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Predicting early signs of dyslexia at a preliterate age by combining behavioral assessment with structural MRI

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ABSTRACT

Background: Recent studies suggest that neurobiological anomalies are already detectable in pre-school children with a family history of developmental dyslexia (DD). However, there is a lack of longitudinal studies showing a direct link between those differences at a preliterate age and the subsequent literacy difficulties seen in school. It is also not clear whether the prediction of DD in pre-school children can be significantly improved when considering neurobiological predictors, compared to models based on behavioral literacy precursors only.
Methods: We recruited 53 pre-reading children either with (N=25) or without a family risk of DD (N=28). Quantitative T1 MNI data and literacy precursor abilities were assessed at kindergarten age. A subsample of 35 children was tested for literacy skills either one or two years later, that is, either in first or second grade.
Results: The group comparison of quantitative T1 measures revealed significantly higher T1 intensities in the left anterior arcuate fascicle (AF), suggesting reduced myelin concentration in preliterate children at risk of DD. A logistic regression showed that DD can be predicted significantly better ($p=.024$) when neuroanatomical differences between groups are used as predictors (80%) compared to a model based on behavioral predictors only (63%). The Wald statistic confirmed that the T1 intensity of the left AF is a statistically significant predictor of DD ($p<.05$).
Conclusions: Our longitudinal results provide evidence for the hypothesis that neuroanatomical anomalies in children with a family risk of DD are related to subsequent problems in acquiring literacy. Particularly, solid white matter organization in the left anterior arcuate fascicle seems to play a pivotal role.

1. Introduction

Five to seven percent of all children have developmental dyslexia (DD), a specific learning disorder that is characterized by severe difficulties in the acquisition of reading and spelling despite adequate cognitive abilities and effective classroom instruction (Moll et al., 2014; Peterson and Pennington, 2012). Studies on families and twins indicate that DD is moderately to highly heritable. A prevalence of 34–77% is observed in children with a dyslexic parent or sibling (Lyytinen et al., 2004; Snowling et al., 2003; Pennington and Lefly, 2001; Gallagher et al., 2000; DeFries et al., 1987; Hallgren, 1950).

At the microstructural level, certain DD-associated genetic variations are related to disruptions of neuronal migration during neocortical development (Tammimies et al., 2013; Szalkowski et al., 2012; Gabel et al., 2011, 2010; Wang et al., 2011; Burbridge et al., 2008; Rosen et al., 2007). It is suggested that these structural

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anomalies in the cortical layers of the perisylvian brain regions lead to a functional disruption of the local microcircuitry (Giraud and Ramus, 2013; Galaburda, et al., 2006; Galaburda and Kemper, 1979). Consistent with this assumption, Darki et al. (2014) found a significantly increased cortical thickness (CortT) of the left temporo-parietal regions, the angular and supramarginal gyri (SMG) in readers with DD-related genetic polymorphisms. Several functional magnetic resonance imaging (fMRI) studies also described hypoactivations during reading and reading-related tasks in individuals with DD in temporo-parietal brain regions as well as in superior temporal, inferior parietal, and in inferior frontal brain regions (pars opercularis of the inferior frontal gyrus, IFG) (for a review, see Richlan et al., 2009). These brain regions belong to the dorsal sublexical reading network and are activated during reading of pseudowords. Further functional hypoactivations were observed in the ventral lexical reading network, which is activated in reading of orthographically irregular words, and particularly in occipito-temporal brain regions including the fusiform gyrus and posterior inferior and middle temporal regions (Richlan et al., 2009). Consistent with these fMRI findings, structural MRI studies reported neuroanatomical differences in the gray matter of the dorsal reading network, including the left superior temporal cortex (Richlan et al., 2013), the left inferior parietal cortex (Darki et al., 2014; Hoeft et al., 2007; Eckert et al., 2005) and the ventral reading network, including the left fusiform gyrus (Skeide et al., 2016; Altarelli et al., 2013).

Recent studies described disruptions of interregional connectivity besides the local findings in specific brain regions as another main problem in dyslexia. Altered structural (Skeide et al., 2015; Vandermosten et al., 2012; Yeatman et al., 2011; Rimrodt et al., 2010) as well as functional connectivity (Schurz et al., 2015; Finn et al., 2014; Norton et al., 2014; van der Mark et al., 2011) has been reported in the dorsal and ventral reading network. Skeide et al. (2015) reported disrupted connectivity in the dorsal reading network in children with DD. The study revealed decreased fractional anisotropy (FA) in the arcuate fascicle (AF), a fiber tract connecting temporo-parietal brain regions with frontal regions. Catani et al. (2005) identified three separate segments of the AF and mapped them on different aspects of phonological processing. The long segment of the AF, directly connecting temporal and frontal brain regions, has been associated with phoneme awareness (Vandermosten et al., 2012; Yeatman et al., 2011), which is relevant for DD. The anterior segment is suggested to be involved in segmental phonological processing (Rimrodt et al., 2010; Fiez and Petersen 1998), while the posterior AF circuit is associated with grapheme-to-phoneme mapping (Thiebaut de Schotten et al., 2014). Furthermore, disrupted connectivity was also reported in the ventral reading network, including anomalies within the inferior fronto-occipital fascicle (IFOF). The IFOF is a long-distance fiber tract which has been related to visual word form recognition (Vandermosten et al., 2012; Jobard et al., 2003).

It is largely unknown whether such anomalies exist before literacy is acquired at school, or, alternatively, whether they are consequences of impaired reading. First indirect evidence in favor of the former hypothesis comes from cross-sectional studies which described disruptions in the connectivity of the dorsal and ventral reading network in pre-school children with a family risk of DD (Vandermosten et al., 2015; Hosseini et al., 2013). Additionally, a longitudinal study reported disruptions in the connectivity of the dorsal reading network in kindergartners who were at risk of DD because of their poor phonological skills (Saygin et al., 2013).

Most of the previous studies investigating the white matter connectivity of the reading network focused on FA (Basser and Pierpaoli, 1996; Basser 1995), a parameter of water diffusion which is based on diffusion tensor imaging (Basser et al., 1994). FA has been characterized as a measure which depends on microstructural fiber tract features such as myelination (Paus et al., 2012), although such interpretation of tensor-derived parameters is still debated. The tensor model is based on the assumption that the diffusion of the water molecules is Gaussian. However, this assumption poorly reflects the more complex non-uniform fiber architecture with crossing, kissing and fanning fibers (Tardif et al., 2015a). The fact that 63–90% of voxels in the brain contain crossing fibers impairs a specific connection of diffusion indices such as FA to physiological consequences (Jones et al., 2013).

Given the fact that FA is a neurobiologically unspecific measure which combines many biological and geometric properties of white matter in a single index, we looked for an alternative, potentially more specific index. Recent studies showed that T1 relaxation time strongly correlates with myelin concentration in the white matter of the brain (Tardif et al., 2015a, 2015b; Sereno et al., 2013; Dick et al., 2012). Accordingly, we analyzed T1 intensity maps as an inverse measure of myelination within fiber pathways relevant for literacy in the present study. Probabilistic tractography (Mori and van Zijl, 2002) was performed to investigate the myelination within fiber tracts of the dorsal and ventral reading network. The network was defined by selecting seed and target regions based on the results of our previous CortT study showing reduced CortT in preliterate children with a family risk of DD compared to children without such risk in the left SMG, the left inferior temporal gyrus (ITG) and in the left superior and transversal occipital sulci (SOS/TOS) (see Figs. S1 and S2; further details of the cross-sectional CortT analysis are provided in Kraft et al., 2015 and Supporting Information S1).

In addition to the cross-sectional investigations of white matter connectivity in the dorsal and ventral reading network in preliterate children at risk of DD, we also performed a longitudinal follow-up assessment in a subsample of 35 children.

The empirical evidence for the neuroanatomical predictability of DD is sparse compared to the intensively investigated behavioral predictors. Phonological development, rapid automatized naming (RAN) and visual attention were identified as reliable predictors for literacy proficiency (Franceschini et al., 2012; Caravolas et al., 2012; Lervåg et al., 2009). Nevertheless, the predictability of DD based on behavioral literacy predictors alone does not provide sufficient specificity when distinguishing between individuals with and without DD (Steinbrink et al., 2010; Marx and Weber, 2006). The involvement of further risk factors such as early variations in the development of specific brain structures might improve the prediction of DD.

The present study addressed one research question from a cross-sectional perspective and two other ones from a longitudinal perspective. Cross-sectionally, we investigated whether preliterate children with a family risk of DD show differences in quantitative T1 measurements in the dorsal and/or ventral reading network compared to children without a family risk of DD. Longitudinally, we investigated (i) whether children with structural brain anomalies at pre-school age will subsequently develop poorer reading abilities and (ii) whether prediction of DD can be improved when neurobiological anomalies are taken into consideration in addition to behavioral precursors of reading.

2. Methods

2.1. Design

The present study relied on two time points of data acquisition. At time point 1, we measured children from kindergartens who did not receive literacy instruction. We acquired structural, quantitative, and diffusion-weighted brain imaging data in children with and without a family risk of DD to extract a potential

neuroanatomical predictor for DD. We investigated behavioral precursors of reading abilities in children with a family risk of DD and compared them to age-, sex and intelligence-matched controls. Regression analyses were also controlled for the potentially confounding effect of intelligence, age and sex. A subsample of the previously examined children was invited back at time point 2 to test their reading and spelling abilities after one or two years of school education.

2.2. Participants

In total, 71 native German-speaking children were recruited from kindergartens on a voluntary basis. The following exclusion criteria were applied: (i) a history of neurological, psychiatric, hearing or vision disorders (based on parental report in the parental questionnaire), (ii) left-handed children (laterality quotient ≤ 0 according to the Edinburgh Handedness Inventory, which was modified into a child-appropriate version for the present study; Oldfield, 1971), (iii) multilingualism (parental questionnaire), (iv) children with second degree relatives with DD (parental questionnaire), (v) termination of the test session in the mock-up scanner because of extensive movement or distress, and (vi) termination of the measurement in the MRI scanner because of extensive movement or distress. From the remaining 59 children, six had to be excluded from the study due to poor image quality of the structural MRI data (i.e. blurring and ringing artifacts, which do not allow correct identification of the gray/white matter border; for more details see Supporting information S1). The finally included 53 children presented an age range from 4 years, 9 months to 6 years, 3 months (mean: 5 years 5 months, SD=0.4; 27 females). Twenty-five of the recruited children were at genetic risk of DD based on their family history. All of these children had one or more first-degree relatives with DD as reported in a parental questionnaire. The 28 children of the control group had neither first nor second degree relatives with DD (demographic information is provided in Table 1). A subgroup of 35 children out of the 53 children that took part in the baseline measurement was tested longitudinally (age range: 7 years, 0 months to 8 years, 9 months; mean: 7 years, 8 months, SD=7.2; 18 females). Eighteen participants were unable to attend follow-up sessions at the end of the school year. Ten participants had finished second grade and 25 had finished first grade at the time of investigation. The returning group was spread over 2 years because the 5-year-old children of the baseline measurement started school one year later than children who were 6 at the time of baseline measurement. Twelve of the 35 children originated from the group of dyslexic children (for classification details, see next paragraph 2.3). There were no statistically significant group differences between the dyslexic children and the control children with respect to age ($t(31)=.845$, $p=.441$), sex ($\chi^2(1)=.038$, $p=.845$) or intelligence ($t(30)=-.831$, $p=.271$). All experimental procedures of the study were approved by the ethics committee of the University of Leipzig.

Table 1
Demographic information.

	Risk	Control	Significance (*p*-value, univariate analysis of variance)
N	25	28	
Age[a]	5;7 ± 0;4	5;6 ± 0;4	.227
Sex[b]	14/11	16/12	.933[d]
Non-verbal IQ[c]	99 ± 13	104 ± 12	.098

[a] years;months, MRI-scan age, mean ± standard deviation.
[b] male/female.
[c] mean ± standard deviation.
[d] chi-square test.

2.3. Psychometric assessment

We investigated six literacy precursor abilities at kindergarten age: quality of phonological representations (PR), phonological awareness on the syllable/rhyme level (PA), rapid automatized naming (RAN), visual attention and verbal working memory. PR was assessed using the pseudoword repetition subtest of the SETK 3–5 (a developmental German language test for children between 3 and 5 years of age; Grimm et al., 2001). Note that only phonemic failures but not failures resulting from articulation disorders (such as sigmatism) are taken into account in this subtest of the SETK 3–5 (Grimm et al., 2001). Verbal working memory was used as a covariate to exclude the potentially confounding effect of verbal working memory on pseudoword repetition in all analyses including PR. The decision for using this task was based on a systematic review of longitudinal studies in German-speaking countries (Pfost, 2015), which revealed that phonological awareness tasks at the syllable or rhyme level were less related to reading and spelling abilities than tasks on the phoneme level. PA was assessed using syllable segmentation and rhyme identification tasks of the BISC (Bielefeld screening of literacy precursor abilities; Jansen et al., 2002). RAN was assessed using the corresponding subtest of the BISC. Visual attention was assessed using the symbol comparison subtest of the BISC. Verbal working memory was assessed using the digit span subtest of the German version of the Kaufman Assessment Battery for Children, third edition (Kaufman et al., 2009). Furthermore, we investigated parental education using a self-constructed parental questionnaire and non-verbal intelligence using the Wechsler preschool and primary scale of intelligence (Wechsler et al., 2009). Note that visual attention, rapid automatized naming, verbal working memory and non-verbal intelligence data were not available for one participant, who was therefore excluded from the data analysis presented in Sections 3.1, 3.2, 3.4 and 3.5.

We investigated reading skills to obtain follow-up information regarding the actual acquisition of literacy abilities using the reading fluency subtest of the SLRT-II (Salzburg test of reading and spelling, second edition; Moll and Landerl, 2010) and the reading comprehension test ELFE 1-6 (Reading comprehension test for 1st to 6th grade; Moll et al., 2006). Furthermore, we investigated spelling skills using the DERET (German spelling test; Stock and Schneider, 2008), a writing test after a dictation of words. We finally assessed phoneme awareness using the BAKO (Test of basic reading and spelling skills; Stock et al., 2003). Spelling and phoneme awareness data were not available for one participant, who was therefore excluded from the final DD prediction analysis (see Section 3.5).

The diagnostic status of DD was defined based on the individual performance in tasks assessing reading fluency, reading comprehension and spelling accuracy. Twelve (9 children with a family risk of DD and 3 without such risk) of the 35 children were assigned to the group of dyslexic children based on poor task performance. These children performed below the 10th percentile rank of the population performance in at least one of the tests (reading fluency, reading comprehension and/or spelling accuracy). Eleven children of the dyslexic group showed reading comprehension deficits (performance below 10th percentile in reading comprehension test). Moreover, 80% of all children of the dyslexic group showed additional reading fluency and/or spelling deficits (performance below 10th percentile in reading fluency and/or spelling accuracy test). To ensure good reading skills in the control group and that there is no overlap between groups, the two children between the 10th and 25th percentile were excluded from the analysis in Section 3.5 (Shaywitz et al., 2002).

2.4. MRI data acquisition

Children were invited to a training session conducted using a mock scanner in order to familiarize them with the MRI procedure. Both the training and the experimental session were adapted for young children and set up as interesting games. These games increased the cooperation of the children and facilitated familiarization with the experimental procedures.

MRI was performed on a 3 T Siemens TIM Trio (Siemens AG) magnetic resonance scanner with a 12 channel radio-frequency head coil. We used the magnetization-prepared 2 rapid acquisition gradient echo (MP2RAGE; Marques et al., 2010) method to acquire T1 maps with the following parameters: TR = 5000 ms; TI1, TI2 = 700, 2500 ms; α1, α2 = 4°, 5°; FOV = 250 × 219 × 187 mm; matrix size = 192 × 168 × 144; voxel size1.3 mm isotropic; GRAPPA factor = 3 (with 32 ref. lines). We also performed simulations of the Bloch equations for these acquisition parameters, to ensure accurate T1-MP2RAGE maps, and particularly robustness against typical (for our MRI system) B1+ variations, within the observed T1 range for white matter (see Fig. S3). The MP2RAGE sequence was validated for T1 estimation against an inversion recovery sequence (Marques et al., 2010), and it was recently shown that this validation approach ensures accurate estimation of T1 relaxation times (Stikov et al. 2015). The T1 relaxation time captured by these images strongly correlates with myelin content in the white matter of the brain (Tardif et al. 2015a, 2015b; Sereno et al., 2013; Dick et al., 2012).

Diffusion-weighted imaging (DWI) data were acquired using the echo planer imaging method with the following parameters: TR = 8 s, matrix size = 100 × 100, voxel size = 1.9 mm isotropic and 66 axial slices. We used 60 diffusion-encoding gradient directions with a b-value of 1000 s/mm^2. Acquisition time was 32 min.

2.5. Data processing

2.5.1. MP2RAGE

The brain images from all uniform T1-weighted volumes of the MP2RAGE sequence were extracted using Freesurfer (http://surfer.nmr.mgh.harvard.edu/). These were then rigidly aligned to the MNI coordinate system and interpolated to 1-mm isotropic voxel size. The same transformation was applied to the quantitative T1 maps.

2.5.2. DWI

Before pre-processing the DWI data, a semi-automatic method (Schreiber et al., 2014) was used to identify DWI volumes corrupted by movement by plotting the average signal intensities for every axial slice of each volume. Signal drop-outs due to subject motion led to noticeably decreased average signal intensity and warranted manual inspection of those volumes. Two directions were removed on average per participant. The spherical deconvolution local model was computed using an order of 8, which requires at least 45 independent diffusion directions. Keeping at least 45 diffusion directions and checking that no more than 3 of these directions were neighboring ensured a sufficient over-determination of the system. The remaining data were also visually inspected to verify the results of this automatic method (Soares et al., 2013; Tournier et al., 2011). The DWI data were then corrected for motion and eddy currents as well as for susceptibility-induced distortions using the Topup tool (Andersson et al., 2003) as implemented in FSL (Smith et al., 2004), aligned to the uniform T1-weighted data and interpolated to 1-mm voxel size. All these procedures were performed with a single step of interpolation to preserve high data quality. Further preprocessing included the separation of background from diffusion data by applying the T1 brain mask and the computation of FA maps using the "dtifit" tool from the FSL software package.

2.6. Differences in quantitative T1 values within literacy relevant fiber pathways

The clusters showing statistically significant differences between children with and without a family risk of DD from a previous whole-brain CortT analysis (Kraft et al., 2015) were used as seed and target regions for tractography (Mori and van Zijl, 2002; Koch et al., 2002). These clusters were located in the left SMG, the left ITG and the left SOS/TOS. All ROIs were projected onto the adjacent gray/white matter border and extended by one voxel to ensure streamline connectivity within the white matter. Two additional target regions were defined in the IFG pars opercularis and IFG pars orbitalis to reconstruct the dorsal and ventral long distance fiber tracts of the reading network. The IFG pars opercularis was drawn in each subject's T1 image because of the high intersubject variability in this region's anatomy. The criteria of prior studies were used for the exact determination of the anatomical borders of the IFG pars opercularis (Amunts et al., 2010; Keller et al., 2007). Rostrally, the IFG pars opercularis was demarcated by the anterior ascending ramus of the Sylvian fissure, caudally by the inferior precentral sulcus and dorsally by the inferior frontal sulcus. For the extraction of IFG pars orbitalis, the *G_front_inf-Orbital* map from the Destrieux Atlas 2009 (https://surfer.nmr.mgh.harvard.edu/fswiki/DestrieuxAtlasChanges) was transformed to individual structural space of each subject. The subsequent visual inspection of each individual mask confirmed successful transformation in each case.

To reconstruct the fiber bundles connecting the aforementioned regions, fiber orientation density functions were computed in every voxel using constrained spherical deconvolution as implemented in MRtrix (Tournier et al., 2007). In contrast to the diffusion tensor (Basser et al., 1994), this model allows distinguishing multiple fiber orientations in each voxel (Zhao et al., 2016; Vanderauwera et al., 2015). Probabilistic tractography (Tournier et al., 2012) based on constrained spherical deconvolution was used to define the connecting pathways between ROIs. For this analysis, 500 000 streamlines were started in the seed locations to propagate to the target regions considering the orientational uncertainty described by the fiber orientation density functions. Probabilistic tractography was used to trace the following specific white matter tracts: connection between the CortT ROI of the SMG and the IFG pars opercularis (anterior AF), connection between the SMG-ROI and the ITG-ROI (posterior AF), connection between the ITG-ROI and the IFG pars opercularis (long AF), and connection between the ITG-ROI and IFG pars orbitalis (IFOF). Streamlines were seeded in the SMG-ROI to reconstruct both the anterior and posterior segment of the AF. Streamlines leading to a hub in the IFG pars opercularis were selected for the anterior segment and only streamlines leading to a hub in the ITG for the posterior one. We seeded in the statistically significant ITG-ROI, and selected streamlines leading to a hub in the IFG pars opercularis to reconstruct the long AF. Finally, we seeded in the statistically significant ITG-ROI, and selected streamlines leading to a hub in the IFG pars orbitalis to reconstruct the IFOF. Furthermore, streamlines were restricted to those fibers running between seed and target ROI.

Finally, mean T1 intensity values were calculated within each tract of interest by using the number of streamlines passing each voxel as weighting factors. This procedure has two major advantages. First, regions at the edge of gray and white matter, which could be contaminated by partial volume effects and contain fewer streamlines, contribute less to the average of an individual fiber

tract. Second, the central regions of the fiber tract with the highest densities of streamlines are more strongly weighted.

2.7. Statistical analyses

2.7.1. White matter

The FSL tool for nonparametric permutation tests within the framework of the general linear model ("Randomize"; Winkler et al., 2014), was used to estimate group effects (risk group versus control group) of averaged T1 intensities at each fiber tract. Results were corrected for family-wise error rate (FWE).

2.7.2. Behavioral test scores

A univariate analysis of variance was conducted for the group comparison of the behavioral data.

2.7.3. Structural MRI measures and precursor abilities

Multiple regression analysis was used to investigate the effect of structural brain anomalies, identified in children with a family risk of DD, on the development of phonological and visual precursor abilities. Gray matter anomalies from our recently published cross-sectional study were used (see Kraft et al., 2015 and Supporting information S1) in addition to predictors derived from the white matter analysis described above. We included a measure of the quality of phonological representations (PR) to investigate phonological precursor abilities and used a visual attention task to investigate visual precursor abilities. The multiple regression analysis was performed while controlling for age, sex and intelligence. Multiple regression analysis, which was used to investigate the effect on the PR, was run controlling verbal working memory in addition to age, sex and intelligence. This approach was used to exclude the potentially confounding effects of working memory on the pseudoword repetition subtest of the SETK.

2.7.4. Prediction of DD

We ran a hierarchical binary logistic regression analysis implemented in SPSS (SPSSInc., Chicago, IL, USA) to investigate whether the gray and white matter differences identified in children with a family risk of DD could predict the disorder better than the literacy precursors and general cognitive development. The independent variables were selected from the longitudinal correlation analysis (provided in Tables S1 and S2) and consisted of all statistically significant predictors of literacy ($p < .05$). During this analysis, three different DD prediction models were specified and hierarchically introduced to the analysis. In order to control for the potential confounding effect of general cognitive development, the first model included the intelligence score as the only predictor. In a second step, the effect of literacy precursors was investigated by adding PR and working memory as further predictors. The third model acknowledged statistically significant structural brain differences as an additional predictor.

3. Results

3.1. Behavioral group comparisons at a preliterate age

There was a statistically significant difference between the risk and control group in RAN ($F(1, 50)=6.84$, $p=.012$) after controlling for the effects of intelligence, age and sex. No statistically significant differences were found for PR ($F(1, 51)=1.07$, $p=.306$), PA ($F(1, 51)=0.38$, $p=.542$), visual attention ($F(1, 50)=0.61$, $p=.439$), working memory ($F(1, 50)=0.02$, $p=.903$) and parental education ($F(1, 51)=0.13$, $p=.722$). Mean raw scores and standard deviations are reported in Table 2.

Table 2
Results of behavioral group statistics: literacy precursor abilities.

	Risk (mean ± SD)	Control (mean ± SD)	Significance (*p*-value, univariate analysis of variance)
N	25	28	
PR	7.88 ± 3.80	8.96 ± 3.90	.306
PA	32.00 ± 6.84	30.93 ± 5.88	.542
RAN	**5.17 ± 2.68**	**6.61 ± 1.07**	**.012***
Visual attention	8.96 ± 1.92	8.43 ± 2.81	.908
Working memory	9.28 ± 2.92	9.37 ± 2.37	.903
Parental education[a]	16.32 ± 5.12	15.79 ± 5.69	.439

* $p < .05$.
[a] questionnaire-derived, single cumulative score per participating child computed by adding the sum of 2 scores (one per parent) for school education (4-point scale; no degree: 1 point; German "Abitur": 4 points) and the sum of 2 scores (one per parent) for further education (9-point-scale; no degree: 1 point; German "Habilitation": 9 points), mean ± standard deviation.

3.2. Behavioral group comparisons after one or two years of literacy education at school

There was a statistically significant difference between the risk and control groups in the reading score (additive score based on results in reading fluency test and reading comprehension test) ($F(1, 31)=7.25$, $p=.011$) and phoneme awareness ($F(1, 25)=1.96$, $p=.002$). The group difference in spelling did not reach statistical significance ($F(1, 30)=3.42$, $p=.074$). Mean scores and standard deviations are reported in Table 3.

3.3. White matter connectivity group comparisons at a preliterate age

The group comparison of averaged T1 intensities within the anterior segment of the left AF revealed significantly higher T1 intensities in pre-school children with a family risk of DD compared to pre-school children without a family risk of DD ($t(51)=1.82$, $p=.034$, Cohen's d=.501 FWE-corrected, Fig. 1). In all other tracts, no statistically significant differences were found between the risk and control group: posterior segment of the left AF ($t(51)=0.52$, $p=.296$, Cohen's d=.143), long segment of the AF ($t(51)=0.34$, $p=.361$, Cohen's d=.094) and IFOF ($t(51)=0.26$, $p=.741$, Cohen's d=.072). We also tested whether similar differences in the left anterior AF could be found when using FA as the dependent variable, but the difference between groups was not statistically significant ($t(51)=0.86$, $p=.194$).

3.4. Link between structural brain differences and literacy precursors

We then investigated the link between structural brain differences in the gray matter (Kraft et al., 2015; Supporting information

Table 3
Results of behavioral group statistics: literacy abilities.

	Risk (mean ± SD)	Control (mean ± SD)	Significance[+] (p-value, univariate analysis of variance)
N	15	20	
Reading score	**32.74 ± 30.75**	**59.19 ± 24.99**	**.011***
Spelling	27.64 ± 26.51	45.85 ± 23.23	.074
Phoneme awareness	**26.35 ± 27.01**	**58.40 ± 24.33**	**.002****

* $p < .05$.
** $p < .005$.

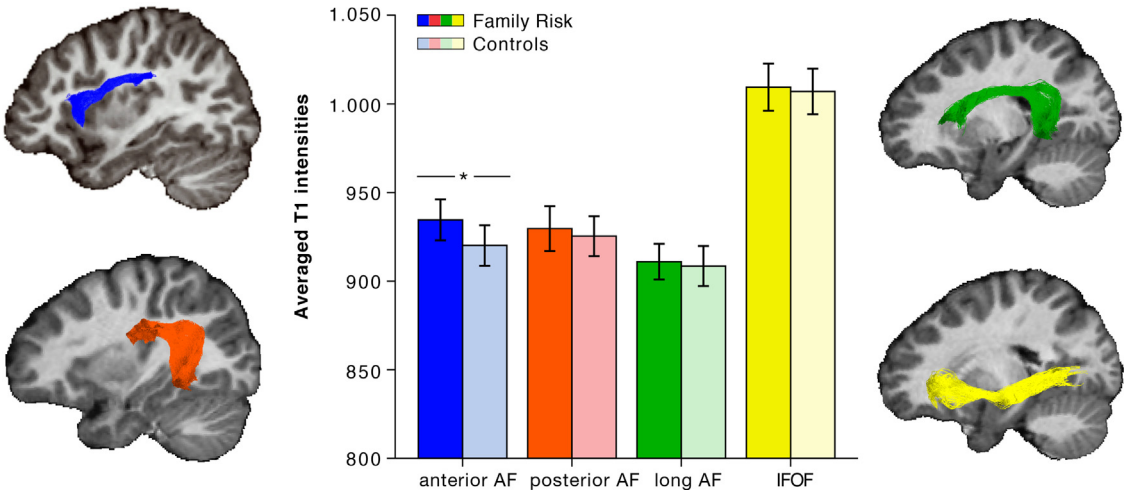

Fig. 1. Comparison of the averaged T1 intensities in the anterior, posterior and long segment of the arcuate fascicle (AF) as well as in the inferior fronto-occipital fascicle (IFOF) in preliterate children. Compared to children without a family risk of DD (N=28), children with a family risk of DD (N=25) showed significantly increased T1 intensities indicating reduced myelin concentration in the left anterior AF ($p < .05$ FWE-corrected, Cohen's d=.501). In all other tracts, no statistically significant differences were found between the risk and the control group. Error bars indicate standard errors of mean (SEM). The anterior segment of the AF connects the supramarginal gyrus (seed region) with the pars opercularis of the inferior frontal gyrus (target region). The posterior segment of the AF connects the supramarginal gyrus (seed region) with the inferior temporal gyrus (target region). The long segment of the AF connects the inferior temporal gyrus (seed region) with the pars opercularis of the inferior frontal gyrus. The IFOF connects the inferior temporal gyrus (seed region) with the pars orbitalis of the inferior frontal gyrus (target region). All tracts are shown for a single representative subject in native space.

Table 4
Results of hierarchical logistic regression analysis: coefficients of the model predicting whether an individual will have DD.

	β	Standard error	Wald	df	p	Exp(β)
Model 1						
Intelligence	−.062	.036	3.030	1	.082	.940
Model 2						
Intelligence	−.046	.040	1.273	1	.259	.955
PR	−.173	.162	1.144	1	.285	.841
Working memory	.005	.220	.001	1	.981	1.005
Model 3						
Intelligence	−.105	.059	3.193	1	.074	.900
PR	−.126	.172	.532	1	.466	.882
Working memory	−.012	.308	.001	1	.970	.988
Cortical thickness SMG	−2.864	1.926	2.212	1	.137	.057
T1 intensities $AF_{anterior}$	**.052**	**.025**	**4.266**	**1**	**.039***	**1.054**

* $p < .05$.

S1), white matter and literacy precursor abilities. Multiple regression analyses were performed to investigate the associations between structural brain differences identified in children at risk of DD and phonological (first analysis) and visual (second analysis) literacy precursor abilities. The results revealed a statistically significant association between the CortT in the left SMG and PR (β=.24, $t(50)=2.07$, $p=.044$) while no such effect was found for the CortT of the left ITG (β=−.14, $t(50)=-1.05$, $p=.301$) or the T1 intensity of the left anterior AF (β=.12, $t(50)=1.00$, $p=.328$). No statistically significant relations were found between the ITG (β=−.11, $t(49)=-.67$, $p=.509$), the SMG (β=−.04, $t(49)=-.26$, $p=.795$), the anterior AF (β=−.08, $t(49)=-.51$, $p=.615$) and visual attention (for more detailed information, see Tables S3 and S4).

3.5. Prediction of DD

Finally, a hierarchical binary logistic regression analysis was computed to investigate the role of behavioral and brain measures at pre-school age as DD predictors. For this, CortT measures were used as described previously (Kraft et al., 2015). The first model investigating the effect of general cognitive development (intelligence) on predictability of DD revealed no statistically significant improvement compared to the null model (Chi-square=3.553, $p=.059$). The second model adding the effect of behavioral literacy precursors (PR and working memory) on predictability of DD failed to detect a statistically significant improvement compared to the first model (Chi-square=1.66, $p=.436$). However, the third model adding the effect of structural brain differences on predictability of DD was statistically significant, demonstrating that inclusion of specific structural brain differences of the model significantly improves prediction of DD (Chi-square=7.482, $p=.024$). Nagelkerke's R^2 was .472, with an overall prediction success of 80% (90% for participants with DD and 64% for participants without DD), in contrast to 63% prediction success of the model including only behavioral predictors. The Wald statistic revealed that the T1 intensity left anterior AF was a statistically significant predictor of DD ($p=.039$) while the gray matter of the left SMG did not reach statistical significance ($p=.137$). The PR ($p=.466$), working memory ($p=.970$) and IQ ($p=.074$) did not significantly predict DD. The beta values, their standard errors and the statistical significance values of all coefficients of the model are reported in Table 4.

4. Discussion

We observed distinct brain structure profiles for children who have a family risk of DD compared to children without such risk. The children with a family risk of DD showed increased T1 intensities in the dorsal reading network, particularly in the left anterior AF, in addition to reduced CortT in previously described brain regions (Kraft et al., 2015). The observed structural brain differences together with behavioral literacy precursor measures showed a DD prediction success of 80%, thereby improving the prediction success based on behavioral literacy precursor measures alone by 17%. The best predictor of DD was an increase in T1 intensities indicating reduced myelin concentration in the left anterior AF.

The left anterior AF belongs to the dorsal reading network, which has been associated with segmental reading of regular words and pseudowords and in particular with phoneme-to-

grapheme mapping (Roux et al., 2012; Jobard et al., 2003). Previous studies investigating school-aged children and adults with DD reported reduced FA in the white matter of the dorsal reading network (e.g. Rimrodt et al., 2010; Deutsch et al., 2005; Klingberg et al., 2000). So far, however, no such anomalies have been found in preliterate children with a family risk of DD (Vandermosten et al., 2015). To our knowledge the present study is therefore the first one showing that such differences in the white matter of the dorsal reading network in children with a family risk of DD (compared to controls) exist before reading is taught at school. This result is in line with another study investigating pre-school children with poor phonological development without taking their family risk of dyslexia into account (Saygin et al., 2013). Saygin and colleagues showed a statistically significant relation between development of the dorsal reading network and the development of phonological skills (PR tasks, e.g. pseudoword repetition).

Given the fact that FA is a neurobiologically unspecific measure which combines many microstructural properties of white matter in a single index, the aim of the present study was to measure myelination using a more specific method. Indeed, the chosen quantitative T1 measure, which was previously shown to reflect myelin content in the white matter of the brain (Tardif et al., 2015a, 2015b; Sereno et al., 2013; Dick et al., 2012), revealed increased T1 intensities. This indicated reduced myelination in the left anterior AF in children at risk of DD (compared to controls), but this effect could not be replicated when we investigated differences in the FA of the left anterior AF. FA is more related to structure than to myelin (Beaulieu, 2002) and hence, quantitative T1 measurement might be a more sensitive method to investigate changes related to myelination in the developing brain.

In contrast to previous studies investigating school-aged individuals and adults with DD (Vandermosten et al., 2012; Yeatman et al., 2011), no anomalies were found in the long and posterior segment of the AF. It might be that the changes in these segments of the AF are not present in preliterates, but only emerge with the beginning of grapheme acquisition (Dehaene et al., 2015). Such reading-associated differences in the posterior AF were previously reported in a study comparing adult beginner readers (ex-illiterates) with illiterates (Thiebaut de Schotten et al., 2012).

The present study revealed no anomalies in the IFOF in preliterate children at risk of DD compared to children with no such risk. This result is in contrast to the result of the previous FA study in pre-reading children with a family risk of DD, which reported reduced FA in the left IFOF in children at risk of DD (Vandermosten et al., 2015). The divergent results might indicate that the difference in FA in preliterate children, which was observed by Vandermosten et al. (2015), is not exclusively driven by myelination but could alternatively be explained by other tissue properties, such as axonal density (Scholz et al., 2009) and axonal diameter (Paus, 2010) or fiber orientation (Beaulieu, 2002). Zhao et al. (2016) found reduced leftward asymmetry of the IFOF using hindrance-modulated oriented anisotropy (HMOA, Dell'Acqua et al., 2013) in school-aged children. Based on our hypotheses and the results of our CortT study (whole brain analysis revealed reduced CortT in left-hemispheric but not in right-hemispheric regions), no further investigation of the left-right-hemispheric asymmetry was performed in the present study. Such asymmetry analysis would nevertheless be an interesting question for future studies in order to investigate the lateralization of the dorsal and ventral reading network pathways in pre-school children with a family risk of DD.

The individual assessment of family risk of DD is an efficient approach to determine the genetic predisposition for DD. Previous research showed that 34% of first-degree relatives of individuals with DD develop DD compared to a rate of only 6% in individuals with no family risk (Pennington and Lefly, 2001). Nevertheless, we are aware of the difficulty of estimating a family risk of DD (Clark et al., 2014). Of the 35 subjects recruited to the longitudinal group in our study, 15 had a family history of DD nine of which (60%) developed dyslexia. Only three of the children without a family history of DD developed dyslexia (15%). This outcome shows that, besides a family history of DD (genetic factor), other factors seem to play a role, which confirms the observation that DD is a heterogeneous disorder with many determinants.

Another goal of the present study was to identify neuroanatomical measures that significantly improve the predictability of DD compared to a prediction model solely based on behavioral precursors. The observed results revealed that only the model considering neuroanatomical predictors was able to classify participants into dyslexics and non-impaired individuals, while the model including only the behavioral predictors was not. The model including neuroanatomical and behavioral predictors revealed a prediction accuracy of 80%, while the prediction based only on behavioral precursors reached a prediction accuracy of 63%. Until now, the main focus of the literature about the predictability of DD has been on behavioral precursors. The identified behavioral precursor abilities, however, could not provide sufficient specificity with regard to separation of individuals with and without DD (Steinbrink et al., 2010; Marx and Weber, 2006). The result of the multifactorial approach introduced here shows that the prediction of DD can be significantly improved by considering neuroanatomical measures. This result is in line with a previous study reporting high prediction accuracy ($>90\%$) for long-term reading abilities in school children when considering brain measures in contrast to a model including only behavioral measures (Hoeft et al., 2011).

5. Limitations

It should be noted that our sample size is relatively small and future studies with larger sample sizes should be warranted to investigate the robustness of our results. The objective of this study was to trace connections from regions where the children with a family risk of DD showed reduced CortT to subregions of Broca's area that are relevant for the development of literacy. Thus, it might be that the tracts reconstructed in this study do not display the complete tracts as they were defined in adult anatomical atlases (e.g. Wakana et al., 2007). Given the recent report of tract specific lateralization differences in school children with DD based on the orientation-specific measure HMOA (Zhao et al., 2016), future studies should include HMOA to investigate such lateralization differences already in pre-school children. Moreover, our findings need to be corroborated by further measurement points in stages of advanced literacy.

6. Conclusion

The present longitudinal study goes beyond previous studies by demonstrating that biologically informative neuroanatomical profiles in children with a family risk are related to subsequent reading difficulties. Moreover, we provide evidence that these profiles can be used to optimize the distinction between children with and without DD. Solid white matter organization in the left anterior arcuate fascicle seems to play a pivotal role in typical literacy acquisition. Future studies employing multimodal quantitative MRI techniques are necessary to better characterize brain tissue microstructure of the developmental trajectories of DD.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuroimage.2016.09.004.

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