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Structural white matter connectometry of reading and dyslexia

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ABSTRACT

Current views on the neural network subserving reading and its deficits in dyslexia rely largely on evidence derived from functional neuroimaging studies. However, understanding the structural organization of reading and its aberrations in dyslexia requires a hodological approach, studies of which have not provided consistent findings. Here, we adopted a whole brain hodological approach and investigated relationships between structural white matter connectivity and reading skills and phonological processing in a cross-sectional study of 44 adults using individual local connectome matrix from diffusion MRI data. Moreover, we performed quantitative anisotropy aided differential tractography to uncover structural white matter anomalies in dyslexia (23 dyslexics and 21 matched controls) and their correlation to reading-related skills. The connectometry analyses indicated that reading skills and phonological processing were both associated with corpus callosum (tapetum), forceps major and minor, as well as cerebellum bilaterally. Furthermore, the left dorsal and right thalamic pathways were associated with phonological processing. Differential tractography analyses revealed structural white matter anomalies in dyslexics in the left ventral route and bilaterally in the dorsal route compared to the controls. Connectivity deficits were also observed in the corpus callosum, forceps major, vertical occipital fasciculus and corticostriatal and thalamic pathways. Altered structural connectivity in the observed differential tractography results correlated with poor reading skills and phonological processing. Using a hodological approach, the current study provides novel evidence for the extent of the reading-related connectome and its aberrations in dyslexia. The results conform current functional neuroanatomical models of reading and developmental dyslexia but provide novel network-level and tract-level evidence on structural connectivity anomalies in dyslexia, including the vertical occipital fasciculus.

1. Introduction

Reading is a complex cognitive process in which the reader constructs meaning by decoding written symbols (Snowling and Melby-Lervåg, 2016). This requires efficient integration and processing of sensory inputs and employment of a complex neural network (Fiez and Petersen, 1998; Kujala et al., 2007; Turkeltaub et al., 2003). Functional neuroimaging studies have established that the neural network sub-serving reading comprises left tempo-parietal, occipitotemporal and inferior frontal regions (for meta-analyses, see Jobard et al., 2003; Richlan et al., 2009) as well as right frontotemporal areas and cerebellum (for a meta-analysis, see Martin et al., 2015).

In efficient reading, the cortically processed information is distributed by a network of white matter pathways which form the structural neural network interconnecting the spatially distributed brain regions. Within the reading network, inferior frontal and temporo-parietal regions constitute a dorsal phonological route and the occipitotemporal region sub-serves a ventral orthographical reading route (for a meta-analysis, see Jobard et al., 2003). Due to the anatomical locations of these routes, it has been assumed that the arcuate fasciculus/superior longitudinal fasciculus underpins the dorsal phonological route and the inferior fronto-occipital and inferior longitudinal fasciculi as well as the uncinate fasciculus subserve the ventral orthographical route (for a review and meta-analysis, see Vandermosten et al., 2012b). Moreover, the corpus callosum is assumed to allow efficient interhemispheric connectivity and to drive the left-lateralized reading network (Jobard et al., 2003; Shaywitz et al., 2007). However, a recent Activation Likelihood Estimation (ALE) meta-analysis of white matter structures subserving

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reading reported no significant findings and the structural connectome supporting reading remains unclear (Moreau et al., 2018).

To determine the critical structural connectivity patterns that support reading, studies on developmental dyslexia – a reading-skill impairment that can emerge irrespective of normal intelligence and adequate reading instruction (American Psychiatric Association, 2013) – have been of great interest in neurology and neuroscience. A review and meta-analysis of nine diffusion tensor imaging (DTI) studies in reading and dyslexia concluded that the most consistent finding has been lower fractional anisotropy (FA) in left temporoparietal and frontal regions in children and adult participants with dyslexia as compared to typical readers (Vandermosten et al., 2012b). However, the most recent meta-analysis with up-to-date methodology failed to replicate these findings and reported no reliable differences between dyslexics and typical readers (Moreau et al., 2018). Studies comparing structural white matter differences between dyslexic and typically reading participants have restricted analyses to a limited number of pathways or suffered from small sample sizes (only two studies with sample size > 40, both in children) (Keller and Just, 2009; H.-L. S. Wang et al., 2019) or methodological issues (Moreau et al., 2018; Vandermosten et al., 2012b). For example, an abundance of studies (Beaulieu et al., 2005; Carter et al., 2009; Deutsch et al., 2005; Keller and Just, 2009; Klingberg et al., 2000; Odegard et al., 2009; Richards et al., 2008; Rimrodt et al., 2010; Steinbrink et al., 2008) have implemented voxel-based approaches such as tract-based spatial statistics (TBSS) that reduces volumetric data onto a white matter skeleton (Smith et al., 2006). While being a widely used method, TBSS has recently been criticized for extensive anatomical inaccuracies in skeleton projections and the substantial bias that it can introduce (Bach et al., 2014). Most crucially, TBSS is not tract-specific and can therefore falsify results.

Another common approach in evaluating white matter connectivity is dissection of specific pathways using tractography algorithms (Conturo et al., 1999). The most studied tract in dyslexia research has been the left arcuate fasciculus (Carter et al., 2009; Hoeft et al., 2011; Niogi and McCandliss, 2006; Van Der Auwera et al., 2021; Vanderauwera et al., 2015; Vandermosten et al., 2012a; J. Zhao et al., 2016) with studies reporting FA changes in its long segment interconnecting frontal and temporal regions in dyslexia (Vandermosten et al., 2012b). However, FA has recently received criticism in regarding its accuracy in presenting the diffusion process. Compared to FA, approaches utilizing quantitative anisotropy (QA) have been shown to be less sensitive to the partial volume effects of crossing fibers and free water as well as to provide better resolution in tractography (Yeh et al., 2016b, 2013b). As concluded by Vandermosten and colleagues (2012b), we are far from identifying the structure-function relation with regard to reading and the underlying structural white matter processes in dyslexia as the systematic evaluation of possible reading-related white matter tracts and their contribution to dyslexia has remained scarce.

To overcome the common limitations of tract-based and voxel-based (TBSS) analyses, a novel diffusion MRI analytic approach termed connectometry was recently introduced (Yeh et al., 2016a). Connectometry analysis utilizes QA and has shown greater sensitivity than conventional TBSS or track-based analysis (Yeh et al., 2016a). It uses permutation testing to identify white matter tracts associated with a variable of interest and has recently been used to uncover white matter connectometry of word production in aphasia (Hula et al., 2020). In dyslexia, connectometry approach has been used to map white matter tracts supporting Chinese character recognition in children (H.-L. S. Wang et al., 2019). The results showed that better Chinese character recognition while reading was associated with left ventral stream, corpus callosum, and cerebellar and thalamic tracts bilaterally. However, Chinese character recognition may not tap many central aspects of phonological processing such as phonological awareness and rapid naming. Connectometry studies directly targeting phonological processing, the core deficit of dyslexia (Ramus, 2014; Snowling and Melby-Lervåg, 2016), have not been published nor studies with whole brain approach comparing white matter pathway deficits in dyslexia (Yeh et al., 2019b).

Here, we combined comprehensive neuropsychological testing of reading-related skills with diffusion MRI connectometry (Yeh et al., 2016a) to study the relationship between reading skills and phonological processing and white matter connectivity in a sample of 44 adult participants (23 dyslexics and 21 matched controls). Moreover, we performed QA-aided differential tractography (Yeh et al., 2019b) that provides a quantitative and objective whole-brain tractography method to uncover structural white matter anomalies in dyslexia and their correlation to reading-related skills. Based on the previous diffusion MRI evidence, we hypothesized that connectivity anomalies in dyslexia as well as reading-related connectometry would be associated with a left-lateralized network situated in the frontotemporal and occipitoparietal areas as well as corpus callosum. Whole brain hodological approach could inform the current debate on the reading-related connectome and its aberrations in dyslexia.

2. Materials and methods

2.1. Participants

This observational study was approved by the Coordinating Ethics Committee of The Hospital District of Helsinki and Uusimaa and performed according to the Declaration of Helsinki. A signed informed consent was obtained from all participants. Forty-four right-handed Finnish-speaking participants completed the diffusion MR imaging, the final sample consisting of 21 typically reading and 23 dyslexic participants (Table 1). A sample of 44 participants should provide power of at least 0.8 to detect relationships between language skills and white matter connectivity patterns as suggested by previously reported data on white matter connectivity in post-stroke aphasia (Hula et al., 2020).

A participant was classified as dyslexic if either a recent statement on dyslexia diagnosis was available from a doctor, or the participant had reading-related problems in childhood based on the Adult Reading History Questionnaire (ARHQ; cut-off at 43% for the childhood-related items) (Lefly and Pennington, 2000), combined with a performance of at least one standard deviation (SD) below the average of age-matched standardized control data (Laasonen et al., 2010) in the speed or accuracy on least two reading tests (word list reading, pseudoword list reading, text reading, see Table 2). Control group participants i) reported no language-related problems in themselves or first-degree relatives, ii) reported no childhood problems in reading or writing in ARHQ or interview, and iii) performed within norm in at least two out of three reading tests in both speed and accuracy. The groups were balanced in age, years of education and music education, and sex as well as in total brain volume and white matter volume (Kujala et al., 2021) (Table 1), but significantly differed in the reading-skill measures and composite scores of phonological processing, reading skills, and working memory (Table 2).

The exclusion criteria were 1) indication of an attention deficit evaluated with the Adult ADHD Self-Report Scale ASRS-v1.1 questionnaire (Kessler et al., 2005), 2) performance IQ (PIQ) below 80 evaluated with a neuropsychological test battery (see below), as well as the following self-reported diagnoses or conditions: 3) developmental or other language impairment, 4) other neurological or psychiatric disorders, 5) substance abuse, 6) medication affecting the brain, 7) uncorrected visual deficit, 8) an individualized school curriculum, 9) early bilingualism, and 10) non-detachable metal in the body or pregnancy.

2.2. Behavioural data

A neuropsychological test battery was used to assess IQ, working memory functions, reading, and phonological processing in all participants. To reduce the number of analyses and the error variance related to single task performance, four composite scores were calcu-

Table 1
Demographic and morphological data.

	Dyslexic (n = 23)	Control (n = 21)	p value	Effect size
Demographic				
Gender (male/female)	11/12	10/11	1.000 (χ^2)	0.02 (V)
Age (years)	31.3 (8.6)	29.9 (6.0)	.538 (t)	0.19 (d)
Education (years)	15.7 (5.2)	16.1 (4.4)	.817 (t)	0.07 (d)
Musical education (years)	3.0 (7.8)	3.7 (5.5)	.730 (t)	0.11 (d)
Morphological				
White matter volume (litres)	0.48 (0.1)	0.49 (0.1)	.592 (t)	0.16 (d)
Total brain volume (litres)	1.24 (0.1)	1.27 (0.1)	.513 (t)	0.20 (d)

Group sizes (n) and mean values of background variables in the Dyslexic and Control groups with standard deviation in parentheses. p-values show Chi Squared (χ^2) and independent-samples t-test (t) statistics for group comparisons. Effect sizes show Cohen's d and Cramer's V for group comparisons.

Table 2
Neuropsychological tests and composites.

Neuropsychological composites (bold)and individual tests	Median (IQR) Dyslexic (n = 23)	Control (n = 21)	Range	p_{corr}	Effect size (r)
Phonological processing [z]	-0.2 (1.2)	0.5 (0.4)	[-2.8 1.3]	<.001	0.61
Pig Latin (accuracy, amount of correct items out of 15)[1)]	9.0 (7.0)	15.0 (1.0)	[0.0 15.0]	<.001	0.57
Non-word span length (accuracy, amount of correctly recalled words out of 35)[2)]	12.0 (3.0)	13.0 (4.0)	[3.0 19.0]	.089	0.26
Rapid Alternate Stimulus naming (RAS) (speed of second trial, seconds)[3)]	30.0 (10.7)	24.1 (6.7)	[20.0 68.8]	<.001	0.58
Reading [z]	-0.3 (0.9)	0.6 (0.2)	[-3.6 0.8]	<.001	0.84
word list reading (accuracy, amount of correctly read words out of 30)	30.0 (1.0)	30.0 (0.0)	[25.0 30.0]	.006	0.43
word list reading (speed, seconds to read 30 words)	31.0 (11.4)	19.3 (3.0)	[14.5 83.5]	<.001	0.78
pseudoword list reading (accuracy, amount of correctly read words out of 30)	21.0 (8.5)	28.0 (3.0)	[6.0 30.0]	<.001	0.71
pseudoword list reading (speed, seconds to read 30 words)	72.9 (32.6)	40.2 (7.5)	[31.7 231.8]	<.001	0.84
text reading (accuracy, % of correctly read words in 3 min)[#]	98.2 (1.1)	99.4 (0.8)	[92.4 100.0]	<.001	0.59
text reading (speed, amount of correctly read words in 3 min)[#]	305.0 (67.0)	453.0 (65.0)	[205.0 479.0]	<.001	0.82
Full Intelligence Quotient	104.5 (17.3)	117.5 (12.3)	[90.5 128.5]	<.001	0.59
Verbal IQ [Wechsler Adult Intelligent Scale (WAIS)-IV Similarities and Vocabulary]	103.0 (20.0)	115.0 (10.0)	[75.0 125.0]	<.001	0.55
Performance IQ (WAIS-IV Block design and Matrix reasoning)	113.0 (11.0)	119.0 (9.0)	[81.0 138.0]	.006	0.43
Working memory functions	19.0 (7.5)	24.0 (6.0)	[13.0 32.0]	.011	0.39
WMS-III Letter-Number Sequencing	10.0 (3.5)	13.0 (3.0)	[7.0 19.0]	<.001	0.54
WMS-III Spatial span	9.0 (5.0)	11.0 (3.0)	[4.0 19.0]	.189	0.20

Group sizes (n) and median values of all variables in the Dyslexic and Control groups with interquartile range (IQR) in parentheses. Group differences were tested with Wilcoxon sign-rank test, p-values are FDR-corrected, and effect sizes (r) are Wilcoxon Effect Sizes. Composite scores (bolded) of the test results were formed for phonological processing and technical reading by converting the raw scores (of subtests below the respective composite) to z-scores and averaging them, and for working memory according to WMS-III (Wechsler, 2008). For all IQ scores, normalized mean = 100 and SD = 15. For WMS-III subtests, normalized mean = 10 and SD = 3. For WMS-III working memory index, normalized mean = 20 and SD = 6. 1) Phonological awareness; 2) Phonological short-term memory; 3) Rapid serial naming

[#] Not included in the reading composite score.

lated: 1) Reading skills (accuracy and speed; Cronbach's α = .87) were assessed with word and pseudoword list reading tests (Nevala et al., 2006); 2) Phonological processing (Cronbach's α = .69) included 'Pig Latin' (Nevala et al., 2006), non-word span length (Laasonen et al., 2002), and rapid alternating stimulus naming (Wolf, 1986), measuring phonological awareness, phonological short-term memory, and rapid access of phonological information, respectively (Torgesen et al., 1994); 3). Working memory functions were evaluated with Wechsler Memory Scale (WMS-III) subtests letter-number sequencing and spatial span (Wechsler, 2008); 4) Verbal IQ (VIQ) assessed with WAIS-III subtests similarities and vocabulary and PIQ with subtests block design and matrix reasoning (Wechsler, 2008). Composite scores were averages over the z-transformed test scores for reading and phonological processing, and averages of the standardized test scores according to the Working Memory Index in WMS-III for working memory and according to PIQ, VIQ, and full IQ (FIQ) in Wechsler Adult Intelligent Scale (WAIS-IV) for IQ (Table 2). Internal consistency of the composite variables was checked with Cronbach's α (see above). The studied groups differed in all IQ indices. In dyslexia, VIQ is more likely to be affected than PIQ (Ingesson, 2006; Laasonen et al., 2009), and therefore, PIQ was used as a covariate in the analyses.

2.3. MRI data acquisition and reconstruction

All neuroimaging data were collected at the Aalto University AMI center (Espoo, Finland). Diffusion-weighted MRI (DW-MRI) scans were acquired on a 3 T MAGNETOM Skyra MRI scanner (Siemens Healthcare, Erlangen, Germany) using single-shot-spin-echo epi sequence (SE-EPI) with GRAPPA technique. DW-MRI images covering the whole brain and brainstem were acquired using the following parameters: 70 continuous transversal slices, slice thickness 2.5 mm, TR = 9000 ms, TE = 80 ms, FOV = 240 mm x 240 mm, voxel size = 2.5 × 2.5 × 2.5 mm^3. At the beginning of the sequence one non-diffusion weighted image and at the end of the sequence 10 non-diffusion weighted images with a b-value = 0 s/mm^2 were acquired as an anatomical reference volume. Diffusion gradients were applied in 64 directions (b = 1000 s/mm^2).

The DW-MRI data were denoised for thermal noise with MP-PCA method (Veraart et al., 2016) using denoise tool from MRTrix (MRTrix 3) (Tournier et al., 2019). Then, a Gibbs ringing correction based on local subvoxel shifts was applied (Kellner et al., 2016). The b-table was checked by an automatic quality control routine to ensure its accuracy (Schilling et al., 2019) and the DW-MRI were reconstructed in the Montreal Neurological Institute (MNI) space using q-space diffeo-

morphic reconstruction (QSDR) (Yeh and Tseng, 2011) that allows the construction of spin distribution functions (SDFs) (Yeh et al., 2010). Normalization was carried out using the anisotropy map of each participant and a diffusion sampling length ratio of 1.25 was used. The data output was resampled to 2 mm isotropic resolution. Quality of the normalization was inspected using the R^2 values denoting goodness-of-fit between the participant's anisotropy map and template. Moreover, each participant's forceps major and minor were inspected and used as an anatomical benchmark to confirm the normalization quality (Hula et al., 2020). The restricted diffusion was quantified using restricted diffusion imaging (Yeh et al., 2017) and QA was extracted as the local connectome fingerprint (Yeh et al., 2016b) and used in the connectometry analysis.

2.4. Connectometry analysis

Diffusion MRI connectometry (Yeh et al., 2016a) analyses were carried out using DSI Studio (http://dsi-studio.labsolver.org, version April 7 2021). Two multiple regression models were used to identify positive local connectomes associated with 1) reading skills (composite score) and 2) phonological processing (composite score) across the whole sample. Age, sex, whole brain mean QA and PIQ were included as covariates in the analyses (Gong et al., 2011; Hedman et al., 2012; Kujala et al., 2021; Ramus et al., 2018). Local connectomes with T-score exceeding 2 were selected (Hula et al., 2020) and tracked using a deterministic fiber tracking algorithm (Yeh et al., 2013b) to obtain correlational tractography. The tracks were filtered by topology-informed pruning (Yeh et al., 2019a) with 4 iterations, and a length threshold of 20 voxel distance was used to identify significant tracts. Bootstrap resampling with 2000 randomized permutations was used to obtain the null distribution of the track length and estimate the False Discovery Rates (FDR).

2.5. Differential tractography

Differential tractography (Yeh et al., 2019b) was conducted using DSI Studio (http://dsi-studio.labsolver.org, version April 7 2021). After pre–processing and reconstruction of the DW-MRI data, average templates of dyslexic and control groups were created (Yeh et al., 2013a). Normalization of the group templates was conducted by a linear regression between the scans. As dyslexia has previously been associated with decreased and increased (e.g., Banfi et al., 2019) structural connectivity, differential tractography determining i) decreased and ii) increased QA in dyslexic group compared to control group was calculated at whole brain with 1,000,000 seeds with random anisotropy threshold (default). The angular threshold was randomly selected from 15 degrees to 90 degrees (default). The step size was randomly selected from 0.5 voxel to 1.5 voxels (default). Tracks with length shorter than 20 mm or longer than 300 mm were discarded. Topology-informed pruning (Yeh et al., 2019a) was applied to the tractography with 16 iterations to remove false connections. The threshold for significantly decreased QA was set to 20%.

Correlations (Spearman, two-tailed) were calculated between significant differential tractography results (i.e., network of results) and the two composite z-scores (reading skills, phonological processing) over the whole sample using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) to determine their relationship with reading abilities. To control for multiple comparisons (n = 4), Bonferroni-correction was applied.

In addition, exploratory correlations (Spearman, two-tailed) were calculated between the independent significant components (i.e., tracts) and the two composite z-scores within each group (control group, dyslexic group) to evaluate possible correlational differences between the two groups. Due to the exploratory nature of these correlations, adjustments for multiple comparisons were not made.

2.6. Data availability

Anonymized data reported in this manuscript are available from the corresponding author upon reasonable request and subject to approval by the appropriate regulatory committees and officials.

3. Results

3.1. Connectometry of reading-related skills

The connectometry analysis of reading skills in the whole sample revealed positive associations (FDR = 0.14) with left cingulum and right fornix, corticospinal and frontal corticopontine tract as well as cerebellum bilaterally (Fig. 1A). Moreover, reading skills were positively associated with the connectivity of the body of corpus callosum, forceps major and minor as well as the tapetum and middle cerebellar peduncle.

The analysis for phonological processing showed several white matter tracts whose connectivity was positively associated with the ability (FDR = 0.03). These comprised the left arcuate fasciulus (i.e., the long segment), the right thalamic radiation and fornix, and cerebellum bilaterally (Fig. 1B). Moreover, the connectivity of the body of corpus callosum, forceps major and minor as well as the tapetum and middle cerebellar peduncle were positively associated with phonological processing.

3.2. Whole brain structural white matter anomalies in dyslexia

Differential tractography analyses showed that the dyslexic group had decreased white matter connectivity in a left-lateralized network (fiber count = 2,794, mean length = 22.0 mm, mean QA difference = 0.16) compared to the control group (Fig. 2A). Decreased QA (>20%) was observed in left uncinate fasciculus and bilaterally in superior longitudinal fasciculus, parietal aslant tract (i.e., the posterior segment of arcuate fasciculus), corticostriatal tract, vertical occipital fasciculus, and thalamic radiation. Moreover, dyslexic group had decreased QA in the body of corpus callosum and forceps major compared to the control group. Higher mean normalized QA in the observed network of results correlated significantly with better reading skills (r = .65, $p < 0.001$, Bonferroni-corrected) and phonological processing (r = .57, $p < 0.001$, Bonferroni-corrected).

In contrast, the dyslexic group had increased white matter connectivity in a left-lateralized network (fiber count = 1,864, mean length = 22.4 mm, mean QA difference = 0.12) compared to the control group (Fig. 2B). Increased QA (>20%) was observed in left superior longitudinal fasciculus and vertical occipital fasciculus, and bilaterally in corticostriatal tract. Higher mean normalized QA in the observed network of results correlated significantly with poor reading skills (r = -.62, $p < 0.001$, Bonferroni-corrected) and phonological processing (r = -.37, $p = 0.012$, Bonferroni-corrected).

Exploratory analyses evaluating correlations between the significant tracts and the two composite z-scores within each group separately showed that better reading skills in the control group correlated with higher mean normalized QA in the left uncinate fasciculus (r = .75, $p < 0.001$, uncorrected), right corticostriatal tract (r = .47, $p = 0.030$, uncorrected) and corpus callosum (r = .44, $p = 0.044$, uncorrected), all belonging to the network of results showing increased QA in the control group compared to the dyslexic group. Within the network of results showing increased QA for the dyslexic group compared to the control group, lower QA in the left vertical occipital fasciculus correlated with better phonological processing in the control group (r = -.51, $p = 0.019$, uncorrected). Moreover, in the dyslexic group, higher mean normalized QA in the right superior longitudinal fasciculus within the network of controls > dyslexics correlated with better phonological processing (r = .45, $p = 0.031$, uncorrected). These correlations should be interpreted with caution and considered exploratory in nature.

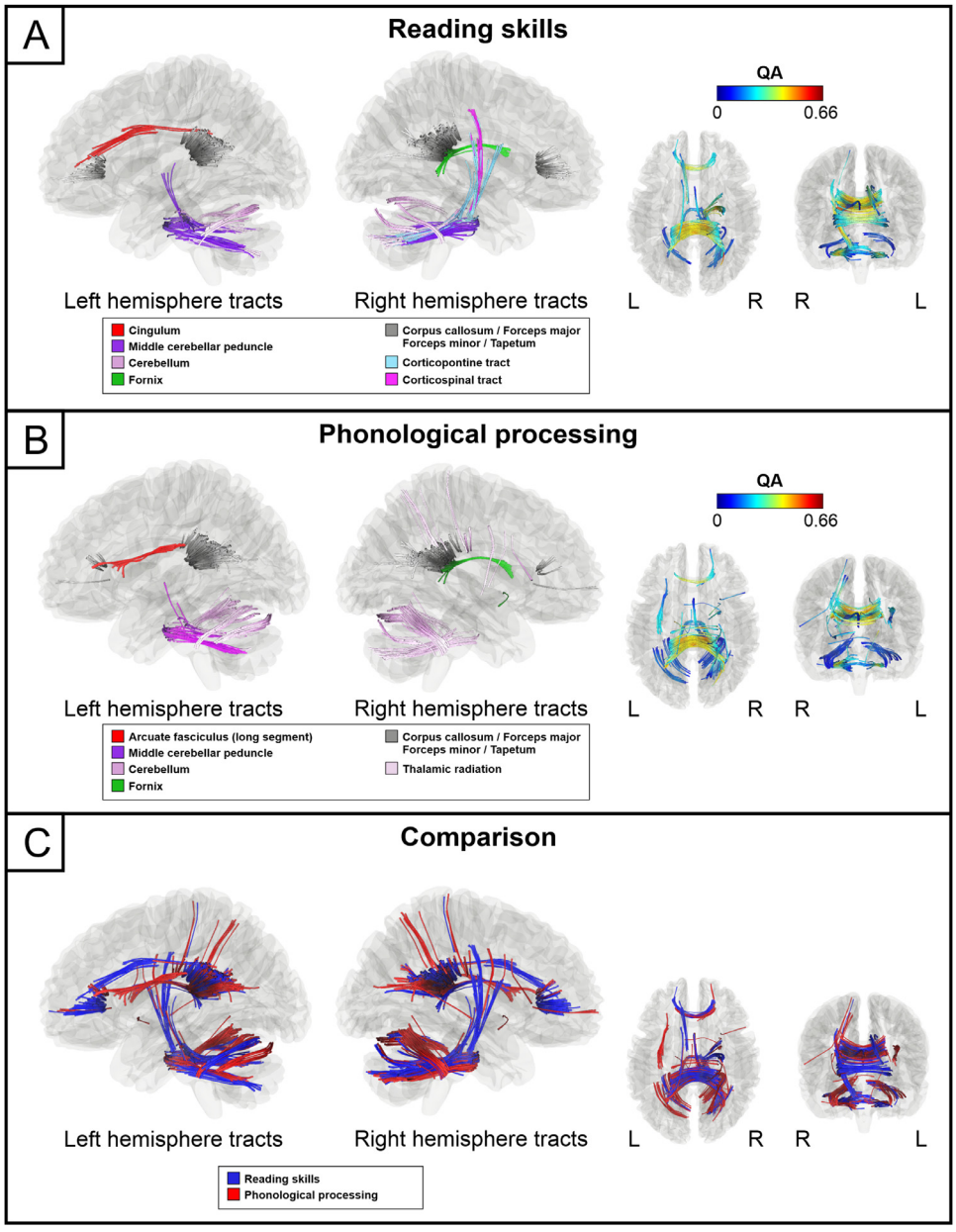

Fig. 1. Connectometry results of reading-related skills. (A) Positively associated reading skills tracts. (B) Positively associated phonological processing tracts. (C) Comparison between white matter tracts positively associated with reading skills (blue) and phonological skills (red). N= 44. L = Left, QA = Quantitative anisotropy, R = Right.

4. Discussion

The present study sought to determine white matter pathways associated with reading skills and phonological processing using diffusion MRI connectometry and rigorous neuropsychological testing of reading-related skills in a sample of 44 adult participants. Moreover, we set out to identify whole brain tractography anomalies in dyslexia and their correlations to core reading-related deficits in dyslexia (Ramus, 2014; Snowling and Melby-Lervåg, 2016). Previous hodological studies using QA-aided connectometry analysis on reading on adult dyslexic participants have not been reported. In children, better Chinese character recognition has been associated with left ventral pathway, corpus callosum, and cerebellar and thalamic tracts bilaterally. QA-aided tractography has been shown to outperform FA by being more specific to individual's connectivity patterns (Yeh et al., 2016b) and less susceptible to the partial volume effect (Yeh et al., 2013b). The present results provide information on the extent of the reading-related connectome comprising corpus callosum and cerebellum as well as left dorsal tracts (phonological processing). Current study also informs the debate regarding the structural white matter aberrations in dyslexia revealing a novel network of results comprising the left ventral route and bilaterally the dorsal route as well as the corpus callosum.

According to the dual route model of reading (Jobard et al., 2003), early visual analysis and pre-lexical processing during reading relies on left inferior temporo-occipital area (the visual word form area) (Cohen et al., 2000). After this, the model suggests two distinct routes for word access: i) the direct route (semantic access) comprising ventral temporal and frontal areas, and ii) the indirect route (grapho-phonological conversion) comprising more dorsal temporoparietal and inferior frontal areas. A number of neuroimaging studies have provided evidence on functional deficits in these areas in developmental dyslexia (Martin et al., 2016; Paulesu et al., 2014; Richlan, 2012) but have also shed light on aberrations in right frontal regions and the cerebellum (Martin et al., 2015). However, findings on structural dysconnectivity have mostly been restricted to the left dorsal route and interhemispheric connections (i.e., corpus callosum; Vandermosten et al., 2012b; but also see Moreau et al., 2018). Along with the superior longitudinal fasciculus, the arcuate fasciculus is a key part of the dorsal language stream

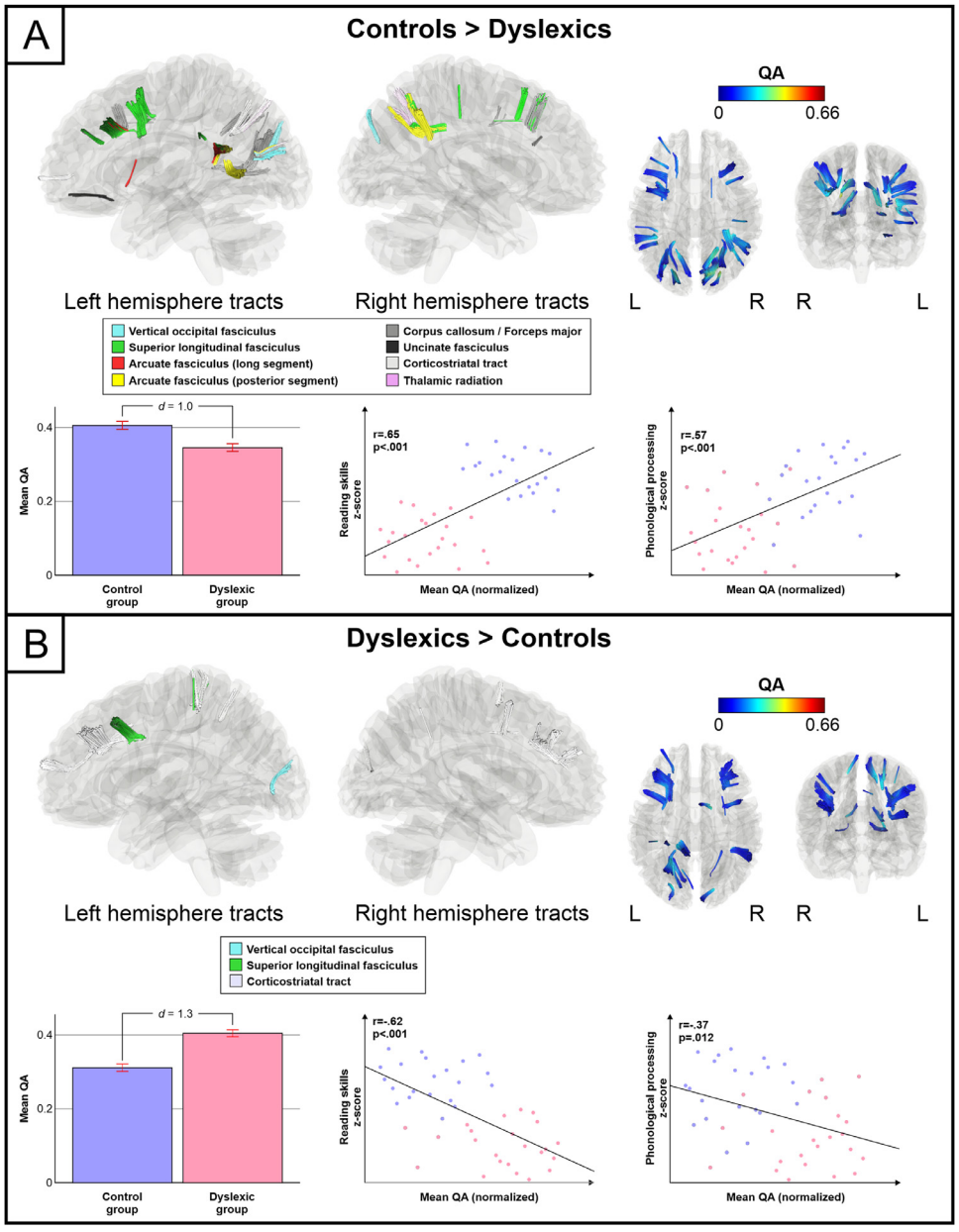

Fig. 2. Differential tractography results for altered connectivity in dyslexia. Structural white matter anomalies in the differential tractography analyses marked by A) decreased QA (>20%) in dyslexics (n = 23) compared to control group (n = 21) and B) increased QA (>20%) in dyslexics compared to control group. Mean normalized QA correlations (Spearman, two-tailed) to reading-related skills are shown with scatter plots. Bar plot for mean QA in significant connectivity differences corrected for age, sex, whole brain mean QA and PIQ is shown: bar = mean, error-bar = standard error of mean, d = Cohen's d. L = left, PIQ = performance IQ, QA = quantitative anisotropy, R = Right.

(Hickok and Poeppel, 2007), interconnecting inferior frontal, temporal and parietal cortical regions for speech and phonological processing (Catani et al., 2007, 2005; Catani and Thiebaut de Schotten, 2008; López-Barroso et al., 2013; Richlan, 2012; Vandermosten et al., 2012b). It has been the most studied white matter tract in dyslexia (Ramus et al., 2018; Van Der Auwera et al., 2021; Vandermosten et al., 2012b) and was implicated in both whole brain connectometry results of phonological processing and in differential tractography results showing decreased connectivity patterns in dyslexia. While the present study supports the role of arcuate fasciculus in dyslexia (and reading), it is not likely that one single dysfunctional white matter pathway can fully explain such heterogenous entity as dyslexia (Perry et al., 2019; Zoubrinetzky et al., 2014). In contrast, a pattern of structural dysconnectivity within the reading network could give rise to dyslexia and its heterogenous variants. Indeed, a recent study utilizing network-based statistics revealed widely distributed white matter connectivity deficits in a network connecting the left-occipital-temporal and temporo-parietal cortex in dyslexic children, beyond previously established white matter abnormalities (Lou et al., 2019). While exploring lateralization indices of the inferior fronto-occipital and superior longitudinal fasciculi, the study was not focused on providing a comprehensive and exact evaluation of the affected white matter pathways beyond these tracts. To this end, we utilized a whole brain hodological approach to capture a network of anomalies in dyslexia and structural connectivity patterns supporting reading (Yeh et al., 2019b, 2016a).

Our present results, emerging from unbiased whole brain analysis, conform with studies on reading (Jobard et al., 2003; Kujala et al., 2007; Schlaggar and McCandliss, 2007) and functional and structural anomalies in dyslexia (Lou et al., 2019; Ramus et al., 2018; Vandermosten et al., 2012b; Zhao et al., 2016). Moreover, the present results parallel a previous connectometry study associating better performance in Chinese character recognition with corpus callosum and cerebellar and thalamic tracts bilaterally (H.-L. S. Wang et al., 2019). The present study also extends these previous results and reveals novel information about the structural white matter connectometry anomalies underlying dyslexia. The results suggest that dyslexia is underpinned by structural dysconnectivity in a left-lateralized network interconnecting frontotemporal (uncinate fasciculus, superior longitudinal fasciculus),

frontoparietal (superior longitudinal fasciculus), temporoparietal (superior longitudinal fasciculus, parietal aslant tract/posterior segment of the arcuate fasciculus) and occipitotemporal (vertical occipital fasciculus) regions (Catani et al., 2003, 2002; Catani and Thiebaut de Schotten, 2008; Panesar et al., 2019; Yeatman et al., 2013). Our results can be viewed as evidence that supports both the dual route model of reading (Jobard et al., 2003) and the direct and the indirect routes as means for word access: i) Vertical occipital fasciculus forms the core of the visual word forming area circuitry that projects dorsally to language and reading related cortical areas and facilitates encoding of written words (Yeatman et al., 2013), ii) the dorsal stream (i.e., arcuate fasciculus, superior longitudinal fasciculus) is important for phonological awareness, an essential skill in reading development (Vandermosten et al., 2012a; Yeatman et al., 2011), and iii) the uncinate fasciculus, part of the ventral stream, subserves semantic processing (Han et al., 2013) and its greater FA values have been shown to correlate with better semantic performance in healthy adults (De Zubicaray et al., 2011). Next, we will further discuss the individual findings.

A noteworthy novel finding was the connectivity deficits in vertical occipital fasciculus in dyslexia. Vertical occipital fasciculus interconnects visual word form area with dorsal parieto-occipital regions (Panesar et al., 2019; Yeatman et al., 2014, 2013) and has been associated with acquired reading deficits in case studies (Greenblatt, 1976), but previously has not been implicated in dyslexia. Dysconnectivity of the vertical occipital fasciculus could impede transformation of reading-related information via both direct and indirect routes in the early stages of processing (Jobard et al., 2003). Indeed, a recent functional MRI study revealed a decreased word-sensitive activation that was associated with reading skills within the left visual word form area in children with dyslexia (Brem et al., 2020). Structural anomalies in the vertical occipital fasciculus could also contribute to visual processing deficits observed in dyslexia, which, alongside phonological deficits, have been argued to play a critical role (Giofrè et al., 2019; Snowling and Melby-Lervåg, 2016).

Structural connectivity deficits in dyslexia were also observed in thalamocortical and corticostrial tracts compared to the controls. Structural anomalies in thalamocortical (Cui et al., 2016; Fan et al., 2014; Žarić et al., 2018) and corticostriatal (Cui et al., 2016) pathways have previously been reported in dyslexic children. It has been suggested that thalamic connectivity plays a role in developing phonemic representations and orthographic forms and that they contribute to typical reading development (Fan et al., 2014). In addition, thalamopontine pathways have been associated with better Chinese character recognition (H.-L. S. Wang et al., 2019). Corticostriatal tracts are implicated in speech and language learning and are involved in implicit learning (for a review, see Krishnan et al., 2016). Previous studies have suggested decreased grey matter volume in the left striatum in dyslexia (Brown et al., 2001; Z. Wang et al., 2019), similar to our recent findings in the current sample (Kujala et al., 2021). Fronto-striatal circuit functional aberrations have also been observed in dyslexia and are thought to reflect increased reliance on these systems during reading to compensate for functional and structural deficits in posterior brain regions (for a review, see Hancock et al., 2017).

Structural white matter anomalies in dyslexia also comprised the corpus callosum. Previous studies have shown that anomalies in the corpus callosum, especially in its posterior portion and projections (tapetum) interconnecting temporal lobes, underlie poor reading performance in dyslexic adults (Frye et al., 2008) and children (Cui et al., 2016; H.-L. S. Wang et al., 2019; Wang et al., 2021). Similarly in adult typical readers, the number of cross-hemispheric connections through the posterior corpus callosum has been associated with better phonological decoding (Welcome and Joanisse, 2014). The present findings are in parallel with these findings: Structural connectivity anomalies were observed in the tapetum as well as in the forceps major connecting occipital lobes in dyslexia. Dysconnectivity in the forceps major (and in the posterior corpus callosum) represents decreased connectivity between the ventral occipital areas crucial for reading (Jobard et al., 2003) and could contribute to occipitotemporal lateralization deficits observed in dyslexia (Shaywitz et al., 2007).

We found no positive associations between reading-related skills and ventral white matter tracts, in contrast with previous connectometry study associating better Chinese character recognition with left ventral pathway (H.-L. S. Wang et al., 2019). However, in the differential tractography analyses, the dyslexic group showed structural connectivity changes in the left uncinate fasciculus that connects the left temporal pole with left inferior frontal areas (Catani and Thiebaut de Schotten, 2008). The uncinate contributes to the dual stream model of language function (Hickok and Poeppel, 2007; Rauschecker and Tian, 2000) subserving semantic and phonological processing (Han et al., 2013; Hula et al., 2020) and has previously been implicated in dyslexia (Lebel et al., 2019). Moreover, we recently reported grey matter structural anomalies in dyslexia in the left temporal termination area of the left uncinate fasciculus in these same participants (Kujala et al., 2021).

In addition to the visual word form area, the early word processing has been associated with the cerebellum that has been found to be a key forward driving node in the reading network, increasing network synchronization and improving text comprehension (Hoeft et al., 2011; Kujala et al., 2007; Stoodley and Stein, 2013). According to the previously more popular “cerebellar deficit hypothesis”, cerebellar anomalies could give rise to developmental dyslexia by impairing articulatory/phonological monitoring (Nicolson et al., 2001). However, neuroimaging studies have not provided consistent evidence and convergent reading-related activations have been observed in adults but not in children (Alvarez and Fiez, 2018; Martin et al., 2015). The current study related cerebellar tracts with reading skills and phonological processing, but, interestingly, structural anomalies in these tracts were not observed in dyslexia in differential tractography analyses. One might speculate that dyslexia is not underpinned by structural cerebellar dysconnectivity but rather functional connectivity deficits: In dyslexic children, the right cerebellum has been shown to have higher functional connectivity between the right parietal cortex compared to the control group during a phonological task (Li et al., 2020). This observation might not hold in adult dyslexics. In the healthy brain, structural and functional connectivity tend to show strong relationship, but neuroimaging studies on children have shown that structure-function relationships are not straightforward (Supekar et al., 2010) and become stronger with age (Hagmann et al., 2010). Evaluation of cerebellar structural connectivity, in addition to vertical occipital fasciculus and reviewing its more detailed structural connectivity deficits in dyslexia, could provide a fertile ground for future larger scale studies combining multimodal functional and structural connectivity approaches on dyslexia. Furthermore, due to the network refinement caused by dynamic and age-dependent functional modifications of white matter maturation (Hagmann et al., 2010) supporting the development of cognitive abilities (Barnea-Goraly et al., 2005; Casey et al., 2000), larger studies on adult, adolescent and children participants with dyslexia as well as longitudinal studies are needed to disentangle the core structural white matter deficits in dyslexia. Compared to children, more extensive neuropsychological test batteries as well as longer MRI sequences are possible to carry through in adult participants. Moreover, further studies on dyslexia utilizing higher-order diffusion models specifically addressing the limitations of single diffusion tensor model framework are needed (Farquharson et al., 2013; Malcolm et al., 2010; Tournier et al., 2011). Evolving diffusion MRI methods will hopefully provide new and more detailed insights into dyslexia and its treatment.

The present study utilized composite scores instead of individual test scores to represent reading skills and phonological processing. The composite scores derived from individual tests that assessed the same general reading-related skill, confirmed with Cronbach’s αs, and were named accordingly. While utilization of a composite score can lead to simplifying a complex cognitive process such as reading and to lose de-

tailed information on a sub-skill within, for example, phonological processing and reading, it helps to reduce the error variance related to a single performance score. Using single performance scores might therefore yield more fine-grained results compared to composite scores, but in turn, reduce reliability as well as increase the problems related to conducting multiple tests.

5. Conclusions

The results of this study revealing a network of dysconnectivity in dyslexia as well as finding associations between reading-related skills and white matter connectivity conform current functional neuroanatomical models of reading and developmental dyslexia. They support the notion of left-hemispheric dominant reading network and its anomalies in dyslexia, but also provide novel network-level and tract-level evidence on structural connectivity anomalies in dyslexia, including the vertical occipital fasciculus. According to the current theories, developmental dyslexia is primarily based on phonological deficits (Ramus, 2014; Snowling and Melby-Lervåg, 2016), but also associated with significant implicit learning deficits (Krishnan et al., 2016; Lum et al., 2013). The present results support these views by associating phonological processing related connectome and structural white matter anomalies in dyslexia to same pathways (i.e., left arcuate fasciculus, thalamic pathways and corpus callosum), and also by revealing dysconnectivity in dyslexia in pathways subserving implicit learning.

Declaration of Competing Interest

The authors report no competing interests.

Credit authorship contribution statement

Aleksi J. Sihvonen: Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Paula Virtala:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – review & editing, Supervision. **Anja Thiede:** Methodology, Formal analysis, Investigation, Data curation, Writing – review & editing. **Marja Laasonen:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Teija Kujala:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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Data and code availability statements

Anonymized data reported in this manuscript are available from the corresponding author upon reasonable request and subject to approval by the appropriate regulatory committees and officials. No custom codes were used in any of the analyses.

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