positive LI score reflects right HMOA lateralization and LI value close to zero means no lateralization. $^{***}p < .0005$; $^{**}p < .005$; $^{*}p < .05$.

regarding the SLF II survived FDR-correction. Fig. 2 displays the individual scatter plots for the Pearson correlations between residuals of the LI values for IFOF and SLF II and residuals of the five behavioral measures after controlling for sex, age, parental education, and head motion parameter. Correlation coefficients for Spearman rank correlation and skipped-correlation may be found in Supplementary Table S10 and Table S11.

4. Validation analysis

Given that spherical deconvolution tractography is relatively new and has not been used before in dyslexia research, we have conducted a number of additional analyses to assess the robustness of the method.

4.1. *Statistical analysis after removing five left-handed subjects*

Significant effects and trends of IFOF and SLF were further confirmed by removing the five subjects who were left-handed in order to eliminate possible confounded effects from left-handedness. All the results remained the same, with even lower p values in most cases (see Supplementary S3). The trend toward a group difference in HMOA of the right IFOF became fully significant: $F_{(1,\ 44)} = 9.988$, $p = .003 <$ FDR-corrected $q^* = .025$, $\eta_p^2 = .185$.

4.2. *Volume lateralization analysis for SLF*

For the purpose of comparing with the previous study using SD tractography to dissect the SLF (in normal adults; Thiebaut de Schotten et al., 2011), we measured the volume of SLF I, II,

Table 2 – Pearson partial correlation coefficients (controlled for gender, age, parental education, and head motion parameter) between behavioral measures (reading accuracy (READACC), reading fluency (READFLU), spelling (SPELL), rapid automatic naming (RAN), and phonological processing abilities (PHONO)) and lateralization index (LI) of inferior fronto-occipital fasciculus (IFOF) and superior longitudinal fasciculus (SLF) II. $^{**}p < .005$ (surviving FDR correction); $^{*}p < .05$; $^{\#}p < .10$.

		READACC	READFLU	SPELL	RAN	PHONO
IFOF_LI	Dyslexia	**$r = -.599^{**}$**	$r = -.157$	**$r = -.586^{**}$**	$r = -.303$	$r = -.278$
		$p = .0016$	$p = .4529$	$p = .0017$	$p = .1328$	$p = .1691$
	Control	$r = .022$	$r = .062$	$r = -.143$	$r = .069$	$r = -.019$
		$p = .9048$	$p = .7388$	$p = .4443$	$p = .7126$	$p = .9178$
SLF II_LI	Dyslexia	**$r = -.363^{\#}$**	$r = .140$	$r = -.242$	$r = -.116$	$r = -.080$
		$p = .0744$	$p = .5061$	$p = .2338$	$p = .5732$	$p = .6963$
	Control	**$r = -.311^{\#}$**	$r = -.022$	**$r = -.386^{*}$**	$r = .172$	$r = -.140$
		$p = .0884$	$p = .9057$	$p = .0319$	$p = .3557$	$p = .4512$

Correlations with p < .10 are marked with bold.

and III and computed the volume lateralization index [volume LI = (right volume – left volume)/(right volume + left volume). We found that the SLF III was strongly right lateralized in both control children and dyslexic children (controls: LI = .38 ± .136, $t = 15.420$, $p < .0001$; dyslexics: LI = .31 ± .148, $t = 10.698$, $p < .0001$), whereas the SLF I and SLF II were not (SLF I controls: LI = −.028 ± .146, $t = -1.074$, $p = .291$; dyslexics: LI = −.036 ± .119, $t = -1.555$, $p = .133$; SLF II controls: LI = .009 ± .17, $t = .300$, $p > .5$; dyslexics: LI = −.013 ± .11, $t = -.572$, $p > .5$). The volume lateralization results for the SLF in our children sample are thus consistent with the report by Thiebaut de Schotten et al. (2011) in an adult population. No difference was found between control and dyslexic children in volume lateralization index for any segment of the SLF.

4.3. *FA analysis for AF with standard DTI models*

The absence of group differences in the left AF from the HMOA analysis is unexpected, given that several earlier studies have suggested it is disrupted in dyslexia, using both voxel-based approaches (Deutsch et al., 2005; Klingberg et al., 2000) and tractography (Rimrodt et al., 2010; Vandermosten, Boets, Poelmans, et al., 2012). Yet, Vanderauwera et al. (2015) previously reported inconsistencies between HMOA and FA measures in a group of young children. To test whether our sample of dyslexic children had lower FA values compared with age-matched controls in AF, we performed tractography analysis and computed FA using standard DTI models offered by ExploreDTI. Tractography parameters were chosen following Thiebaut de Schotten, Cohen, Amemiya, Braga, and Dehaene (2014). The whole-brain tractography was imported to TrackVis using home-made software written in Matlab. The same ROIs defined in the HMOA analysis were used to delineate the three segments of the AF in TrackVis. The mean FA value for each segment of the AF was then computed for each hemisphere. For 15 participants, the AF could not be reliably reconstructed (eight in the right long segment, four in the left anterior segment, two in the left posterior segment, and one in

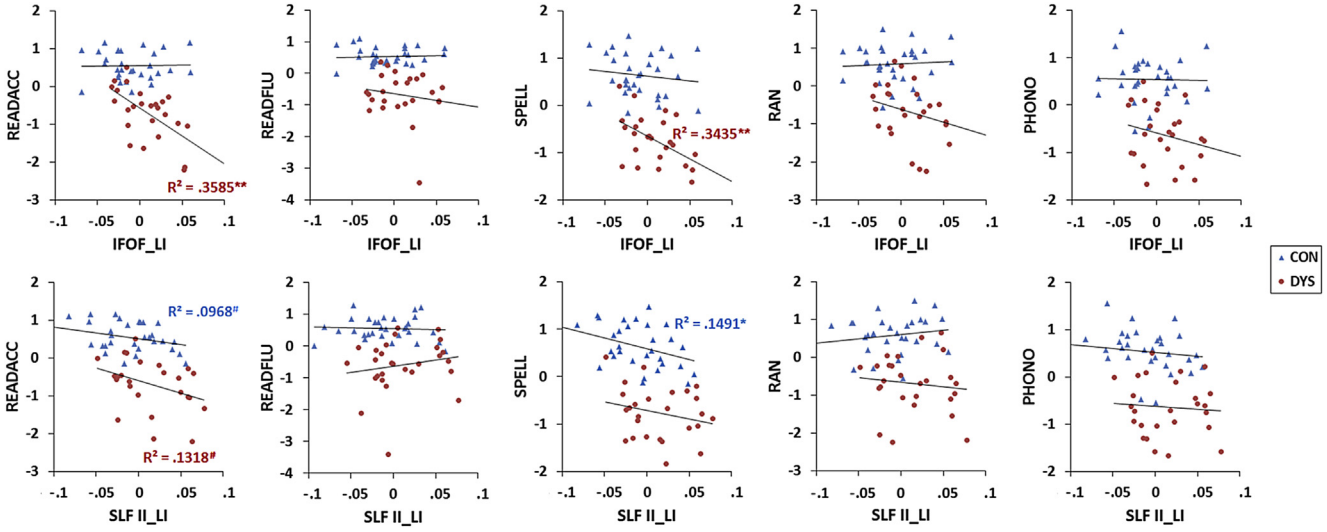

Fig. 2 – Individual scatter plots for the correlations between residuals of the lateralization index (LI) values of hindrance-modulated oriented anisotropy (HMOA) for the inferior fronto-occipital fasciculus (IFOF) and the superior longitudinal fasciculus (SLF) II and residuals of the behavioral measures [reading accuracy (READACC), reading fluency (READFLU), spelling (SPELL), rapid automatic naming (RAN), and phonological processing abilities (PHONO)] after controlling for sex, age, parental education, and head motion parameter for the group of dyslexics (DYS) and for the group of controls (CON), respectively. $^{**}p < .005$ (surviving FDR correction); $^{*}p < .05$; $^{\#}p < .10$.

the left long segment), a common problem with standard DTI (e.g., Catani et al., 2007; Vandermosten, Boets, Poelmans, et al., 2012; Yeatman et al., 2011). The same general linear model as HMOA analysis was used to analyze FA values of the AF for the remaining subjects (20 dyslexics and 23 controls for the full model; 23 dyslexics and 27 controls for the posthoc analysis of left hemisphere segments; 23 dyslexics and 26 controls for the posthoc analysis of right hemisphere segments).

Statistical analyses revealed a trend toward lower FA in dyslexic children than the controls [controls: .457 ± .01, dyslexics: .452 ± .01; $F_{(1, 35)} = 2.978$, $p = .093$] and a significant hemisphere by group interaction across the entire AF [$F_{(1, 35)} = 11.909$, $p = .001$, $\eta_p^2 = .254$]. No interaction between group and segment was found. Post-hoc analyses within each hemisphere of AF aiming to unpack the hemisphere by group interaction across the entire AF revealed a significant group effect in the left hemisphere with dyslexic children having lower FA than controls [controls: .460 ± .016, dyslexics: .450 ± .014; $F_{(1, 42)} = 5.254$, $p = .027$, Cohen's d = −.6666], but not in the right hemisphere [controls: .450 ± .015, dyslexics: .454 ± .014; $F_{(1, 41)} < 1$].

To assess whether the lateralization of FA is consistent with the results of Catani et al. (2007) in normal adults and those of Vandermosten et al. (2013) in adult dyslexics and controls, we further computed the FA lateralization index [FA LI = (right FA − left FA)/(right FA + left FA)] for each segment of the AF. We performed one-sample t-tests for each FA LI with zero for controls and dyslexics separately. Similar to the lateralization pattern in HMOA (anterior segment controls: $t = 3.325$, $p = .002$; dyslexics: $t = 4.545$, $p = .0001$; long segment controls: $t = -5.975$, $p < .0001$; dyslexics: $t = -6.784$, $p < .0001$; see Fig. 1), our results show that the anterior segment of AF is right lateralized (controls: LI = .0159 ± .034, $p = .019$; dyslexics: LI = .035 ± .033, $p < .0001$), whereas the long segment of AF is left lateralized (controls: LI = −.0215 ± .026, $p < .0001$; dyslexics: LI = −.020 ± .028, $p = .002$). A left lateralization was found for the posterior segment only in controls but not in dyslexics (controls: LI = −.0179 ± .035, $p = .01$; dyslexics: LI = .005 ± .038, $p > .5$). The FA lateralization patterns for the anterior and long segments of AF are thus consistent with the report of Catani et al. in an adult population. We then performed independent-sample t-tests for each FA LI between controls and dyslexics. Dyslexic children showed greater right lateralization of the anterior segment of AF than controls ($t = 2.086$, $p = .042$, Cohen's d = .5701). Dyslexic children also differ in the lateralization pattern of the posterior segment of AF from controls ($t = 2.289$, $p = .026$, Cohen's d = .6269), with only controls showing left-lateralization. Finally, the two groups did not differ in FA LI for the long segment of AF ($t = .182$, $p > .5$), showing equal left-lateralization. Thus, while our results replicate previously observed lateralization patterns of the AF, we do not replicate a group difference in the long segment, as reported by Vandermosten et al. (2013) in an adult population.

5. Discussion

In the present study, we have shown that the lateralization patterns of the microstructure of two association white matter pathways related to reading (IFOF and SLF II) differ between a group of dyslexic children and their age-matched controls. These lateralization patterns were also correlated with measures of literacy skills in dyslexic children. The results provide evidence for an atypical asymmetry of the occipito-frontal and parieto-frontal connections in developmental dyslexia.

This work represents a major methodological advance over previous diffusion studies of developmental dyslexia. Indeed, a high diffusion weighting ($b = 1400$ sec/mm^2) combined with high angular (60 directions) and spatial (1.7 mm) resolutions has allowed us to apply for the first time state-of-the-art spherical deconvolution tractography techniques to the study of white matter integrity in dyslexia. The main benefit of this methodology is to provide a resolution of fiber-crossing events and attribute a properly apportioned connectivity and microstructure measure (hindrance modulated oriented anisotropy, HMOA) to each specific tract. This methodological advance allowed us to explore for the first time in dyslexia research the integrity of the SLF with precisely defined subsegments, as well as to systematically study the hemispheric lateralization pattern of the main association fiber pathways in dyslexics.

Our main result on lateralization patterns is that dyslexic and control children differ in the lateralization of two tracts: IFOF and SLF II. Dyslexic children show a weaker left-lateralization of IFOF than control children, and a right-lateralization of SLF II (where control children show no hemispheric difference in SLF II), and these deviant lateralization patterns are related to reading capacity in dyslexic children. These results are consistent with long-standing suggestions of an atypical brain lateralization pattern in dyslexia (Galaburda et al., 1985; Orton, 1937; Witelson, 1977).

More specifically, previous work on the IFOF in adults suggested a relationship between the integrity of left IFOF and orthographic processing in reading (Vandermosten, Boets, Poelmans, et al., 2012). Together with other studies indicating a semantic involvement of the left IFOF (Duffau et al., 2005; Han et al., 2013; Turken & Dronkers, 2011), this tract might be a structural basis for the direct orthographic to semantic reading route defined by both computational and neurobiological models (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Pugh et al., 2001; Schlaggar & McCandliss, 2007; Seidenberg & McClelland, 1989). The weaker left lateralization of the IFOF observed in dyslexic children may therefore plausibly reflect an under-developed direct reading route. Alternatively, a recent study illustrated that the IFOF might play a role in phonological decoding (Welcome & Joanisse, 2014). It is therefore unclear whether IFOF is a pure orthographic processing route or whether it also participates in a phonological route. Given that our results showed correlations in dyslexic children between the lateralization of IFOF and reading accuracy and spelling, but also a trend with phonological skills, they are potentially consistent with both interpretations. Furthermore, the negative correlations between the lateralization of IFOF and literacy measures in the dyslexic group suggest that the shift from left-lateralization to no lateralization of IFOF in the dyslexics is maladaptive (associated with poorer reading skills).

With respect to SLF II, previous work in normal adults indicated a role in visuospatial attention, with greater rightward volume asymmetry associated with a greater left bias in the line bisection task (Thiebaut de Schotten et al., 2011). This might suggest that dyslexic children would show a greater left bias than control children in the line bisection task. While we have not collected such behavioral data in the present study, this would conflict with previous suggestions of a left mini-neglect in dyslexia (Hari, Renvall, & Tanskanen, 2001; Sireteanu, Goertz, Bachert, & Wandert, 2005). It would also conflict with the alternative hypothesis that reading acquisition induces a visual attentional bias toward the left in left-to-right writing systems (Chokron & DeAgostini, 1995; Chokron & Imbert, 1993), and that this bias is attenuated in poor readers (Gabay, Gabay, Schiff, Ashkenazi, & Henik, 2013). Alternatively, the lateralization of SLF II might be implicated in the rightward bias of the perceptual span in reading (Rayner, 2009), an effect that is acquired by learning to read in left-to-right writing systems and reversed in right-to-left systems (Pollatsek, Bolozky, Well, & Rayner, 1981). Thus dyslexic readers might show, just like beginning readers (Rayner, 1986), a reduced rightward bias of their perceptual span, and this might be reflected in an increased rightward asymmetry of the SLF II. Further research would be needed to clarify whether SLF II becomes progressively less rightward asymmetric in the course of reading acquisition to reach as the symmetry observed in our control children as in adults (Thiebaut de Schotten et al., 2011). Our results on the SLF II might also be consistent with a recent intrinsic functional connectivity finding in dyslexic children (Koyama et al., 2013), in which the authors observed significantly weaker intrinsic functional connectivity between left intraparietal sulcus and the left middle frontal gyrus in dyslexic children compared with typically developing children. Intraparietal sulcus and middle frontal gyrus are indeed regions connected by SLF II. Thus, an atypical lateralization of the SLF II in dyslexia is consistent with a variety of data on the involvement of fronto-parietal networks in reading acquisition, but a definitive interpretation will await further research.

Our connectivity findings in IFOF and SLF II are also consistent with results from a recent meta-analysis of PET and fMRI activation studies of dyslexia (Paulesu et al., 2014), in which the authors highlighted that dyslexia might involve dysfunctions in multiple systems across distributed brain regions associated with reading (e.g., conversion from orthography to phonology and phonological manipulation) and visuo-attentional processes respectively. In particular, the study found hypo-activations for dyslexia in the reading network and the visuo-attentional network in the left hemisphere and hyper-activations in the visuo-attentional network in the right hemisphere. Our finding of reduced leftward asymmetry of IFOF in the dyslexic group might be a structural reflection of the dysfunction within the reading network found by Paulesu et al., which included two key cortical regions connected by IFOF: the left inferior frontal cortex and the left infero-temporal and fusiform region. Our finding of increased rightward asymmetry of SLF II in the dyslexic group might be a counterpart of the dysfunction in the visuo-attentional network that Paulesu et al. found, which included two key cortical regions connected by SLF II: the inferior parietal lobule and the precentral gyrus.

To what extent do our results replicate previous studies on dyslexia on IFOF and SLF? There are in fact remarkably few points of meaningful comparison. One previous study analyzed the left IFOF only, reporting no group difference (consistently with ours). However they did not report results from the right IFOF and therefore did not compute asymmetry, so it is not possible to make a more direct comparison with our results (Vandermosten, Boets, Poelmans, et al., 2012). Only one previous study reported analyses of the SLF in relation to dyslexia. Their finding was that the right SLF, as indexed by FA, predicted future reading gains in dyslexic children (Hoeft et al., 2011). However, beyond methodological differences (no distinction between SLF and AF, FA *vs* HMOA), that study did not report group differences, so the results are again impossible to compare.

Regarding the AF, previous DTI studies have suggested that its microstructure (as measured by FA) either is disrupted in dyslexia, or positively correlates with reading-related measures (Deutsch et al., 2005; Klingberg et al., 2000; Rimrodt et al., 2010; Vandermosten, Boets, Poelmans, et al., 2012; Yeatman et al., 2011, 2012). Our own analysis of the FA of the AF in the present study does confirm the group difference in the left AF (although not for the lateralization index). However, an unexpected finding is that HMOA analyses of AF do not confirm this result (although they perfectly replicate the hemispheric asymmetry patterns of the AF measured with FA). This may reflect the limitations of DTI modelling and FA measurement, which can be affected by a number of factors, and notably fiber crossing (e.g., Dubois et al., 2014). While the dominant interpretation for lower FA in the left AF is worse connectivity (either fewer fibers or less myelination leading to lower efficient connectivity) in dyslexics than in controls, an alternative interpretation is that dyslexic readers might have more fibers crossing in the left low corona radiata between arcuate, callosal and sensori-motor fibers (Wandell & Yeatman, 2013). Putatively, atypical cerebral dominance may have led to an increase in interhemispheric connections (e.g., corpus callosum fibers) crossing with association fibers and spuriously decreasing FA in the left AF of the dyslexic subjects. A recent tractography study directly compared FA and HMOA in the AF of a young children population (5–6 years old) and found that FA in the AF was highly contaminated by fiber crossings (Vanderauwera et al., 2015). This suggests that significant group differences of FA found in the left AF between dyslexics and controls should be considered with caution and further increases the interest of measuring HMOA in dyslexia. Only future investigations will be able to provide insights on how differences in corpus callosum may relate to atypical lateralization in dyslexia, and potentially explain FA differences in the left AF. Other factors also reduce the possibility of directly comparing the present study with previous ones. Many studies based on DTI modeling and deterministic tractography have failed to distinguish the AF from the SLF (with the exception of Saygin et al., 2013; Yeatman et al., 2011; Yeatman et al., 2012). Studies that have dissected the AF and/or the SLF have typically not distinguished their three segments (Vandermosten, Boets, Poelmans, et al., 2012 being the only exception for the AF). Some studies have measured

FA over the entire tract, while others have measured it in specific clusters or sections along the tract. In addition, some studies have investigated children in a normally developing population (Yeatman et al., 2011, 2012), some adult dyslexic and control individuals (Vandermosten, Boets, Poelmans, et al., 2012), some both children and adolescents with dyslexia (Rimrodt et al., 2010), and some compared children at risk and not at risk of dyslexia ahead of reading instruction (Saygin et al., 2013; Vanderauwera et al., 2015). Finally, the fact that the standard DTI model fails to reconstruct segments of the AF in a substantial portion of the population is a clear worry, which gives a biased view of the variations of the AF across the population, and which truncates the comparison with our results obtained using SD tractography. Therefore, it is very difficult to directly compare the findings of the present study with those of previous ones, but they do not necessarily conflict. In order to obtain a more integrative view of white matter disruption in dyslexia, it will become increasingly important for diffusion imaging studies to converge on common methodological standards. We suggest that high diffusion-weighting (b values) and spherical deconvolution tractography may provide a good basis to avoid the pitfalls of standard DTI.

Overall, our study suggests that the severity of dyslexia during childhood is associated with an atypical brain lateralization of the IFOF and the SLF II, two tracts that may participate in orthographic-semantic/phonological and visuo-spatial pathways respectively. One limitation may be the large age range of our sample of children (between 9 and 14 years old). However, age did not seem to be a significant factor in any of our analyses. Whether there are any age-related effects that potentially interact with group differences in white matter integrity between control and dyslexic children will be a matter for future studies. Another limitation is that our study is correlational and therefore does not address the direction of causality. Group differences in the lateralization of white matter tracts might reflect pre-existing differences leading to dyslexia, or might reflect a divergent maturation of white matter pathways. Alternatively, white matter disruptions in developmental dyslexia might also be caused by poorer reading experience, and/or a compensation mechanism subsequent to dyslexia, since a recent study has shown that learning to read caused demonstrable changes in white matter microstructure (Thiebaut de Schotten et al., 2014). Future studies based on spherical deconvolution tractography comparing dyslexic with reading-matched (i.e., younger) control children (like in Altarelli et al., 2013; Hoeft et al., 2007; Krafnick, Flowers, Luetje, Napoliello, & Eden, 2014), or longitudinal studies starting before the onset of reading acquisition (e.g., Clark et al., 2014) will hopefully be able to tease apart these different causal mechanisms.

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Supplementary data

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