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Research Report

Atypical gray matter in children with dyslexia before the onset of reading instruction

Caroline Beelen [a], Jolijn Vanderauwera [a,b], Jan Wouters [b], Maaike Vandermosten [b,*,1] and Pol Ghesquière [a,1]

[a] Parenting & Special Education Research Unit, Faculty of Psychology & Educational Sciences, KU Leuven, Belgium
[b] Research Group ExpORL, Department of Neurosciences, KU Leuven, Belgium

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ABSTRACT

Many studies have focused on neuroanatomical anomalies in dyslexia, yet primarily in school-aged children and adults. In the present study, we investigated gray matter surface area and cortical thickness at the pre-reading stage in a cohort of 54 children, 31 with a family risk for dyslexia and 23 without a family risk for dyslexia, of whom 16 children developed dyslexia. Surface-based analyses in the core regions of the reading network in the left hemisphere and in the corresponding right hemispheric regions were performed in FreeSurfer. Results revealed that pre-readers who develop dyslexia show reduced surface area in bilateral fusiform gyri. In addition, anomalies related to a family risk for dyslexia, irrespectively of later reading ability, were observed in the area of the bilateral inferior and middle temporal gyri. Differences were apparent in surface area, as opposed to cortical thickness. Results indicate that the neuroanatomical anomalies, since they are observed in the pre-reading phase, are not the consequence of impoverished reading experience.

1. Introduction

Developmental dyslexia (henceforth, dyslexia) is a neurobiological learning disorder marked by persistent difficulties with accurate and/or fluent visual word recognition, poor spelling and/or poor decoding skills, regardless of intellectual abilities, intact sensory abilities and adequate teaching instructions (Lyon, Shaywitz, & Shaywitz, 2003; Peterson & Pennington, 2015). Dyslexia is considered a multifactorial deficit, originating from a complex interaction of genetic, neural, cognitive and environmental factors (Peterson & Pennington, 2015).

At the neural level, reading recruits in experienced readers a network of regions in the left hemisphere of the brain, which is referred to as the reading network. The classical, yet simplified model on the neural correlates of typical reading development encompasses left temporoparietal, occipito-temporal and inferior frontal regions (Pugh et al., 2000). According to the model, the dorsal temporoparietal region is

* *Corresponding author*. Research Group Experimental Oto-rino-laryngology (ExpORL), O&N II Herestraat 49 - bus 721, 3000 Leuven, Belgium.
E-mail address: maaike.vandermosten@kuleuven.be (M. Vandermosten).
[1] Both should be considered joint last author.
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involved in phonological processes and grapheme-phoneme conversions, whereas the ventral occipitotemporal region, and specifically the visual word form area (VWFA), contributes to the pre-lexical coding of letter strings (Cohen et al., 2000, 2002) and visual whole-word recognition based on orthographic word representations (Schurz et al., 2010; Zhao et al., 2017). The pars opercularis of the inferior frontal region, encompassing Broca's area, maps phonological representations to speech output and regulates higher order phonological processes, such as the sequencing of phonemes and words (Boets et al., 2013; Price, 2010; Shaywitz & Shaywitz, 2008). Furthermore, recent findings suggest additional recruitment of few surrounding areas in reading, i.e., precentral regions, motor regions and the cerebellum (see Martin, Schurz, Kronbichler, & Richlan, 2015).

In readers with dyslexia the neural reading network differs in function from typical readers, showing decreased activation in left temporoparietal and occipitotemporal regions (Richlan, Kronbichler, & Wimmer, 2009; 2011). Concerning the analyses on structural neural differences in individuals with dyslexia, most studies performed were voxel based morphometry (VBM) studies (Richardson & Price, 2009). VBM is an automated approach for whole-brain analyses at a voxel-by-voxel level (Ashburner & Friston, 2000). A vast majority of the VBM studies on dyslexia reported anomalies in the classical reading network of the dyslexic brain, as indicated by gray matter volume reductions in left temporoparietal (Brown et al., 2001; Eckert et al., 2005; Silani et al., 2005), occipitotemporal (Brambati et al., 2004; Brown et al., 2001; Silani et al., 2005) and inferior frontal regions (Brown et al., 2001; Eckert et al., 2003). However, three independent meta-analyses (Eckert, Berninger, Vaden, Gebregziabher and Tsu, 2016; Linkersdörfer, Lonnemann, Lindberg, Hasselhorn, & Fiebach, 2012; Richlan, Kronbichler, & Wimmer, 2013) showed low consistency in regions differing between readers with dyslexia and typical readers, which may be the result of methodological differences between meta-analyses, such as the particular studies included, the analyses chosen or the type of statistical corrections applied (Ramus, Altarelli, Jednoróg, Zhao & Scotto di Covella, 2018). Hence, up until now it remains unclear at which locations in the brain dyslexia manifests itself. Part of the problem relates to the fact that due to brain plasticity throughout development and difficulty in measuring causality, it remains largely unknown whether observed differences in the dyslexic brain are a cause or consequence of the reading impairment (Carreiras et al., 2009; Golestani, Price, & Scott, 2011; Ramus, Altarelli, Jednoróg, Zhao, & di Covella, 2018; Xia, Hancock, & Hoeft, 2017).

Few structural studies have opted for a reading-level matched design in order to take some first steps in identifying causal factors, yet also providing inconsistent results (Hoeft et al., 2007; Krafnick, Flowers, Luetje, Napoliello, & Eden, 2014; Xia, Hoeft, Zhang, & Shu, 2016). Krafnick et al. (2014) suggested that reductions in gray matter volume that are related to dyslexia are a consequence rather than a potential cause of dyslexia, since they observed that no differences in gray matter volume were present in regions typically associated with dyslexia when children with dyslexia were compared to reading-level matched children. Contrary, Xia et al. (2016) reported that children with dyslexia compared to reading-matched children showed reduced grey matter volume in frontal, temporoparietal and occipitotemporal regions, and Hoeft et al. (2007) reported that adolescents with dyslexia compared to reading-matched individuals had reduced gray matter volume in the left parietal region only. Pre-reading magnetic resonance imaging (MRI) studies offer insight into anomalies in dyslexia *prior* to reading experience and can therefore better reveal whether anomalies might be a potential cause or consequence of a different reading experience (Vandermosten, Hoeft, & Norton, 2016; Xia et al., 2017). Since dyslexia is suggested to be first and foremost caused by a phonological deficit (Shaywitz & Shaywitz, 2005; Snowling, 2000) and the classical neuroanatomical model of dyslexia localized this primary phonological deficit in left temporoparietal regions (Richlan, 2012), it is generally assumed that dyslexia is first displayed in left temporoparietal regions. Moreover, it is assumed that beginning readers rely more on the left dorsal temporoparietal circuit, whereas advanced readers activate to a larger extent the left ventral occipitotemporal circuit. Recruitment of conscious, effortful grapheme-phoneme conversions would gradually decrease, whereas automatic activation of the VWFA would gradually become more prominent (McCandliss & Noble, 2003; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003). Yet, the classical neuroanatomical model of dyslexia is based on studies involving adults and older children. Indeed, several structural MRI studies in pre-readers with a family risk for dyslexia (Black et al., 2012; Hosseini et al., 2013; Im, Raschle, Smith, Ellen Grant; Gaab, 2016; Raschle, Chang, & Gaab, 2011) and behavioural risk for dyslexia (Black et al., 2012) reported neuroanatomical anomalies in a more distributed network in the brain, more specifically in the left temporoparietal region (Black et al., 2012; Im, Raschle, Smith, Ellen Grant, & Gaab, 2016; Raschle et al., 2011), the left occipitotemporal region (Im et al., 2016; Raschle et al., 2011) and the left inferior frontal gyrus (Black et al., 2012; Hosseini et al., 2013), in right counterparts (Black et al., 2012; Raschle et al., 2011) and outside the reading network (Raschle et al., 2011; Hosseini et al., 2013; see also the review of; Vandermosten et al., 2016). However, not all of the children in these studies develop dyslexia. Although dyslexia is highly heritable, i.e., 30–50% of children with a family risk for dyslexia will develop dyslexia, more than half of the family risk group will develop typical reading skills. Longitudinal studies in pre-reading children who are later classified as having dyslexia or not would clarify which neuroanatomical differences can be related to either dyslexia *per se* or a family risk for dyslexia.

Up until recently, only few structural MRI studies used a longitudinal design to study dyslexia starting prior to formal reading instruction (Clark et al., 2014; Kraft et al., 2016; Vanderauwera, Wouters, Vandermosten, & Ghesquière, 2017; Wang et al., 2017). Most of these studies focused on white matter properties with Wang et al. (2017) and Kraft et al. (2016) showing white matter differences in the left arcuate fasciculus in good versus poor readers. Vanderauwera et al. (2017) followed-up pre-readers until they could be classified as dyslexic and confirmed white matter anomalies in the left arcuate fasciculus. In addition, they revealed that anomalies in the right arcuate fasciculus and the left inferior frontal

occipital fasciculus are related to dyslexia *per se* and to a family risk for dyslexia. To the best of our knowledge, Clark et al. (2014) performed the only brain morphology study (i.e., T1 MRI data) on dyslexia focusing on gray matter and using a longitudinal design in which pre-readers are later classified as having dyslexia or not. In the study of Clark et al. (2014), a small group of children were followed-up from pre-reading until a few years of reading experience. Thinner cortices in primary sensory areas and regions involved in executive functioning, instead of areas belonging to the reading network, were observed in pre-readers developing dyslexia. A reduction of cortical thickness in the reading network was only observed after these children had learned how to read. They concluded that abnormalities in the reading network are a consequence of limited reading experience, instead of a cause of dyslexia, and that neuroanatomical deviances in dyslexia have their origin in primary sensory cortices and core executive function areas. However, the Clark et al. (2014) study had a lack of power due to a very limited sample size (pre-reading n = 17, of which only 7 children were later identified as a dyslexic reader). Hence, their results should be interpreted with caution. In addition, Clark et al. (2014) focused on cortical thickness without including surface area. Cortical thickness and surface area are genetically independent and emerge at different stages of human development, due to which it is more informative to investigate both independently (Panizzon et al., 2009; Winkler et al., 2010). To be more specific, surface area would reflect cortical folding patterns largely determined prenatally, whereas cortical thickness would develop more excessively after birth; increase until adolescence, decline after this period and stabilize in adulthood (Black et al., 2012; Im et al., 2008; Kapellou et al., 2006).

The purpose of the current study is to examine *whether and where* in the neural reading network pre-reading neuroanatomical gray matter anomalies can be found in children who develop dyslexia (DR), as opposed to children who become typical readers (TR), and in children with a family risk for dyslexia (FRD^+), as opposed to children without a family risk for dyslexia (FRD^-). By investigating dyslexia *in the pre-reading phase* an answer can be given to whether observed neuroanatomical differences potentially are either a cause or consequence of the reading impairment. By studying dyslexia in a *longitudinal cohort*, later dyslexia status can be used for analyzing pre-reading data, and neuroanatomical differences can be related to either dyslexia *per se* or a family risk for dyslexia. In our study, dyslexia status was determined via reading measures that yearly were obtained from our participants from grade 2 until grade 5 of primary school. These measures were used to classify our participants in retrospect as a reader with dyslexia or not. The current study is unique, because it is the first study in pre-readers with a longitudinal design, in which groups are compared based on a family risk for dyslexia as well as on dyslexia *per se* and in which we take into account measures of surface area and cortical thickness. As a consequence, our study may provide new insights into the morphology of the brain in dyslexia, especially at its onset.

In our study, we adopt an automated surface-based region-of-interest (ROI) registration approach in FreeSurfer, because we have specific hypotheses regarding the locations were differences can be observed, and since in this approach the components of cortical volume, i.e., cortical thickness and surface area, can be studied independently. ROIs of the reading network are chosen based on a meta-analysis of Richlan et al. (2009) and include the left inferior, middle and superior temporal gyri, the left inferior parietal lobule, the left fusiform gyrus and the left pars opercularis of the inferior frontal gyrus. Additionally, we also include corresponding right hemispheric regions, since meta-analyses of structural studies on dyslexia reported bilateral hemispherical anomalies in children with dyslexia (Eckert et al., 2016; Linkersdörfer et al., 2012; Richlan et al., 2013) and since anomalies might not be restricted to the left hemisphere in the pre-reading phase (Vandermosten et al., 2016).

In line with the classical model on reading development, we expect that structural anomalies in pre-readers who develop dyslexia will be found in the reading network. At this developmental stage, in particular in left temporoparietal regions, as the classical model on the neural correlates of reading predicts that in dyslexia dorsal temporoparietal deficits are present early in development and ventral occipitotemporal deficits arise later in development (Pugh et al., 2001, 2000; Turkeltaub et al., 2003). However, it should be noted that until recently very little empirical research was performed on neuroanatomical anomalies in pre-readers who develop dyslexia (Clark et al., 2014; Kraft et al., 2016; Vanderauwera et al., 2017). Furthermore, for pre-readers with a family risk for dyslexia who become typical readers we do not have specific expectations yet regarding the manifestation of anomalies in the reading network, since family risk for dyslexia and dyslexia status were intertwined in most former pre-reading studies focusing on similar ROIs (see for instance Raschle et al., 2011, 2017; Black et al., 2012). Regarding counterpart regions, we expect to observe anomalies in these regions, because several past studies have indicated bilateral anomalies in individuals with dyslexia (Brambati et al., 2004; Brown et al., 2001; Kronbichler et al., 2008; Williams, Juranek, Cirino, & Fletcher, 2018) and two meta-analyses specifically predicted anomalies in the right superior temporal gyrus (Linkersdörfer et al., 2012; Richlan et al., 2013). Finally, evidence is conflicting on whether differences in cortical thickness (Altarelli et al., 2013; Clark et al., 2014; Williams et al., 2018) or in surface area (Altarelli et al., 2014; Black et al., 2012; Vanderauwera et al., 2018) can be expected.

2. Methods

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Participants

The original sample consisted of 87 Flemish children, of which 44 children had a family risk for dyslexia (FRD^+) and 43 children had no family risk for dyslexia (FRD^-) (see also Vanderauwera et al., 2017; Vandermosten et al., 2015). Family risk was defined as having a first degree relative (a parent or a sibling) with a clinical diagnosis of dyslexia. FRD^- children

were individually matched to FRD$^+$ children on age, gender, educational environment (same school and class), non-verbal IQ and socio-economic status (SES) of the parents. SES was assessed by the Family Affluence Scale (Boudreau & Poulin, 2009; Boyce, Torsheim, Currie, & Zambon, 2006), a self-report questionnaire of family wealth that was filled in by one of the parents.

All children fulfilled the following inclusion criteria: 1) born in 2006 (5 to 6 years old during the MRI session); 2) no history of brain damage, articulatory problems, visual or auditory impairments (i.e., Pure Tone Average of 20 dB HL or lower); 3) Dutch as native language and spoken language at home; 4) a non-verbal IQ of 80 or higher on the Coloured Progressive Matrices (Raven, Court, & Raven, 1984; 5) no elevated risk for developing attention deficit hyperactivity disorder (ADHD), as determined by a cut-off score of 9 or 10 out of 10 on the scale of hyperactivity in the Strengths and Difficulties Questionnaire (Goodman & Goodman, 2009). The latter helped to assure that observed group differences in readers with dyslexia (who have a higher prevalence of ADHD) were related to dyslexia and not ADHD. Additionally, non-verbal and verbal intelligence were tested (again) by means of the WISC-III-NL subtests Block Design and Vocabulary at the start of grade 2 (Kort et al., 2005). Furthermore, handedness had been tested with the Edingburgh Handedness Inventory (Oldfield, 1971). Importantly, in line with the Flemish educational system, none of the participants had received formal reading instruction (http://www.ond.vlaanderen.be/).

The original sample of 87 participants performed a cognitive-behavioural test battery every year from the last year of kindergarten to the 5th grade of primary school. Besides reading and spelling, different aspects of phonological processing, speech perception and auditory processing were assessed. In addition, the sample underwent EEG and MRI acquisitions every two years in turn (see Vanvooren, Poelmans, Hofmann, Ghesquière & Wouters et al., 2014; Vandermosten et al., 2015; Vanvooren, Poelmans, De Vos, Ghesquière, & Wouters, 2017; Vanderauwera et al., 2018, 2017; Vandermosten, Cuynen, Vanderauwera, Wouters, & Ghesquière, 2017; De Vos, Vanvooren, Vanderauwera, Ghesquiere, & Wouters, 2017a; b). From the original sample, 71 children (mean age: 74 months; SD: 3 months), participated in the first MRI session, which was assessed before the start of the 1st grade. A child-friendly 'submarine' protocol was introduced to the participants to make them acquainted with the scanning procedure (Theys, Wouters, & Ghesquiere, 2014). Visual inspection of the T1-weighted images revealed that images of 17 participants showed severe motion as defined by Blumenthal's criteria, i.e., severe ringing and blurring artifacts due to which they are unusable for analyses purposes (Blumenthal, Zijdenbos, Molloy, & Giedd, 2002; Phan, Smeets, Talcott, & Vandermosten, 2017). These images were excluded from our study. The remaining study sample consisted of 54 children of whom 31 children were FRD$^+$ and 23 children were FRD$^-$. Children were retrospectively classified as typical readers (TR, n = 38) or readers with dyslexia (DR, n = 16) based on standardized word reading (Brus & Voeten, 1973) and pseudo-word reading (Van den Bos, Spelberg, Scheepstra, & de Vries, 1994) tests. These tests were obtained during the first semester of the 2nd, 3rd and 4th grade, and the second semester of the 5th grade of primary school. Dyslexia was classified by applying both a severity (i.e., below the 10th percentile) and persistence (i.e., at the last two or three time points) criterion at the (pseudo-)word level (Gersons-Wolfensberger & Ruijssenaars, 1997). More specifically, children scoring below the 10th percentile on the same reading test (word reading or pseudo-word reading) at the last three time points were classified as reader with dyslexia (n = 15). In case reading was only assessed at two time points, the child's reading scores had to be below the 10th percentile on the same reading test at both time points to be classified as reader with dyslexia (n = 1). Furthermore, difficulties with spelling (i.e., scoring below the 10th percentile at the last three time points) were observed in 7 children who were classified as reader with dyslexia. In addition, all 16 children who were classified as reader with dyslexia had spelling problems at least at one time point. Nearly 30% of our study sample fulfilled our dyslexia criteria (n = 16), 45% of our FRD$^+$ sample (n = 14) and 9% of our FRD$^-$ sample (n = 2). Demographics and behavioural assessments are listed in Tables 1A and B. The study was approved by the local ethical committee of the university hospital (UZ Leuven) and is in accordance with ethical standards described within the declaration of Helsinki. Study procedures or analyses were not pre-registered prior to the research being conducted. Parents had given their informed consent. The conditions of our ethics approval do not permit public archiving of anonymised study data, since consent had only been obtained for the participation in the study, and not to share data with third parties. Researchers seeking access to the study data should contact the last author (pol.ghesquiere@kuleuven.be) explaining the purpose of their request. In accordance with the EU general data protection regulation (GDPR), data will be released to requestors upon the following conditions: consent of the representative of the minor and a formal agreement between parties. Please note that the MRI data cannot be shared under any circumstance, as MRI data are person-specific and therefore cannot be considered anonymous.

2.2. *Reading assessment*

The reading tests assessed were a Dutch standardized one-minute word reading task ('Een-Minuut Test' (EMT)) (Brus & Voeten, 1973) and Dutch standardized two-minute pseudo-word reading task ('Klepel') (Van den Bos et al., 1994). For both reading tests, the score takes into account reading accuracy and speed, and is expressed as the number of (pseudo-)words read accurately within the time limit. Both tests were assessed in the 2nd, 3rd, 4th and 5th grade of primary school. Mean scores and standard errors of the raw scores and the norm scores of these tests are provided in Tables 1A and B. The word reading ('EMT') and pseudo-word reading ('Klepel') tests have legal copyright restrictions and can be ordered via the company Pearson Clinical & Talent Assessment (https://www.pearsonclinical.nl/). Furthermore, cognitive-behavioural precursors of reading, i.e., letter knowledge, phonological awareness and rapid automatized naming, were assessed at the end of kindergarten. Mean scores and standard errors of these tests are also provided in Tables 1A and B.

Table 1A – Demographics and Behavioural Assessments of typical readers (TR) versus readers with dyslexia (DR). Mean score and standard error of raw scores and norm scores are given*. Group means are compared using test statistics (chi-square, independent samples t-tests and Mann–Whitney *U*).

Participants		TR (n = 38) −FRD$^+$ (n = 17) −FRD$^-$ (n = 21)	DR (n = 16) −FRD$^+$ (n = 14) −FRD$^-$ (n = 2)	Test Statistics
Sex (M/F)		24/14	11/5	$\chi^2_{(2)} = .848$, $p = .357$
Age (in months)		74.6 (.5)*	73.3 (.9)	$t_{(52)} = 1.323$, $p = .192$
Non-verbal IQ (Block Design, WISC-III-NL)		99.6 (2.0)	103.1 (3.9)	$t_{(52)} = -.873$, $p = .387$
Verbal IQ (Vocabulary, WISC-III-NL)		95.7 (2.1)	93.1 (2.5)	$t_{(52)} = .685$, $p = .496$
Handedness (L/R)		32/6	14/2	$\chi^2_{(1)} = .097$, $p = .756$
SES		5.3 (.4)	5.7 (.2)	$t_{(52)} = 1.031$, $p = .307$
Pre-reading				
Letter knowledge		11.2 (.6)	8.1 (1.0)	$t_{(52)} = 2.841$, $p = .006$
Phonological Awareness		7.2 (.3)	5.2 (.5)	U = 134, $p = .001$
Rapid Automatized Naming		.7 (.0)	.5 (.0)	U = 151, $p = .004$
Grade 2				
Word reading	Raw score	27.1 (2.1)	10.8 (1.1)	U = 540, $p < .001$
	Norm score	105.7 (2.2)	85.9 (1.8)	
Pseudo-word reading	Raw score	20.4 (1.5)	8.1 (.7)	U = 547, $p < .001$
	Norm score	106.3 (2.1)	84.5 (1.6)	
Grade 3				
Word reading	Raw score	45.2 (1.9)	19.2 (2.0)	$t_{(52)} = 8.231$, $p < .001$
	Norm score	107.7 (1.5)	81.8 (2.0)	
Pseudo-word reading	Raw score	32.6 (1.7)	13.9 (1.5)	$t_{(52)} = 6.554$, $p < .001$
	Norm score	107.1 (1.7)	83.6 (2.6)	
Grade 4				
Word reading	Raw score	55.7 (2.1)	28.3 (2.2)	$t_{(48)} = 7.681$, $p < .001$
	Norm score	107.7 (1.9)	83.3 (1.5)	
Pseudo-word reading	Raw score	42.9 (2.4)	17.8 (1.7)	$t_{(47)} = 8.385$, $p < .001$
	Norm score	107.2 (1.8)	83.4 (2.2)	
Grade 5				
Word reading	Raw score	70.7 (2.3)	41.5 (2.5)	$t_{(46)} = 7.766$, $p < .001$
	Norm score	107.8 (1.9)	85.8 (3.1)	
Pseudo-word reading	Raw score	62.7 (2.4)	29.2 (3.3)	$t_{(42)} = 8.066$, $p < .001$
	Norm score	107.7 (1.5)	81,8 (2.0)	

2.3. *Image acquisition*

In our study, 71 MRI scans were acquired at the last year of kindergarten. T1-weighted MR images were gathered on a Philips 3T-scanner (Best, The Netherlands) with 3D Turbo field echo acquisition using a 32-channel head coil. In the scanner, 182 contiguous coronal slices were collected with the following parameter settings: TR = 9.6 msec; TE = 4.6 msec; flip angle = 8°; FOV = 250 × 250 × 218 mm^3; voxel size = 1 × 1 × 1.2 mm^3. Scans were taken at the university hospital of Leuven (UZ Leuven). Scanning sessions lasted around half an hour and T1-weighted images were acquired in 6 min and 22 sec.

2.4. *Image processing*

All images were (pre)processed in FreeSurfer (http://www.freesurfer.net/) version 5.3 via the automated reconstruction process. Details on this process can be found in prior publications (Dale, Fischl, & Sereno, 1999; Fischl et al., 2002; Fischl, Liu, & Dale, 2001; Reuter, Rosas, & Fischl, 2010; Ségonne et al., 2004; Sled, Zijdenbos, & Evans, 1998). In brief, the automated reconstruction process includes removal of non-brain tissue via a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automatic Talairach transformation, segmentation of gray/white matter structures (Fischl et al., 2002), intensity normalization (Sled et al., 1998), gray/white matter boundary tessellation, automated topological correction (Fischl et al., 2001) and surface deformation following intensity gradients to optimally place gray matter/white matter/CSF borders (Dale et al., 1999).

Regions of interest (ROIs) were a priori defined and were the left inferior, middle and superior temporal gyri, the pars opercularis of the inferior frontal gyrus, the inferior parietal lobule and the fusiform gyrus of the reading network (see the meta-analysis of Richlan et al., 2009). In addition, corresponding right hemispheric regions were included. These ROIs were selected from the Desikan-Killiany atlas, which was implemented in FreeSurfer. The Desikan-Killiany atlas automatically subdivides the human cortex into 34 gyral regions-of-interest based on anatomical markers of curvature and sulcal information on the inflated brain images (Desikan et al., 2006).

As recommended by FreeSurfer, T1-weighted images were visually inspected and manually edited in the supporting toolbox Freeview in order to remove segmentation errors.

Table 1B – Demographics and Behavioural Assessments of children without a family risk for dyslexia (FRD$^-$) versus (Children with a family risk for dyslexia (FRD$^+$). Mean score and standard error of raw scores are given*. Group means are compared using test statistics (chi-square, independent samples *t*-tests and Mann–Whitney *U*).

Participants		FRD$^-$ (n = 23) -TR (n = 21) -DR (n = 2)	FRD$^+$ (n = 31) -TR (n = 17) -DR (n = 14)	Test Statistics
Sex (M/F)		13/10	19/12	$\chi^2_{(2)} = .124$, $p = .724$
Age (in months)		74.9 (.7)*	73.8 (.6)	$t_{(52)} = 1.186$, $p = .241$
Non-verbal IQ (Block Design, WISC-III-NL)		98.9 (2.8)	101.9 (2.4)	$t_{(52)} = -.811$, $p = .421$
Verbal IQ (Vocabulary, WISC-III-NL)		92.2 (2.7)	96.9 (2.1)	$t_{(52)} = -1.415$, $p = .163$
Handedness (L/R)		22/1	24/7	$\chi^2_{(1)} = 3.478$, $p = .062$
SES		5.5 (.4)	5.6 (.2)	$t_{(52)} = -.219$, $p = .828$
Pre-reading				
Letter knowledge		11.5 (.6)	9.3 (.8)	$t_{(52)} = 2.080$, $p = .042$
Phonological Awareness		6.8 (.4)	6.5 (.4)	U = 331.5, $p = .660$
Rapid Automatized Naming		.7 (.0)	.6 (.0)	U = 252.5, $p = .007$
Grade 2				
Word reading	Raw score	27.4 (3.0)	18.8 (2.2)	U = 490, $p = .009$
	Norm score	105.8 (3.0)	95.7 (2.6)	
Pseudo-word reading	Raw score	19.7 (2.0)	14.8 (1.7)	U = 459, $p = .040$
	Norm score	105.0 (3.1)	96.3 (2.6)	
Grade 3				
Word reading	Raw score	45.1 (2.6)	31.8 (2.9)	$t_{(52)} = 3.290$, $p = .002$
	Norm score	107.7 (2.2)	94.3 (2.8)	
Pseudo-word reading	Raw score	32.8 (2.6)	22.8 (2.1)	$t_{(52)} = 3.019$, $p = .004$
	Norm score	106.8 (2.5)	95.2 (2.8)	
Grade 4				
Word reading	Raw score	54.1 (3.1)	42.7 (3.3)	$t_{(48)} = 2.462$, $p = .017$
	Norm score	106.2 (2.8)	96.1 (2.8)	
Pseudo-word reading	Raw score	42.1 (3.5)	30.5 (3.0)	$t_{(48)} = 2.498$, $p = .016$
	Norm score	106.4 (2.6)	95.5 (2.9)	
Grade 5				
Word reading	Raw score	68.0 (3.3)	56.6 (3.7)	$t_{(46)} = 2.261$, $p = .029$
	Norm score	105.6 (2.8)	97.3 (3.0)	
Pseudo-word reading	Raw score	59.3 (3.9)	46.5 (4.2)	$t_{(42)} = 2.157$, $p = .037$
	Norm score	105.7 (2.8)	95.8 (3.1)	

Freeview allows manual editing of the images, i.e., adding or deleting of voxels, to ensure that pial, gray and white matter surfaces are well-segmented. Details on manual editing (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TroubleshootingData) are provided by FreeSurfer and editing guidelines were followed in strict sequential order to ensure consistency of the editing process. In short, manual editing consisted of fixing: a) skull stripping errors, b) intensity normalization errors, c) white matter errors, d) topological errors and e) pial errors. Edits were made in coronal, sagittal and axial views, and checked on the inflated 3D surfaces. Per child, editing took approximately 15 h. After editing, the images underwent the automated reconstruction process again. Finally, surface area and cortical thickness measures were extracted per ROI.

2.5. *Statistical analyses*

Analyses were run in IBM SPSS version 25.0 (IBM Corp., 2017) and in FreeSurfer version 5.3 on an Ubuntu 14.02 OS. Demographics were analyzed with Chi-Square (for the variables sex, handedness) and independent samples *T*-tests (for the variables age, non-verbal IQ, SES). Surface-based ROI analyses were performed using full factorial linear mixed effect models in SPSS in order to compare between groups surface area and cortical thickness of the six ROIs in the reading network and the corresponding right hemispheric regions. First, we compared TR versus DR, and FRD$^-$ versus FRD$^+$ groups. Second, in order to cross-check the neuroanatomical substrate of dyslexia while controlling for family risk, we additionally compared TR_FRD$^+$ versus DR_FRD$^+$ (i.e., 2 subgroups that are matched for family risk, but differ in reading level). In addition, in order to cross-check the neuroanatomical correlates of family risk for dyslexia while controlling for reading level, we additionally compared TR_FRD$^-$ versus TR_FRD$^+$ (i.e., 2 subgroups that are matched for reading level, but differ in family risk for dyslexia). For the main and subgroup analyses of surface area and cortical thickness, a best model fit was searched for and the model with the lowest AIC-value was selected. The best fitting models were identical for the main and subgroup analyses, and were: surface area = group + region + hemisphere + group*region + region*hemisphere and cortical thickness = group + region + hemisphere + region*hemisphere. The independent factors in the model were fixed, and subject was included as random intercept. Intra-class correlations of all selected models were moderate (i.e., between .043 and .055) and the variances of the intercept were highly significant ($p < .001$). For surface area, residuals of

the selected models were normally distributed. For cortical thickness, residuals of the selected models were normally distributed for the subsample analyses in contrast to the whole group analyses. Yet, mixed model analysis is robust in analyzing semi-normally distributed data (Verbeke & Lesaffre, 1997). Bonferroni-adjusted results were presented. In the mixed model analyses, only significant results with group as a factor were analyzed post hoc, since we were interested in group differences. Furthermore, whole brain analyses were performed in which group differences were investigated via general linear models that were run in FreeSurfer. The whole brain analyses are additional analyses to see whether certain results from the ROI-analyses failed to show up due to averaging across relatively large areas. Relevant outcomes of these analyses are provided as supplementary material, since they are not directly related to our hypotheses. Finally, across the whole sample correlation analyses were performed between regions displaying morphometric group differences and cognitive-behavioural precursors of reading, i.e., letter knowledge, phonological awareness and rapid automatized naming. Correlation analyses were performed to examine which cognitive functions might be sustained by each of these regions.

3. Results

3.1. *Demographics & behavioural assessments*

Tables 1A and B shows demographics and behavioural assessments of all participants (n = 54), including test statistics. Data were presented for TR versus DR and FRD^- versus FRD^+.

3.2. *Group comparisons on morphological brain differences*

3.2.1. *Surface area*

❖ Dyslexia-related group differences

Results comparing TR and DR groups revealed that the main effects of region ($F_{(5,594)} = 1131.756$; $p < .001$) and hemisphere ($F_{(1,594)} = 21.552$; $p < .001$) were significant, whereas the main effect of group ($F_{(1,54)} = 2.809$; $p = .100$) was not. In addition, there was a significant region by hemisphere interaction ($F_{(5,594)} = 54.592$; $p < .001$) and group by region interaction ($F_{(5,594)} = 5.045$; $p < .001$). Bonferroni-adjusted post-hoc analyses of the group by region interaction indicated that there was a significant difference in the surface area of the fusiform gyrus between DR and TR ($F_{(1,103)} = 13.764$; $p < .001$), revealing a smaller surface area in DR (Fig. 1). Contrary, there were no significant differences between the groups in the surface area of the inferior parietal, inferior temporal, middle temporal, pars opercularis of the inferior frontal or superior temporal gyrus. Results are summarized in Table 2A (Supplementary Material).

Results comparing TR_FRD^+ and DR_FRD^+ subgroups (controlling for a family risk for dyslexia) confirmed the above analysis that the main effects of region ($F_{(5,341)} = 887.673$; $p < .001$) and hemisphere ($F_{(1,341)} = 21.783$; $p < .001$) were significant, whereas the main effect of group ($F_{(1,31)} = .349$; $p = .559$) was not. In addition, it was confirmed that there was a significant region by hemisphere interaction ($F_{(5,341)} = 35.293$; $p < .001$) and group by region interaction ($F_{(5,341)} = 5.494$; $p < .001$). Bonferroni-adjusted post-hoc analyses of the group by region interaction indicated that there was a significant difference in the surface area of the fusiform gyrus ($F_{(1,52)} = 7.965$; $p = .007$) between DR_FRD^+ and TR_FRD^+, revealing a smaller surface area in DR_FRD^+. Contrary, there were no significant differences between the groups in the surface area of the inferior parietal, inferior temporal, middle temporal, pars opercularis of the inferior frontal or superior temporal gyrus. Results are summarized in Table 2B (Supplementary Material).

❖ Family risk-related group differences

Results comparing FRD^- and FRD^+ groups revealed that the main effects of region ($F_{(5,594)} = 1320.085$; $p < .001$) and hemisphere ($F_{(1,594)} = 21.612$; $p < .001$) were significant, whereas the main effect of group ($F_{(1,54)} = 1.782$; $p = .188$) was not. In addition, there was a significant region by hemisphere interaction ($F_{(5,594)} = 54.744$; $p = < .001$) and group by region interaction ($F_{(5,594)} = 5.390$; $p < .001$). Bonferroni-adjusted post-hoc analyses of the group by region interaction indicated that there was a significant difference in the surface area of the inferior temporal gyrus ($F_{(1,102)} = 11.636$; $p = .001$) and middle temporal gyrus ($F_{(1,102)} = 3.979$; $p = .049$) between FRD^+ and FRD^-, revealing a smaller surface area in FRD^+ (Fig. 2). Contrary, there were no significant differences between the groups in the surface area of the fusiform, inferior parietal, pars opercularis of the inferior frontal or superior temporal gyrus. Results are summarized in Table 2C (Supplementary Material).

Results comparing TR_FRD^- and TR_FRD^+ subgroups (controlling for reading level) confirmed the above analysis that the main effects of region ($F_{(5,418)} = 907.428$; $p < .001$) and hemisphere ($F_{(1,418)} = 17.229$; $p < .001$) were significant, whereas the main effect of group ($F_{(1,38)} = 1.138$; $p = .293$) was not. In addition, it was confirmed that there was a significant region by hemisphere interaction ($F_{(5,418)} = 41.007$; $p < .001$) and group by region interaction ($F_{(5,418)} = 5.230$; $p < .001$). Bonferroni-adjusted post-hoc analyses of the group by region interaction indicated that there was a significant difference in the surface area of the inferior temporal gyrus ($F_{(1,69)} = 7.453$; $p = .008$) and middle temporal gyrus ($F_{(1,69)} = 4.181$; $p = .045$) between TR_FRD^+ and TR_FRD^-, revealing a smaller surface area in TR_FRD^+. Contrary, there were no significant differences between the groups in the surface area of the fusiform, inferior parietal, pars opercularis of the inferior frontal or superior temporal gyrus. Results are summarized in Table 2D (Supplementary Material).

3.2.2. *Cortical thickness*

❖ Dyslexia-related group differences

Results comparing TR and DR groups revealed that there was no main effect of group ($F_{(1,54)} = 1.145$; $p = .289$). Contrary, there was a main effect of region ($F_{(5,594)} = 163.800$; $p < .001$)

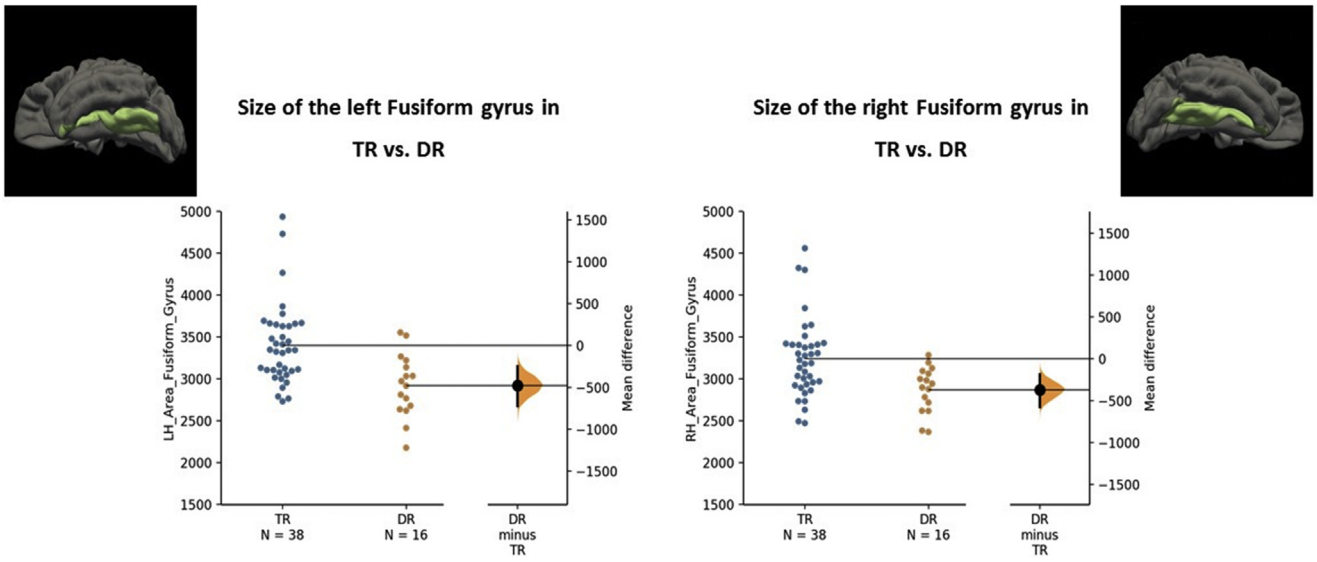

Fig. 1 – Size of the left and right fusiform gyrus in typical readers (TR) versus readers with dyslexia (DR). The left axis shows for TR and DR per individual the size of the left and right fusiform gyrus, respectively. The right axis shows for TR and DR the corresponding effect size (i.e., the mean difference between DR and TR). The filled curve represents the mean difference distribution, given the data. Horizontally aligned with the mean of DR, the mean difference is illustrated by the black circle. The 95% confidence interval of the mean difference is indicated by the black vertical line. Plots have been created via www.estimationstats.com (Ho, Tumkaya, Aryal, Choi, & Claridge-Chang, 2019).

and hemisphere ($F_{(1,594)} = 47.754$; $p < .001$). In addition, there was a significant region by hemisphere interaction ($F_{(5,594)} = 8.236$; $p < .001$). There were no significant interactions with group. Results are summarized in Table 3A (Supplementary Material).

Results comparing TR_FRD$^+$ and DR_FRD$^+$ subgroups (controlling for family risk) confirmed the above analysis that there was no main effect of group ($F_{(1,31)} = .005$; $p = .942$), whereas there was a main effect of region ($F_{(5,341)} = 87.313$; $p < .001$) and hemisphere ($F_{(1,341)} = 27.041$; $p < .001$). In addition, it was confirmed that there was a significant region by hemisphere interaction ($F_{(5,341)} = 4.487$; $p = .001$). Again, there were no significant interactions with group. Results are summarized in Table 3B (Supplementary Material).

❖ Family risk-related group differences

Results comparing FRD$^-$ and FRD$^+$ groups revealed that there was no main effect of group ($F_{(1,54)} = .176$; $p = .676$). Contrary, there was a main effect of region ($F_{(5,594)} = 163.800$; $p < .001$) and hemisphere ($F_{(1,594)} = 47.754$; $p < .001$). In addition, there was a significant region by hemisphere interaction ($F_{(5,594)} = 8.236$; $p < .001$). There were no significant interactions with group. Results are summarized in Table 3C (Supplementary Material).

Results comparing TR_FRD$^-$ and TR_FRD$^+$ subgroups (controlling for reading level) confirmed the above analysis that there was no main effect of group ($F_{(1,38)} = 1.029$; $p = .317$), whereas there was a main effect of region ($F_{(5,418)} = 119.756$; $p < .001$) and hemisphere ($F_{(1,418)} = 35.187$; $p < .001$). In addition, it was confirmed that there was a significant region by hemisphere interaction ($F_{(5,418)} = 6.600$; $p < .001$). Again, there were no significant interactions with group. Results are summarized in Table 3D (Supplementary Material).

3.3. *Correlation analyses*

❖ Dyslexia-related correlation analyses

For the left and right fusiform gyrus that according to the surface-based ROI analyses are linked to dyslexia *per se*, it was investigated whether they are related to letter knowledge, phonological awareness and rapid automatized naming. Correlation analyses revealed that pre-reading the left fusiform gyrus is related to phonological awareness ($r = .382$; $p = .009$), whereas the right fusiform gyrus is not ($r = .297$, $p = .056$). There were no further significant correlations (see Supplementary Material).

❖ Family risk-related correlation analyses

For the left and right inferior temporal and middle temporal gyrus that according to the surface-based ROI analyses are linked to a family risk for dyslexia, it was investigated whether they are related to letter knowledge, phonological awareness and rapid automatized naming. The analyses revealed no significant correlations (see Supplementary Material).

3.4. *Whole brain analyses*

Results of the whole brain analyses revealed that neuroanatomical anomalies can be found in the left fusiform gyrus (see Supplementary Material).

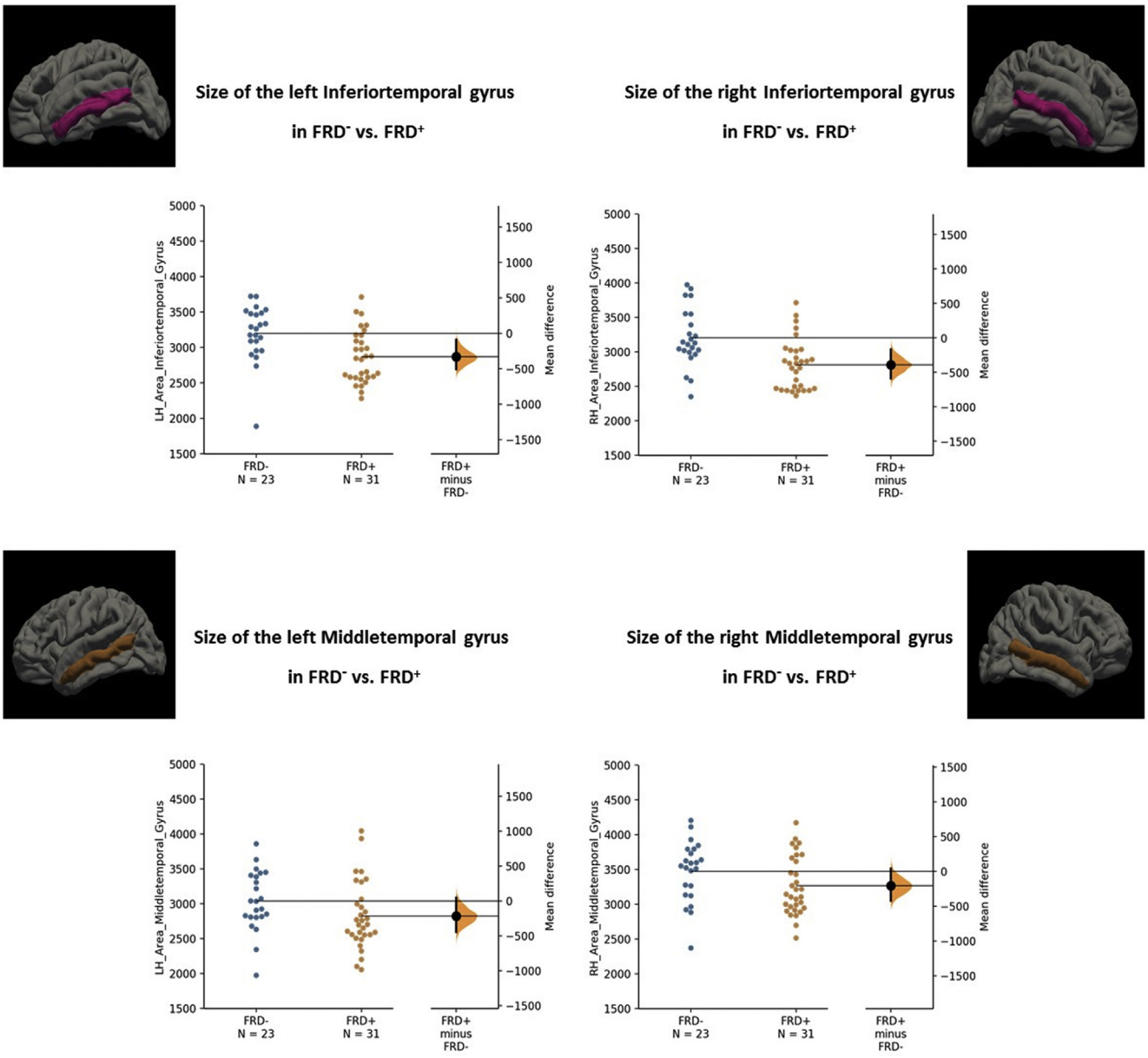

Fig. 2 – Size of the left and right inferior temporal gyrus and middle temporal gyrus in children without a family risk for dyslexia (FRD^-) versus children with a family risk for dyslexia (FRD^+). The left axis shows for FRD^- and FRD^+ per individual the size of the left and right inferior temporal gyrus (above) and middle temporal gyrus (below), respectively. The right axes show for FRD^- and FRD^+ the corresponding effect size (i.e., the mean difference between FRD^+ and FRD^-). The filled curves represent the mean difference distribution, given the data. Horizontally aligned with the mean of DR, the mean difference is illustrated by the black circle. The 95% confidence interval of the mean difference is indicated by the black vertical line. Plots have been created via www.estimationstats.com (Ho et al., 2019).

4. Discussion

The current study is one of the few studies focusing on morphological gray matter differences in developmental dyslexia prior to formal reading instruction. The study is unique because of its design allowing independent investigation of family risk for dyslexia and dyslexia *per se*, i.e., children with and without a family risk for dyslexia were followed-up from the last year of kindergarten until the 5th grade of primary school and in retrospect defined as pre-reader developing typical reading skills or pre-reader developing dyslexia. In addition, the study included both measures of surface area and cortical thickness. In the study, we focused on specific regions of the reading network, i.e., the fusiform gyrus, the inferior parietal gyrus, the inferior temporal gyrus, the middle temporal gyrus, the pars opercularis of the inferior frontal gyrus and the superior temporal gyrus as well as their homologous right hemispheric counterparts. More specifically, we investigated pre-reading if gray matter differences

in surface area and cortical thickness in these regions are present in children developing dyslexia or in children with a family risk for dyslexia. As a consequence, it is possible to give some valuable insights on neuroanatomical anomalies in size or thickness of these regions related to either a family risk for dyslexia or dyslexia *per se*. The main findings in our study are that the bilateral fusiform gyrus has a smaller surface area in children developing dyslexia, and that a smaller bilateral inferior and middle temporal gyrus area are specifically related to a family risk for dyslexia. In addition, morphological differences are observed in surface area, as opposed to cortical thickness.

One important observation in our study is that group differences related to dyslexia are mainly found in a ventral region of the reading network, i.e., the fusiform gyrus, in contrast to more dorsal temporoparietal regions. The finding is supported by the whole brain analyses, revealing a cluster in the left fusiform gyrus nearby the suggested location of the VWFA (Vogel, Petersen, & Schlaggar, 2012) with less gray matter in pre-readers who will develop dyslexia as opposed to pre-readers who become typical readers. However, the finding is in contrast with the classical model on the neural correlates of reading, which suggests early onset recruitment of temporoparietal regions and later onset recruitment of occipitotemporal regions. In addition, the model predicts that temporoparietal deficits in dyslexia are present during early reading development, whereas occipitotemporal deficits in dyslexia arise during later reading development (Pugh et al., 2001, 2000; Turkeltaub et al., 2003). Yet, also other pre-reading studies revealed early onset of ventral deficits in children with a family risk for dyslexia (see the review of Vandermosten et al., 2016). Richlan, Kronbichler, and Wimmer (2011) reported in their functional magnetic resonance imaging (fMRI) meta-analysis that underactivation in the occipitotemporal cortex, as opposed to the temporoparietal cortex, is apparent in children with dyslexia. They suggested that an early failure of the occipitotemporal cortex in dyslexia is an indication of its early involvement in typical reading development. Indeed, early recruitment of the ventral occipitotemporal cortex in reading has been supported by studies of Brem et al., 2010 and Dehaene-Lambertz, Monzalvo, and Dehaene (2018). Brem et al. (2010) revealed in their fMRI and event-related potential (ERP) study that the occipitotemporal cortex is recruited in pre-reading children when learning grapheme-phoneme coupling. Dehaene-Lambertz et al. (2018) recently discovered in their fMRI study that the VWFA at the onset of reading acquisition rapidly emerges at its final location within the fusiform gyrus, nearby an organized region with originally a high selectivity to faces, houses, bodies or tools. At this location the VWFA quickly becomes fine-tuned for written whole-words. Another important observation in our study is that prior to reading the left fusiform gyrus sustains an important behavioural precursor of later reading skills, i.e., phonological awareness. Hence, the left fusiform gyrus is involved in phonological processes besides orthographic processes, at least in the pre-reading stage. However, this contrasts the classical model on the neural correlates of reading, since the model assumes that ventral areas in the brain contribute to orthographical processes and dorsal areas in the brain to phonological processes. Yet, a recent fMRI study of Zhao et al. (2017) on typical reading adults revealed that the middle and anterior fusiform gyrus represent both phonological and orthographic processes. In addition, other pre-reading studies suggest that phonological awareness relates to the left occipitotemporal region (Raschle et al., 2011; Raschle, Zuk, & Gaab, 2012; Vandermosten et al., 2015; see Vandermosten et al., 2016).

Our study reveals that dyslexia in the pre-reading phase is not accompanied with morphological differences in dorsal temporoparietal regions of the brain. Contrary, several structural (Black et al., 2012; Brambati et al., 2004; Im et al., 2016; Raschle et al., 2017, 2011; Vanderauwera et al., 2018; Yamada et al., 2011) and functional (Brambati et al., 2006; Dębska et al., 2016; Raschle et al., 2012) studies on children at family risk for dyslexia reported differences in temporoparietal regions. However, each of these studies differed in design from our study. For instance, Im et al. (2016) studied sizes of sulcal basin areas in pre-readers with familial risk for dyslexia and school-aged children with dyslexia, and revealed atypical sulci (i.e., more sulci of smaller sizes) in left temporoparietal and occipitotemporal areas. Because they obtained similar results for both groups, they suggested that these are an inherent feature of dyslexia. Yet, sizes of sulcal basin areas are difficult to relate to sizes of surface area *per se*, due to which their result may differ from ours, i.e., the sulcal basins of certain brain regions may be atypical (i.e., more sulci of smaller sizes), whereas the total surfaces of these areas may not differ. From studies on children at family risk for dyslexia that reported differences in temporoparietal regions, Black et al. (2012) and Vanderauwera et al. (2018) are most similar to our study in their design. Black et al. (2012) did a morphological study in which they, similar to our study, implemented an automatized surface-based registration approach in FreeSurfer. They reported smaller bilateral prefrontal and temporoparietal gray matter volumes. However, Black et al. (2012) included pre-readers with and without a family *and* behavioural risk for dyslexia in a single group, regardless of their dyslexia status. Vanderauwera et al. (2018) revealed that atypical asymmetry of the planum temporale is related to a family risk for dyslexia in pre-readers with and without a family risk for dyslexia. Our study sample largely overlapped with the study sample of Vanderauwera et al. (2018), yet we failed to observe anomalies in the superior temporal region. However, Vanderauwera et al. (2018) specifically investigated lateralization of the planum temporale, whereas we focused on morphological differences in the left and right hemisphere of the superior temporal gyrus, respectively. These examples indicate that differences between studies in sample composition or analysis method singly may result into different findings. Future studies adopting a similar study design should confirm whether anomalies in pre-readers at family risk for dyslexia or developing dyslexia are absent in temporoparietal regions.

Whereas a smaller fusiform gyrus is related to dyslexia *per se*, a smaller surface area of the inferior and middle temporal gyri is related to a family risk for dyslexia. Specifically, our results indicate that the temporal cortex is smaller in children with a family risk for dyslexia, regardless of whether they will develop dyslexia or not. However, the obtained results related to a family risk for dyslexia (i.e., a smaller area of the inferior and middle temporal gyrus) seem less robust than the finding

of left fusiform differences between TR and DR, as the whole brain analyses (in which a more strict correction for multiple comparisons is applied) could not confirm these differences. Hence, they should be interpreted with caution. An fMRI study of Cohen, Jobert, Le Bihan, and Dehaene (2004) indicated another region besides the VWFA involved in written and spoken word processing, i.e., the lateral inferior temporal multimodal area (LIMA). The LIMA is located at the border of (lateral and slightly anterior to) the VWFA in the inferior temporal gyrus. It is activated both by spoken and written words - i.e., multimodal - as opposed to the VWFA, which is activated only by written words - i.e., unimodal -, and is thought to be involved in the integration of phonology, orthography and semantics (Danelli et al., 2013; Devlin, Jamison, Gonnerman, & Matthews, 2006; Paulesu, Danelli, & Berlingeri, 2014). Recently, it was mentioned that during reading the LIMA, the VWFA and a third undefined region within the posterior fusiform become co-activated, and that functional integration of these three regions is needed for fast and efficient reading (Danelli et al., 2017). Our results suggest that typical development of the VWFA before the onset of reading is a prerequisite for achieving efficient reading skills later on, as they reveal that the left fusiform gyrus is related to dyslexia *per se*. Typical development of the LIMA might be needed in addition, as our results indicate that the inferior temporal cortex is related to a family risk for dyslexia and since 30–50% of the at-riskers for dyslexia will develop dyslexia. Our results are congruent with the view that normal functioning of, and between, both regions is needed to obtain fluid reading skills.

Results of our study are not restricted to the left hemisphere. Surprisingly, a smaller surface area in pre-readers with (a family risk for) dyslexia is observed in both left and right ventral regions. Yet, similar to the obtained results related to a family risk for dyslexia (i.e., a smaller area of the inferior and middle temporal gyrus), the finding of right fusiform differences between TR and DR seems to be less robust and should be interpreted with caution, as the whole brain analyses could not confirm these differences. As far as known, only a small number of studies reported right hemispheric differences in occipitotemporal regions (Brambati et al., 2004; Debska et al., 2016; Kronbichler et al., 2008; Raschle et al., 2012; Williams et al., 2018). Raschle et al. (2012) and Debska et al. (2016) revealed in their fMRI studies that children at family risk for dyslexia have decreased activation in the bilateral occipitotemporal cortex pre-reading and at early reading onset. Williams et al. (2018) indicated in their MRI study a thinner bilateral occipitotemporal cortex in children with dyslexia. Brambati et al. (2004) and Kronbichler et al. (2008) reported in their VBM studies reduced gray matter volume of the right fusiform gyrus in adolescents and adults with (a family risk for) dyslexia. In line with these results, we suggest that bilateral anomalies in occipitotemporal regions might be present over the course of development.

Finally, differences are observed in surface area, in correspondence with Black et al. (2012), Altarelli et al. (2014) and Vanderauwera et al. (2018). Differences in surface area are more related to prenatal influences. Prenatal influences suggest that they do not develop slowly over the developmental course, but predominantly in utero, and are therefore present from birth onwards. Hence, dyslexia is considered to manifest in utero, suggesting that genes or cortical neural migration processes play a dominant role in its onset. Differences in cortical thickness are absent in our study, in contrast to what has been reported by Altarelli et al. (2013), Clark et al. (2014) and Williams et al. (2018). Yet, note that we studied our participants pre-reading, whereas these studies (also) included children of approximately ten years on average. Cortical thickness is assumed to develop post-natal due to which it is possible that anomalies in cortical thickness may not be absent in dyslexia altogether, but slightly reveal itself throughout the first ten years. Clark et al. (2014) support the latter, as they revealed that differences in cortical thickness in the reading network could not be observed pre-reading in children developing dyslexia, but were present when these children were eleven years old.

The current study has a few limitations. First, it is not known to what extent parents offered their children reading instructions at home. However, since children were below the level they learn to read at school (i.e., last year of kindergarten) differences in reading skills should be minimal, as none of the children had received any formal reading instruction yet. Second, an experimental limitation of our study is that young children tend to move inside the scanner. Even though we had applied a child friendly protocol and we had carefully prepared the children for their scanning session, a significant amount of the data showed moderate or severe motion according to Blumenthal's criteria. However, two independent raters rated the images and came to an agreement with regards to assigning the images to movement categories in correspondence with Blumenthal's criteria. Importantly, all images with severe ringing and blurring artifacts that were unusable for analyses purposes, were excluded. Third, results on the right fusiform gyrus, bilateral inferior temporal gyrus and bilateral middle temporal gyrus were absent for the surface-based whole brain analyses. However, the whole brain analyses were vertex-based, and on top of a correction for all vertices in the brain, an additional cluster-wise correction was performed (keeping clusters with a p-value below .05). These corrections were stricter than the hypotheses-driven analyses we conducted, indicating that the group differences in the right fusiform, bilateral inferior and middle temporal regions are less robust than in the left fusiform gyrus. Finally, the study has limited power, although it contains a relatively high amount of children with a family risk for dyslexia that were willing to undergo an MRI at a young age (74 months on average).

To summarize, children who develop dyslexia show already in the pre-reading phase anomalies in a core region of the reading network, i.e., the left fusiform gyrus, and in its right hemispheric counterpart. In addition, in children with a family risk for dyslexia, whether developing dyslexia or not, anomalies are observed in the bilateral inferior and middle temporal gyri. The observed differences are in surface area, suggesting predominantly prenatal causes. Finally, since

anomalies are observed in the pre-reading phase, they are not the consequence of impoverished reading experience.

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CRediT authorship contribution statement

Caroline Beelen: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization. **Jolijn Vanderauwera:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing - review & editing. **Jan Wouters:** Methodology, Visualization, Resources, Supervision, Project administration, Funding acquisition. **Maaike Vandermosten:** Conceptualization, Methodology, Validation, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Pol Ghesquière:** Conceptualization, Methodology, Validation, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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Supplementary data

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