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Structural brain alterations associated with dyslexia predate reading onset

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Abstract

Functional magnetic resonance imaging studies have reported reduced activation in parietotemporal and occipitotemporal areas in adults and children with developmental dyslexia compared to controls during reading and reading related tasks. These patterns of regionally reduced activation have been linked to behavioral impairments of reading-related processes (e.g., phonological skills and rapid automatized naming). The observed functional and behavioral differences in individuals with developmental dyslexia have been complemented by reports of reduced gray matter in left parietotemporal, occipitotemporal areas, fusiform and lingual gyrus and the cerebellum. An important question for education is whether these neural differences are present before reading is taught. Developmental dyslexia can only be diagnosed after formal reading education starts. However, here we investigate whether the previously detected gray matter alterations in adults and children with developmental dyslexia can already be observed in a small group of pre-reading children with a family-history of developmental dyslexia compared to age and IQ-matched children without a family-history (N = 20/mean age: 5:9 years; age range 5:1–6:5 years). Voxel-based morphometry revealed significantly reduced gray matter volume indices for pre-reading children with, compared to children without, a family-history of developmental dyslexia in left occipitotemporal, bilateral parietotemporal regions, left fusiform gyrus and right lingual gyrus. Gray matter volume indices in left hemispheric occipitotemporal and parietotemporal regions of interest also correlated positively with rapid automatized naming. No differences between the two groups were observed in frontal and cerebellar regions. This discovery in a small group of children suggests that previously described functional and structural alterations in developmental dyslexia may not be due to experience-dependent brain changes but may be present at birth or develop in early childhood prior to reading onset. Further studies using larger sample sizes and longitudinal analyses are needed in order to determine whether the identified structural alterations may be utilized as structural markers for the early identification of children at risk, which may prevent the negative clinical, social and psychological outcome of developmental dyslexia.

Keywords

fMRI; Children; Dyslexia; Voxel-based morphometry; Reading; Family history

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Introduction

Developmental dyslexia, which affects 5–17% of all children, is a specific learning disability characterized by difficulties with accurate and/or fluent word recognition, poor spelling and decoding skills (Beitchman et al., 1986). Difficulties in reading are disproportionate to other cognitive abilities (such as IQ) and cannot be explained by poor vision, hearing difficulty or a lack of motivation or educational opportunities (World Health Organization, 1992). Familial occurrences and twin studies suggest that developmental dyslexia is highly heritable, occurring in up to 40% of individuals who have a first-degree relative with developmental dyslexia (Fisher and Francks, 2006; Smith et al., 1983). Several candidate susceptibility genes for developmental dyslexia have been reported (Galaburda et al., 2006). The majority of these genes are shown to be important for brain development and it has been suggested that developmental dyslexia may be caused by abnormal migration and/or maturation of neurons during early development (Galaburda et al., 2006). Currently, developmental dyslexia can only be diagnosed after the onset of formal reading instruction (around second or third grade in the United States). However, identifying a child after reading onset limits the time available for early interventions that may prevent the serious clinical, psychological and social impact of developmental dyslexia. Educational neuroscience offers methods for identifying early biomarkers of educational risk, for example via structural differences in the dyslexic brain that pre-date being taught to read.

To date, studies focusing on the early detection of children at risk for developmental dyslexia have mainly centered on behavioral correlates of reading abilities. These studies suggest that linguistic impairments such as deficits in language comprehension, phonological processing or impaired letter name knowledge prior to formal reading instruction predict reading ability in children with and without a family history of developmental dyslexia (e.g.; Flax et al., 2008; Gallagher et al., 2000; Pennington and Lefly, 2001; Puolakanaho et al., 2008; Scarborough, 1990; Snowling et al., 2003). Additionally, several studies have found deficits in rapid automatized naming prior to formal reading instruction which predict later reading abilities (De Jong and Van der Leij, 1999; Kirby et al., 2003; Kobayashi et al., 2005; Wolf, 1986; Wolf et al., 1986). Furthermore, research suggests that both phonological processing and rapid automatized naming contribute uniquely and substantially to word reading from grade 1 to grade 6 (Vaessen and Blomert, 2010). However, the feasibility of these behavioral correlates as effective screening measures remains a challenge (Gabrieli, 2009).

Several studies have utilized brain measures to study young children at risk for developmental dyslexia and healthy controls. Electrophysiological differences have been reported for infants with familial risk for developmental dyslexia for basic auditory and language processing (e.g.; Guttorm et al., 2001, 2003; Pihko et al., 1999; Leppanen et al., 2002). However, to date only one study has reported neural predictors of reading abilities (Maurer et al., 2009) in children with and without a familial risk of dyslexia. In a 5-year longitudinal study, neurophysiological and behavioral measures obtained in 6 year old kindergarteners with and without a family history of dyslexia predicted reading outcome after reading instruction. Neurophysiological measures in kindergarten furthermore improved reading prediction in comparison to behavioral measures alone and were the only predictor for reading success in fifth grade.

Previous neuroimaging studies revealed differences in brain structure and function between school-age children and adults with a diagnosis of developmental dyslexia and controls. Using functional magnetic resonance imaging (fMRI), individuals with developmental dyslexia showed reduced activation during reading and reading related tasks in left-

hemispheric occipitotemporal regions which correlated with reduced reading skills (Hoeft et al., 2007b; Temple, 2002; Specht et al., 2009).

Structural magnetic resonance imaging (MRI) with voxel-based morphometry (VBM) revealed decreased gray matter volume indices in individuals with developmental dyslexia, when compared to typical reading controls, in several brain regions, such as left occipitotemporal and temporoparietal areas (Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005; Hoeft et al., 2007a; Kronbichler et al., 2008; Pernet et al., 2009; Silani et al., 2005), bilateral fusiform (Kronbichler et al., 2008) and lingual gyrus (Eckert et al., 2005) as well as the cerebellum (Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005). Moreover, gray matter volume indices in these areas were positively correlated with pre-reading and reading skills, such as timed and untimed (pseudo-)word reading (Kronbichler et al., 2008; Pernet et al., 2009; Silani et al., 2005; Steinbrink et al., 2008), phonological processing (Kronbichler et al., 2008; Pernet et al., 2009), spelling performance (Pernet et al., 2009) and rapid automatized naming (RAN) (Kronbichler et al., 2008). Similarly, white matter organization, as characterized by diffusion tensor imaging (DTI), is found to be weaker in left posterior brain regions in individuals with developmental dyslexia and correlate positively with reading skills, such as reading speed or word and pseudo-word reading (Klingberg et al., 2000; Silani et al., 2005; Steinbrink et al., 2008).

It remains unclear whether these morphological differences exist at birth, develop during the first few years of life, or are due to experience-dependent structural changes that occur after the onset of formal reading education. In the current study we utilized VBM (Ashburner and Friston, 2005) to investigate whether the previously reported differences in gray matter volume indices in individuals with developmental dyslexia can already be observed in a small group of five year old pre-readers with a family-history of developmental dyslexia.

Our focus on an understudied age group (pre-reader to beginning readers) within the dyslexia population is highly significant, as it provides an opportunity to examine potential predictors for an age group for which intervention might be most efficacious. For example, it has been shown that children with learning disabilities are less likely than their peers to enroll in programs of higher education (Wagner, 1993) or complete high school (Marder, 1992) and are more likely to enter the juvenile justice system (Quinn et al., 2001). Early identification of predictors of reading disability in pre-reading children offers a chance to eliminate these significant personal and social costs. A modified approach to the way we teach children how to read must include early identification and the development of early preventive strategies. The identification of a child with reading disabilities in mid-elementary school may be too late. By this stage, the delayed development of reading has already affected children's vocabulary skills (Cunningham and Stanovich, 1991) and motivation to read (Oka and Paris, 1986), thus leading to missed opportunities for the development of comprehension strategies (Brown et al., 1986). Studies have shown that children who are weak readers at the end of first grade remain poor readers by the end of elementary school (Francis and Shaywitz, 1996; Torgesen and Buress, 1998). Improved early identification of children at risk (behavioral or family risk) using neural pre-markers may further lead to changes in educational policies and will make it possible to assign independent educational plans and customized curriculums for children at risk prior to formal schooling.

Methods

Subjects

Twenty healthy, native English speaking children with (FHD+/n=10) and without (FHD–/n=10) a family-history of developmental dyslexia, have been included in the present

analyses. All children are enrolled in our larger longitudinal study which also employs functional imaging, psychophysical measures as well as conducts genetic testing. FHD+ children (mean age 5 years and 11 months) had at least one first degree relative with a clinical diagnosis of developmental dyslexia. Children with a family-history of reading difficulties, but no clinical diagnosis of developmental dyslexia in the family were excluded from the study. FHD– children (mean age 5 years and 7 months) had no first degree relatives with developmental dyslexia and no self-reported history of reading difficulties or language delays in their families. Children were screened for hearing and vision difficulties, neurological disease or psychiatric disorders through a parent questionnaire. The two groups of FHD+ and FHD–children were matched by group for age, gender and non-verbal IQ (Kaufman Brief Intelligence Test, 2nd edition; Kaufman and Kaufman, 1997). Data obtained in the national early childhood longitudinal study (ECLS-K, kindergarten class of 1998–1999) indicate that by kindergarten entry only 2% of all children are able to identify sight words and no more than 1% recognize words in context (Denton et al., 2000). Based on this study, only pre-reading children were enrolled in our study. During an initial telephone/email-screening with the parents, we screened for pre-reading status in all children. Only pre-reading children (parent report) planning to receive formal reading instruction within the next months were invited to take part in the study. Furthermore, the Word Identification subtest of the Woodcock Reading Mastery Test (WRMT; Woodcock, 1998) was administered to assure pre-reading status. For the Word Identification subtest the child is required to identify isolated words presented in the test booklet. For an answer to be scored as correct, the child must produce a natural or fluent reading of the word within about five seconds. Seventeen children (9 FHD+/8 FHD–) were not able to read a single word, two children (1 FHD+/1 FHD–) recognized two and one child (FHD+) recognized seven isolated words. All children were tested between May and November of their kindergarten entry year (based on the reading curriculum, children should be able to read first words by the end of November of their kindergarten year). This study was approved by the ethics committee of Children's Hospital Boston. Verbal assent and informed consent was obtained from each child and guardian, respectively.

Behavioral group characteristics

Participants were characterized by a test battery of standardized assessments examining language and pre-reading skills, such as expressive and receptive vocabulary (Clinical Evaluation of Language Fundamentals (CELF Preschool 2nd edition); Semel et al., 1986), phonological processing (Comprehensive Test of Phonological Processing (CTOPP); Wagner et al., 1999) and RAN (Rapid Automatized Naming Test; Wolf and Denckla, 2005). Additionally, potential confounds included socioeconomic status and home literacy environment. All participating families were given a socioeconomic background questionnaire (questions adapted from the MacArthur Research Network: http://www.macses.ucsf.edu/Default.htm) and answered questions concerning the home literacy environment (based on Denney et al., 2001 as cited in Katzir et al., 2009). For a complete overview of SES and HLE questions see SI1 and SI2).

Imaging procedure

For all participants an age-appropriate neuroimaging protocol was used, which included an intensive familiarization with the MRI equipment in a mock scanner area prior to the actual neuroimaging session (Raschle et al., 2009). T1-weighted MPRAGE MRI sequences were acquired on a Siemens 3 T whole body scanner with the following specifications: 128 slices, TR 2000 ms; TE 3.39 ms; flip angle 9°; field of view 256 mm; voxel size 1.3×1.0×1.3 mm. Whole brain structural brain images were collected for all children between August and November prior to their or within the first few weeks of their first kindergarten year.

VBM analysis and statistics

We utilized optimized voxel-based morphometry (Ashburner and Friston, 2005), a whole-brain analysis technique, to examine differences in gray matter volume indices between pre-reading FHD+ and FHD– children. In particular, the VBM5.1 toolbox (http://www.dbm.neuro.uni-jena.de/vbm) was employed using SPM5 software (http://www.fil.ion.ucl.ac.uk/spm) executed in MATLAB (Mathworks, Natick, MA). All images were segmented, bias-corrected and spatially normalized to a customized pediatric brain template specific to the group's characteristics (e.g. age and gender) to account for brain size and development within our pediatric population (mean: 5 years and 9 months). The template was generated using Template-O-Matic, a toolbox to create customized brain templates of high quality, especially in smaller subject samples (Wilke et al., 2008). Using unified segmentation, the images were segmented into gray matter, white matter and cerebrospinal fluid. Data quality was assured with a sample homogeneity test by plotting the standard deviation of the normalized, gray matter segmented brain volumes across all subjects. The covariance between each gray matter volume is hereby visualized using a boxplot and covariance matrices (for VBM manual and details see http://www.dbm.neuro.uni-jena.de/vbm). Finally, bias-corrected, whole brain Jacobian modulated images (preserving total gray matter volume) were smoothed with a 12-mm full width at half maximum isotropic Gaussian kernel (Ashburner and Friston, 2005).

Regional variations in gray matter volume indices (GMVI, corresponding to the percentage of gray matter in a given voxel) between FHD+ and FHD– children were calculated using a two-sample *t*-test. Statistical significance thresholds were applied at the voxel-level ($p<0.001$, uncorrected). Results for the whole brain analysis were obtained using non-stationary correction ($p<0.01$ cluster size extent value), which is essential to adjust cluster sizes according to local roughness (Hayasaka et al., 2004). To examine the relationship between structural and behavioral measures, we defined two main regions of interests. The ROIs were defined by an 8 mm radius sphere, centered around parietotemporal and occipitotemporal activation peaks as identified in a meta-analysis of 35 neuroimaging studies of word and pseudoword reading (Jobard et al., 2003). They further overlap with the observed anatomical differences between pre-reading children with and without a family-history of developmental dyslexia in the current study. Using the brain imaging toolbox (BIT, Gabrieli Lab, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA) a parietotemporal ROI was created at $x=–44±4$; $y=–58±5$; $z=–15±6$ and a more occipitotemporal ROI at $x=–60±4$; $y=–41±6$; $z=25±6$. The two ROIs were normalized to our customized pediatric template, which accounts for brain size and development within our pediatric population. Next, mean GMVIs of these ROIs were extracted for each individual. Finally, the average of GMVIs within each ROI for the whole experimental group ($n=20$; 10 FHD+/10 FHD–) was correlated with standardized behavioral measures, which have shown to predict reading ability: phonological processing (e.g. Flax et al., 2008; Gallagher et al., 2000; Pennington and Lefly, 2001; Puolakanaho et al., 2008; Scarborough, 1990; Snowling et al., 2003;) and RAN (De Jong and Van der Leij, 1999; Kirby et al., 2003; Kobayashi et al., 2005; Wolf, 1986; Wolf et al., 1986). Statistical correlation analysis was performed using SPSS software package, version 16.0 (SPSS Inc., 1999). Significance thresholds of this ROI correlation analysis were corrected for multiple comparisons by controlling for the false discovery rate (FDR, Benjamini and Hochberg, 1995).

Results

Demographics and behavioral data

Demographic characteristics of all participants are listed in Table 1. We observed significant differences in standardized behavioral assessments of RAN between children with a family history of developmental dyslexia (FHD+) compared to children without a family-history of developmental dyslexia (FHD–) ($p \leq 0.001$; Table 1). Mean scores of expressive and receptive language skills and phonological processing appeared to be lower in FHD+, compared to FHD–, children but did not reach significance ($p > 0.05$). There were no group differences in age ($p = 0.241$) and no group differences in verbal or non-verbal IQ (Verbal: $p = 0.489$/Non-verbal: $p = 0.452$). Furthermore, there was no significant difference ($p > 0.05$) in socioeconomic status (SES; e.g. parental education and total family income over the last 12 month) or home literacy environment (HLE; e.g. age of child when first read to, total number of adult or children books at home) between groups (Table 1, SI1 and SI2).

VBM

Voxel-based morphometry (VBM5) revealed significantly reduced gray matter volume indices (GMVIs) for FHD+ compared to FHD– children in left occipitotemporal area (LOT: $x = -43$, $y = -66$, $z = 4$), left and right temporoparietal regions (LTP: $x = -57$, $y = -34$, $z = 26$; / RTP: $x = 46$, $y = -29$, $z = 24$), left fusiform (LFG; $x = -45$, $y = -60$, $z = -14$) and right lingual gyrus (RLG; $x = 23$, $y = -87$, $z = -11$) at $p < 0.001$ (corrected for non-stationarity; $p < 0.01$) (see Fig. 1a–c and Table 2). The reported differences are displayed on our customized pediatric brain template and MNI coordinates also reflect our pediatric brain template generated with Template-O-Matic (Wilke et al., 2008), which optimally reflects our age range (mean: 5 years and 9 months) and hence the average brain development stage of our participant group. There were no significant differences in gray matter volume indices for the inverse contrast (FHD+ >FHD–; at $p < 0.001$) and no differences in total gray matter ($p = 0.760$) or total intracranial volume ($p = 0.772$) between FHD+ compared to FHD– children.

Region of interest (ROI) analyses

Correlation analyses for standardized behavioral measures of phonological processing and RAN with GMVIs revealed significant positive Pearson correlations for the left temporoparietal and left occipitotemporal ROI with RAN (LTP: $r = 0.26$, $p = 0.023$/LOT/LFG $r = 0.32$, $p = 0.009$; Fig. 1d–e). No significant correlations were found for the two ROIs with phonological processing. Because of the previously reported strong relationship between left occipitotemporal brain region and phonological processing in functional and structural studies (e.g. Hoeft et al., 2007b; Temple, 2002; Kronbichler et al., 2008; Pernet et al., 2009) we additionally extracted GMVIs from a non-independent ROI within our left occipitotemporal region (LOT) which exhibited significantly less gray matter volume in FHD+, compared to FHD–, children. GMVIs in LOT significantly correlated with phonological processing ($r = 0.25$, $p = 0.024$) and RAN ($r = 0.47$, $p = 0.037$).

Discussion

We observed reduced gray matter volume indices in a small group of pre-reading children with a family-history of developmental dyslexia, compared to children without a family-history, in brain areas known to be involved during reading and reading development (McCandliss and Noble, 2003; Schlaggar and McCandliss, 2007). If these structural brain differences are replicated in future studies with larger samples, reduced gray matter volume may provide a biomarker useful for education. These regions include the left occipitotemporal area, bilateral temporoparietal regions, left fusiform gyrus and right lingual gyrus. Furthermore, GMVIs within left hemispheric temporoparietal and occipitotemporal

ROIs (created based on a meta-analysis on reading networks, Jobard et al., 2003) correlated with RAN skills. There were no significant differences in early literacy experience or socioeconomic background between children with compared to children without a family-history of developmental dyslexia, and therefore these variables do not account for the present findings.

The observed structural brain differences in pre-readers at risk for developmental dyslexia, compared to control children, correspond to brain regions that have been shown to differ (structurally and functionally) between individuals with developmental dyslexia and typical readers. In particular, our results are consistent with VBM studies that demonstrated gray matter differences in left occipitotemporal and bilateral temporoparietal areas (Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005; Hoeft et al., 2007a; Kronbichler et al., 2008; Pernet et al., 2009; Silani et al., 2005), fusiform (Kronbichler et al., 2008) and lingual gyrus (Eckert et al., 2005) in children and adults with a diagnosis of developmental dyslexia compared to typical-reading controls. Furthermore, our findings are supported by VBM and DTI studies demonstrating reduced white matter connectivity and white matter indices in left-hemispheric occipitotemporal regions in adults (Klingberg et al., 2000; Steinbrink et al., 2008) and children (Deutsch et al., 2005; Niogi and McCandliss, 2006; Rimrodt et al., 2009) with developmental dyslexia.

Previous research using fMRI shed light on the role of brain structures that significantly differ in individuals with developmental dyslexia when compared to typical readers. These studies indicate that the left occipitotemporal area is activated during tasks of phonological processing (Temple, 2002) and tasks requiring the visual analysis of letters and words (Cohen et al., 2003; McCandliss et al., 2003; Vinckier et al., 2007). The left fusiform gyrus is involved in rapid recognition of visual words (McCandliss et al., 2003; Vinckier et al., 2007) and gains particular importance during the later stages of reading development within the typical reading brain (McCandliss et al., 2003; Turkeltaub et al., 2003). The temporoparietal area is known to be important for the integration of letters and speech sounds (Van Atteveldt et al., 2004, 2007), a key skill for reading in starting readers. Furthermore, research has shown that individuals with developmental dyslexia display deficits in letter sound integration within the temporal-parietal network (Blau et al., 2009; Blau et al., 2010).

In the current study in a small group of pre-reading children, GMVIs extracted from left hemispheric parietotemporal and occipitotemporal brain regions significantly correlated with rapid automatized naming. Rapid automatized naming is commonly impaired in children and adults with dyslexia and was reported to be one of the main precursors of later reading ability in children (De Jong and Van der Leij, 1999; Kirby et al., 2003; Kobayashi et al., 2005; Wolf, 1986; Wolf et al., 1986). Furthermore, previous research reported significant correlations between gray matter volume in a left occipitotemporal region and digit naming (Kronbichler et al., 2008). Previous research has suggested that RAN reflects the automatization or efficiency of matching visual/orthographic units to their phonological counterparts (e.g.; Vaessen et al., 2009; Vaessen and Blomert, 2010) or the efficient retrieval of phonological codes (e.g. Wagner and Torgesen, 1987). This is in line with our finding which shows a correlation between brain regions previously reported to be involved in phonological processing and RAN. However, RAN significantly differentiated our children with and without a family-risk of developmental dyslexia behaviorally before reading onset. Here, the observed anatomical differences may therefore reflect either a family-history or behavioral risk for developmental dyslexia. Further studies need to determine whether pre-reading children without a family history of dyslexia but a strong behavioral risk for dyslexia (e.g.; as determined by psychometric testing) also display the here observed anatomical alterations.

Several studies have shown a reduction of gray and white matter in children and adults with DD which correlate with phonological processing (e.g. Kronbichler et al., 2008; Pernet et al., 2009) and correlations between functional differences in occipitotemporal and parietotemporal regions and phonological skills have also been reported (Hoeft et al., 2007b; Temple, 2002; Specht et al., 2009). In our present study, we only observed a significant correlation between gray matter volume indices in the left occipitotemporal area (LOT) and phonological processing in a ROI which was defined by our observed anatomical differences but not when using independent ROIs defined by coordinates from previous publications which reported a similar correlation or meta-analysis. Therefore, the results of this analysis need to be interpreted with caution (see discussion by Poldrack and Mumford, 2009; Vul et al., 2009). Although this lack of a relationship between phonological skills and GMVI in left hemispheric regions in our sample may suggest that this relationship develops after reading onset, or that RAN has a higher specificity at this age, there may be a methodological explanation for the missing correlation. In the present study, a pediatric template was utilized and previously reported results were reported for adult templates. Although independent ROIs can be normalized to the pediatric template (as performed here), the areas within occipitotemporal and parietotemporal regions that exhibited a difference in GMVIs between the two groups is relatively small and therefore ROIs defined based on coordinates from previous papers (with adult templates) were most likely not targeting the appropriate areas in our age group of pre-readers.

In contrast to VBM studies in individuals with developmental dyslexia, we did not observe structural brain alterations in left inferior frontal brain regions (Brown et al., 2001; Eckert et al., 2003) or the cerebellum (Brambati et al., 2004; Brown et al., 2001). However, we examined structural brain alterations in pre-readers at risk for dyslexia as opposed to individuals with diagnosed developmental dyslexia or reading difficulties. It has been suggested that the alterations in frontal brain regions observed in children and adults with developmental dyslexia develop after the age of reading onset, mirroring the influence of experience and reading education (Hoeft et al., 2007a). Structural (Brambati et al., 2004; Brown et al., 2001) and functional MRI studies (Fulbright et al., 1999; Vlachos et al., 2007) have shown an involvement of the cerebellum during reading processes, such as word identification, phonological assembly and semantic processing. Our results complement these studies and suggest that structural differences in the left occipitotemporal area, bilateral temporoparietal regions, left fusiform gyrus and right lingual gyrus in children with a family-history of dyslexia prior to reading-onset are likely a pre-existing biological deficit. Further alterations, such as those seen in frontal regions and the cerebellum, might reflect experience-dependent changes that typically coincide with the process of learning to read.

A comprehensive model of dyslexia

Progress toward understanding developmental dyslexia has come from multiple levels. It has been suggested that developmental dyslexia may be a developmental disorder of genetic origin with a neurobiological basis (Galaburda et al., 2006; Silani et al., 2005). In line with the most recent neurobiological and genetic findings, our results seem to support a comprehensive model of developmental dyslexia which incorporates variant function in genes involved in brain development, structural and functional brain alterations and pre-reading skills (Galaburda et al., 2006). To date, several genes (e.g.; ROBO1, DCDC2, DYX1C1, KIAA0319) have been reported to be candidates for dyslexia susceptibility and it has been suggested that the majority of these genes plays a role in brain development (Galaburda et al., 2006; Hannula-Jouppi et al., 2005; Meng et al., 2005; Paracchini et al., 2006). Since the structural alterations revealed in the present study predate the onset of formal reading instruction and as there are no significant group differences in socioeconomic status or home literacy environment, it can be hypothesized that genetic

factors critical for brain development may be responsible for the observed cortical alterations. More specifically, the cortical alterations in pre-reading children at risk for developmental dyslexia may originate from abnormal migration and/or maturation of neurons during early development which may lead to altered functional brain circuits and result in impaired pre-reading and reading skills (Galaburda et al., 2006). Interestingly, we observed reduced and not increased gray matter indices in children with compared to without a family history of developmental dyslexia which speaks against effects of synaptic pruning at this young age where one would expect increased abnormality being associated with increased gray matter in certain cortical areas. Our reduced gray matter findings support previous hypotheses that reading disabilities, such as developmental dyslexia, are characterized by neural migration failure (e.g.; Chang et al., 2005, 2007; Galaburda et al., 2006) and are further in line with the finding that four of the main candidate susceptibility genes (DYX1C1, KIAA0319, DCDC2, ROBO1) are linked to neuronal migration and other developmental processes (Galaburda et al., 2006). Furthermore, deviations in the migration of neurons from proliferative zones towards the cortex have also been found in post-mortem examination of individuals with developmental dyslexia (Galaburda et al., 1985) and reading and processing speed deficits have been reported for patients with neuronal migration disorder of periventricular nodular heterotopia (Chang et al., 2005).

Nevertheless, no specific cognitive processes are known to be directly influenced by the reported susceptibility genes (Schumacher et al., 2007). It remains unclear whether any of the reported genes are associated with specific cognitive phenotype dimensions or whether there are any interactions among the genes. Gene–environment interactions should not be underestimated. A series of major environmental risks are known to play a crucial role in the manifestation of developmental dyslexia, such as socio-economic status, educational opportunities and home literacy environment. Although the risk for dyslexia is greater among first degree relatives of individuals with dyslexia, one needs to keep in mind that only approximately 40% of all children with a family history of dyslexia will later develop reading disabilities themselves (Pennington and Smith, 1988). This suggests that gene–gene interactions, early compensation strategies and environmental factors not shared by siblings as well as educational (e.g.; teaching style), psychological factor and their interaction with genetics may play a larger role in the manifestation of developmental dyslexia than anticipated.

Follow-up studies in young infants with and without a family history of developmental dyslexia may help to explain the underlying developmental mechanism for the here observed reduced gray matter indices in 5 year olds. Further examinations of models incorporating genetic vulnerability, structural and functional neuroimaging measures, environmental factors and behavioral skills will be crucial for a complete understanding of the etiology of developmental dyslexia.

Conclusion

Structural brain alterations have previously been observed in children and adults with developmental dyslexia. Developmental dyslexia can only be diagnosed after formal reading instruction begins. However, our findings in a small group of pre-reading children demonstrate that previously described gray matter alterations in children and adults with developmental dyslexia in parietotemporal, occipitotemporal brain areas and left fusiform and right lingual gyrus are already observable in pre-readers with a family-history of developmental dyslexia and correlate with pre-reading skills. These findings cannot be explained by differences in socioeconomic background or early literacy experiences. This discovery suggests that structural alterations in developmental dyslexia may be present at birth or may develop in early childhood. Future research using larger sample sizes and

longitudinal designs are needed to determine whether these structural alterations may be utilized for the identification of children at risk for developmental dyslexia in infancy and/or early childhood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

FHD+	children with a family-history of dyslexia
FHD–	children without a family-history of dyslexia
VBM	voxel-based morphometry
DTI	diffusion tensor imaging
RAN	rapid automatized naming
WRMT	Woodcock Reading Mastery Test
CELF	Clinical Evaluation of Language Fundamentals
CTOPP	Comprehensive Test of Phonological Processing
SES	socioeconomic status
HLE	home literacy environment
GMVI	gray matter volume indices
ROI	region of interest
LOT	left occipitotemporal area
LTP	left temporoparietal region
RTP	right temporoparietal region
LFG	left fusiform gyrus
RLG	right lingual gyrus

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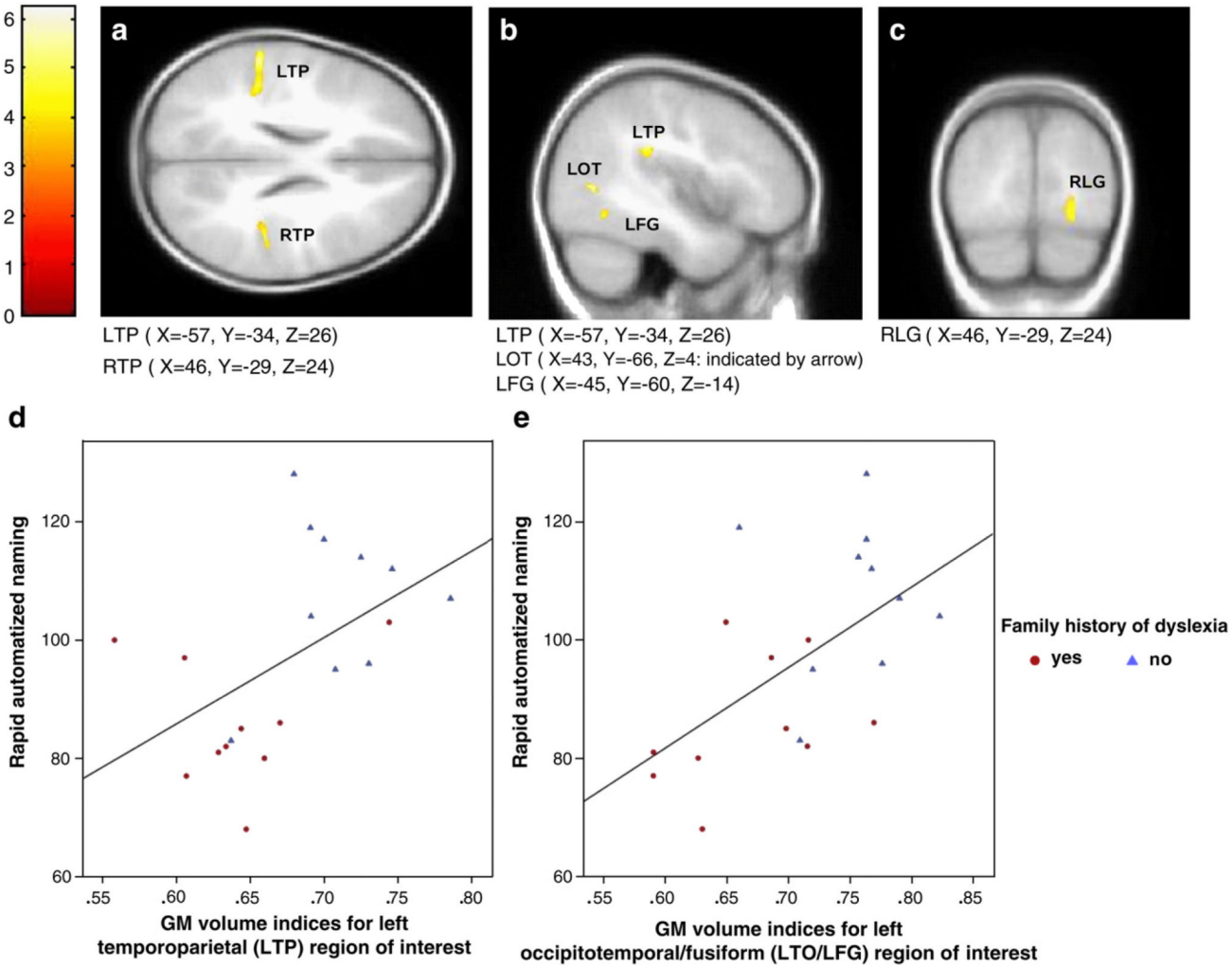

Fig. 1.

[a–c] Statistical parametric maps showing brain areas with significant decreased gray matter volume indices in pre-reading FHD+ compared to FHD– children (a=axial, b=sagittal, c=coronal view). [d–e] Correlations between gray matter volume indices in the left parietotemporal (d) and left occipitotemporal (e) ROI and rapid automatized naming.

Table 1

Subject demographics.

	FHD+	FHD–	*p* FHD+ vs. FHD– sig. 2-tailed *Independent samples t-test*
N	10	10	
Age (years)	5:11	5:7	0.241
Age (range in years)	5:5–6:5	5:1–6:2	

Behavioral Measures		**Mean ± SD**	**Mean ± SD**	**sig. 2-tailed** *Independent samples t-test*
CELF	Core Language	105.6 ± 8.9	109.9 ± 11.7	0.366
	Receptive Language[a]	105.3 ± 16.6	110.2 ± 10.8	0.455
	Expressive Language	102.1 ± 8.2	110.0 ± 13.0	0.121
	Language Content[a]	100.4 ± 11.9	110.1 ± 11.7	0.093
	Language Structure[a]	105.6 ± 11.8	109.5 ± 12.1	0.483
CTOPP	Elision	8.9 ± 1.8	10.2 ± 2.3	0.181
	Blending	10.7 ± 2.4	11.9 ± 1.6	0.199
	Non-Word Repetition	9.8 ± 2.5	10.8 ±1.9	0.334
RAN	Objects	85.9 ± 11.0	107.5 ± 13.4	0.001*
	Colors	84.2 ± 11.1	110.1 ± 10.5	0.000**
KBIT	Verbal Ability	110.9 ± 10.4	113.7 ± 7.0	0.489
	Non-Verbal Ability	97.6 ± 8.4	100.9 ± 10.6	0.452

Socioeconomic Status and Home Language Environment	**Mean ± SD**	**Mean± SD**	**sig. 2-tailed** *Independent samples t-test*
Parental Education[b]	6.2 ± 0.5	6.23 ± 0.7	0.749
Age (in months) of child when first read to	4.4 ± 5.0	9.8 ± 19.0	0.429
Some one at home reads to the child [hours/week]	2.7 ± 1.4	3.4 ± 1.7	0.336

	Mean Rank	**Mean Rank**	**sig. 2-tailed** *Kruskal-Wallis test*
Income (total family income for last 12 months)[c]	8.83	9.19	0.865
Total number of parents/adult books at home[d]	9.72	9.28	0.844
Total number of children's books at home[d]	8.50	10.50	0.146

Measures (standard scores are reported).

two-tailed *t*-test; all other *t*-tests non-significant at threshold of $P = .05$.

* $P < .01$

** $P < .001$

[a] 10 FHD+/9 FHD– (One child did not finish all testing).

[b] Parental Education scores are calculated according to the 7-point Hollingshead Index Educational Factor Scale, summed for husband and wife and divided by two (Hollingshead, 1975).

[c] Scale where 1 = 50,000-74,999 $, 2 = 75,000-99,999 $, 3 = 100,000+ $.

[d] Scale where 1 = 0–50books, 2 = 50–100 books, 3 = 100+ books.

Table 2

Significant differences in gray matter volume indices between FHD+ and FHD– children (at $p<0.001$ uc; adjusted for non-stationarity).

Brain region	Volume (mm)	Z score	X	Y	Z
Left occipitotemporal region (LOT)	144	4.51	–43	–66	4
Left temporoparietal regions (LTP)	767	4.27	–57	–34	26
Left fusiform gyrus (LFG)	116	3.83	–45	–60	–14
Right temporoparietal regions (RTP)	565	3.69	46	–29	24
Right lingual Gyrus (RLG)	517	4.09	23	–87	–11