◆ Human Brain Mapping 34:3055–3065 (2013) ◆

Structural Abnormalities in the Dyslexic Brain: A Meta-Analysis of Voxel-Based Morphometry Studies

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Abstract: We used coordinate-based meta-analysis in order to objectively quantify gray matter abnormalities reported in nine Voxel-Based Morphometry studies of developmental dyslexia. Consistently across studies, reduced gray matter volume in dyslexic readers was found in the right superior temporal gyrus and left superior temporal sulcus. These results were related to findings from previous meta-analyses on functional brain abnormalities in dyslexic readers. Convergence of gray matter reduction and reading-related underactivation was found for the left superior temporal sulcus. Recent studies point to the presence of both functional and structural abnormalities in left temporal and occipito-temporal brain regions before reading onset. *Hum Brain Mapp 34:3055–3065, 2013.* © 2012 Wiley Periodicals, Inc.

Key words: dyslexia; reading; magnetic resonance imaging; meta-analysis; cerebral cortex

INTRODUCTION

The underlying neural dysfunctions in developmental dyslexia were the focus of review articles published on both functional and structural brain abnormalities in dyslexic readers [Démonet et al., 2004; Eckert, 2004; Heim and Keil, 2004; McCandliss and Noble, 2003; Pugh et al., 2000; Sandak et al., 2004; Schlaggar and McCandliss, 2007; Shaywitz and Shaywitz 2005]. In the case of functional abnormalities, three quantitative, coordinate-based meta-analyses summed up the large body of existing literature [Maisog et al., 2008; Richlan et al., 2009, 2011]. Functional abnormalities were mainly found in left hemisphere occipito-temporal, temporo-parietal, and inferior frontal language regions [for a review see Richlan, in press]. In the case of structural abnormalities such an objective quantification of abnormalities is missing. Therefore, this study provides a meta-analysis of Voxel-Based Morphometry studies of gray matter abnormalities in developmental dyslexia.

Starting with 19th century neurological examinations [Dejerine, 1891, 1892], there is a long history of studying neuroanatomical abnormalities in acquired dyslexic readers. With respect to developmental dyslexia, significant progress was made in the 70s and 80s of the last century with the histological postmortem brain examinations by Galaburda et al. Specifically, Galaburda and Kemper [1979] found reduced left-right asymmetry of the planum temporale—localized on the dorsal bank of the superior temporal gyrus, posterior to Heschl's gyrus—in a postmortem examination of the brain of a developmental dyslexia

Contract grant sponsor: Austrian Science Foundation; Contract grant number: P18832-B02; Contract grant sponsor: European Union's 6th Framework Programme [NEURODYS].

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Received for publication 27 June 2011; Revised 19 April 2012; Accepted 20 April 2012

DOI: 10.1002/hbm.22127

Published online 19 June 2012 in Wiley Online Library (wileyonlinelibrary.com).

case. In addition, Galaburda et al. [1985] and Humphreys et al. [1990] reported findings of neuronal ectopias and architectonic dysplasias in left perisylvian regions of several additional dyslexia cases. These cortical anomalies were assumed to develop prenatally during neuronal migration. However, some of the eight cases examined by the Galaburda group may have suffered from comorbid problems which may have been reflected in the reported brain abnormalities. It was also suggested that the dyslexic brains had been stored for a longer period of time than those of the control subjects and therefore were more prone to suffering from cell shrinkage and other postmortem alterations [Heim and Keil, 2004].

With computed tomography (CT) and magnetic resonance imaging (MRI), it became possible to study the structure of a larger number of brains in vivo. Still, analysis of these brain images was difficult and required manual tracing of specific regions of interest based on expert neuroanatomical knowledge. Statistical comparisons were mainly limited to these subjectively defined regions (e.g., the planum temporale) and to rather coarse anatomical measures such as global cerebral volume. This unsatisfactory state of affairs was overcome by statistical methods capable of examining differences between brain images in an unbiased and objective way such as Statistical Parametric Mapping [Friston et al., 1990]. A major advance in the analysis of structural T1-weighted MR scans was the introduction of Voxel-Based Morphometry (VBM) by Ashburner and Friston [2000], and the subsequent optimization of this method [Mechelli et al., 2005]. VBM is an objective and powerful tool to study local tissue concentrations on the voxel-level together with automatic segmentation of gray matter (GM), white matter (WM), and cerebro-spinal fluid (CSF). The basic idea behind VBM is to identify a particular tissue type — usually gray matter — in the scan of each subject (segmentation) and to warp these tissue maps to a common anatomical space (normalization). The normalized tissue maps are then spatially blurred (smoothing) and a voxel-by-voxel statistical analysis of this preprocessed data is performed. VBM provides a general measure of local GM volume or density which is the product of several aspects of cortical architecture such as surface area, folding complexity, and thickness [Hutton et al., 2009]. VBM has been used to investigate both normal brain development [e.g., Good et al., 2001] and pathological alterations [e.g., Mummery et al., 2000]. A PubMed search with the keyword "voxel-based morphometry" identified over 1700 studies and a number of meta-analyses were performed on these studies [e.g., Honea et al., 2005]. However, the VBM method was shown to suffer from potential limitations, which will be considered in the Discussion.

With respect to developmental dyslexia, a number of VBM studies of gray matter (GM) abnormalities were published [Black et al., 2012; Brambati et al., 2004; Brown et al., 2001; Eckert et al., 2005; Hoeft et al., 2007; Kronbichler et al., 2008; Menghini et al., 2008; Pernet et al., 2009a, 2009b; Raschle et al., 2011; Silani et al., 2005; Steinbrink et al., 2008; Vinckenbosch et al., 2005]. Inspection of the results of these studies, at first sight, revealed only limited convergence. By meta-analyzing the original studies, this work aimed at quantifying objectively on a voxel-by-voxel basis which regions were consistently reported with GM abnormalities. In the Discussion we relate the present meta-analytic results of structural abnormalities to our previous meta-analyses on functional abnormalities [Richlan et al., 2009, 2011].

Two of the VBM studies—in addition to GM abnormalities—investigated white matter (WM) abnormalities in dyslexic readers [Eckert et al., 2005; Silani et al., 2005]. Specifically, Eckert et al. [2005] reported WM reduction in a right temporo-parietal region, whereas Silani et al. [2005] reported WM reduction in three left hemisphere regions (underneath inferior frontal, postcentral, and supramarginal gyri, respectively). Because of the small number of peaks and their obvious inconsistency with respect to localization, meta-analytic quantification of these WM abnormalities was omitted.

Another method in the study of WM abnormalities became available with diffusion tensor imaging (DTI) techniques allowing examination of the integrity of fiber tracts [e.g., Basser et al., 1994]. The emergence of this technique was paralleled by a conceptual focus on functional integration among different brain regions in contrast to a focus on functional specialization of discrete brain regions. Several neuroimaging studies investigated dyslexic abnormalities in structural connectivity [Beaulieu et al., 2005; Carter et al., 2009; Deutsch et al., 2005; Dougherty et al., 2007; Frye et al., 2008, 2011; Jäncke et al., 2007; Keller and Just, 2009; Klingberg et al., 2000; Nagy et al., 2004; Niogi and McCandliss, 2006; Odegard et al., 2009; Qiu et al., 2008; Richards et al., 2008; Rimrodt et al., 2010; Rollins et al., 2009; Steinbrink et al., 2008]. However, these abnormalities in structural connectivity are frequently not reported in terms of 3D coordinates in standard stereotactic space, and therefore cannot be included in the present coordinate-based meta-analytic approach (see Material and Methods).

MATERIALS AND METHODS

We performed several PubMed searches with the Keywords "dyslexia" and "imaging" to identify relevant structural studies. For meta-analytic quantification of GM abnormalities, only VBM studies reporting direct group comparisons between nonimpaired and dyslexic readers of an alphabetic script in a standardized stereotactic space (Talairach or MNI) were used. On the basis of these criteria we identified nine studies: Brambati et al. [2004], Brown et al. [2001], Eckert et al. [2005], Hoeft et al. [2007], Kronbichler et al. [2008], Menghini et al. [2008], Silani et al. [2005], Steinbrink et al. [2008], and Vinckenbosch et al. [2005]. For homogeneity we did not include a VBM study with Chinese dyslexic readers [Siok et al., 2008].

TABLE I. Main characteristics of the included studies and number of peaks used in the meta-analysis

Year	First author	*N*	Dys	Con	Native language	Age mean (SD)	Modulated VBM (absolute volumes preserved)	ROI analysis	Threshold		No. of foci (reduced/increased GM)
									Voxel-level (height) $P <$	Cluster-level (extent) $P <$ or no. of voxels	
2008	Kronbichler	28	13	15	German	15.7 (0.7)	X	X	0.05 corr.	100	9/0
2008	Menghini	20	10	10	Italian	40.8 (6.9)	X	X	0.005 unc.	0.05 corr.	2/0
2008	Steinbrink	16	8	8	German	21.9 (4.1)	X	—	0.05 corr.	650	2/0
2007	Hoeft	38	19	19	English	14.4 (2.2)	X	—	0.01 corr.	0.01 corr.	6/0
2005	Eckert	26	13	13	English	11.4 (8.2)	X	—	0.00001 unc.	0.001 corr.	5/0
2005	Silani	64	32	32	English, French, Italian	25.3 (5.0)	X	X	0.05 corr.	—	1/1
2005	Vinckenbosch	23	13	10	French	range 17–30	—	—	0.01 corr.	0.05 corr.	1/1
2004	Brambati	21	10	11	Italian	29.5 (range 13–57)	X	—	0.05 corr.	25	9/0
2001	Brown	30	16	14	English	24.0 (5.0)	—	—	0.05 unc.	0.05 corr.	8/0

Two VBM studies were not eligible for inclusion in the meta-analysis because they studied prereading kindergarteners with a family history of developmental dyslexia rather than diagnosed dyslexics [Black et al., 2012; Raschle et al., 2011]. However, a substantial proportion of these children can be expected to experience major difficulties in the course of learning to read [Scerri and Schulte-Körne, 2010], and therefore these studies are very interesting and useful for discussion. Another VBM study examined changes in GM volume following an eight week reading instruction in dyslexic children, but was not eligible for inclusion in the meta-analysis because it did not include a nonimpaired sample [Krafnick et al., 2011]. Also not included were the VBM studies by Pernet et al. [2009a, 2009b]. Specifically, Pernet et al. [2009a] failed to find direct group differences in GM volume, and instead reported group differences in correlations between GM volume and behavioral measures. Likewise, Pernet et al. [2009b] did not report direct group comparisons but rather used a classification approach to search for voxels in which GM volume of dyslexic readers was found to lie outside the normal range.

A total number of 266 participants (134 dyslexic and 132 nonimpaired readers) were included in the 9 selected studies. These studies and their main characteristics are listed in Table I. Three of the studies were done with English participants, two each with German and Italian participants, and one with French participants. One study [Silani et al., 2005] included English, French, and Italian dyslexic readers. With respect to age, the participants were mainly adolescents and young adults; that is, they were not in early stages of their reading career. All of the nine studies reported peaks of dyslexic GM reductions which survived statistical thresholds corrected for multiple comparisons. In contrast, peaks of GM increases surviving a corrected threshold were only reported in two studies [Silani et al., 2005; Vinckenbosch et al., 2005]. These peaks were localized in the left posterior middle temporal gyrus [Silani et al., 2005] and in the right precentral gyrus [Vinckenbosch et al., 2005] respectively. A total number of 45 peaks (43 for GM reduction and 2 for GM increase) entered the present meta-analysis.

For meta-analysis, Effect-Size Signed Differential Mapping (ES-SDM; http://www.sdmproject.com) software, version 2.14 was used [Radua and Mataix-Cols, 2009; Radua et al., in press]. Signed Differential Mapping combines positive features from other methods such as Multilevel Kernel Density Analysis (MKDA) and Activation Likelihood Estimation (ALE), and was used in one of our previous meta-analyses on functional dyslexic abnormalities [Richlan et al., 2011]. All peaks were transformed to Talairach space and meta-analysis was restricted to a specific GM template provided by the software. For each study, effect-size maps (Hedge's *g*) and variance maps were created. For peak voxels, effect sizes were calculated from their respective *t* values and the number of included

TABLE II. Gray matter reductions in developmental dyslexia identified in the present meta-analysis

Region	Talairach-coordinates			ES-SDM	
	x	*y*	*z*	*z*-value	Voxels
R superior temporal gyrus	50	−36	18	1.93	86
	52	−42	18	1.89	
L superior temporal sulcus	−54	−50	10	1.70	24
	−48	−52	12	1.55	
	−56	−46	6	1.48	

participants per group (dyslexic vs. nonimpaired). For the rest of the voxels, effect sizes were estimated by their respective distance to peak voxels by means of an unnormalized Gaussian kernel (FWHM = 20 mm). A random effects model was used to combine the data from the nine studies. To examine statistical significance, the location of the voxels was randomized within the GM template (500 permutations). Finally, the meta-analytic map was thresholded using a voxel-level (height) threshold of $P < 0.005$ (uncorrected) and a cluster-level (extent) threshold of 10 voxels. For ES-SDM, this uncorrected threshold was found to optimally balance sensitivity and specificity, and to be an approximate equivalent to a corrected threshold of $P < 0.05$ in original neuroimaging studies [Radua et al., in press]. However, we also applied a false discovery rate (FDR) threshold of $q < 0.05$ but none of the results survived this correction. To evaluate the robustness of the findings, we relied on inspecting how many of the original studies contributed to the identification of the meta-analytic clusters (see below)—a method already applied in our previous meta-analyses [Richlan et al., 2009, 2011].

RESULTS

Table II shows the brain regions identified with GM reduction in the meta-analytic map. No brain regions were identified with GM increase. The clusters are characterized by the Talairach coordinates and the ES-SDM *z*-values of the maxima and submaxima of the reduction, as well as by the spatial extent. In Figure 1A the clusters with GM reduction are rendered on a template brain. Figure 1B shows coronal slices at $y = -50$ and $y = -34$, respectively.

Figure 1A,B and Table II show convergent GM reduction in dyslexic compared to nonimpaired readers in the right superior temporal gyrus (STG) and in the left superior temporal sulcus (STS). Specifically, the cluster in the right hemisphere was localized in the posterior dorsal bank of the STG near the temporo-parietal junction, while the cluster in the left hemisphere was localized in the posterior STS between the superior and middle temporal gyri (MTG). As the right STG cluster was localized more anterior and superior than the left STS cluster, these regions may not be treated as homologous. With respect to spatial extent, the right STG cluster was more than three times bigger than the left STS cluster.

For further evaluation of convergence of GM reductions, Table III shows which of the original VBM studies reported peaks of GM reductions contributing to the identification of the present meta-analytic clusters. Substantial convergence was found for both clusters with five (of nine) studies contributing to each cluster. Furthermore, Table III reports additional findings of the original studies which found no support in the present meta-analysis. Notably, four studies found GM reduction in left ventral occipito-temporal (OT) regions including inferior temporal and fusiform gyri, but these peaks were too scattered for reliable meta-analytic clustering. Similarly, the left cerebellum was reported with GM reduction in four original VBM studies, but again, this region failed to survive the meta-analytic threshold. Further peaks of GM reduction were identified in regions typically associated with phonological or articulatory output processes such as the inferior frontal gyrus, precentral gyrus, supplementary motor area, insula, and basal ganglia, as well as in regions associated with visual processing such as the lingual and medial occipital gyri.

DISCUSSION

This article provides an objective summary of studies reporting gray matter (GM) abnormalities in samples of dyslexic readers by quantitatively meta-analyzing nine original Voxel-Based Morphometry (VBM) studies. The meta-analysis, based on 45 peaks, identified GM reduction in the right superior temporal gyrus (STG) and in the left superior temporal sulcus (STS). In the following, we discuss the evidence for these structural abnormalities and relate them to functional abnormalities.

Right Superior Temporal Gyrus

Peaks contributing to the cluster of GM reduction in the posterior dorsal bank of the right STG near the temporo-parietal junction were reported in five of the nine original VBM studies. This right hemisphere GM reduction was rather unexpected as previous studies identified structural abnormalities primarily in the left temporal lobe. As noted in the Introduction, the seminal histological postmortem brain examinations of Galaburda and colleagues found perisylvian anomalies (i.e., ectopias and dysplasias) primarily—although not exclusively—in the left hemisphere [e.g., Galaburda et al., 1985; Humphreys et al., 1990]. A brain imaging study by Eliez et al. [2000], not included in the present meta-analysis, measured GM volume in the major lobes of the brain and reported reduced GM volume only for the left but not for the right temporal lobe of dyslexic adults. The present finding of GM reduction in the

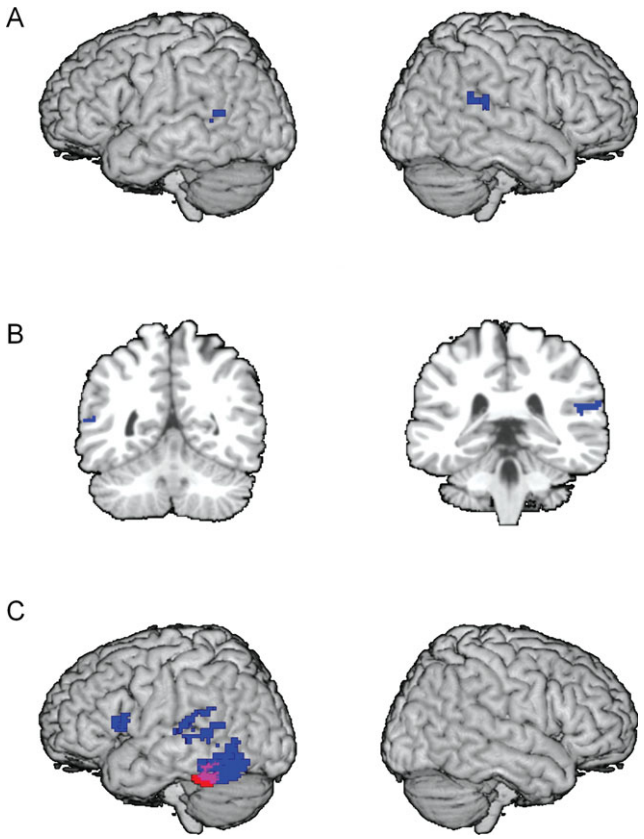

Figure 1.

A: Surface rendering of gray matter reductions identified in the present meta-analysis of structural brain abnormalities. **B**: Coronal slices at (Talairach coordinates) $y = -50$ and $y = -34$, respectively. **C**: Underactivation in dyslexic children (red) and dyslexic adults (blue) identified in our previous meta-analysis of functional brain abnormalities [Richlan et al., 2011].

right STG is also difficult to reconcile with early reports which measured extents of the planum temporale, a region in the dorsal bank of the STG, posterior to Heschl's gyrus. These studies were based on early findings that nonimpaired readers typically exhibit planum temporale asymmetry (i.e., larger left than right) and that dyslexic readers

TABLE III. Convergence of gray matter reductions

Year	First author	R STG	L STS	Additional regions
2008	Kronbichler	X		L/R fusiform, L/R cerebellum
2008	Menghini			R supplementary motor, R superior parietal
2008	Steinbrink	X	X	—
2007	Hoeft	X	X	L inferior frontal, L/R insula, L anterior cingulate, L lentiform, L/R pre-/postcentral, L/R inferior parietal
2005	Eckert			L lentiform, L supramarginal, L/R lingual, L cerebellum
2005	Silani		X	—
2005	Vinckenbosch			L inferior temporal
2004	Brambati	X	X	L/R planum temporale, L inferior temporal, L/R fusiform, L/R cerebellum
2001	Brown	X	X	L/R frontal pole, L/R inferior frontal, L/R caudate, R precentral, L inferior temporal, R medial occipital, L/R cerebellum

VBM studies reporting peaks of gray matter reduction contributing to the identification of the present meta-analytic clusters are marked with an X. Furthermore, additional findings of the original studies which found no support in the present meta-analysis are reported.

fail to exhibit this asymmetry due to abnormally large extent of the right planum temporale [e.g., Galaburda and Kemper, 1979; Geschwind and Levitsky, 1968]. From larger extent of the right planum temporale, one would have expected dyslexic readers to exhibit increased GM in the right STG, but this was not the case. However, the finding of abnormal planum temporale symmetry in developmental dyslexia found no support in newer studies [e.g., Leonard et al., 2006].

A recent finding by Carreiras et al. [2009] is of interest for interpretation of the present results. This VBM study compared ex-guerillas who did or did not learn to read as adults and found increased GM volume in bilateral temporo-parietal (TP) and dorsal occipital regions to accompany learning to read. This finding points to the possibility that the right STG GM reduction found in our meta-analysis reflects the reduced reading experience of dyslexic readers. Against this interpretation stand the results of Raschle et al. [2011], who found pre-readers with a high genetic risk for dyslexia to exhibit reduced GM in both left and right TP regions. In a similar study, Black et al. [2012] found maternal history of reading disability to be associated with reduced bilateral TP GM volume in a sample of 5 to 6 year old beginning readers. For these young children the reduction in GM volume cannot be attributed to a reduced amount of reading experience. In summary, the GM reduction in the right STG was an unexpected finding which in earlier work was not paid as much attention as left hemisphere abnormalities. However, as evidenced by two recent studies with young children, right STG GM reduction—together with left temporal GM reduction—may be an early neuroanatomical signature for later reading problems.

Left Superior Temporal Sulcus

Similar to the cluster in the right STG, peaks contributing to the cluster in the left posterior STS (between superior and middle temporal gyri) were reported in five of the nine original VBM studies. As mentioned in the previous section, this finding is in line with evidence for left perisylvian cortical anomalies identified in post-mortem brain examinations [e.g., Galaburda et al., 1985; Humphreys et al., 1990], as well as with evidence from early neuroimaging studies [Eliez et al., 2000]. Damage to the left STS was classically associated with a disruption in auditory speech comprehension (Wernicke's aphasia). In newer conceptions [e.g., Hickok and Poeppel, 2007], the left STS—as opposed to the bilateral STG, which is associated with auditory spectrotemporal analysis—is thought to be an important region for the representation and/or processing of phonological information. Thus, it is activated during both the perception and production of speech, as well as during active maintenance of phonemic information.

In functional neuroimaging studies of developmental dyslexia, the left STS frequently exhibits underactivation during reading or reading-related tasks [e.g., Blau et al., 2010; Meyler et al., 2007; Paulesu et al., 2001]. In the dominant version of the phonological deficit explanation, a language-phonological deficit localized in left STG/STS regions is assumed to affect the emergence of phoneme awareness at the beginning of learning to read, which constitutes the proximal cause for developmental dyslexia [e.g., Shaywitz and Shaywitz, 2005; Snowling, 2000; Vellutino and Fletcher, 2005]. However, other studies suggest that the left STS plays a central role in the integration of auditory and visual information [e.g., van Atteveldt et al., 2004]. Therefore, during reading, its main function may be more directly related to serial grapheme-phoneme conversion. Dyslexic underactivation of this region in response to demands on letter-speech sound integration was interpreted as resulting from a failure to develop neural systems specialized for efficient interactive processing of auditory and visual linguistic inputs [Blau et al., 2010]. The convergence between studies of structural brain abnormalities and studies of functional brain abnormalities in dyslexic readers will be discussed in more detail in the following section.

Convergence of Structural and Functional Brain Abnormalities

The right STG and left STS regions with convergent GM reduction only partially overlap with regions identified in the meta-analyses of regions exhibiting reduced activation in response to reading or reading-related tasks [Maisog et al., 2008; Richlan et al., 2009, 2011; for a review see Richlan, in press]. Figure 1C presents the regions with underactivation in dyslexic children (red) and underactivation in dyslexic adults (blue) identified by Richlan et al. [2011]. The comparison with Figure 1A shows structure–function convergence for the left STS abnormalities, although the extent of the functional abnormalities appears enlarged compared with the structural ones. In contrast, the GM reduction in the right STG found no functional correspondence. Additionally, we did not identify structural equivalents to the underactivation in the left ventral occipito-temporal (OT) regions and in the left inferior frontal gyrus (IFG) shown in Figure 1C.

The convergence between functional and structural abnormalities in the left STS and the nonconvergence in the right STG (i.e., reduced GM, no reduced activation) is of interest. One may speculate that the reduced GM in both the left and the right hemisphere is caused by abnormalities in prenatal brain development, but only the reduced GM in the left STS affects learning to read, with the consequence of reduced functional engagement. The left STS dysfunction is commonly interpreted as reflecting impaired phonological reading of unfamiliar letter strings in the early stage of learning to read, which secondarily affects the build-up of orthographic word memories for

efficient word recognition in the left ventral OT cortex [e.g., Pugh et al., 2000].

The results of our functional meta-analysis in Figure 1C are difficult to reconcile with this developmental hypothesis, as the studies with dyslexic children provided convergent evidence for left ventral OT underactivation (marked in red), whereas the studies with adults exhibited underactivation in an extended left OT and in left superior temporal areas (marked in blue). Consistent with the early emergence of left OT underactivation in dyslexic children are studies showing early engagement of left OT regions by nonimpaired reading development. Brem et al. [2010] found prereaders in kindergarten—after a few weeks of letter-sound training—to exhibit an increased left OT response in reading-related tasks. Correspondingly, Maurer et al. [2007] found that second graders with a familial risk for dyslexia and poor progress in learning to read exhibited reduced tuning of the electrophysiological response in the left OT. In addition, even before learning to read, the at-risk children exhibited a reduced bilateral OT response to symbols. Recently, Bach et al. [in press] found that prediction of reading skills in 2nd grade based on behavioral measures was significantly improved by adding ERP and fMRI responses of the left OT region before learning to read to the prediction model. A further recent study with prereaders found underactivation in bilateral OT and left superior and middle temporal regions in children with a family history of developmental dyslexia in response to a phonological matching task [Raschle et al., 2012].

With respect to GM abnormalities, the present meta-analysis failed to identify left ventral OT regions. However, as already noted, four of the nine original VBM studies (see Table III) reported reduced GM in this region (including inferior temporal and fusiform gyri). A possible explanation for the absence of left ventral OT GM reduction in the meta-analytic results is that the peaks of the original studies were too scattered for reliable clustering. In particular, the location of the peaks varied most along the posterior-anterior direction with some peaks located in posterior fusiform regions (at around $y = -60$) and others in anterior inferior temporal regions (at around $y = -10$). The location of the former corresponds to the typical left ventral OT region with dyslexic underactivation identified in functional studies [Richlan, in press; Richlan et al., 2009, 2011] while the location of the latter corresponds to a region associated with heteromodal semantic memory [Binder and Desai, 2011] typically not identified with functional abnormalities in dyslexic readers.

Although the studies in the present meta-analysis failed to identify convergent structural abnormalities in left ventral OT regions, other studies are suggestive of such abnormalities. Specifically, Frye et al. [2010] provided evidence for a left OT abnormality by reporting reduction of GM volume and of cortical surface area in dyslexic adults. This study was not included in the present meta-analysis as no coordinates were reported for group differences. For dyslexic children, a recent VBM study by Krafnick et al. [2011] showed that behavioral gains following an eight week reading training were accompanied by GM increases in the left fusiform gyrus, left precuneus, right hippocampus, and right cerebellum. For interpretation of possible left OT abnormalities the VBM study by Raschle et al. [2011] is of specific importance. This study found reduced GM volume of prereaders with a family history of developmental dyslexia not only in bilateral TP regions but also in a left OT region. Furthermore, across children with and without a risk for dyslexia, GM volume in left OT and left TP regions correlated positively with rapid automatized naming performance, which is an important predictor for later reading skills [e.g., Landerl and Wimmer, 2008]. These findings suggest that GM reduction in the left OT—similar to GM reduction in the left STS and in the right STG—may not arise secondarily but may be present even before learning to read.

To draw accurate conclusions on the structure–function relationship, longitudinal studies with measurement of both structural abnormalities and functional abnormalities in response to reading or reading-related tasks would be important. Apparently, such studies do not exist yet. To our knowledge there are only three studies which investigated both structural and functional abnormalities. Hoeft et al. [2007] found GM reduction and reading-related underactivation in a left TP region, whereas Silani et al. [2005] found reduced GM volume in a left posterior MTG region that was previously identified with underactivation in a PET study of the same adult participants [Paulesu et al., 2001]. Investigating Chinese dyslexic children, Siok et al. [2008] found co-occurrence of GM reduction and fMRI underactivation and in the left middle frontal gyrus, which is assumed to be engaged by memorizing the stroke patterns of the Chinese words.

As evident from Table III, 4 original VBM studies reported GM reduction in the cerebellum. Although the present meta-analysis failed to identify convergent GM abnormalities in cerebellar regions, there are other findings suggestive of such abnormalities. Specifically, Pernet et al. [2009b] found cerebellar GM volumes of dyslexic readers to be either above or below the normal range, and reported volume of the right cerebellum (together with the right lentiform nucleus of the basal ganglia) to most reliably separate dyslexic and nonimpaired readers. In addition, Leonard et al. [2001] reported increased leftward asymmetry of the cerebellar lobes of dyslexic readers. The possible cerebellar abnormalities are of potential interest, as both the skill automatization deficit hypothesis of Nicolson et al. [2001] and the magnocellular deficit hypothesis of Stein and Walsh [1997] posit a dysfunction of the cerebellum in developmental dyslexia.

White Matter Abnormalities in Developmental Dyslexia

As mentioned in the Introduction, a number of recent studies focused on dyslexic abnormalities of white matter

(WM) tracts. These diffusion tensor imaging (DTI) studies frequently found reduced organization of fiber tracts in left temporal and left temporo-parietal regions [Beaulieu et al., 2005; Carter et al., 2009; Deutsch et al., 2005; Klingberg et al., 2000; Nagy et al., 2004; Niogi and McCandliss, 2006; Richards et al., 2008; Rimrodt et al., 2010; Rollins et al., 2009; Steinbrink et al., 2008]. However, there is still little agreement on which fiber tracts within the WM are specifically affected [Ben-Shachar et al., 2007]. Possible candidates include the corpus callosum (left-right direction, connecting the cerebral hemispheres), the corona radiata (inferior–superior direction, connecting the cerebellum, thalamus, and brain stem with cortical motor and somatosensory regions), and the main fiber tracts running in the posterior–anterior direction. These are the superior longitudinal fasciculus (SLF, connecting occipito-temporal, temporo-parietal, and inferior frontal language regions), the inferior longitudinal fasciculus (ILF, connecting occipital and temporal regions), and the inferior fronto-occipital fasciculus (IFOF, connecting occipital, parietal and prefrontal regions).

The SLF is of specific interest because it connects the occipito-temporal, temporo-parietal, and inferior frontal regions identified as major components of the left hemisphere reading network in numerous functional neuroimaging studies. Further fMRI studies found evidence for functional coupling of these regions in response to reading demands in nonimpaired readers and functional disruption in dyslexic readers [Cao et al., 2008; Richlan et al., 2010; Shaywitz et al., 2003; van der Mark et al., 2011]. Two of the 9 original VBM studies reported left inferior frontal GM reduction but this was not sufficient to reach statistical significance [Brown et al., 2001; Hoeft et al., 2007]. Interestingly, one of the VBM studies which—in addition to GM—investigated WM abnormalities in dyslexic readers reported reduced WM in the depth of the left inferior frontal and left temporo-parietal cortex, respectively [Silani et al., 2005]. However, the relationship between WM, GM, and functional activation as measured by fMRI is still very unclear. Even more difficult to answer are the questions about how abnormalities in these domains might be related to each other, and how they might exert influence over each other during development. Certainly, more basic research on these issues is required before comprehensive models integrating the various findings on brain abnormalities in developmental dyslexia can be put forward.

Voxel-Based Morphometry: Methodological Concerns

Although Voxel-Based Morphometry (VBM) has been extensively used in order to study structural brain abnormalities in various diseases, several potential limitations exist when comparing patients to control subjects. Specifically, the normalization step during the VBM procedure was the subject of much debate [Ashburner and Friston, 2001; Bookstein, 2001; Mechelli et al., 2005]. It was put forward that abnormalities in the brain scans of patients may lead to systematic group-specific misregistration when trying to match these images to an average brain template. As a result, the VBM method would be sensitive to this registration bias rather than to structural abnormalities per se. On the contrary, it was argued that the normalization step relies on a relatively simple warping method, which attempts to find a global match between brain images (i.e., matching overall size and shape). Therefore, only severe pathologies on the macroscopic level (i.e., tumors and artero-venous malformations) would lead to misregistration. The presence of such atypical tissue types would additionally lead to misclassification during the segmentation step, which relies on tissue probability maps for GM, WM, and cerebro-spinal fluid obtained from healthy brains. With respect to developmental dyslexia, no evidence for macroscopic brain abnormalities exists, thus rendering the possibility of misregistration or misclassification unlikely.

However, even in the absence of severe pathologies, one may use an additional processing step in order to compensate for subtle volumetric changes introduced by the normalization step (e.g., artificial enlargement of smaller regions). This optional step is referred to as "modulation," and is basically a multiplication of the spatially normalized image by its relative volume before and after normalization. Thus, the absolute volume of the normalized image is preserved. As evident from Table III, seven of the nine VBM studies of the present meta-analysis included this step. Inclusion of the modulation step also has an effect on the interpretation of VBM results: modulated VBM can be thought of as a measure of absolute volume of a tissue class in a region, whereas unmodulated VBM can be thought of as a measure of relative concentration of a tissue class (in relation to the other classes) in a region.

A further critique of the VBM method concerns its volume-based registration approach. As mentioned previously, it uses a relatively simple warping method attempting to match the overall size and shape of brains. It was shown that a surface-based registration approach, which attempts to match cortical (gyral/sulcal) folding patterns, can lead to improved intersubject registration [e.g., Fischl et al., 2008]. Another advantage of the surface-based approach is that it allows the measurement of more specific properties of GM architecture such as cortical thickness, as opposed to VBM which provides a more general measure of GM volume. The presently described limitations of the VBM method, together with the well-known problems of classical significance testing, may have led to false positive results or misses. However, this makes the attempt to objectively synthesize original findings through meta-analysis even more essential.

CONCLUSIONS

The present quantitative, coordinate-based meta-analysis of nine Voxel-Based Morphometry studies of gray matter

abnormalities associated with developmental dyslexia found converging evidence for reduced gray matter in the right superior temporal gyrus and left superior temporal sulcus. Reports of gray matter reduction in left occipito-temporal and cerebellar regions failed to reach statistical significance. The structural abnormalities were related to functional abnormalities identified in previous meta-analyses. Structure–function convergence was found for the left superior temporal sulcus, which is consistently reported with underactivation in dyslexic readers during reading or reading-related tasks. Recent evidence from prereaders with a family history of developmental dyslexia suggests early presence of both functional and structural abnormalities in left temporal and occipito-temporal brain regions.

ACKNOWLEDGMENTS

The authors would like to thank Joaquim Radua for helpful comments and Anna Martin, Joe Miller, and Philipp Schwartenbeck for proofreading the manuscript.

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