Brief Communications

A Functionally Guided Approach to the Morphometry of Occipitotemporal Regions in Developmental Dyslexia: Evidence for Differential Effects in Boys and Girls

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Developmental dyslexia is a learning disability that specifically affects reading acquisition. Cortical anomalies and gray matter volume differences in various temporal regions have been reported in dyslexic subjects compared with controls. However, consistency between studies is lacking. In the present experiments, we focused our structural analyses on the ventral occipitotemporal regions, defined by their functional response to visual categories. We applied a subject-by-subject functionally guided approach on a total of 76 participants (31 dyslexic children). Cortical thickness was estimated for each participant around his/her peak of specific functional activation to visual words, faces, or places. Results from two independent datasets showed a reduction in thickness in dyslexic children compared with controls in the region responsive to words, in the left hemisphere. Additionally, a gender-by-diagnosis interaction was observed at the same location, due to differences in girls only. To avoid the potential confound of reading level, we also contrasted dyslexic and control children matched for reading performance, and we observed a similar difference, although in a smaller extent of cortex. The present study thus provides the first account of a focal cortical thickness reduction in dyslexia in the subregion of ventral occipitotemporal cortex specifically responsive to visual words, when age, gender, and reading performance are taken into account.

Introduction

Dyslexia is a neurodevelopmental disorder under genetic influence, affecting 3–7% of school-age population. It is characterized by a severe difficulty in reading acquisition despite normal intelligence, education, and sensory functions. Understanding the links between genetic variations, brain disruptions, and specific cognitive impairments remains an important challenge for research on dyslexia (Giraud and Ramus, 2013). To this end, finely characterizing potential neuroanatomical markers of the disorder appears essential.

From a functional point of view, a recent meta-analysis of functional magnetic resonance imaging (fMRI) studies (Richlan et al., 2011) revealed that the most consistent hypo-activation in dyslexic children is found in the left occipitotemporal region, which is thought to play a key role in visual word form recognition and processing (Dehaene and Cohen, 2011; Price and Devlin, 2011). This finding is congruent with experiments suggesting an early failure to engage this system in children with dyslexia (Maurer et al., 2007), or in kindergartners bearing a genetic predisposition for the disorder (Raschle et al., 2012).

At the structural level, following the seminal postmortem work by Galaburda et al. (1985), many attempts have been made to describe the brain of dyslexic patients *in vivo* by MRI. Gray matter volume reductions have been reported in several cerebral regions, comprising temporoparietal and left occipitotemporal areas (Richardson and Price, 2009), in dyslexic adults, children, and at-risk prereaders (Raschle et al., 2011). However, complete consistency between studies is lacking, possibly due to small samples of subjects differing in factors such as age, gender, and severity of the disorder.

In the present experiments, we aimed at characterizing the structure of ventral occipitotemporal regions in developmental dyslexia with refined anatomical detail. Congruently with the functional literature, our prediction was that, instead of a widespread defect, only the region responsive to written words would structurally differ in dyslexic children compared with controls.

Received Dec. 21, 2012; revised May 31, 2013; accepted June 2, 2013.

Author contributions: I.A., K.M., J.F., C.B., F.R., and G.D.-L. designed research; I.A., K.M., S.I., and J.F. performed research; S.I. contributed unpublished reagents/analytic tools; I.A., F.R., and G.D.-L. analyzed data; I.A., F.R., and G.D.-L. wrote the paper.

This work was supported by Ecole des Neurosciences de Paris, Agence Nationale de la Recherche (Grants Nos. ANR-06-NEURO-019-01, ANR-11-BSV4-014-01, ANR-11-0001-02 PSL*, and ANR-10-LABX-0087), European Commission (Grant No. LSHM-CT-2005-018696), University Paris-Sud (BQR), CNRS, INSERM, and the Bettencourt-Schueller Foundation. We thank Rémi Lebigre for his help with image preprocessing. We also like to thank Nadège Villiermet, Camille Chabernaud, Laure Bricout, and the clinical and technical staff at Bicêtre Hospital and at Neurospin for their contribution to children testing in a welcoming environment, and all children and families for their participation.

The authors declare no competing financial interests.

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DOI:10.1523/JNEUROSCI.5854-12.2013

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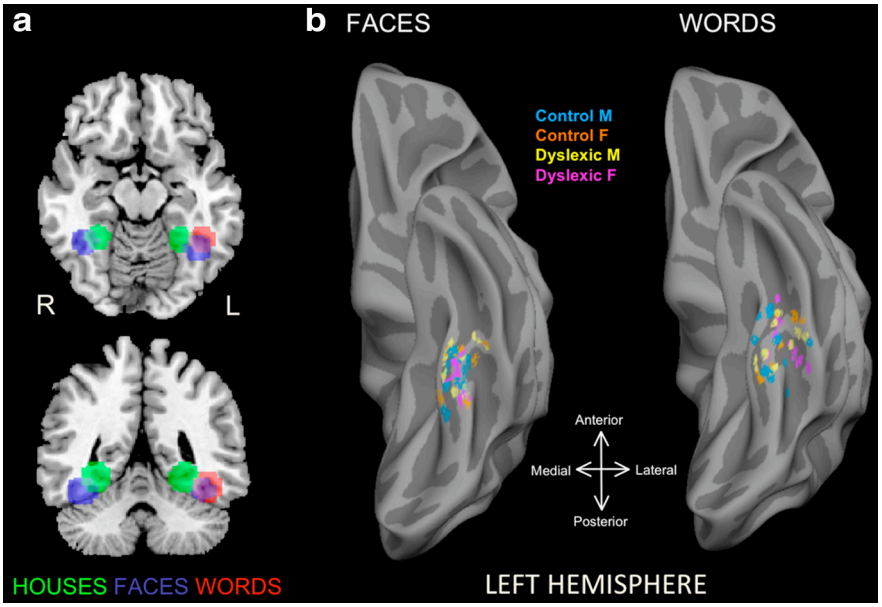

Figure 1. ***a***, Spherical search space around the group reference peak for each category. ***b***, Each subjects' response peak to words and faces is projected on the left ventral surface of an inflated template brain, for all participants in Study 1.

We applied a subject-by-subject region-of-interest approach, restricting our analysis to functionally defined territories, where we estimated cortical thickness. We analyzed data from two independent datasets, differing in age and imaging characteristics, to exclusively report replicated results. Finally, a major issue being the potential confound between effects of developmental dyslexia per se versus effects of reading experience, we further tested the obtained results in a comparison between dyslexic participants and control children matched for reading performance.

Materials and Methods

Participants. Forty-five control (25 boys) and 31 dyslexic children (17 boys) participated in our experiments. No child with a history of neurological or psychiatric disorder, with a hearing or uncorrected visual deficit was included. Nonverbal IQ was in the normal range (standard scores in the block design subtest from the Wechsler Intelligence Scale for Children or WISC III or IV $\geq$7 or overall nonverbal IQ $\geq$80; Wechsler, 2005). Children and their parents gave written informed consent; all experimental procedures received approval from the local ethics committee.

In Study 1, dyslexic participants (mean age, 11 years 9 months) were matched with controls for age and gender. In Study 2, dyslexic children (mean age, 9 years 10 months) were paired with two distinct control groups, one matched for age, gender, and parental education (age-matched group), and the other for gender and reading level (reading-matched group; mean age, 6 years 8 months). The dyslexic and age-matched control children of Study 2 were selected from the study of Monzalvo et al. (2012) so as to be paired one-by-one for age and gender. All dyslexic participants were previously diagnosed by a dedicated learning disability center (Dr. Billard, CHU Bicêtre). Parental education was determined through a sociodemographic questionnaire; only maternal education was available in Study 2.

Behavioral tests. A battery of behavioral tests was administered to determine participants' intellectual, verbal, and reading abilities. Children's verbal skills and working memory were evaluated through WISC similarities and digit span subtests, respectively. Reading level was assessed by the standardized French test "L'alouette" (Lefavrais, 1967) and dyslexic children were expected to present a delay $\geq$18 months. Phonological skills (using a phoneme deletion task; Sprenger-Charolles et al., 2005) and rapid automatized naming of pictures (Plaza and Robert-Jahier, 2006) were also assessed. All tests are age-standardized, except for phoneme deletion and rapid automatized naming tasks.

MRI procedure. All children underwent a 3-T MRI exam (Siemens Tim Trio), comprising the acquisition of both functional and structural images. The functional paradigm aimed at describing category-specific visual areas in ventral occipitotemporal cortices. A revolving checkerboard, houses, faces, words, and also tools in the case of Study 1 (30 black and white pictures in each category and 30 frequent regular words) were presented in a block paradigm (Monzalvo et al., 2012). No explicit reading of the words was requested. The child was instructed to press a button as soon as he/she detected a star (two of them being randomly presented in each block), to keep his/her attention focused on the visual stimuli.

Whole-brain images were acquired using a 32-channel head coil in Study 1 (T1 sequence parameters: acquisition matrix = 230 × 230 × 224, TR = 2300 ms, TE = 3.05 ms, flip angle = 9 deg, FOV = 230 mm, voxel size = 0.9 × 0.9 × 0.9 mm) and a 12-channel head coil in Study 2 (T1 sequence parameters: acquisition matrix = 256 × 256 × 176, TR = 2300 ms, TE = 4.18 ms, flip angle = 9 deg, FOV = 256 mm, voxel size = 1 × 1 × 1 mm). For functional imaging, the sequence parameters were the same in both studies (TR = 2400 ms, TE = 30 ms, matrix = 64 × 64 × 40, voxel size = 3 × 3 × 3 mm) with 108 volumes acquired in one run in Study 1, and four runs of 84 volumes each in Study 2.

fMRI analyses. All preprocessing and analyses of functional data were performed in SPM5. Images were aligned to the first functional image, coregistered with the individual anatomical image, normalized to the MNI adult brain, and smoothed (5 mm Gaussian kernel). fMRI data modeling used the canonical SPM hemodynamic response function and its time derivative, convolved with the experimental conditions (corresponding to each visual category presented). The 6 movement parameters were entered as regressor of no interest. No group differences in movement were found, in either study (for mean translation and rotation respectively, Study 1: $t = -1.3$ $p > 0.2$, $t = -1.1$ $p > 0.2$ Study 2: age-matched $t = -0.3$ $p > 0.7$, $t = -0.6$ $p > 0.5$, reading-matched $t = 1.2$ $p > 0.2$, $t = 1.5$ $p > 0.1$). For each subject and each visual category, the peak location was determined as the voxel of maximal t value within a sphere of 10 mm centered on a reference peak [in MNI, left: words (−42 −48 −15), faces (−39 −54 −16.5), houses (−27 −48 −9); right: faces(39 −49.5 −18), houses (30 −46.5 −9); Fig. 1*a*] in the t-map corresponding to the contrast of interest [i.e., (words > others), (faces > others), (houses > others)]. The reference peaks were the peak specific responses for each category reported in Monzalvo et al. (2012), computed across 46 dyslexic and control children. In that study, there was no significant specific response for words in the right hemisphere.

Cortical thickness estimation. A surface-based cortical reconstruction was applied to all subjects, using Freesurfer (Dale et al., 1999). This software reconstructs cortical surfaces, registers them to a common surface template and estimates cortical thickness (Fischl and Dale, 2000).

For each subject, each category peak was localized on the reconstructed cortical surface, thanks to the Talairach transformation estimated by Freesurfer (the dispersion of those peaks across subjects in Study 1 is represented in Fig. 1*b*). By successive dilatations around those peaks, disks of ~4 and 10 mm radius were built on the cortical surface. Mean cortical thickness was estimated within these disks, in each subject's own native space.

Statistical analyses. Statistical analyses were conducted in SPSS (version 8, SPSS). Demographic differences between groups were tested through independent sample t tests. Analyses of covariance were first applied to behavioral measures, with diagnosis and gender as between-subject factors and parental education and age (except for the reading-matched comparison in Study 2) as covariates.

Table 1. Group composition in Studies 1 and 2

	Gender	Age, months	*t* test	Reading age, months	*t* test
Study 1					
19 control children (age-matched)	11 M 8 F	139 (16)	$p > 0.8$	147 (19)	$p < 0.001$
18 dyslexic children	10 M 8 F	141 (17)		90 (13)	
Study 2					
13 control children (age-matched)	7 M 6 F	117 (5)	$p > 0.3$	123 (15)	$p < 0.001$
13 dyslexic children	7 M 6 F	118 (6)		85 (6)	
13 control children (reading-matched)	7 M 6 F	80 (6)	$p < 0.001$	84 (5)	$p > 0.7$

Mean and SD (in brackets) are reported for age and reading age, as well as *p* values obtained from an independent samples *t* test comparing dyslexic children and controls.

Table 2. Behavioral scores for control and dyslexic children

	Study 1				Study 2						
	Age-matched				Age-matched				Reading-matched		
	Ctr	Dys	$F_{(1,30)}$	*p* value	Ctr	Dys	$F_{(1,20)}$	*p* value	Ctr	$F_{(1,21)}$	*p* value
Block design	12 (3)	11 (4)	0.03	>0.8	9 (2)	10 (2)	1.53	>0.2	12 (4)	0.48	>0.4
Similarities	14 (3)	12 (3)	1.05	>0.3	13 (3)	10 (4)	4.92	0.04	11 (3)	1.08	>0.3
Digit span	11 (3)	7 (2)	23.12	<0.001	9 (4)	7 (3)	2.24	0.15	11 (3)	8.96	0.007
Rapid picture naming (s/picture)	0.7 (0.2)	1 (0.2)	21.23	<0.001	0.8 (0.2)	1 (0.2)	10.37	0.004	1 (0.3)	0.04	>0.8
Phoneme deletion (correct items/24)	23 (1)	20 (3)	14.22	0.001	22 (2)	18 (4)	6.28	0.02	19 (6)	0.01	>0.9
Reading lag (months)	8 (16)	−42 (15)	131.7	<0.001	7 (14)	−34 (5)	97.38	<0.001	5 (5)	206.6	<0.001
Reading age (months)	147 (19)	90 (13)	190.8	<0.001	123 (15)	85 (6)	97.38	<0.001	84 (5)	0.17	>0.6

Mean and SD (in brackets) are reported, as well as *F* and *p* values obtained from an analysis of covariance.

Regarding cortical thickness, mixed analyses of covariance were run, with region of interest (left-hemisphere words, faces, houses; right-hemisphere faces, houses) as within-subject factor, diagnosis and gender as between-subject factors and parental education, age, and mean hemispheric thickness as covariates. Significant interactions were further investigated by separate between-subject analyses of covariance for each region, with the same factors and covariates. Effect sizes were calculated using Cohen's d formula.

To test the possibility that the location of peak coordinates or its variability might differ between groups, we ran multivariate analyses of variance and Box's M tests, entering the Talairach *x*, *y*, and *z* coordinates for each category peak as dependent variables and diagnosis and gender as between-subject factors.

Results

Demographic and behavioral results

Demographic characteristics are reported in Table 1. As for behavioral tests (Table 2), no differences were found in nonverbal abilities between dyslexic and control children, in any study. In most other tests, dyslexic participants performed significantly worse than their age-matched peers. When paired with children of the same reading level, only working memory (assessed by the age-standardized test of digit span) remained significantly lower in dyslexic children.

No consistent effect of gender across studies and no diagnosis by gender interaction was identified for any behavioral measure.

Peak response locations

Individual peak locations for each visual category did not differ between dyslexic and control children, as no effect of diagnosis on the combined *x*, *y*, *z* Talairach coordinates was found in either study. Moreover, the peaks were not more widely dispersed among dyslexic participants than among controls, as Box's M tests were not significant. Similarly, gender showed no effect on peak location and dispersion.

Group differences in cortical thickness

No difference in mean hemispheric thickness was observed between dyslexic children and their age-matched controls, in Studies 1 and 2, whereas reading-matched (and therefore younger) controls presented significantly greater left mean hemispheric thickness than dyslexic individuals ($t_{(24)} = 2.2$, $p = 0.04$). This result is consistent with previously documented age trends (Sowell et al., 2004). As mentioned earlier, mean hemispheric thickness was included as a covariate in all analyses.

In Study 1, a significant diagnosis*gender*region interaction was found ($F_{(4,112)} = 3$, $p = 0.02$). Analyses computed on the individual regions revealed a thicker cortex in controls relative to dyslexic children around the specific peak for words in the left hemisphere ($F_{(1,29)} = 4.45$, $p = 0.04$, $d = 0.5$) and a diagnosis by gender interaction around that same peak ($F_{(1,29)} = 6.59$, $p = 0.02$): girls, but not boys, presented significantly thicker cortices in the control than in the dyslexic group (girls $F_{(1,10)} = 30.65$, $p < 0.001$, $d = 2$, boys $F_{(1,15)} < 1$), as displayed in Figure 2*a*. Crucially, no main effect of diagnosis was observed around the specific peaks to faces and houses, in either hemisphere. A gender by diagnosis interaction was however significant around the left-hemisphere response peak to houses ($F_{(1,28)} = 8.66$, $p = 0.007$) driven by opposite marginal effects in girls and boys (girls, $F_{(1,10)} = 3.78$, $p = 0.08$, $d = 1$; boys, $F_{(1,14)} = 2.40$, $p = 0.14$, $d = 1.2$).

In Study 2, a significant diagnosis*gender*region interaction ($F_{(4,76)} = 3.7$, $p = 0.008$) for the age-matched comparison was also observed. Controls showed thicker cortices than dyslexic children around the specific peak for words ($F_{(1,19)} = 9.68$, $p = 0.006$ $d = 1$) and the diagnosis by gender interaction ($F_{(1,19)} = 6.65$, $p = 0.018$) was again explained by a difference in cortical thickness between control and dyslexic girls ($F_{(1,7)} = 14.47$, $p = 0.007$, $d = 2$), but not boys ($F_{(1,9)} < 1$), as shown in Figure 2*b*. However, the diagnosis by gender interaction around the peak of response to (houses > others), reported in Study 1, did not reach significance ($F_{(1,19)} = 3.51$, $p = 0.08$). No other main effect of diagnosis or interaction was observed in either hemisphere.

Finally, we compared reading-matched controls to dyslexic children in the region found to be different between age-matched subjects in both Studies 1 and 2, i.e., the response peak to

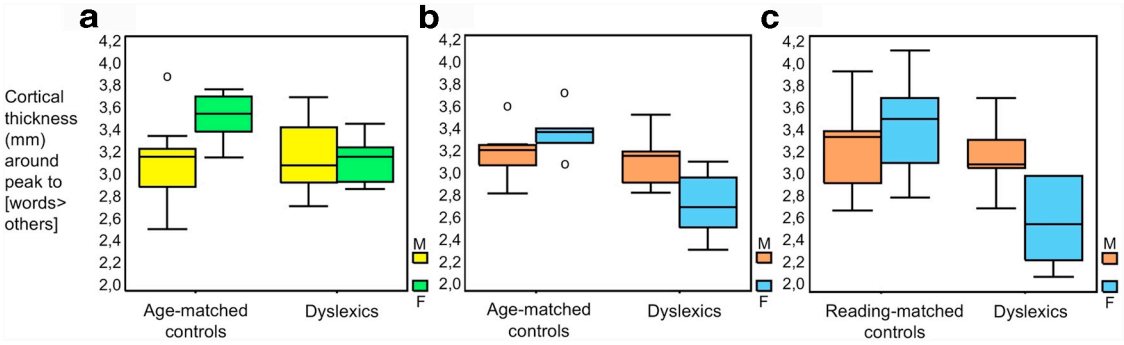

Figure 2. Boxplots for left hemisphere cortical thickness around the response peak to the contrast (words > others). ***a***, Study 1, 11-year-old age-matched groups. ***b***, Study 2, 9-year-old age-matched groups. ***c***, Study 2, reading-matched groups. Plots ***a*** and ***b*** are based on disks of 10 mm radius, whereas ***c*** is based on a 4 mm radius.

(words > others). The effect of diagnosis did not reach significance ($F_{(1,20)} = 1.71$, $p = 0.2$), nor did the diagnosis by gender interaction ($F_{(1,20)} = 2.27$, $p = 0.15$). However, when estimating cortical thickness within a disc of smaller radius (~4 mm), both the effect of diagnosis ($F_{(1,20)} = 5.45$, $p = 0.03$, $d = 0.5$) and the diagnosis by gender interaction became significant ($F_{(1,20)} = 6.49$, $p = 0.02$). Control girls, but not boys, showed significantly thicker cortices than dyslexic girls in this specific region (girls, $F_{(1,8)} = 7.82$, $p = 0.02$, $d = 1.4$; boys, $F_{(1,10)} < 1$), as can be seen in Figure 2*c*. For consistency, we retested the comparison between the age-matched groups using a 4 mm radius disc, and we found that in Study 1 the main effect of diagnosis ($F_{(1,29)} = 2.26$, $p = 0.1$, $d = 0.4$) and the diagnosis by gender interaction ($F_{(1,29)} = 3.4$, $p = 0.08$) were marginally significant, whereas they were significant in Study 2 (respectively, $F_{(1,19)} = 9.8$, $p = 0.006$, $d = 1$; $F_{(1,19)} = 6.15$, $p = 0.02$).

Discussion

In the present experiments, we analyzed the cortical thickness of left and right ventral occipitotemporal regions. We refined traditional analyses by applying a subject-by-subject functionally based approach and measured the structural properties of individually defined functional territories. We found a cortical thickness reduction in dyslexic children, specifically located around the response peak to words in the left hemisphere; furthermore, the global group difference was carried exclusively by girls. These results were replicated in two independent datasets of dyslexic and control children, whereas no consistent difference was observed around the functional peaks of other visual categories (houses and faces).

A reduction of gray matter tissue across occipitotemporal regions in dyslexia has been inconsistently reported. Although increased gray matter volume was observed in the left fusiform gyrus of dyslexic subjects by Silani et al. (2005), the opposite effect was subsequently described bilaterally (Kronbichler et al., 2008; Brambati et al., 2004). Recent meta-analyses of voxel-based morphometry (VBM) studies have not managed to resolve these inconsistencies (Linkersdörfer et al., 2012; Richlan et al., 2013). However, methodological approaches like VBM, which are relatively insensitive to individual anatomical characteristics, might miss the type of subtle differences reported in the present study. This might be particularly relevant for ventral occipitotemporal regions, given their complexity in terms of anatomical landmarks (Frost and Goebel, 2012) and cytoarchitecture (Caspers et al., 2013). Moreover, Frost and Goebel (2012) reported that functional regions in the fusiform gyrus can be quite variable across subjects in relation to anatomical landmarks, even after accurate alignment. As can be seen in Figure 1*b*, the dispersion of our functional peaks was indeed not negligible. The method used in the present study is thus likely to be more effective than previous investigations in detecting subtle differences between populations.

Cortical thickness decreases with maturation across most of the brain, probably due to an increase of the myelin sheet in lower cortical layers (Sowell et al., 2004). Variations in thickness can also be associated with the density of elements in perineuronal space, among which glial cells and mainly dendrites, whose arborization follows synaptogenesis and pruning cycles (Jiang et al., 2009). Either of these aspects could underlie the observed results in dyslexic participants.

Interestingly, postmortem studies have revealed ectopias, dysplasias, and heterotopias in the brains of dyslexic patients, and susceptibility genes for the disorder appear to be involved in neuronal migration (Poelmans et al., 2011). These lines of evidence have led to the hypothesis of a neuronal migration disruption in dyslexia (Galaburda et al., 1985). In this perspective, the reported cortical thickness differences between dyslexic and control children could be related to a thinner cortical plate in the former; this could either be due to insufficient numbers of cells in place in the cortex, or to a reduction in synaptic connections, because of cells ending up in abnormal positions.

The area surrounding the visual word form area, which develops a specific functional response to words in literates (Dehaene et al., 2010) and whose activity is found reduced in dyslexics (Shaywitz et al., 2002; Monzalvo et al., 2012), is a good candidate for functional and structural plasticity consecutive to reading acquisition. Nevertheless, the fact that Raschle et al. (2011) found gray matter volume reductions in at-risk prereaders in the left hemisphere, in proximity to our own reference peak for words, is an argument against gray matter differences depending exclusively on differential reading experience. Furthermore, hypoactivations in this region have also been observed, even in reading-matched comparisons (Hoeft et al., 2007). In the present study, we replicated cortical thickness differences between control and dyslexic participants when equalizing reading skills (Fig. 2*c*), although within a smaller patch of cortex (4 vs 10 mm radius) compared with age-matched comparisons. The absence of a clear group difference within a 10 mm sphere weakens the reading age group comparison, and would make it desirable to replicate this result. Nevertheless, the reduction of the area of interest in this second comparison, involving younger controls, is consistent with the idea of an expansion of visual category-specific regions in the course of development and/or expertise acquisition (Gola-

rai et al., 2007; Dehaene et al., 2010), with less expert readers showing a smaller region specialized for visual words and thus a smaller region of increased thickness due to reading expertise. Therefore, although requiring cautious interpretation, our reading-matched comparison suggests that there might be a primary structural defect in dyslexic children precisely in the left occipitotemporal subregion that eventually becomes the visual word form area.

Although a group difference around the response peak to words was expected, the diagnosis by gender interaction was more surprising. A few studies are however consistent with the idea that the biological basis of dyslexia might to some extent differ between boys and girls. Humphreys et al. (1990) described the presence of myelinated glial scars, rather than ectopias, in the brains of three women with dyslexia. Very few structural MRI studies have included balanced numbers of male and female dyslexic participants, partly because of the known sex ratio in dyslexia (Flannery et al., 2000) making it more difficult to recruit affected females. Thus, very little is known about possible patterns of structural variation between genders. Among the few exceptions, Sandu et al. (2008) showed that dyslexic girls differed from control girls in global hemispheric measures, whereas no such difference was observed in boys. The findings of both Sandu et al. (2008) and the present study could be interpreted as the presence of a more severe cerebral phenotype in dyslexic girls compared with boys. This could result either from an entirely distinct etiology in girls and in boys, or from the impact of sex-related variations on a shared primary cause. Studies assessing heritability estimates of reading difficulties in males and females have been inconclusive, finding either higher heritability in males (Harlaar et al., 2005) or no difference between sexes (Hawke et al., 2006), thus providing little evidence for a distinct genetic etiology. Some steroid hormones (McCarthy, 2009), as well as other potential nonhormonal factors (Zhang et al., 2003), might give females greater resilience to brain insult across life (Rosen et al., 1999; Ramus, 2006). Trajectories of brain development appear to peak earlier in females than in males (Lenroot et al., 2007), and brains at different developmental stages are not equally vulnerable. All these factors could conceivably contribute to a greater functional resilience of females to structural brain disruptions, thus requiring a more severe neural phenotype to produce similar cognitive impairments.

Future research should aim to clarify the interaction between predispositions to dyslexia and gender on the associated brain phenotypes. At the very least it now seems crucial for any brain imaging study of dyslexia to take gender differences into account.

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