



Early dynamics of white matter deficits in children developing dyslexia

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ABSTRACT

Neural anomalies have been demonstrated in dyslexia. Recent studies in pre-readers at risk for dyslexia and in pre-readers developing poor reading suggest that these anomalies might be a cause of their reading impairment. Our study goes one step further by exploring the neurodevelopmental trajectory of white matter anomalies in pre-readers with and without a familial risk for dyslexia ($n = 61$) of whom a strictly selected sample develops dyslexia later on ($n = 15$). We collected longitudinal diffusion MRI and behavioural data until grade 3. The results provide evidence that children with dyslexia exhibit pre-reading white matter anomalies in left and right long segment of the arcuate fasciculus (AF), with predictive power of the left segment above traditional cognitive measures and familial risk. Whereas white matter differences in the left AF seem most strongly related to the development of dyslexia, differences in the left IFOF and in the right AF seem driven by both familial risk and later reading ability. Moreover, differences in the left AF appeared to be dynamic. This study supports and expands recent insights into the neural basis of dyslexia, pointing towards pre-reading anomalies related to dyslexia, as well as underpinning the dynamic character of white matter.

1. Introduction

Reading is a relatively recent cultural invention (around 5000 years ago) (Dehaene, 2009). In evolutionary terms this is a relatively short time span for our brain to develop a genetically imprinted reading network. Hence, when a child learns to read, pre-existing brain networks are reorganized within only a few years of time (Dehaene, 2009). Although the vast majority of children becomes literate rather easy within their early lives, 3–7% of the children struggles with learning to read and/or write. They are diagnosed with developmental dyslexia (Peterson and Pennington, 2015; Snowling, 2000), a learning disability characterized by severe and persistent reading and/or spelling impairments not accounted for by intellectual and sensory deficits (Peterson and Pennington, 2015; Vellutino and Fletcher, 1964). The diagnosis of dyslexia is typically given after several years of reading/writing instruction, when the impairments show up to be severe and persistent. This implies that targeted interventions do not start during the first stages of literacy acquisition, when they are most effective (Ozernov-Palchik and Gaab, 2016; Torgesen, 2002). Yet, early intervention is important because children experiencing a lifelong reading failure, are likely to display lower educational attainment and more psychiatric and health problems (Undheim, 2003). A thorough understanding of neurodevelopmental reading processes can aid our understanding of the

aetiology of developmental dyslexia. Moreover, a thorough understanding might enhance early detection of dyslexia, that can consequently lead to more effective remediation. The neural reading network consists of three distinct left hemispherical regions in advanced readers, i.e. inferior frontal, temporo-parietal and occipito-temporal cortex (for reviews, see Martin et al., 2015; Norton et al., 2015; Paulesu et al., 2014; Sandak et al., 2004). Functional neural deficits associated with dyslexia have been consistently shown in the left posterior regions of the reading network, mostly in adults (Richlan et al., 2009; Turkeltaub et al., 2003) but also in children (Richlan et al., 2011) and pre-readers at risk for dyslexia (Vandermosten et al., 2016), with mixed evidence for deficits in frontal or right hemispheric regions (Richlan et al., 2009). Given the interactive and dynamic character of the brain, previous research suggested that the neural deficit in dyslexia might not originate within cortical regions, but rather in the white matter connections between them (Boets et al., 2013; Saygin et al., 2013; Wang et al., 2016). The three main regions of the reading network are dorsally connected through the arcuate fasciculus (AF), while a ventral connection is sustained by the inferior fronto-occipital fasciculus (IFOF) (Vandermosten et al., 2012a). In adults and school-aged children with dyslexia, white matter anomalies have been shown in the left dorsal pathway, more specifically in the direct segment of the AF connecting the frontal region to the temporo-parietal region

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(Rauschecker et al., 2009; Vandermosten et al., 2012a, 2012b). Recent studies have demonstrated that these anomalies are already present prior to reading onset in those children at familial risk (Langer et al., 2015; Wang et al., 2016; but see Vandermosten et al., 2015) or at cognitive risk for dyslexia (Saygin et al., 2013). These studies point towards a causal role of dorsal white matter anomalies in developmental dyslexia, rather than these anomalies being a consequence of reading failure. However, evidence is scarce on the developmental trajectory of white matter anomalies paralleling the very first stages of reading acquisition, specifically in those children who demonstrate severe and persistent reading deficits, i.e. children who develop dyslexia. First attempts have recently been made to address this gap of knowledge. Wang et al. (2016) demonstrated slower development of white matter fractional anisotropy (FA) in a temporo-parietal node of the left direct AF segment in children who developed poor relative to good reading skills. Another recent study by Kraft et al. (2016) showed higher T1 intensities, an indirect measurement of myelin, in the anterior segment of the AF in pre-readers who developed poor reading skills. However, they did not observe differences in white matter FA, the most common used measure for quantitative description of white matter pathways. In addition to the involvement of the dorsal AF in reading, the ventral IFOF has been suggested to be involved in orthographic aspects of reading in adults (Vandermosten et al., 2012a). Yet, the specific role of this pathway is unclear in early reading stages, which rely more on phonological processes. The investigation of ventral white matter connections prior to reading onset and through the first stages of reading acquisition is therefore important, as this might entail information on the neurodevelopmental reorganization paralleling reading acquisition, and plausibly reading failure. One study that investigated the IFOF in the pre-reading brain, by means of T1 intensities, demonstrated no effect of family risk (Kraft et al., 2016).

The last decade, studies have indicated that a familial risk for dyslexia is related to neural deviances (e.g. Raschle et al., 2011; Raschle et al., 2012). It is, however, not clear whether these neural differences are associated with both the disorder and the familial risk (Leppänen et al., 2010), or with the familial risk regardless of reading/writing outcome (Hakvoort et al., 2015; Vanderauwera et al., 2016). The present study fills this gap by investigating structural white matter reorganization through the very first stages of reading and writing acquisition both in children who develop dyslexia and in children who are merely at familial risk for dyslexia. The first aim of the present study is to investigate whether atypical pre-reading neural connectivity is specific to those children developing *severe and persistent* reading and/or spelling difficulties, i.e. developmental dyslexia. This study thereby aims at enlarging recent insights in poor readers (Kraft et al., 2016; Wang et al., 2016). The dynamic pattern of the potentially observed deficits through the initial stages of reading acquisition will also be tracked, by means of a longitudinal study design ($n = 61$). We hypothesize that if neural differences will be found prior to reading onset in those children developing dyslexia, these differences will be located in the left long AF segment, as differences in this pathway have most consistently been demonstrated in older subjects (e.g. Vandermosten et al., 2012a). Second, we aim to investigate whether we can observe, in addition to dyslexia-related white matter anomalies, white matter differences that are merely related to the familial risk for dyslexia, which would define dyslexia as a continuum, also at the neural level. These differences can be expected in the ventral IFOF (Kraft et al., 2016) or in the dorsal AF (Langer et al., 2015; Wang et al., 2016). Finally, the predictive value of cognitive, familial risk and neural factors for developmental dyslexia will be investigated. It is our special interest to investigate whether potentially observed pre-reading white matter differences between children developing typical reading skills and children developing dyslexia can attribute to the prediction, on top of familial risk and cognitive predictors including phonological skills, that we hypothesize will provide the strongest prediction.

2. Methods

2.1. Participants

MRI scans were administered in 75 children before the start of literacy acquisition, i.e. during the summer holidays prior to first grade when the children were aged 5–6 years old. Since acquiring MRI scans in this population is challenging, a submarine protocol was developed that sufficiently prepared the children on the MRI assessment (Theys et al., 2014). After two years of reading and writing instruction, i.e. during summer holidays prior to third grade, MRI scans were conducted again in a subsample of 65 children using a knight and damsel protocol. Similar as in the submarine protocol (Theys et al., 2014), the knight and damsel protocol prepared the children for the MRI scanner in a playful manner. In a first step, the child watched a movie at home with his/her parents, in which an introduction and explanation was given of the scanning session. Second, before entering the MRI examination room, a set of different games was played together with the child in a small castle, explaining every aspect of MRI scanning and training adequate within scanner behaviour. Because of inadequate data acquisition in four participants, longitudinal diffusion images are available of 61 children. Thirty-four of these children had a familial risk for dyslexia (FRD⁺), defined by having at least one first-degree relative with dyslexia, while 27 children had no familial risk (FRD⁻). In the initial sample (Vanvooren et al., 2014), children with and without a familial risk were pairwise matched based on sex, age, parent's socio-economic status (SES) assessed with the Family Affluence Scale (Boudreau and Poulin, 2009; Boyce et al., 2006), non-verbal intelligence assessed with the Coloured Progressive Matrices (Raven et al., 1984), and school environment (i.e. same class). In the sample included in this study, no group differences are present in these matching variables (see Table 1). Participants were selected in kindergarten based on five inclusion criteria (Vanvooren et al., 2014): (1) a non-verbal IQ above 80, (2) normal hearing (i.e. a Fletcher index of less than 20 dB HL), (3) monolingual native Dutch speaking, (4) no history of brain damage, vision deficits, or articulatory problems, and (5) no high risk for developing ADHD. Non-verbal intelligence has again been tested at the start of second grade by the WISC-III-NL subtest Block Design (Wechsler, 2005) (Table 1). One child was diagnosed with attention deficit disorder (ADD), however, results did not change by removing this participant. At the early reading stage, all participants had two years of reading instruction, except for one child who had one, and another child who had three years of reading instruction. One child changed after one year of reading instruction from a Dutch school to a French school. Similarly, removing these participants from the analyses did not change the results.

Two sets of criteria were applied to classify children as dyslexic readers (DR) or as typical readers (TR). For these classifications word reading, pseudo-word reading and spelling scores conducted at the start of the second and third grade were used. The first set of criteria selected children with reading problems that are severe and persistent, i.e. a score below percentile 10 on the same reading test at the two time points. Based on this set of criteria, 11 children were classified as dyslexic. The second set of criteria selected children with severe and persistent spelling problems, i.e. below percentile 10 at the two time points. As dyslexia is mostly defined as a reading impairment, children that were selected based on severe and persistent spelling problems were additionally required to have reading scores below percentile 16 at both measurement times, to assure that these children also had poor reading skills. Based on this set of criteria, four additional children were classified as dyslexic. Hence, of the 61 children included in this study, 15 children developed dyslexia: 7% ($n = 2$) of the children without a familial risk and 38% ($n = 13$) of the children with a familial risk. These results are in line with the expected prevalence described in these two populations (Gilger et al., 1991; Snowling, 2000).

In kindergarten, the children of this study did not receive reading

Table 1
Demographic and cognitive characteristics of the participants.

	DR (n = 15)	TR (n = 46)	Test statistics	FRD ⁺ (n = 34)	FRD ⁻ (n = 27)	Test statistics
Participant characteristics						
Sex (male/female)	8/7	31/15	$\chi^2(1) = 0.969, p = 0.325$	21/13	18/9	$\chi^2(1) = 0.157, p = 0.692$
SES	5.5 (0.5)	5.4 (0.2)	$\chi^2(1) = 9.532, p = 0.146$	5.4 (0.3)	5.4 (0.3)	$\chi^2(1) = 10.001, p = 0.125$
Non-verbal intelligence ^a	97.0 (4.4)	101.7 (1.9)	$F_{(1,59)} = 1.265, p = 0.265$	99.1 (2.5)	102.4 (2.6)	$F_{(1,59)} = 0.805, p = 0.373$
Age at pre-reading MRI (in months)	73.3 (0.8)	73.7 (0.5)	$F_{(1,59)} = 0.140, p = 0.709$	73.5 (0.5)	73.7 (0.6)	$F_{(1,59)} = 0.067, p = 0.797$
Age at early reading MRI (in months)	95.0 (0.8)	95.4 (0.4)	$F_{(1,59)} = 0.150, p = 0.700$	95.2 (0.5)	95.4 (0.6)	$F_{(1,59)} = 0.112, p = 0.739$
Pre-reading cognitive skills						
Phonological awareness (CS)	-0.35 (0.21)	0.12 (0.11)	$F_{(1,59)} = 4.209, p = 0.045$	-0.03 (0.15)	0.05 (0.12)	$F_{(1,59)} = 0.168, p = 0.684$
End-rhyme identification ^b	7.6 (0.8)	8.8 (0.3)	$U = 265, p = 0.176$	8.1 (.5)	9.1 (.4)	$U = 361, p = 0.149$
End-phoneme identification ^b	3.4 (0.4)	4.3 (0.4)	$F_{(1,59)} = 2.026, p = 0.160$	4.4 (0.4)	3.8 (0.5)	$F_{(1,59)} = 0.852, p = 0.360$
Rapid naming colours & pictures (CS)	-0.23 (0.25)	0.07 (0.14)	$F_{(1,59)} = 5.609, p = 0.021$	-0.13 (0.17)	0.16 (0.16)	$F_{(1,59)} = 1.467, p = 0.231$
Rapid naming of colours	0.63 (0.05)	0.75 (0.03)	$F_{(1,59)} = 4.556, p = 0.037$	0.70 (0.03)	0.75 (0.04)	$F_{(1,59)} = 1.116, p = 0.295$
Rapid naming of pictures	0.62 (0.04)	0.74 (0.02)	$U = 214, p = 0.028$	0.68 (0.03)	0.74 (0.03)	$U = 389, p = 0.309$
Letter knowledge (CS)	-0.51 (0.26)	0.17 (0.13)	$U = 218.5, p = 0.034$	-0.19 (0.18)	.24 (0.15)	$U = 344, p = 0.095$
Productive letter knowledge	7.3 (1.1)	10.1 (.6)	$U = 210, p = 0.023$	8.5 (0.7)	10.5 (0.7)	$U = 326, p = 0.052$
Receptive letter knowledge	8.5 (1.0)	11.0 (0.5)	$U = 233, p = 0.059$	9.8 (0.7)	11.1 (0.6)	$U = 369, p = 0.186$
Grade 2 cognitive skills						
Word reading	84.3 (1.6)	106.1 (2.0)	$U = 23.5, p < 0.001^*$	97.4 (2.7)	104.6 (2.8)	$U = 311.5, p = 0.068$
Pseudo-word reading	80.0 (1.9)	102.1 (1.8)	$U = 27.5, p < 0.001^*$	93.8 (2.7)	100.0 (2.6)	$F_{(1,59)} = 2.713, p = 0.105$
Spelling	40.5 (3.2)	51.8 (1.4)	$U = 126, p < 0.001^*$	46.6 (2.0)	51.8 (2.1)	$U = 281, p = 0.021$
Grade 3 cognitive skills						
Word reading	64.0 (3.5)	94.5 (2.3)	$U = 60, p < 0.001^*$	80.6 (3.6)	95.0 (3.0)	$U = 286.5, p = 0.012^*$
Pseudo-word reading	70.7 (2.7)	96.6 (1.8)	$F_{(1,59)} = 55.228, p < 0.001^*$	85.3 (2.9)	96.5 (2.4)	$F_{(1,59)} = 8.002, p = 0.006^*$
Spelling	29.0 (2.1)	46.0 (7.0)	$F_{(1,59)} = 60.697, p < 0.001^*$	37.8 (1.9)	47.0 (1.2)	$F_{(1,59)} = 14.315, p < 0.001^*$

All characteristics were compared between dyslexic children (DR) and typical readers (TR) and between children with (FRD⁺) and without (FRD⁻) a familial risk for dyslexia. The mean (and standard error) of the raw scores is presented for the participants' characteristics, and on the standardized raw scores and composite scores (CS) for the cognitive tasks. Group means are compared by one-way independent ANOVA test or Mann-Whitney *U* test, except for sex and socio-economic status (SES) which have been analysed by a Chi-square test.

^a The scores of the intelligence and reading tests are standardized (mean = 100, SD = 15).

^b The scores on the rapid naming subtests are defined based on accuracy and speed. For more information see method Section 2.2.

*Remains significant after Bonferroni correction for multiple comparisons, i.e. three to four comparisons at each grade.

and writing instruction, as determined by the Flemish government (<http://www.ond.vlaanderen.be/>). Hence, all children except one were illiterate at the time of the first MRI acquisition (see Results Section 3.1 for more information). This study was approved by the local ethical board of the University Hospital. Informed consents were obtained from all parents of the participants according to the Declaration of Helsinki.

2.2. Cognitive measurements

Cognitive skills, known as precursors of reading, were tested at the start of each school year. In this section all relevant cognitive measurements are reported. A first cognitive skill that was assessed is *phonological awareness*, i.e. the awareness of the sound structure of language (Wagner and Torgensen, 1987). In pre-readers, a phonological awareness composite score was assessed based on an end-phoneme and end-rhyme identification task, as described in a previous study (Vandermosten et al., 2015). At the start of first grade a *letter knowledge* composite score was conducted based on a productive and receptive subtest (Boets et al., 2008). Sixteen frequent Dutch letters were visually presented in each subtest. For the productive subtest the child was asked to name all letters while in the receptive subtest the child had to point to the letter that was spoken to the child. For each test the score was defined as the number of correctly answered items. At the same time a *serial rapid naming speed* composite score was assessed by two subtests, i.e. rapid naming of colours and rapid naming of objects (van den Bos et al., 2002). For both subtests a card with 50 symbols, consisting of randomly ordered ten times five colours or ten times the picture of five high frequent one-syllable words, was presented. All symbols had to be named as accurate and fast as possible, and the score was defined as the number of correctly named items divided by the time to complete the test.

At the start of second and third grade, reading and spelling skills have been administered with standardized achievement tests. Reading

was assessed by an identical word reading test (Brus and Voeten, 1973) and pseudo-word reading test (Van den Bos et al., 1994) at both grades. The child was asked to read the items as accurate and fast as possible, and the score was defined as the number of correct read items in one or two minutes, respectively. Half-year norms on a standardized scale from 1 to 19 are present for both reading tests from grade 1 to grade 7. Spelling skills were administered by a writing on dictation test (Dudal, 1997), adjusted to the grade of the child.

2.3. DW-MRI acquisition

Pre-reading and early reading MRI acquisitions were identical. Single shot EPI with SENSE (parallel) MRI scans were conducted with a 32-channel head coil on a 3T MRI scanner (Philips, Best, The Netherlands). Sagittal diffusion imaging slices were obtained using the following parameters: repetition time 7600 ms, echo time 65 ms, flip angle 90°, voxel size 2.5 × 2.5 × 2.5 mm, 60 non-collinear directions, b-value 1300 s/mm², 6 nondiffusion-weighted images. The scan acquisition time was 10:32 min.

2.4. DW-MRI processing

The software ExploreDTI (version 4.8.3) (Leemans and Jones, 2009) was used to pre-process the data, applying the diffusion tensor model (DTI). Images were corrected for subject motion and eddy current-induced distortions and whole-brain tractography was conducted using the following parameters: minimum fractional anisotropy (FA-threshold) = 0.20, step length between calculations = 1 mm, maximum turning angle between voxels = 40°. For each individual a value for head motion in the scanner, defined as the root mean square of the absolute motion in all three directions (Theys et al., 2014), was obtained for both diffusion imaging scans. Motion parameters for the subjects of this study have been described previously at the pre-reading

stage (Theys et al., 2014), indicating that the applied scanning procedure sufficiently avoided excessive subject motion. There were no differences in subject motion for the reading groups and familial risk groups at both reading stages ($p_s > 0.17$). Adding subject motion as a covariate did not change the reported results. White matter properties were characterized by mean fractional anisotropy (FA), an indirect measure of white matter organization that is driven by microstructural properties such as myelination and axon density, and macro structural properties such as fiber crossings (Beaulieu, 2009).

Deterministic tractography was performed in TrackVis (trackvis.org). White matter pathways were manually delineated using a region of interest (ROI) approach. Each individual brain was analysed in native space, avoiding artefacts due to conversion of the individual child brain to a standard atlas. The three segments of the dorsal arcuate fasciculus (i.e. the long fronto-temporal, the anterior fronto-parietal and the posterior temporo-parietal segment) and the ventral inferior fronto-occipital fasciculus were delineated. For more information on the delineation procedure see Vandermosten et al., 2012a and Wakana et al. (2007). The right long AF segment, that is known not to be traceable in all individuals (Catani et al., 2007; Yeatman et al., 2011), could not reliably be traced in this study in 12 typical readers and four dyslexic readers prior to reading onset. After two years of reading instruction, the pathway could not be traced in four typical readers and one dyslexic reader. The left long AF segment could not be traced in one participant prior to reading onset and in two participants (1 TR, 1 DR) at the early reading stage. The left AF anterior segment could not be delineated in one typical reader at both reading stages.

All manual delineations reported in this study, at both time-points, are conducted by the first author (J.V.). Inter-rater reliability of the anisotropy index of J.V. and M.V. has been reported in Vandermosten et al. (2015), for the left long AF segment and the left IFOF, and was very high (correlation coefficient > 0.96). The ROIs used for the manual delineation at both time points are identical for each subject. Based on anatomical knowledge, NOT-ROIs were added for each individual pathway by the first author to exclude undesired streamlines. Streamlines that intersected the NOT-ROI were considered no part of the pathway of interest and were therefore deleted. Intra-rater reliability of the first author has been reported for the anisotropy index of the long AF segment in Vanderauwera et al. (2015) (correlation coefficient = 0.98).

2.5. Statistical analyses

A Shapiro-Wilk test was conducted in order to define whether the data and the residuals were normally distributed. If data were not normally distributed, non-parametric tests were applied. One extreme FA-value (> 1.5 interquartile range) was removed from the early reading left IFOF. There were no other outliers. First, group means of the demographic and cognitive characteristics of the participants were compared by a one-way independent ANOVA test or a Mann-Whitney *U* test, except for sex and socio-economic status (SES) which has been analysed by a Chi-square test. Correction for multiple comparisons was conducted by means of Bonferroni correction. For the first aim, FA in the white matter pathways was compared between the DR and TR groups across the two time points applying repeated measures ANOVA with time point (pre-reading and early reading) as within subject factor and group (TR and DR) as between subject factor. Significant interaction effects were further explored by independent *t*-tests. For these *t*-tests Bonferroni correction is reported as well. Note that post hoc power analyses indicate that these repeated measures analyses have a power of 99% to detect medium effects (effect size $f = 0.20$) and a power of 83% to detect small effects (effect size $f = 0.10$) (Faul et al., 2007). To further explore the reading related differences, we investigated whether white matter differences between TR and DR children were driven by reading ability regardless of familial risk. Therefore, the typical reading group was restricted to the FRD⁺ TR children, as 87% of the DR group

also consisted of FRD⁺ children. Similar repeated measures ANOVA were run with time point (pre-reading and early reading) as within subject factor and group (FRD⁺ TR and DR) as between subject factor. For the second aim, we investigated whether we can observe white matter deficits specific to the familial risk for dyslexia. White matter FA was compared between the FRD⁺ and FRD⁻ group at the pre-reading and early reading stage applying repeated measures ANOVA with time point (pre-reading and early reading) as within subject factor and group (FRD⁻ and FRD⁺) as between subject factor. Significant interaction effects were again further investigated by means of pairwise post-hoc comparisons applying Bonferroni correction. Power analyses indicate a power of 99% to detect medium effects and a power of 58% to detect small effects. We investigated whether observed differences were purely driven by the familial risk by restricting the analyses to the typical readers. Therefore, repeated measures ANOVA were run with time point (pre-reading and early reading) as within subject factor and group (FRD⁻ TR and FRD⁺ TR) as between subject factor. Finally, to define the best pre-reading predictor of dyslexia (categorical variable: TR or DR), stepwise forward logistic regression is applied. Three models have been conducted: a first model including cognitive and familial risk variables, a second model including neuroanatomical measurements, and a final model combining all predictors into one model. For significant predictors, the increase in percentage of correctly classified cases relative to the percentage of correctly classified cases based on the amount of typical readers/dyslexic readers in the group is presented.

3. Results

3.1. Cognitive and demographic characteristics of participants

Participants' cognitive and demographic characteristics are presented in Table 1. Prior to reading instruction onset, scores on the letter knowledge tasks confirmed that children had no substantial reading experience, i.e. for the productive subtest the mean score was 9.3 (SD = 4.1) and for the receptive subtest the mean score was 10.3 (SD = 3.7). As expected, at this pre-reading stage, reading-related skills already differed between DR and TR children. After two years of formal reading and writing instruction, at the start of grade 3, the DR group scored lower on all reading and writing tasks compared to the TR group. When restricting the typical reading group and the dyslexic group to the children with a family risk (FRD⁺ TR, $n = 21$; FRD⁺ DR, $n = 13$), for the aims of result section 3.2, similar results were obtained. There were no significant differences between the FRD⁺ and FRD⁻ group in the pre-reading cognitive skills. There were, however, differences in spelling in grade 2 and grade 3, and reading in grade 3. A comparison between typical readers with (FRD⁺ TR, $n = 21$) and without (FRD⁻ TR, $n = 25$) a familial risk for dyslexia revealed that there were no differences in pre-reading cognitive skills ($p_s > 0.09$), neither in grade 2 nor grade 3 reading and spelling scores ($p_s > 0.21$). Hence, the differences observed between the FRD⁺ and FRD⁻ children in grade 2 and grade 3 were driven by the high proportion of DR children in the FRD⁺ group (38%). For statistical analyses comparing typical readers and dyslexic readers, all children developing typical reading skills, regardless of their familial risk, were included in one group.

3.2. White matter deficits in developmental dyslexia

The developmental trajectory of white matter organization of the three segments of the dorsal AF (i.e. the long, anterior and posterior segment) and of the ventral IFOF were compared between children developing typical reading skills (TR; $n = 46$) and children developing dyslexia (DR; $n = 15$) prior to reading onset and after two years of reading instruction by means of repeated measures ANOVA with time point (pre-reading and early reading) as within subject factor and group (DR and TR) as between subject factor (see Fig. 1). Note that in all

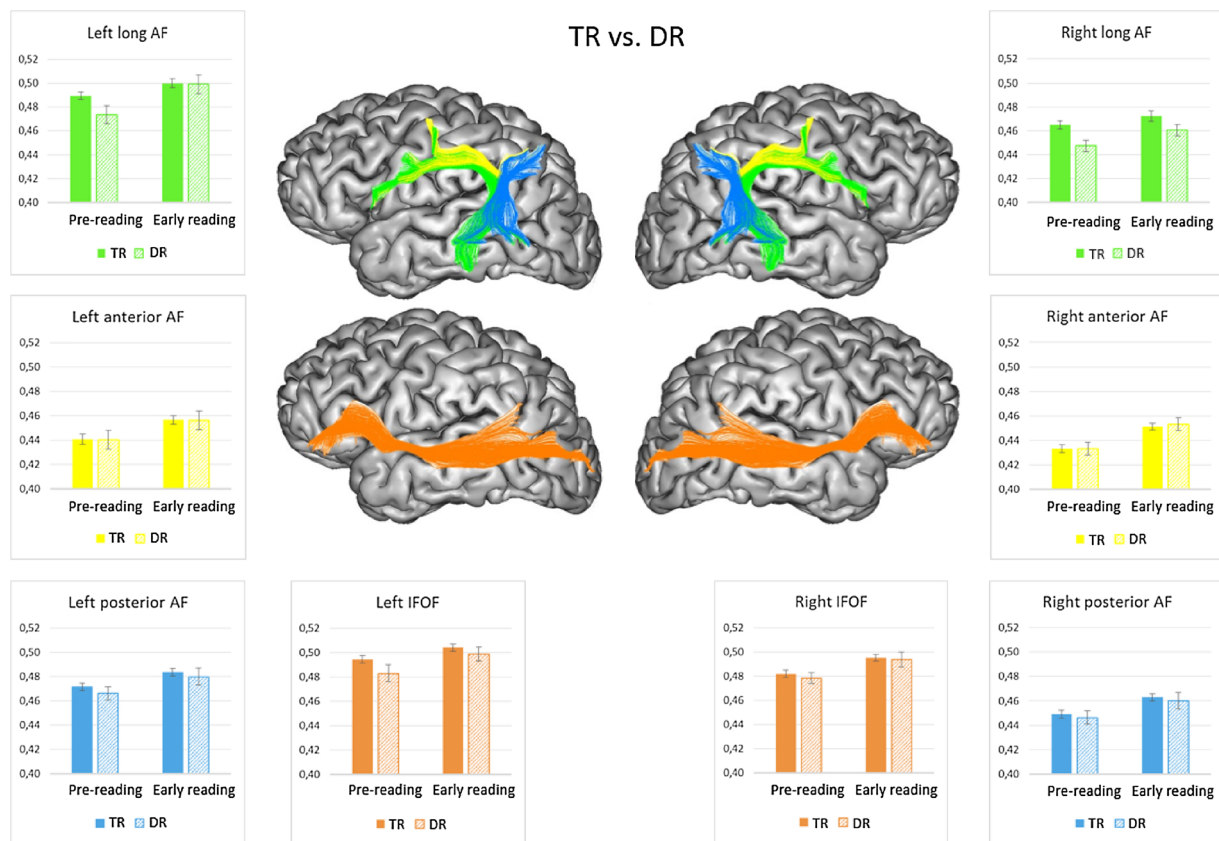


Fig. 1. White matter properties of typical readers (TR) and dyslexic readers (DR).

Mean FA-values of bilateral segments of the arcuate fasciculus (AF), i.e. the long, anterior and posterior segment, and the inferior fronto-occipital fasciculus (IFOF) are presented for the TR and DR groups, prior to reading/writing onset and after two years of reading/writing instruction.

white matter pathways, a significant increase in FA over time was present ($p_s < 0.001$). For the left long AF segment ($n = 59$), the results show a time point by group interaction ($F_{(1,57)} = 10.161, p = 0.002$), in the absence of a main effect of group ($F_{(1,57)} = 1.357, p = 0.249$). Independent t -tests indicate that the interaction effect was driven by a lower FA within the DR group compared to the TR group prior to reading onset ($t_{(59)} = 2.2, p = 0.032$, p -value does not survive Bonferroni correction for multiple comparisons), whereas no difference was present at the early reading stage ($t_{(57)} = 0.3, p = 0.730$). For additional analyses that explore why this group effect might fade please see Supplementary results section A. In the right long AF segment ($n = 45$), a main effect of group was present ($F_{(1,43)} = 6.383, p = 0.015$). There was no group by time point interaction ($F_{(1,43)} = 0.033, p = 0.858$). These results indicate that overall an effect of group was present, characterized by lower FA in the DR group compared to the TR group (Fig. 1). For the left IFOF ($n = 60$), the main effect of group was close to significance although the effect did not reach significance ($F_{(1,58)} = 3.326, p = 0.073$). There was no significant group by time point interaction ($F_{(1,58)} = 1.249, p = 0.268$). For all other white matter pathways, no significant main effect of group was present ($p_s > 0.45$) as well as no significant group by time point interaction ($p_s > 0.60$). In a next step, we investigated to which extent the observed white matter differences between typical readers and children developing dyslexia was purely driven by reading ability, regardless of familial risk. Therefore, both the typical reading group and the dyslexic group were restricted to the FRD⁺ children. For the left long AF segment ($n = 33$), the time point by group interaction was confirmed ($F_{(1,31)} = 4.635, p = 0.039$), in the absence of a main effect of group ($F_{(1,31)} = 1.214, p = 0.279$). Independent t -tests in this subsample showed lower FA seemed to be present prior to reading onset in the DR group, although the effect did not reach significance ($t_{(32)} = 1.848,$

$p = 0.074$) whereas at the early reading stage again no significant group difference was present ($t_{(31)} = 0.468, p = 0.643$). For the right long AF ($n = 26$), no main effect of group ($F_{(1,24)} = 2.149, p = 0.156$) and no time point by group interaction effect were present ($F_{(1,24)} = 0.313, p = 0.581$). Further exploration of group differences within the FRD⁻TR children to the DR children can be found in Supplementary results (section B).

3.3. White matter deficits specific to the familial risk for dyslexia

A family history of dyslexia is known as a risk factor for developing dyslexia, elevating the chance of developing dyslexia to 30–50% (Gilger et al., 1991). Therefore, we also investigated the presence of white matter deficits in children with a familial risk for dyslexia, regardless of the presence of a reading and/or writing disorder. White matter properties were compared between those children with a familial risk, defined by having a first-degree relative with dyslexia (FRD⁺, $n = 34$) and children without a family history of dyslexia (FRD⁻, $n = 27$). Note that group comparisons between the FRD⁺ pre-readers and the FRD⁻ pre-readers have been reported in a previous study (Vandermosten et al., 2015) and therefore, the present study focusses on the developmental trajectory of potential white matter deficits. Repeated measures ANOVA were run with group (FRD⁺ and FRD⁻) as between subject factor and time point (pre-reading and early reading) as within subject factor. For the left IFOF ($n = 60$), a main effect of group was present ($F_{(58)} = 8.156, p = 0.006$). However, a group by time point interaction was present as well ($F_{(58)} = 4.212, p = 0.045$). Independent t -tests indicated that the difference between the two groups decreases at the early reading stage ($t_{(58)} = 2.1, p = 0.042$, p -value does not survive Bonferroni correction for multiple comparisons) compared to the pre-reading stage ($t_{(59)} = 2.788, p = 0.007$, p -value survives Bonferroni

correction for multiple comparisons). In addition, a main effect of group was found for the right long AF segment ($F_{(1,43)} = 6.030, p = 0.018; n = 45$), in the absence of a time point by group interaction ($F_{(1,43)} = 0.001, p = 0.971$). No main effect of group was observed in other pathways ($p_s > 0.14$) as well as no group by time point interaction ($p = 0.068$ for the left posterior AF segment, $p_s > 0.14$ for all other pathways). The main effect of time point has been reported in section 3.2. Note that prior to literacy acquisition we did not find cognitive differences between the FRD^- and FRD^+ group. After one year of formal reading and writing instruction the FRD^+ children already scored lower for spelling and after two years of instruction, the FRD^+ children scored lower on all reading and spelling tests. However, when restricting these analyses to the typical readers, thereby excluding the effect of reading ability, no differences were present anymore at the cognitive level. In line with these analyses, white matter FA in the left IFOF and in the right long AF segment was compared between the FRD^+ and the FRD^- typical readers by means of repeated measures analyses. For the left IFOF ($n = 45$), the main effect of group was no longer significant in this subsample ($F_{(1,43)} = 3.010, p = 0.090$). In addition, no interaction effect was present ($F_{(1,43)} = 1.470, p = 0.232$). For the right long AF ($n = 34$), no main effect of group was present ($F_{(1,32)} = 2.313, p = 0.138$) as well as no time point by group interaction effect ($F_{(1,32)} = 0.581, p = 0.452$). Hence, similar to the results obtained at the behavioural level, the effect of family risk observed in the left IFOF and in the right AF seems, at least partially, driven by the presence of a large portion of participants who developed dyslexia in the FRD^+ group (Fig. 2).

3.4. Predictors of developmental dyslexia

In a next step, the variables that best predict developmental dyslexia prior to reading instruction were investigated. Pre-reading cognitive skills (i.e. phonological awareness, rapid naming and letter knowledge composite scores, see Table 1), familial risk (i.e. FRD^- vs. FRD^+) and neuroanatomical measures (i.e. mean FA values of bilateral dorsal and ventral pathways) were combined in a stepwise way in three logistic regression models to predict which children develop typical reading skills (TR) and which children develop dyslexia (DR). Note that the analyses including white matter pathways was performed in the subset of individuals for whom all white matter pathways were traceable ($n = 45$). Based on the amount of typical readers in the group (i.e. 46 children of the total sample of 61 children), 75.4% of the cases can be classified correctly without entering any predictor in the model. Since all subjects were classified as typical readers, 0% of the individuals with dyslexia was correctly classified without entering any predictor in the

model. The first model including familial risk and the pre-reading cognitive skills, defined two unique predictors of dyslexia, i.e. familial risk ($B = 2.0, SE = 0.8, Wald = 6.3, df = 1, p = 0.012, Exp(B) = 7.7$) and rapid naming ($B = -0.8, SE = 0.4, Wald = 5.5, df = 1, p = 0.050, Exp(B) = 0.4$). This model increases the percentage of correctly classified cases to 80.3%. On top of these predictors, phonological awareness and letter knowledge did not significantly contribute to the model ($p_s > 0.26$).

A second model included all mean FA-values of the bilateral dorsal and ventral pre-reading white matter pathways. Confirmatively, the results showed that FA in the left long AF segment significantly predicted who will develop dyslexia ($B = -42.5, SE = 17.0, Wald = 6.2, df = 1, p = 0.013, Exp(B) < 0.001$). The left long AF is the only neural feature that relates to the emergence of developmental dyslexia. Including this predictor increases the number of correctly classified cases to 84.4% (45.5% of the individuals with dyslexia were correctly classified). On top of the left long AF, no other white matter pathways were significant predictors ($p_s > 0.24$). Note that this analysis was performed in the subset of individuals for whom all white matter pathways were traceable ($n = 45$). Hence, out of the 11 participants with dyslexia included in the model, 5 were correctly classified. However, removing the right long AF segment that was not traceable in 16 individuals from the model did not change the results ($p = 0.033$).

Finally all cognitive, familial risk and neuroanatomical predictors were combined into one model in order to define the strongest unique predictors of developmental dyslexia. This analysis showed that the left long AF segment is the only significant predictor ($B = -42.5, SE = 17.0, Wald = 6.2, df = 1, p = 0.013, Exp(B) < 0.001$). The implementation of this predictor again increased the percentage of correctly classified cases to 84.4% (45.5% of the individuals with dyslexia were correctly classified). On top of the left long AF segment, there were no other significant contributors, neither familial risk nor cognitive skills, to the prediction ($p_s > 0.13$). Hence, the present analyses suggest that the left long AF segment might be a unique predictor of who will develop dyslexia, above and beyond the familial risk and cognitive predictors that we took into account in the our study. Adding an additional subject motion variable to all three models did not change the results.

4. Discussion

The brain is a complex and dynamic system, changing due to constant interaction between distant brain regions but also due to the individual's interaction with the environment. Hence, atypical neural connectivity in adults and school-aged children who struggle with

FRD⁻ vs. FRD⁺

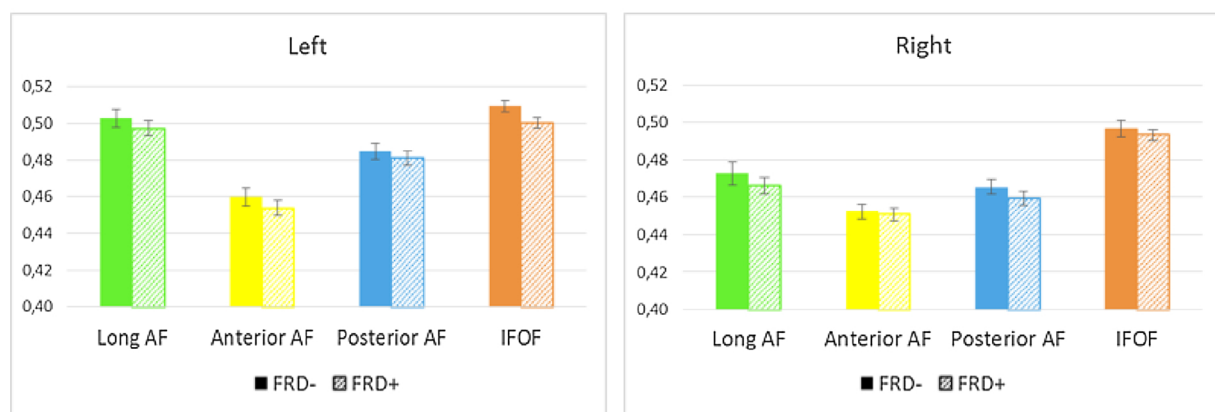


Fig. 2. White matter properties of children with (FRD^+) and without (FRD^-) a familial risk for dyslexia after two years of reading acquisition.

Mean FA-values of bilateral segments of the arcuate fasciculus (AF), i.e. the long, anterior and posterior segment, and the inferior fronto-occipital fasciculus (IFOF) are presented for the FRD^- and FRD^+ groups.

reading impairments might be the result of a lack of reading experience or might represent build-up compensational strategies. The question remains whether anomalies were present prior to literacy acquisition in individuals with dyslexia, hence might be a cause of the emergence of dyslexia, or whether these anomalies emerge throughout (the early stages of) reading and writing acquisition (Eden et al., 2016). Recent studies in children at risk for dyslexia (for a review see Ozernov-Palchik and Gaab, 2016; Vandermosten et al., 2016) and in children developing poor reading skills (Kraft et al., 2016; Wang et al., 2016) suggest that neural differences are present prior to reading instruction onset. We expanded these recent findings by investigating the development of the structural neural connectivity network for reading in a strictly selected set of children who developed dyslexia through the very first stages of reading and writing acquisition. The results confirm that neural deviances at the level of the white matter are already present before the start of reading and writing acquisition in children who develop severe and persistent reading problems. These findings support contemporary views on dyslexia, emphasizing the importance of connectivity to understand the multifactorial cause of dyslexia. For example, the distinctiveness of phonological representations measured with specific well-suited fMRI techniques has been demonstrated not to be altered in adults with dyslexia, yet the representations were less accessible due to decreased neural connectivity (Boets et al., 2013; Vandermosten et al., 2012a). However, our study cannot rule out whether the origin of the observed deficits is within white matter pathways or whether these anomalies represent underlying regional grey matter impairments. A recent study did suggest that early connectivity influences functional cortical development of the visual word form area (VWFA) (Saygin et al., 2016), although it remains to be determined whether this process is specific to the VWFA or whether it represents a general mechanism of cortical development. The neural deviances we observed before the start of reading and writing instruction in children developing dyslexia, were located in bilateral dorsal pathways. Other studies in adults and school-aged children have also shown deviances in the structural organization of the left dorsal pathway, playing a key role in the communication between the different regions of the reading network and sustaining essential processes in reading (for an overview see Vandermosten et al., 2012b). A relation between lower phonological awareness skills, as a risk factor for developing dyslexia, and the left dorsal pathway has been suggested in pre-readers (Saygin et al., 2013; Vandermosten et al., 2015). Remarkably, white matter properties within the left dorsal pathway represent the best predictor of the development of dyslexia prior to reading and writing acquisition, on top of familial risk and the standard cognitive skills that are widely used to indicate a risk for dyslexia. Although neural differences were present in bilateral dorsal pathway, in-depth analyses of the observed group difference revealed that only the difference in the left dorsal pathway seemed to be exclusively related to the development of dyslexia, in the absence of a relation with the familial risk for dyslexia, and only the left pathway provided a unique prediction of developmental dyslexia. It should be noted, however, that the observed difference in the left dorsal AF prior to reading instruction onset did not survive Bonferroni correction for multiple comparisons. Although Bonferroni correction is a conservative correction that significantly reduces statistical power, the current results should be interpreted with caution and the replication of these findings specific to the group of individuals who develop dyslexia is required. Wang et al. (2016) did suggest for similar findings in poor readers. Concerning the results obtained for the right dorsal pathway, plausibly, white matter organization, that was also decreased in children at familial risk for dyslexia, plays a role in the emergence of developmental dyslexia, but only in interaction with other influencing factors. The right dorsal pathway has been suggested to play a compensatory role for the reading impairments of school-aged children with dyslexia (Hoeft et al., 2011). However, in our study we found an overall group difference, that was significant at the pre-reading stage ($t_{43} = 2.7, p = 0.011$). Hence, the results do not seem to confirm a

compensatory role of the right pathway. In school-aged children (8–14 years of age), initial white matter FA of the left arcuate fasciculus has also been shown to be predictive of further reading development (Gullick and Booth, 2015). Moreover, development from kindergarten to grade 3 in a left temporo-parietal white matter cluster, through which the arcuate fasciculus passes, had been presented to be predictive for reading outcome (Myers et al., 2014). Nevertheless, while our study defines the strongest unique predictor(s), the most variance can presumably be predicted by combining cognitive factors, familial risk factors and left dorsal white matter organization as proposed by Wang et al. (2016) in a backward regression model. Hence, this pathway seems to be highly important for reading development.

The current study also demonstrates that the complexity of reading and writing disorders cannot be explained by one single static factor, but rather is the result of dynamic interplay between genetic, environmental and cognitive factors, expressed at the neural level, in line with the multiple deficit model by Pennington (2006). Although the left dorsal pathway is crucial in predicting dyslexia, and deviances were observed in bilateral dorsal pathways prior to reading acquisition in those children who were developing dyslexia, other white matter pathways might be closely interacting with the dorsal pathway, and presumably the weighting of different factors eventually results in the development (or not) of dyslexia. One pathway that seems to be important is the left ventral IFOF. Recent studies indicated an effect of having a familial risk for dyslexia in the pre-reading brain in bilateral dorsal and left ventral regions and connections (Kraft et al., 2016; Langer et al., 2015; Raschle et al., 2011; Vandermosten et al., 2015). However, until now no study was able to investigate whether the observed deviances in the pre-reading and early reading brain were specific to developmental dyslexia, or to the elevated familial risk for dyslexia. While deficits in the left dorsal pathway were most consistently related to reading and writing impairments, children with an elevated genetic risk for dyslexia presented deficits in the left ventral pathway as well as in the right dorsal pathway. For both pathways, a main effect of family risk group was observed. For the left IFOF a group by time point interaction was present as well. This interaction effect revealed that the effect of family risk seemed to fade over time. Whereas the pre-reading group difference survived Bonferroni correction for multiple comparisons, the early reading group difference did not. Further analyses restricted to the typical readers with and without a family risk for dyslexia revealed that these differences observed between children with and without a familial risk were not independent of reading ability. For the right dorsal AF this result is not surprising, given that a group difference was also present between children developing typical reading skills and children developing dyslexia. However, when comparing typical readers to children developing dyslexia, no difference was present in the left IFOF. It seems that both differences observed in the ventral IFOF and in the right dorsal AF are to some extent driven by both the familial risk and reading ability. These anomalies might add and interact with other risk factors for dyslexia (Bishop, 2013), resulting in impaired reading ability in some of the children and in normal reading skills in other children.

The current study demonstrates that white matter deficits are dynamic. The effect of family risk on the left ventral IFOF might fade over time. Although a significant group difference was present at both time points, only the pre-reading difference survived Bonferroni correction for multiple comparisons. Moreover, while there was a group difference in the left dorsal pathway between typical readers and children developing dyslexia prior to reading and writing onset, this difference was no longer present after two years of formal reading and writing instruction. In an exploratory analysis present in Supplementary results, we investigated whether the development of the left dorsal AF might be associated with the amount of clinical intervention a child received. Although no detailed information on the intensity and content of the intervention was available, this analysis seems to indicate that the development within the left direct AF segment is related to the amount of

clinical language/reading/spelling intervention a child received per week. The results suggest that early intervention might have a positive influence on the structural organization of the left dorsal arcuate fasciculus, a pathway that seems to play a key role in dyslexia. White matter organization has been shown to remain plastic during the school years (Keller and Just, 2009; Lebel et al., 2008) and structural plasticity following reading instruction has been demonstrated in ex-illiterates (see Carreiras et al., 2009; Thiebaut De Schotten et al., 2014). The location of this preliminary effect of clinical intervention is not unexpected as the left direct AF pathway has repeatedly been demonstrated to be involved in phonological processing (e.g. Saygin et al., 2013; Vanderauwera et al., 2015; Vandermosten et al., 2012a). Although the exact content of the interventions cannot be retrieved, it is common practice for speech therapists to focus on phonological processing for the remediation of reading impairment. However, it should be noted that this analysis has a high exploratory character as it is merely based on an indirect and limited measurement of clinical therapy that needs to be further investigated. Therefore, it would be of interest for future studies to perform a more in-depth analyses of the specific interventions, in a controlled intervention study design. Moreover, to fully understand the developmental course of the arcuate fasciculus, further longitudinal follow up in larger samples is required.

Further, we potentially observed an influence of environmental factors on the reading intervention the children in our study received. In our study, 15 children developed dyslexia, of whom 13 children had a family history of dyslexia. Only the 13 children with a family history of dyslexia received reading intervention by the end of grade 2. These children with a family history of dyslexia might grow up in a specific environment where the parents are extremely attentive to the reading and spelling development of their child. Moreover, as a result of being part of the current longitudinal study, the parents of the participating children were well informed on the reading and spelling development of their children, as we provided them a yearly overview of their cognitive skills. Hence, the well-informed parents with a family history of dyslexia might increase their alertness with regard to their children's reading/spelling development, increasing the chance for seeking early intervention. In addition to this plausible effect of family risk, we hypothesize that other environmental factors such as parental educational level, a measurement of socio-economic status (SES) might influence the chance that parents seek for early intervention.

Although the results of the present study are of interest to the research field, the study has some limitations that should be considered. First, the amount of children developing dyslexia is limited in the present study ($n = 15$), and therefore results should be interpreted with caution. Although the longitudinal MRI study started with a large number of children ($n = 75$), due to inadequate data acquisition and a small dropout, 61 longitudinal scans were available. Hence, given the pre-reading selection of at risk children of whom 30–50% is considered to develop dyslexia, a group of 15 children eventually developed dyslexia. It should be noted, however, that all dyslexic children were selected based on strict criteria ensuring both the severity and the persistence of their reading and spelling impairment. Given the small sample size and the number of comparisons, some group comparisons do not survive multiple comparisons. The robustness of important findings was tested by repeated measures analyses. Nevertheless, replication of the present findings is surely required and this study aims to guide future studies.

Altogether, this study shows that commonly observed brain differences characterizing developmental dyslexia are present before children have significant reading and writing experience and therefore are more likely involved in the emergence of dyslexia, rather than being consequences of dyslexia. These results stress the importance of addressing developmental disabilities as a complex dynamic interplay between different factors, and urges to abandon the static approach current imaging studies often apply.

Conflict of Interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.dcn.2017.08.003>.

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