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Developmental Dyslexia: Gray Matter Abnormalities in the Occipitotemporal Cortex

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Abstract: Functional neuroimaging studies have consistently demonstrated less activation of the left occipitotemporal cortex in dyslexic readers. This region is considered critical for skilled reading and damage to it in adult readers leads to severe deficits in reading ability. In contrast to these findings, structural abnormalities in the occipitotemporal cortex were not consistently found to date. We used optimized Voxel Based Morphometry with T1 weighted MR images to investigate gray matter volume in 13 dyslexic and 15 nonimpaired reading adolescents (age 14–16). Less gray matter volume for dyslexic readers was found in the left and right fusiform gyrus, the bilateral anterior cerebellum and in the right supramarginal gyrus. Decreased gray matter volume in the left and right fusiform gyrus of dyslexic readers highlights the importance of this brain region for developmental dyslexia. The structural abnormalities in the right occipitotemporal cortex suggest that dyslexia may be such a persistent disorder because an occipitotemporal reading area, critical for skilled reading, cannot develop in any hemisphere. The extended areas of reduced gray matter volume in dyslexic readers in the cerebellum suggest that structural abnormalities in the cerebellum are also strongly associated with dyslexia and warrant further investigation. *Hum Brain Mapp 29:613–625, 2008.* ©2007 Wiley-Liss, Inc.

Key words: dyslexia; brain; voxel based morphometry; gray matter; occipitotemporal cortex; reading impairment; fusiform gyrus; cerebellum

INTRODUCTION

Numerous studies have examined the neuroanatomical correlates of developmental dyslexia, the failure to develop adequate reading skill despite normal intelligence, learning ability, educational, and socioeconomic opportunities [for recent reviews see Demonet et al., 2004; Shaywitz and Shaywitz, 2005]. In their pioneering work, Galaburda and colleagues reported abnormalities in perisylvan areas, the thalamus and absent left–right asymmetry of the planum temporale in postmortem examinations of a small number of dyslexic brains [Galaburda and Kemper, 1979; Galaburda et al., 1985, 1994; Humphreys et al., 1990; Livingstone et al., 1991]. Since then, neuroanatomical correlates of developmental dyslexia have been examined using CT and MRI

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[Eckert, 2004; Habib, 2000]. Despite considerable inconsistency, three regions were associated with structural abnormalities relative consistently [Eckert, 2004]: the inferior frontal gyrus [e.g., Brown et al., 2001; Eckert et al., 2003], the superior temporal and temporoparietal cortex [e.g., Brambati et al., 2004; Brown et al., 2001; Leonard et al., 2001] and the cerebellum [e.g., Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2003; Rae et al., 2002]. The involvement of temporal and tempororparietal regions in dyslexia was also found in functional neuroimaging studies [e.g., Rumsey et al., 1997; Shaywitz et al., 2002; Temple et al., 2001].

Functional neuroimaging studies also revealed that the left occipitotemporal cortex is strongly associated with dyslexia [McCandlis and Noble, 2003; Pugh et al., 2000; Shaywitz and Shaywitz, 2005]. This brain region, including the fusiform gyrus and posterior aspects of the inferior and middle temporal gyrus, contains the so called Visual Word Form Area [VWFA Cohen et al., 2000, 2002]. This area exhibits reliable activity during skilled reading [Jobard et al., 2003; Price and Mechelli, 2005], but decreased activity in dyslexic readers [e.g., Kronbichler et al., 2006; Paulesu et al., 2001; Shaywitz et al., 2002]. Although the specificity of the VWFA for reading is under discussion [Price and Mechelli, 2005], its importance for visual word processing is undisputed. Less activation of this area in dyslexic readers was also found during object naming [McCrory et al., 2005]. Rapid object naming is commonly impaired in dyslexic readers and was found to be the main precursor of later reading difficulties in German-speaking children [Wimmer and Mayringer, 2002].

Despite this converging evidence on the involvement of the left occipitotemporal cortex in dyslexia, structural abnormalities of this region have not been reported consistently. No volumetric studies, in which regions of interest are traced and measured manually, have examined this region. This may be due to the fact that this area is hard to define and trace manually [Eckert, 2004]. Voxel Based Morphometry (VBM) [Ashburner and Friston, 2000] may be better suited to reveal occipitotemporal brain abnormalities, as it enables an unbiased whole brain voxel-wise examination of brain tissue.

To date, only one VBM study reported gray matter abnormalities in the left occipitotemporal cortex in dyslexic readers [Silani et al., 2005]. In this study, English, French, and Italian dyslexic readers exhibited less gray matter density in a left posterior middle temporal region and increased gray matter density in an adjacent region. Silani et al. [2005] used a small volume correction for the left occipitotemporal cortex, which allowed a more sensitive statistical analysis by reducing the massive multiple comparison problems present when examining the whole brain.

Four other recent VBM studies on developmental dyslexia did not reveal occipitotemporal abnormalities [Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005; Vinkenbosch et al., 2005]. Gray matter abnormalities were detected in anterior inferior temporal regions [Brambati et al., 2004; Brown et al., 2001; Vinkenbosch et al., 2005] and in the lingual gyrus [Eckert et al., 2005]. However, these regions do not correspond to the occipitotemporal reading areas identified in functional neuroimaging studies [Jobard et al., 2003]. Structural brain abnormalities were found in other regions, most consistently in the cerebellum and in temporal and temporoparietal regions.

The failure of most previous VBM studies to identify structural abnormalities in the left occipitotemporal cortex could indicate that such abnormalities are only present in some dyslexic readers. On the other hand, the failure to consistently identify such abnormalities may suggest that the finding of less activation in dyslexic readers in this region reflects insufficient input from other structurally abnormal brain areas, in other words a functional disconnection. These heterogeneous results may also be caused by differences in MR techniques, analysis strategies and differences in the diagnosis of dyslexia.

These explanations seem unsatisfactory, given the highly consistent finding of less activation of the occipitotemporal cortex in dyslexic readers and the fact that damage to the left occipitotemporal cortex leads to pure alexia and dysfluent letter-by-letter reading [Binder and Mohr, 1992; Cohen et al., 2003; Damasio and Damasio, 1983; Dejerine, 1892; Gaillard et al., 2006].

In light of these considerations we thought that further investigations on potential structural abnormalities of the occipitotemporal cortex are needed for a better understanding of the neurobiological basis of developmental dyslexia. In the present study we used optimized VBM [Good et al., 2001] to examine potential structural abnormalities of the occipitotemporal cortex in developmental dyslexia. To enable increased sensitivity for the detection of abnormalities in this region we used a small volume correction for these regions. In contrast to Silani et al. [2005] who focussed only on left hemisphere areas, we also examined whether potential left occipitotemporal abnormalities would be mirrored in the right hemisphere and, therefore, defined volumes of interest in both hemispheres. The investigation of the right occipitotemporal cortex was motivated by findings showing that lesions in the right hemisphere after prior damage to the left hemisphere can seriously disrupt residual reading abilities in pure alexic patients [e.g., Bartolomeo et al., 1998]. Furthermore, recent VBM studies [Brambati et al., 2004; Brown et al., 2001] revealed extended gray matter abnormalities in right hemisphere brain regions in dyslexic regions. To assess potential structural alterations in other regions, we used small volume corrections also for inferior frontal, temporoparietal, and cerebellar regions, which were previously reported as consistently abnormal in dyslexia [Eckert, 2004].

German dyslexic and normally reading adolescents from a longitudinal sample participated in the present study. Because data from the beginning of formal schooling are available for these adolescents we can ensure that these dyslexic readers suffered from a persistent reading impairment.

As differences in subject characteristics and the severity of reading difficulties, as well as differences in associated

TABLE I. Behavioural measures and total gray and white matter volume

	Nonimpaired readers ($n = 15$)		Dyslexic readers ($n = 13$)		
	M	SD	M	SD	t[1]
Age (years)	15.46	0.58	15.89	0.75	0.43
Nonverbal IQ	106	14.31	106.6	11.34	0.12
Sentence reading (N sentences)	21.33	3.77	10.54	2.18	−9.41*
Spelling (% correct)	68.8	19.43	27.69	14.28	−6.43*
Digit naming (syl/min)	214.81	39.06	154.82	27.86	−4.61*
Reading aloud					
Words (syl/min)[2]	189.45	24.19	99.78	30.59	−8.48*
Pseudowords (syl/min)[2]	137.66	18.54	72.37	24.32	−7.8*
Grade 1					
Rhyme detection (% correct)	94.67	5.16	81.03	17.60	−2.7**
Pseudoword repetition (% correct)	71.56	15.62	50.26	22.55	−2.94***
Object naming (syl/min)	50.18	10.19	39.18	7.24	−3.17***
Peg moving task (N pegs)	42.98	5.07	45.69	4.4	1.5
Grade 7					
Coherent motion detection[3] (% threshold)	11.28	4.17	10.44	6.61	0.39
Auditory illusion proneness[3] (% illusion perceived)	50.00	12.99	46.15	18.07	0.62
Total gray matter (ml)	871.80	66.66	814.10	62.86	−2.35**
Total white matter (ml)	449.71	33.43	420.55	37.24	−2.18**

Syl/min, syllables per minute.
[1] Negative t-values reflect poorer performance of dyslexic readers.
[2] Data is missing from one nonimpaired reader.
[3] Data is missing from two nonimpaired readers.
* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

cognitive deficits may partly explain inconsistencies in the literature, we think that the present sample is ideal for studying the neuroanatomical correlates of developmental dyslexia. For the presently studied subjects the reliability and persistence of the reading deficits is firmly established and data on associated deficits like sensory processing, verbal skills, and motor skills, are available. Dyslexic readers in the rather regular German orthography suffer mainly from impaired reading speed, but not from impaired reading accuracy, compared with readers from less regular orthographies like English [e.g., Landerl et al., 1997]. However, even for English dyslexic readers fluent reading poses the main problem in adulthood, even when relatively accurate reading is achieved [Shaywitz and Shaywitz, 2005]. Because of the specific impairment in reading fluency and the deficits in object naming speed, even before learning to read [Wimmer and Mayringer, 2002], these dyslexic adolescents may be well suited to reveal structural abnormalities of the occipitotemporal cortex, as this brain region is strongly associated with skilled reading and object naming [e.g., McCrory et al., 2005; Shaywitz et al., 2002].

METHODS AND MATERIALS

Participants

Thirteen dyslexic and 15 nonimpaired reading German-speaking boys (14–16 years) were recruited from a longitudinally studied sample. Written informed consent was obtained from all participants and one of their parents. The study was approved by the ethical committee of the University of Salzburg. For inclusion in the dyslexic group, a participant had to exhibit a persistent reading impairment, reflected by a reading score below Percentile 11 in Grades 3 and 7 and at the present assessment in Grade 9. Exclusion criterion was a nonverbal IQ of below 85 in Grade 1 [Huttenlocher and Cohen-Levine, 1990]. For inclusion in the control group, the reading scores had to be above Percentile 20. Additionally, it was checked that all participants were right-handed by showing consistent right hand preference for nine different activities. The Grade 3 reading score was based on reading aloud a list of pseudowords and a text passage, the Grades 7 and 9 reading scores were based on tests, in which lists of sentences had to be read silently and evaluated as semantically correct within certain time limits (3 min in Grade 7, 1 min in Grade 9). A spelling test, consisting of 25 words, was administered at the present assessment.

As can be seen from Table I the dyslexic participants suffered from a substantial impairment in reading speed during silent sentence reading and from a massive spelling impairment. At the present assessment the mean performance of the dyslexic readers corresponded to Percentile 5 for sentence reading and Percentile 7 for spelling, for nonimpaired readers the mean performance for reading and spelling corresponded to Percentiles 68 and 72, respectively.

Table I also reports speed during reading aloud lists of words and pseudowords and digit naming speed (for both measures speed is reported in syllables per minute).

For a more complete neurocognitive characterization of our dyslexic participants we report performance on previous assessments of possible neurocognitive deficits. Table I shows that at the school entrance assessment, dyslexic boys exhibited lower performance on rhyme detection, pseudoword repetition and rapid naming tasks, but they did not show an impairment on a speeded visual-motor task (peg moving). In Grade 7 they showed no deficit in dynamic sensory processing (coherent motion detection, auditory illusion proneness). For a detailed description of these tasks see Kronbichler et al. [2002].

Data Acquisition and Analysis

A 1.5-Tesla Philips MR Scanner (Philips Medical System, Best, The Netherlands) was used to acquire a T1-weighted MPRAGE scan from each participant (130 slices, 1.3-mm slice thickness, FOV 220 × 220 mm^2, Matrix 256 × 256, TE 4 ms, FA 12°, TR 17 ms, TI 600 ms). SPM2 (http://www.fil.ion.ucl.ac.uk/spm) with custom scripts created by Christian Gaser (http://dbm.neuro.unijena.de/vbm.html) was used for optimized VBM [Ashburner and Friston, 2000; Good et al., 2001]. A custom whole brain template and custom prior probability maps for gray matter, white matter and CSF were constructed from all participants. The T1 images were segmented and non-brain tissue was removed. The SPM2 segmentation algorithm used 1 Gaussian function per brain tissue class and 2 Gaussian functions for non-brain background voxels. The gray matter images were normalized to the custom gray matter template and the resulting parameters were used to normalize the T1 images, which were then optimally segmented. The resulting images were resliced to 1 × 1 × 1 mm^3 voxels, using 4th degree B-splines. To enable analysis of gray matter volume the images were modulated by the Jacobian determinants from the normalization step. All images were smoothed with a 12-mm FWHM Gaussian Kernel.

The statistical analysis focused on gray matter volume differences using an ANCOVA (AnCova-model as implemented in SPM2's basic models), which included total gray matter as a covariate to test for regionally specific effects. We identified voxels with group differences in gray matter volume with a small volume correction for the volume of interest consisting of a priori anatomically defined brain regions, based on the AAL parcellation of the MNI single subject brain [Tzourizo-Mazoyer et al., 2002] and created with the MarsBar toolbox [Brett et al., 2002; http://marsbar.sourceforge.net/].

All regions were defined bilaterally by selecting the appropriate regions of the AAL parcellation, constrained in extent as indicated later, and then combined into one single region, which constituted the volume of interest for the small volume correction. The main region of interest was the occipitotemporal cortex and included parts of the inferior and middle temporal and fusiform gyri, restricted to y coordinates posterior to −45 and anterior to −70 and z coordinates superior to −18 and inferior to +1. This region included occipitotemporal coordinates, for which less activation in dyslexic readers was reported [Brunswick et al., 1999; Kronbichler et al., 2006; McCrory et al., 2005; Paulesu et al., 2001; Rumsey et al., 1997; Shaywitz et al., 2002]. Additionally, we included regions which consistently exhibited structural brain abnormalities in dyslexic readers in previous studies [Eckert, 2004]. These regions were the temporoparietal cortex and temporal perisylvan areas (superior temporal, rolandic operculum, and supramarginal regions), the cerebellum and the triangular and opercular parts of the inferior frontal gyrus.

The resulting volume of interest for the small volume correction therefore contained 361,304 cubic 1 × 1 ×1 mm^3 voxels and included the following bilateral regions of the AAL parcellation: all cerebellar regions (Cerebellum Crus 1 + 2, Cerebellum 3–10, Vermis 1–10), temporal inferior and fusiform regions (posterior to $y = -45$ and anterior to $y = -70$, inferior to $z = -1$ and superior to $y = -18$), temporal superior, rolandic operculum, supramarginal, frontal inferior triangular, and frontal inferior operculum regions.

The statistical threshold was set to a false discovery rate (FDR) of $q < 0.05$ [Genovese et al., 2002], corrected for multiple comparison for the volume of interest. Additionally, a whole brain search was conducted to identify potential brain abnormalities outside this volume of interest. Regions surviving an uncorrected threshold of $P < 0.005$ with a minimum extent of 100 mm^3 are also reported for exploratory purposes. One should note, that effects in regions surviving only the uncorrected threshold should just be considered as tendencies.

We also performed correlation analyses to explore (a) possible intercorrelations between gray matter volumes in regions with reliable group differences, and (b) the relationship between gray matter volume in regions with group differences and reading speed (performance on the sentence reading test), spelling ability, digit naming speed, and rhyme detection in Grade 1. The interest in possible intercorrelations between the gray matter volume of regions with group differences was prompted by previous studies that showed correlations of gray matter volume and cortical thickness between diverse brain regions [e.g., Lerch et al., 2006; Mechelli et al., 2005]. A relationship between gray matter volume in diverse brain regions may indicate that common genetic and/or environmental influences underlie gray matter volume in these regions. For all these correlation analysis we extracted the gray matter volume of the clusters with reliable group differences for each subject with the MARSBAR toolbox. Partial correlations (controlling for total gray matter volume) were then calculated (a) between gray matter volume of the clusters with group differences, and (b) between gray matter volumes of the clusters with group differences and behavioral performance.

TABLE II. Brain regions with group differences in gray matter volume

Region	Extent (voxels)	MNI coordinates			Z
		x	*y*	*z*	
Nonimpaired readers > dyslexic readers					
R anterior cerebellum	**27,314**	**27**	**−54**	**−33**	**4.88**
		46	**−46**	**−33**	**4.22**
R fusiform gyrus		**35**	**−64**	**−8**	**3.53**
		33	**−53**	**−19**	**3.37**
L anterior cerebellum	**5,896**	**−34**	**−41**	**−31**	**3.35**
		−28	**−51**	**−30**	**3.08**
L fusiform gyrus	**491**	**−30**	**−58**	**−6**	**2.86**
		−38	**−67**	**−15**	**2.85**
R supramarginal gyrus	**168**	**48**	**−40**	**27**	**4.19**
L parietooccipital cortex	163	−30	−61	33	3.03
R middle temporal gyrus	431	40	−57	6	3.31
Dyslexic readers > nonimpaired readers					
R precuneus	802	14	−46	44	3.02
L superior temporal sulcus	753	−50	−26	3	3.13
R postcentral gyrus	581	17	−38	60	3.26
R precentral gyrus	465	56	0	23	3.06
R superior frontal gyrus	2,506	20	11	51	3.59
R SMA		6	12	54	2.93
L medial superior frontal gyrus	3,372	−6	50	18	3.36
R medial superior frontal gyrus	192	12	51	5	2.91

Regions surviving a corrected FDR threshold of $q < 0.05$ for the a priori defined volume of interest (see Methods & Materials section) are printed in **bold**. Regions not in bold exhibit group differences at a threshold of $P < 0.005$, uncorrected.

RESULTS

Generally, dyslexic adolescents had less total gray matter volume than normally reading adolescents (Table I).

As can be seen from Table II and Figure 1 dyslexic readers had reliable less gray matter volume in a number of brain regions in the a priori defined volume of interest at a FDR of $q < 0.05$. In the occipitotemporal cortex less gray matter for dyslexic readers was found in the left and right fusiform gyrus, the region with less gray matter volume being more extended in the right hemisphere. The largest areas of decreased gray matter volume in the dyslexic group were located in the anterior cerebellum, bilaterally, again more extended on the right. Additionally, a region in the right supramarginal gyrus exhibited reliable less gray matter in dyslexic readers.

Decreased gray matter volume in the right cerebellum and the right occipitotemporal cortex were found in one contiguous cluster. One may be concerned that this result indicates that the decrease in gray matter volume in the right occipitotemporal cortex is solely an artificial extension (caused by smoothing) of the large group differences in the right cerebellum. However, when using a more stringent statistical threshold (FDR < 0.01) two distinct clusters, one in the right cerebellum and the other in the right occipitotemporal cortex, were identified. Furthermore, when repeating the analysis with a smaller smoothing kernel of 8-mm FWHM we also identified these two separate clusters. These additional analyses showed that less gray matter volume was present in the right occipitotemporal cortex and in the right cerebellum in two separate clusters, which formed one contiguous cluster in the original analysis because of the chosen threshold and smoothing with a 12-mm FWHM kernel.

We did not identify any regions where dyslexic readers exhibited more gray matter volume at the corrected FDR threshold.

In addition to these group differences in gray matter volume in the a priori volume of interest, which were found at at the FDR-corrected threshold, we also examined group differences in gray matter volume at a more liberal threshold of $P < 0.005$, uncorrected. One should note that these group differences at the uncorrected threshold were only performed for exploratory purposes. These tendencies towards group differences will therefore generally not be discussed in detail.

At an uncorrected threshold of $P < 0.005$, less gray matter volume in the dyslexic readers was found in the left parieotoccipital and in the right middle temporal cortex. In inferior frontal areas, for which a number of previous studies reported structural brain abnormalities in dyslexic readers, no regions with less gray matter volume for the dyslexic groups were identified, even when lowering the threshold to $P < 0.01$, uncorrected.

More gray matter volume in dyslexic readers at the uncorrected threshold was found in a region in the left superior temporal cortex. More gray matter volume for dyslexic readers at $P < 0.005$, uncorrected, was also found in a number of other regions, including the superior frontal cortex, the SMA, precentral and postcentral regions, as well as the posterior cingulate and the precuneus.

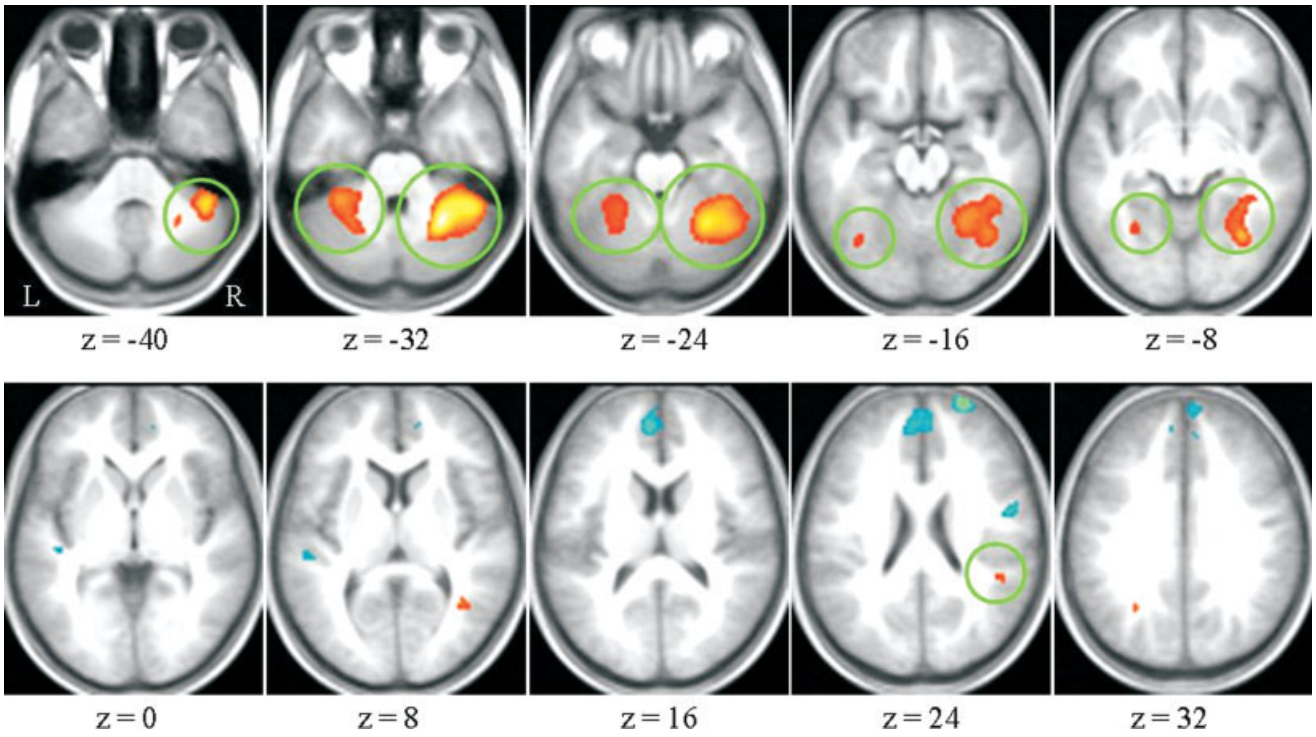

Figure 1.

Brain regions with group differences in gray matter volume shown on axial slices (neurological convention, L = L). The threshold is set to $P < 0.005$, uncorrected for display purposes, all regions surviving a corrected FDR threshold of $q < 0.05$ for the a priori defined volume of interest (see Methods and Materials section) are encircled in green.

To investigate the relationship between gray matter volume in the neighboring or homologous regions in the left and right cerebellum and the left and right occipitotemporal cortex, we extracted gray matter volume for the cerebellar and occipitotemporal voxels with less gray matter (at a FDR < 0.05) in dyslexic readers from each subject and calculated pair-wise partial correlations (controlling for total gray matter volume) between these regions. In the whole sample there were strong partial correlations between gray matter volume in all 4 regions (all rs > 0.642, all ps < 0.001). These partial correlations between the 4 regions were also reliable when each group was analyzed separately.

Furthermore, we explored the relationship between gray matter volume in the five brain regions with reliably less gray matter in dyslexic readers and reading skill by performing partial correlation analysis (controlling for total gray matter volume) between reading skill (as measured by the sentence reading test) and gray matter volume in these clusters. Gray matter volume in the left and right occipitotemporal regions, in the right cerebellar region and in the right supramarginal region showed reliable correlations with the number of sentences read in 1 min, the partial correlation of gray matter volume with reading skill just missed significance for the left cerebellar region (Fig. 2 and Table III).

We also examined the relationship between gray matter volume in these brain regions and spelling performance, digit naming speed and rhyme detection (measured in Grade 1). As can be seen from Table II nearly all of these partial correlations were positive and reliable or at least showed a trend towards significance. These correlations remained essentially the same when repeating the analysis without controlling for total gray matter volume. Generally, all correlations seemed to be mainly caused by the group differences in gray matter volume in the five regions and in the behavioural measures. No reliable correlations between the behavioural measures and gray matter volume were obtained when the analyses were performed for each group separately.

The main focus of the present study were group differences in gray matter volume. However, we additionally performed an analysis of white matter volume. Dyslexic readers had less total white matter than nonimpaired readers (Table I). However, no group differences in regional white matter volume were found at the FDR-corrected

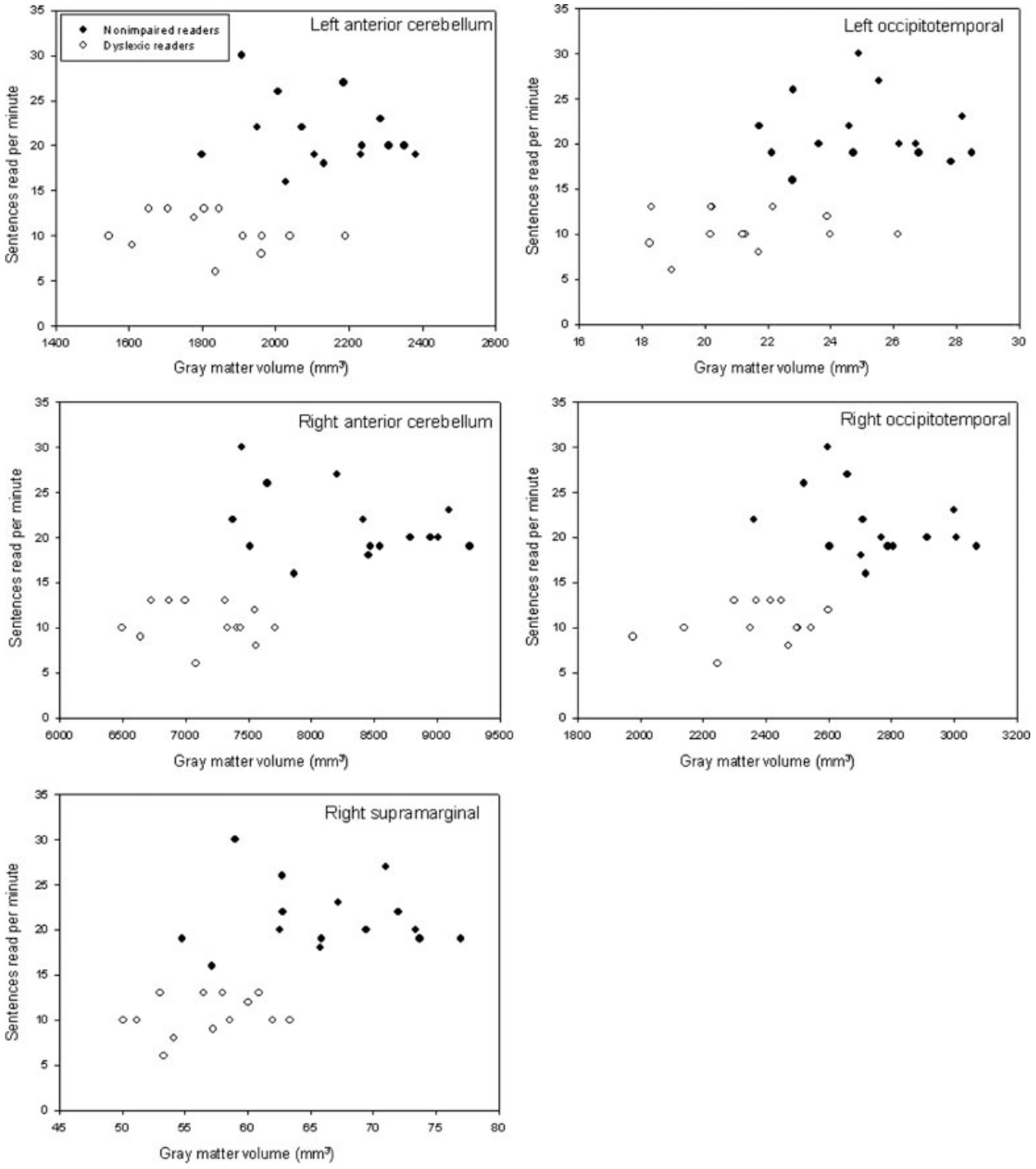

Figure 2.

Scatterplots showing the relation between gray matter volume for the five regions with reliably less gray matter volume in dyslexic readers and performance on the sentence reading speed test for both groups.

threshold. At an uncorrected threshold of $P > 0.005$, dyslexic readers exhibited less white matter in the bilateral cerebellum, somewhat inferior to the regions showing less gray matter. At this uncorrected threshold, dyslexic readers exhibited more white matter volume in a number of regions, including the left superior frontal cortex, the SMA, the right precentral gyrus, and the left superior parietal lobule.

TABLE III. Partial correlations (controlling for total gray matter volume) between gray matter volume in five regions of interest and behavioural performance

	Reading	Spelling	Digit naming	Rhyme detection
Left cerebellum	0.378*	0.313	0.344*	0.553**
Left occipitotemporal	0.502**	0.337*	0.400***	0.372*
Right cerebellum	0.480***	0.559**	0.520**	0.590#
Right occipitotemporal	0.497**	0.553**	0.502**	0.632#
Right supramarginal	0.503**	0.410***	0.592#	0.229

dfs = 22.
#$P < 0.1$.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

DISCUSSION

The present study found reduced gray matter volume in the occipitotemporal cortex of German speaking dyslexic readers who mainly suffer from a persistent reading speed impairment. Because the dyslexic participants came from a longitudinally studied sample, for which data is available from the beginning of formal schooling, not only the persistence but also the reliability of the reading impairment could be ensured. Additionally, less gray matter for dyslexic adolescents was found in the right temporoparietal cortex and in bilateral cerebellar regions, replicating gray matter abnormalities reported previously [Brambati et al., 2004; Brown et al., 2001; Eckert, 2004; Eckert et al., 2003, 2005]. Generally, dyslexic readers had less total gray matter volume, as in previous studies [e.g., Eckert et al., 2003, 2005].

Correlation analyses revealed that gray matter volume in the cerebellar and occipitotemporal regions were strongly correlated, even when dyslexic and nonimpaired readers were analyzed separately. This finding corresponds to previous reports showing intercorrelations of the gray matter volume of brain areas [e.g., Mechelli et al., 2005] and intercorrelations of the cortical thickness of brain regions [Lerch et al., 2006]. The strong association between gray matter volume in these regions suggest that one or more common factors may influence the brain structure of these regions. It is tempting to speculate that gray matter volume in these regions is under genetic control, given the high heritability of reading skill [Fisher and Francks, 2006], but such speculations must be confirmed in future studies.

We did not find clear evidence for a differential relationship of gray matter volume in the five regions, exhibiting reliably less gray matter in dyslexic readers, with performance on the behavioural tasks. Generally, gray matter volume in these regions correlated strongly with reading and spelling performance as well as digit naming speed and phonological awareness (measured with a rhyme detection task). However, no reliable correlations between gray matter volume and behavioural performance were obtained when the groups were analyzed separately. This finding shows that the obtained correlations were mainly caused by the group differences in gray matter volume and behavioural performance. Future studies with larger samples, more sensitive behavioural tests and a larger range of scores on these tests are needed to further explore whether gray matter volume in these regions can be associated with performance on different behavioural tasks.

In contrast to the reliable group differences in regional gray matter volume we did not find group differences in regional white matter volume at a corrected threshold, although dyslexic readers had less total white matter. In previous studies, abnormalities of white matter tracts were found in the temporoparietal cortex in dyslexic readers using diffusion-weighted imaging [e.g., Klingberg et al., 2000; Niogi and McCandliss, 2006]. The use of diffusion-weighted imaging could have revealed more profound white matter abnormalities in the present sample. Diffusion-weighted MRI could also be used to examine whether an anatomical disconnection of left occipitotemporal reading areas exists in dyslexia.

In the present study less gray matter in dyslexic readers was found in the left and right fusiform gyrus. The left fusiform gyrus, located in the occipitotemporal cortex, contains the VWFA [Cohen et al., 2000, 2002] and is considered critical for skilled and fluent reading [Shaywitz et al., 2002; see Pugh et al., 2000]. However, the presently identified region of less gray matter in dyslexic readers was located somewhat medial and posterior to the originally reported coordinates of the VWFA [Cohen et al., 2000, 2002]. It seems to be relatively close to coordinates ($y = -44$, $x = -68$, $z = -8$) recently reported by Cohen et al. [2004a] for the VWFA, in contrast to a more lateral and anterior multimodal word processing area. Our finding is partly in line with a recent report of gray matter abnormalities in the left occipitotemporal cortex in dyslexic adults [Silani et al., 2005], although this study found less gray matter mainly in a more superior and anterior middle temporal region and also more gray matter in dyslexic readers in an adjacent region.

A critical new result of the present study and an extension of the Silani et al. [2005] study is the finding that less

gray matter volume in dyslexic readers is also present in the right occipitotemporal cortex. The use of a small volume correction for the occipitotemporal cortex may explain why we and Silani et al. [2005] found gray matter abnormalities associated with dyslexia in this region, whereas other studies, which did not use a small volume correction, did not find occipitotemporal abnormalities.

The left occipitotemporal cortex has mainly been linked to visual word processing, but is also involved in other tasks, for example object naming [McCrory et al., 2005], orthographic and phonological decisions in response to auditory words [Booth et al., 2002; Cohen et al., 2004a] and forming links between orthography and phonology [Hashimoto and Sakai, 2004]. Interestingly, object naming, phonological processing and spelling ability are impaired in dyslexic readers, and the dyslexic adolescents of the present study showed impairments in all these skills.

The finding of less gray matter volume in the occipitotemporal cortex highlights the importance of this brain area for developmental dyslexia by showing that the occipitotemporal cortex of dyslexic readers is not only less activated during reading [e.g., Kronbichler et al., 2006; Paulesu et al., 2001; Shaywitz et al., 2002] and object naming [McCrory et al., 2005], but also structurally abnormal. Damage to the left occipitotemporal cortex in adults results in pure alexia [Binder and Mohr, 1992; Cohen et al., 2003; Damasio and Damasio, 1983; Dejerine, 1892; Gaillard et al., 2006]. Patients suffering from pure alexia often exhibit letter-by-letter reading, which is characterized by extremely slow reading and an abnormally large word length effect (i.e., word reading times increase linearly with increasing letter length). Interestingly, not only slow dysfluent reading, but also an abnormally pronounced word length effect is observed in developmental dyslexics [e.g., Martens and de Jong, 2006; Ziegler et al., 2003; Zoccolotti et al., 2005].

Furthermore, recent evidence suggests that damage to the left occipitotemporal cortex also impairs spelling [Rapczak and Beeson, 2004]. The present study demonstrates that the same brain region, in which damage leads to acquired disorders of reading and spelling, exhibits a structural abnormality in developmental dyslexia. The convergent finding of structural brain abnormalities in the occipitotemporal cortex in the study of Silani et al. [2005] and in the present study suggests an important role of the occipitotemporal cortex in the neurobiology of dyslexia. In many previous neurobiological accounts of dyslexia it is assumed that structural abnormalities in the left superior temporal and temporoparietal cortex are mainly responsible for developmental dyslexia [e.g., McCandliss and Noble, 2003; Pugh et al., 2000; Ramus, 2004]. We think, that the finding of structural abnormalities in the occipitotemporal cortex, the consistently observed decreased activation of this region in dyslexics and the association of left occipitotemporal damage in formerly competent readers with pure alexia and letter-by-letter reading suggests a more important role of the occipitotemporal cortex in the psychophysiology of dyslexia then previously thought.

Whereas functional neuroimaging highlights the specific importance of the left occipitotemporal cortex for reading [e.g., Cohen et al., 2000, 2002; Kronbichler et al., 2004], we found less gray matter in dyslexic readers also in the right occipitotemporal cortex. This right occipitotemporal abnormality of developmental dyslexic readers, which has not been reported before, may be important to understand the persistence of reading fluency deficits [e.g., Shaywitz et al., 1999] as well as the fact that fluency impairments are hard to remediate [e.g., Thaler et al., 2004]. A recent case study reported, that after destruction of the left occipital lobe, before learning to read, a right hemisphere shift of the occipitotemporal VWFA occurred, allowing the development of relatively normal reading skill [Cohen et al., 2004b]. We suggest that, if structural abnormalities in dyslexic children affect the occipitotemporal cortex bilaterally, occipitotemporal reading areas cannot develop, which leads to severe and persistent reading impairment. Interestingly, a study reported the case of a child, which never developed normal reading proficiency after bilateral damage to the occipital cortex before learning to read [O'Hare et al., 1998]. However, some differences between developmental and acquired disorders clearly exist. Successful therapeutic interventions can lead to at least a partly normalization of brain activity in developmental dyslexics [e.g., Eden et al., 2004], even in the left occipitotemporal cortex [Shaywitz et al., 2004]. Such changes in brain activity after successful remediation highlight that the structural brain abnormalities observed in developmental dyslexia are not as severe as the damage observed in cases of acquired reading disorders. Although we think that the convergence of functional neuroimaging and neuropsychological studies supports our conclusion that the bilateral occipitotemporal brain abnormalities may cause the persistence of dyslexia, the abnormalities in other brain regions as well as other factors may also explain this persistence. Clearly, more studies are needed to clarify the causes of the persistence of developmental dyslexia.

In line with previous studies [Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2003, 2005; Rae et al., 2002] dyslexic readers had less gray matter volume in the cerebellum, especially in the right hemisphere. The consistent finding of cerebellar abnormalities in dyslexic readers is noteworthy. Furthermore, in the present study, the most extended areas of gray matter abnormalities in dyslexic readers were located in the cerebellum. These findings suggest an important role of the cerebellum in dyslexia as predicted by the cerebellar deficit theory [Nicolson et al., 2001]. The cerebellum is associated with skill acquisition and skill automatisation [Nicolson et al., 2001]. A cerebellar deficit provides a plausible interpretation of the persistent reading fluency impairments by assuming a deficit in the automatisation of reading. Nevertheless, according to the cerebellar deficit theory, dyslexic readers should also exhibit motor difficulties. This prediction was not confirmed in our sample, as the dyslexic readers performed normally on the visuomotor peg moving task. Further-

more, a recent study from our laboratory revealed that motor difficulties are not associated with dyslexia [Raberger and Wimmer, 2003]. This discrepancy indicates that damage to the cerebellum can cause cognitive impairments without affecting motor skills [Fabbro et al., 2004]. In the case of dyslexia this finding could have the implication that cerebellar abnormalities may be present even in the absence of behaviorally measured motor impairments. However, cerebellar abnormalities could also reflect an effect of altered brain development rather than a cause of dyslexia [Ramus, 2004].

Structural brain abnormalities were also found in a left parietooccipital region, in the right supramarginal gyrus and, only at an uncorrected threshold, in the right middle temporal gyrus and in the left superior temporal sulcus. In the left superior temporal sulcus more gray matter was found in dyslexic readers. There is no a priori reason to assume that behavioural impairments can only be associated with less brain volume. Increased brain volume could equally likely be related to developmental disability. Given the importance of left temporal regions for language and phonological processing, one may speculate that the increase in gray matter volume corresponds to the cell migration abnormalities found in the perisylvan cortices of dyslexics [Galaburda and Kemper, 1979; Galadburda et al., 1985; Humphreys et al., 1990; see Silani et al., 2005]. In line with this speculation, temporal and temporoparietal brain areas are highlighted as responsible for dyslexia in the phonological deficit theory [Ramus, 2004] and our dyslexic readers exhibited impairments on verbal tasks at the beginning of formal schooling. In contrast to the phonological deficit theory, no reliable evidence for abnormalities of left inferior frontal regions was found in our sample. This result is interesting as left inferior frontal regions have previously been linked to phonological processing [Jobard et al., 2003; Price, 2000] and damage to left inferior frontal regions is associated with acquired phonological dyslexia and phonological processing impairments [Fiez et al., 2006].

Surprisingly, given the importance of the left hemisphere for language processing, the areas of decreased gray matter volume in dyslexic readers were more extended in the right hemisphere. The functional significance of this finding remains unclear, but two previous VBM studies of dyslexic readers found a similar pattern of more extended abnormalities in the right hemisphere [Brambati et al., 2004; Brown et al., 2001].

We cannot exclude the possibility that less gray matter in the occipitotemporal cortex reflects an effect rather than a cause of dyslexia. Because experience can powerfully alter brain structure [e.g., Draganski et al., 2004; Maguire et al., 2000] less reading experience in dyslexic readers could cause decreased gray matter volume in occipitotemporal reading areas. Such an explanation can only be ruled out by demonstrating less gray matter volume before reading acquisition in children, who are later diagnosed as dyslexic. Nevertheless, we consider such an explanation unlikely for two reasons. First, if less reading experience would be the sole cause of decreased gray matter volume in the occipitotemporal cortex it should be restricted to reading areas in the left hemisphere, whereas we found less gray matter volume also in the right hemisphere. Second, the presently studied dyslexic children exhibited object naming speed deficits before learning to read. As object naming deficits have been linked to an occipitotemporal dysfunction [McCrory et al., 2005], it is tempting to assume that these early deficits were caused by structural abnormalities of the occipitotemporal cortex. Therefore, we assume that the presently found occipitotemporal brain abnormalities are not simply caused by less reading experience.

Most of the dyslexic participants in the present study received reading intervention (mostly at the beginning of reading instruction). One may ask whether such interventions could affect brain structure. Given the earlier mentioned findings on the influence of experience on brain structure one would expect to see an effect of intervention on brain structure. The exact nature of this influence remains to be clarified in future studies. However, we do not think that the presently found decreases in gray matter volume can be explained by effects of intervention as previous studies generally found that training of skills leads to an increase of brain volume in regions associated with these skills [e.g., Draganski et al., 2004; Maguire et al., 2000].

In summary, the present results provide evidence for the importance of the occipitotemporal cortex in developmental dyslexia by revealing a structural brain abnormality in this region. Together with functional neuroimaging studies on dyslexia, and lesion studies with patients with pure alexia, these findings suggest that the occipitotemporal cortex is one of the most important regions for skilled reading and that structural alterations in this region are associated with reading difficulties. In many previous accounts of the neurobiological basis of developmental dyslexia, left superior temporal and temporoparietal areas are considered as being directly responsible for the phonological processing impairment and the reading difficulties of dyslexic readers [e.g., Pugh et al., 2000; McCandliss and Noble, 2003; Ramus, 2004]. In contrast the decreased activation of left occipitotemporal regions is considered as just reflecting an impaired development of the occipitotemporal region, responsible for skilled, automatic word recognition, due to insufficient input from left superior temporal and temporoparietal reading areas [McCandliss and Noble, 2003; Pugh et al., 2000]. The finding of structural brain abnormalities in the left and right occipitotemporal cortex in dyslexic readers should, in our opinion, lead to a stronger emphasis on considering abnormalities in these brain regions as being at least partly responsible for developmental dyslexia.

The extended areas of less gray matter in the bilateral cerebellum replicated one of the most consistent finding in studies on structural brain abnormalities in dyslexia and

indicate that the cerebellum may have an important role in developmental dyslexia.

These findings have to be replicated in future studies, preferably in prospective MRI studies with children at risk for dyslexia. Future studies could also reveal whether gray matter volume in these regions can be used to classify readers as dyslexic or nonimpaired. Studies on the neurobiological correlates of developmental dyslexia have often found inconsistent results. However a pattern is now emerging from the literature with relatively consistent findings pointing to structural abnormalities mainly in the temporal and temporoparietal brain regions, the cerebellum and in occipitotemporal brain regions. Nevertheless, the inconsistency between different studies is still remarkable. We think that a major goal of future studies (besides using advanced MR scanning techniques and data analysis strategies) should be to examine the replicability of this brain abnormalities by focusing specifically on these candidate regions.

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