A structural–functional basis for dyslexia in the cortex of Chinese readers

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Developmental dyslexia is a neurobiologically based disorder that affects ≈5–17% of school children and is characterized by a severe impairment in reading skill acquisition. For readers of alphabetic (e.g., English) languages, recent neuroimaging studies have demonstrated that dyslexia is associated with weak reading-related activity in left temporoparietal and occipitotemporal regions, and this activity difference may reflect reductions in gray matter volume in these areas. Here, we find different structural and functional abnormalities in dyslexic readers of Chinese, a nonalphabetic language. Compared with normally developing controls, children with impaired reading in logographic Chinese exhibited reduced gray matter volume in a left middle frontal gyrus region previously shown to be important for Chinese reading and writing. Using functional MRI to study language-related activation of cortical regions in dyslexics, we found reduced activation in this same left middle frontal gyrus region in Chinese dyslexics versus controls, and there was a significant correlation between gray matter volume and activation in the language task in this same area. By contrast, Chinese dyslexics did not show functional or structural (i.e., volumetric gray matter) differences from normal subjects in the more posterior brain systems that have been shown to be abnormal in alphabetic-language dyslexics. The results suggest that the structural and functional basis for dyslexia varies between alphabetic and nonalphabetic languages.

brain function | Chinese language | culture | reading disorder | neuroimaging

Developmental dyslexia is characterized by unexpectedly low reading ability in people who have adequate intelligence, typical schooling, and sufficient sociocultural opportunities (1–10). Early investigations of postmortem dyslexic brains revealed structural abnormalities in both cortical and subcortical areas (11, 12). Recent neuroimaging studies examining structure–function relationships with alphabetic languages have further identified several brain regions with atypical function and anomalous structure in dyslexia, including left temporoparietal areas, which are thought to be involved in letter-to-sound conversions in reading (1–8, 13–18), the left middle-superior temporal cortex, which is thought to be involved in speech sound analysis (17–22), and the left inferior temporo-occipital gyrus, which may function as a quick word form recognition system (18, 20, 22–27). Together, these findings support a prominent neurophysiological model of reading skill acquisition and its disorders according to which dyslexia is associated with atypical structural and functional development of posterior brain systems (1–10).

The neural circuits involved in reading and reading disorders may vary across languages, because of differences in how a writing system links print to spoken language (4–7, 28–30). For example, in logographic Chinese, graphic forms (characters) are mapped to syllables, which differs markedly from an alphabetic system (e.g., English) in which graphic units (letters) are mapped to phonemes. These differences can lead to differences in how reading is supported in the brain. Readers of Chinese show relatively more engagement of visuospatial areas and left middle frontal regions for verbal working memory, presumably for recognizing complex, square-shaped characters whose pronunciations must be memorized by rote instead of being learned by using letter-to-sound conversion rules (31–35). In an fMRI study, we previously showed that, unlike impaired reading in English and other Western languages, impaired reading in logographic Chinese is associated with functional disruption of processes localized to the left middle frontal gyrus (28). Although Chinese dyslexia is manifested by a phonological deficit (i.e., graphic form to sound conversion), which is similar to dyslexia in alphabetic languages (29), cortical regions mediating this deficit in Chinese and alphabetic languages are spatially separated. Therefore, the neural mechanisms underlying impaired reading may depend on the writing system used.

With fMRI alone, however, it is difficult to know whether activation differences found in a behavioral task are a cause or effect of a brain disorder, such as dyslexia. We hypothesized that there may be a different structural basis for reading impairment in Chinese dyslexics that differs from that found in Western language readers.

To determine brain structure differences indexed by gray matter volume between Chinese dyslexic and control groups, we used an established whole-brain assessment technique, voxel-based morphometry (VBM) (1) to analyze the high-resolution 3D anatomical images acquired with MRIs from 16 Chinese dyslexic subjects and 16 age-matched normal controls (average age 11; Table 1). In addition, a functional MRI (fMRI) experiment was conducted, in which a subset of 12 of the 16 dyslexics and 12 of the 16 control subjects (average age 11) who were available for the additional fMRI scan were asked to decide whether two characters viewed simultaneously rhymed with each other. The rhyme judgment task involves phonological processing, allowing us to make a close comparison between the present findings with those from recent neuroimaging experiments using the similar task to study dyslexia in English readers (1, 14, 23).

Results

Atypical Brain Structure in Chinese Dyslexia. The VBM analysis showed that, while there was no significant difference in total gray matter volume between the two groups [$t(30) = 1.52$, $P = 0.14$], regional gray matter volume in the left middle frontal gyrus was significantly smaller in dyslexic readers than in normal subjects [Brodmann area (BA) 9; $x = -32$, $y = 31$, $z = 28$; Z-score = 5.61; $P < 0.05$ corrected for multiple comparisons using the family-wise error (FWE) , correction for the whole brain] (Fig. 1 *a*, *b*, and *d*). No other brain regions survived this statistical level, although at a less stringent uncorrected statistical threshold of $P < 0.001$ reduced gray matter volume was seen

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Table 1. Demographic characteristics of the two groups

Characteristic	Normal readers, mean (SD)	Dyslexic readers, mean (SD)	*t* tests, *P*
Age, months	132.4 (7.1)	131.63 (5.86)	0.35; 0.73
Gender	3 female, 13 male	8 female, 8 male	
Handedness	16 right-handed	16 right-handed	
Reading (maximum = 120)	90.8 (3.3)	42.8 (3.0)	42.77; < 0.001
Raven, in percentile	89 (9)	83 (9)	1.91; 0.07
Rhyme judgment RT, ms	1,054 (129)	1,400 (308)	3.56; <0.005
Rhyme judgment accuracy, %	92.6 (4.0)	89.8 (8.0)	1.03; 0.315
Font-size decision RT, ms	666 (80)	918 (94)	7.05; <0.001
Font-size decision accuracy, %	97.2 (2.6)	92.8 (3.2)	3.46; <0.005

RT, reaction time.

in the dyslexics' left middle frontal gyrus (BA 9; $x = -32$, $y = 31$, $z = 28$; Z-score = 5.61), left anterior temporal gyrus (BA 38/21; $x = -55$, $y = 4$, $z = -16$; Z-score = 3.61), and left Sylvian fissure ($x = -33$, $y = 18$, $z = 10$; Z-score = 3.28) (Fig. 1*c*).

To better characterize the relationship between individual variability in brain structure and reading performance, we performed correlation analyses on the entire sample of subjects and for each group. A region of interest (ROI) was defined in the left middle frontal region where dyslexic children showed decreased gray matter volume thresholded at $P < 0.05$ FWE-corrected (we label this the VBM ROI). We found that mean gray-matter volume in this left middle frontal ROI was strongly correlated with individual scores on reading achievement for the entire group of 32 participants ($r = 0.85$, $P < 0.0005$). In addition, a significant correlation between reading scores and gray matter volume within the VBM ROI was observed in the control group ($r = 0.697$, $P < 0.001$, one-tailed), and there was a trend toward a significant correlation in the dyslexic group ($r = 0.326$, $P = 0.109$, one-tailed), suggesting that the structure–behavior relationship appears to encompass both normal and dyslexic readers rather than resulting only from the difference between the two groups.

Because the left posterior temporoparietal region, the left middle temporal gyrus, and the left inferior occipito-temporal cortex have been repeatedly demonstrated to have an altered gray matter volume in dyslexia in readers of alphabetic languages (1, 18, 20, 21, 25, 26), we conducted further ROI-based analyses to examine whether there are regional differences in gray matter volume between normal and dyslexic Chinese readers. Based on the findings of the current study and those of previous investigations, we defined three spherical ROIs (10-mm radius), centered according to Talairach coordinates at $x = -58$, $y = -47$, $z = 45$ for the left posterior temporoparietal region (1), $x = -56$, $y = -51$, $z = 2$ for the middle temporal gyrus (26), and $x = -30$, $y = -56$, $z = -2$ for the inferior occipito-temporal cortex (25). We found no statistically significant between-group differences in gray matter volume in any of these regions (Fig. 1 *e–g*). Correlations between individual reading scores and mean gray matter volume in each of these ROIs were, respectively, 0.055 ($P = 0.766$), 0.277 ($P = 0.125$), and 0.126 ($P = 0.491$), none of which approached statistical significance.

Behavioral Results of the fMRI Experiment. Subjects' behavioral performance indicated that normal readers performed significantly better than dyslexic readers both in rhyme decisions and font-size judgments (Table 1), reflecting a phonological deficit and a visuospatial deficit (indexed by font-size judgments). However, there was no significant interaction between reading group (normal vs. dyslexic) and task (rhyme vs. font), $F(1,22) = 0.816$ and $P = 0.316$ for reaction times, and $F(1,22) = 0.266$ and $P = 0.611$ for response accuracy, suggesting that the neuroimaging results from comparisons of rhyme and control conditions

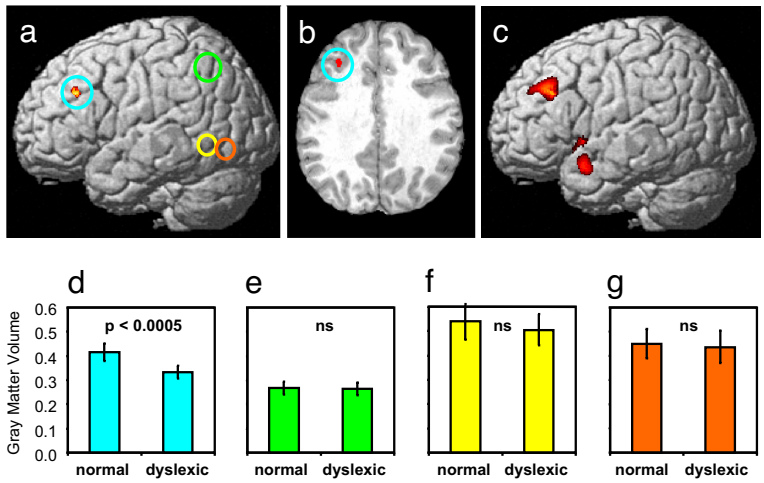

Fig. 1. Group differences in gray matter volume. (*a*, *b*, and *d*) A region in the left middle frontal gyrus (BA 9; $x = -32$, $y = 31$, $z = 28$) exhibited reduced volume in the dyslexic group, $P < 0.05$ corrected using the FWE correction for the whole brain. (*c*) At a less stringent uncorrected threshold of $P < 0.001$, reduced gray matter volume was seen in the left anterior temporal gyrus (BA 38/21) and the left Sylvian fissure, in addition to the left middle frontal gyrus. (*e–g*) ROI analysis of gray matter volume difference in the left posterior temporoparietal region (in green), the left middle temporal gyrus (in yellow), and the left inferior occipito-temporal cortex (in orange). No significant alteration was observed in these regions.

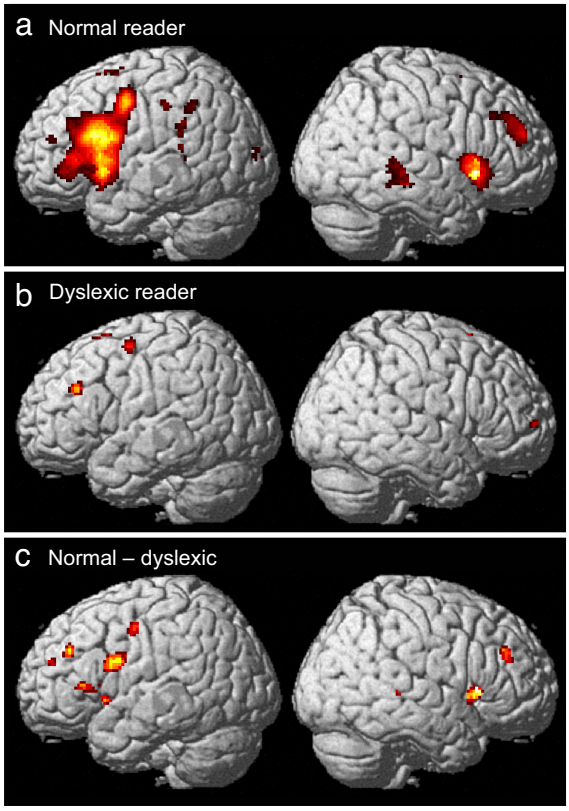

Fig. 2. Brain regions with significant activation during rhyme judgment. (*a* and *b*) Cortical activation associated with rhyme judgment contrasted with font-size decision in normal and dyslexic Chinese readers. (*c*) Brain regions showing group differences during rhyme judgment.

in the two groups were not caused by performance differences or task difficulty.

Brain Structure–Function Correlation. In examining the relationship between regional gray matter volume and reading task-related activity in dyslexic and normal readers, we first computed a functional map associated with rhyme decision. Contrasted with a comparison task involving font size decision, rhyme judgment activated several regions, including bilateral middle-inferior frontal gyrus and left precentral cortex for normal subjects. Dyslexic readers exhibited activations in left middle-superior frontal and precentral regions, bilateral visual cortex, and the putamen (see Fig. 2 and Table 2). Direct comparisons of blood oxygen-level-dependent (BOLD) contrast activity between the two groups revealed stronger activations for normal controls than dyslexic readers in bilateral middle frontal gyrus, inferior prefrontal cortex, precentral cortex, left insula, cingulate, putamen, and cerebellum.

Normal readers also showed significant activity in left inferior parietal lobule in the rhyming task versus the control task, whereas dyslexics did not (Fig. 2). However, the between-group comparison did not reveal these differences to be statistically reliable (β values were -0.12 for font-size decisions and 0.09 for rhyme decisions for normal readers and -0.14 for font-size decisions and -0.11 for rhyme decisions for dyslexics). The failure to detect a significant difference in rhyming task-related activity in these more posterior brain systems between the dyslexia and control groups is consistent with the results of previous Chinese dyslexia studies (28) but differs from findings in English dyslexics (1, 2, 6, 13–18).

Next, we performed correlation analyses between rhyme task-related activity and gray matter volume within the left middle frontal region in the 24 children who participated in both the structural and the functional studies (Fig. 3). We selected a functional ROI in the left middle frontal region centered on the region in which dyslexic subjects exhibited significantly less activation than normal readers during rhyme judgment. There was a significant correlation between brain activity level of this

Table 2. Coordinates of activation peaks

Regions activated	BA	Coordinates X	Y	Z	Z score
Normal readers					
Frontal					
L middle frontal gyrus	9/46	−48	32	24	3.84
	46	−32	45	16	3.24
L inferior frontal gyrus	44/45	−38	17	21	5.24
L precentral gyrus	6	−46	0	41	4.88
L insula		−32	−38	18	5.04
L cingulate gyrus	32	−4	21	41	4.87
R superior frontal gyrus	9	30	44	27	3.45
R middle frontal gyrus	10	34	50	21	3.63
	9	36	31	32	3.23
R inferior frontal gyrus	45	46	14	1	4.61
R cingulate gyrus	32	12	21	36	4.89
Temporal					
R middle temporal gyrus	21	46	−37	4	4.49
Parietal					
L inferior parietal lobule	40	−53	−29	40	3.51
	40	−50	−45	41	3.35
Occipital					
L cuneus	17	−16	−89	10	3.93
L lingual gyrus	18	−20	−72	4	3.86
Subcortical areas					
Caudate nucleus		−18	−1	15	4.97
Putamen		−22	−4	0	3.88
Thalamus		−16	−7	11	4.80
Cerebellum					
L cerebellum		−8	−40	−23	4.89
R cerebellum		8	−69	−12	4.79
Dyslexic readers					
Frontal					
L superior frontal gyrus	6	−2	17	58	4.49
L middle frontal gyrus	9/46	−46	32	24	3.73
	9/46	−36	30	26	3.61
L precentral gyrus	6	−44	−1	55	3.83
Occipital					
L cuneus	17	−6	−75	9	3.39
L lingual gyrus	18	−10	−74	0	3.46
R cuneus	17	14	−83	2	3.94
Subcortical areas					
Putamen		−22	−2	−5	3.43
Normal controls > dyslexic readers					
Frontal					
L middle frontal gyrus	9/46	−46	36	28	3.61
	10	−34	48	20	2.80
L inferior frontal gyrus	44	−55	5	22	3.91
L precentral gyrus	6	−48	−6	43	2.98
L Insula		−32	12	−1	3.49
L cingulate gyrus	32	−2	15	36	3.00
R middle frontal gyrus	9/46	30	38	24	3.01
R inferior frontal gyrus	45	46	14	3	3.97
R cingulate gyrus	32	14	15	36	3.64
Occipital					
L cuneus	17	−18	−74	6	3.13
Subcortical areas					
Putamen		−20	2	7	3.65
Thalamus		−12	−7	8	3.45
Cerebellum					
L cerebellum		−8	−59	−21	3.07
R cerebellum		10	−55	−19	4.18

L, left; R, right.

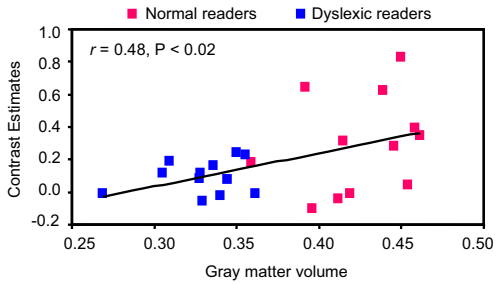

Fig. 3. Correlation between gray matter volume and BOLD signal at the left middle frontal gyrus.

ROI and reading performances for the 24 subjects ($r = 0.43, P < 0.037$). Importantly, we followed an established procedure (1) and extracted mean contrast estimates (linear combination of β estimates) from this functional ROI for each individual's rhyme > font size contrast images, and mean gray matter volume from the VBM ROI in the left middle frontal region. Remarkably, a significant correlation was obtained between these two measures ($r = 0.48, P < 0.02$) for the 24 subjects, that is, children with less gray matter in the left middle frontal region tended to show a smaller functional activation difference across the rhyming and control tasks. The significant correlation between brain activation level within the ROI and reading scores or between brain activation level and gray matter volume mainly reflected group difference because there was no significant correlation for each group on its own ($P > 0.105$). The nonreliable correlations within groups may be caused by limited power.

Discussion

Our present study has demonstrated atypical development of gray matter in the left middle frontal gyrus in dyslexic Chinese readers in comparison with normal controls. This finding presents a sharp contrast to the atypical patterns of regional gray matter in posterior brain systems previously observed in dyslexic readers of alphabetic languages (1, 18, 20, 21, 25, 26). A direct correlation of the gray matter volume and the reading task-related activity level in the left middle frontal region suggests that this structural variation contributes to regional brain dysfunctions associated with dyslexia.

Activation differences between Chinese dyslexics and normal subjects were seen in several brain areas (Fig. 2); nonetheless, only the left middle frontal gyrus showed both functional and morphological anomalies. Regions exhibiting functional, but not anatomical, irregularities may be recruited to support compensatory reading strategies that might be expected to differ between dyslexic and normally developing readers (1). Because there are different gender proportions in the two groups in this study, future research will be needed to investigate whether there are sex differences in the structural–functional basis for reading in normal and dyslexic groups.

The left middle frontal gyrus may play a particularly important role in Chinese reading and reading acquisition because of the arbitrary association between Chinese character forms and their pronunciation. This association must be learned by rote memorization of Chinese characters, demanding an intensive coordination of various kinds of linguistic information contained in written Chinese (28, 30–35). The left middle frontal gyrus is thought to be involved in the allocation and coordination of cognitive resources in working memory (36, 37) and may therefore be recruited to serve this function (34, 35, 38). Strategies that school children adopt in learning to read may also help tune the underlying neural circuits (39, 40). In primary school, Chinese children spend a great amount of time repeatedly copying newly learned characters, which may lead to a close association between reading performance and children's handwriting skills, which are mediated by the left middle frontal region just anterior to the primary motor cortex governing motor functions.

This study has provided insights into our knowledge of associations between structural and functional abnormalities in dyslexic individuals that may yield neurobiological clues to the cause of developmental dyslexia. The fact that Chinese and Western dyslexics show structural abnormalities in different brain regions suggests that dyslexia may even be two different brain disorders in the two cultures.

Methods

Subjects. Thirty-two children participated in a structural MRI experiment, 16 dyslexics (8 boys and 8 girls; mean age = 11 years, 0 months, range 10 years, 2 months to 11 years, 6 months), and 16 typically developing age-matched controls (13 boys and 3 girls; mean age = 11 years, 0 month, range from 9 years, 11 months to 12 years, 4 months). The participants were fourth- or fifth-graders from two Beijing primary schools and were physically healthy and had no history of neurological disease, head injury, or psychiatric disorder. Because there is no standardized reading ability test in Chinese, the classification of children's reading performance was based primarily on their school performance in the Chinese language course and their teacher's evaluation. Children defined as dyslexic had reading scores in the school below the fifth percentile among all children in the same grade assessed by their language examinations ($n > 800$). Children defined as normal readers had reading scores above the 60th percentile. To more quantitatively measure reading ability, a commonly used type of reading test (41) comprising 120 Chinese characters was administered to 800 children in grades 4 and 5 of the two schools. The mean reading scores were 43 (SD = 3) for dyslexics and 91 (SD = 3) for the normal subjects ($t = 42.77, P < 0.001$). All subjects had normal nonverbal Raven IQ above the 75th percentile (average 89th and 83rd percentile for normal readers and dyslexics), and none of them met diagnostic criteria for attention-deficit hyperactivity disorder.

All subjects were native speakers of Putonghua, the official dialect of Mainland China and the language of instruction in school. They were strongly right-handed as judged by the handedness inventory (42). Informed consent was obtained from each subject and their parents before testing.

Twenty-four children from the above two groups, 12 dyslexics (5 boys and 7 girls, mean age = 10 years, 11 months) and 12 typically developing controls (10 boys and 2 girls, mean age = 11 years, 0 month), were available for participating in a fMRI experiment using rhyme judgment as an experimental task and font-size decision as a baseline in a blocked design.

Design and Materials. The fMRI experiment used a phonological processing task, i.e., character rhyme judgment. A blocked design was used, where three blocks of rhyme judgments were alternated with three blocks of font size judgments, which served as the baseline. Each block consisted of a 2-s instruction and 12 trials. In each trial, a pair of characters was synchronously exposed for 2,000 ms, one above and one below a fixation cross-hair, followed by a 1,000-ms blank interval. All Chinese characters used in the experiment were commonly encountered and selected from Chinese language textbooks of primary school grades 1–3. The visual complexity of the characters was matched across all conditions. Subjects indicated a positive response by pressing the key corresponding to the index finger of their right (dominant) hand and a negative response by pressing the key corresponding to the index finger of their left (nondominant) hand. They were asked to perform the tasks as quickly and accurately as possible.

MRI Acquisition. MRI scans were performed on a 2-T GE/Elscint Prestige MRI scanner at Beijing 306 Hospital. Visual stimuli were presented to the subjects through a projector onto a translucent screen. Subjects viewed the stimuli through a mirror attached to the head coil. A T_2*-weighted gradient-echo echo planar imaging (EPI) sequence was used for fMRI scans, with the slice thickness = 6 mm, in-plane resolution = 2.9 mm x 2.9 mm, and repetition time (TR)/echo delay time (TE)/flip angle = 2000 ms/ 45 ms/ 90°. Eighteen contiguous axial slices were acquired parallel to the AC-PC line covering the whole brain. High-resolution anatomical images were acquired by using a T_1-weighted, 3D gradient-echo sequence, with the slice thickness = 2 mm, in-plane resolution = 1 mm × 1 mm, TR/TE/flip angle = 25 ms/ 6 ms/ 28°.

fMRI Data Analysis. The data were preprocessed and analyzed with SPM2 (Wellcome Department of Cognitive Neurology, University College London,

London) using Matlab 6.5.1 (Mathworks). The first four volumes of each subject's data set were discarded to allow for T1 equilibration, and the remaining 187 volumes were realigned to the first volume. They were then normalized to the EPI template in SPM2, based on the Montreal Neurological Institute (MNI) stereotactic space, and then resampled into $2 \times 2 \times 2$-mm cubic voxels. The images were spatially smoothed with an isotropic Gaussian kernel [10-mm full width at half-maximum (FWHM)]. Individual activation maps were generated by using the general linear model in which time series were convolved with the canonical hemodynamic response function. The data were globally scaled and high-pass-filtered at 128 s. The contrast images between task and baseline conditions from each subject were taken into a second-level random-effects model for group analysis. For each group, whole-brain activation was computed for rhyme > font size by using a one-sample *t* test ($P = 0.001$ uncorrected; extent threshold = 10). To evaluate significant difference in brain activation between normal and dyslexic children, a two-sample *t* test was performed ($P = 0.005$ uncorrected; extent threshold = 10).

VBM Analysis. Optimized VBM analysis (43) was performed by using the VBM toolbox by Christian Gaser (http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2). A customized template and prior images of gray and white matter and cerebrospinal fluid (CSF) were first created from T1-weighted images of all subjects, which were normalized to the SPM T1 template with a 12-parameter affine linear transformation and nonlinear normalization with $7 \times 8 \times 7$ basis function, and were smoothed with FWHM of 8 mm for use with the subsequent segmentation procedures. The raw structural images were then segmented into gray matter, white matter, and CSF partitions. Gray matter partitions were spatially normalized linearly and nonlinearly by using customized gray matter template previously generated. Images were modulated by multiplying the voxel values by the Jacobian deformation parameters defined during normalization to preserve the total amount of original gray matter before normalization (44). The modulated images were smoothed with a 12-mm FWHM isotropic Gaussian kernel. We also created another set of normalized images by using the SPM adult T1 templates with the same segmentation, modulation, and smoothing procedures. We performed analyses with both a customized template and the SPM template and obtained similar results. To serve the purposes of direct comparisons between the fMRI and VBM data, we report the results from images that were normalized by using the SPM template.

For the statistical analysis, regional differences in gray matter volume between groups were tested with a one-way analysis of covariance using total gray matter volume as a covariate of no interest. Height threshold was set at $P = 0.05$ corrected for multiple comparisons by using the FWE correction for the whole brain and an extent threshold of 50 contiguous voxels. Brain regions were estimated from Talairach and Tournoux (45), after adjustments for differences between MNI and Talairach coordinates.

To examine the relationship between individual variability in brain structure and reading performance, mean gray matter volume measure in the left middle frontal region that exhibited decreased gray matter volume in dyslexics at $P < 0.05$ FWE-corrected (labeled as the VBM ROI) was extracted and subject to correlation with individual's reading score. To measure differences in gray matter volume between the two groups in regions that have been reported to have decreased gray matter volume in dyslexics in alphabetic languages, three sphere ROIs (10-mm radius) were defined, one centered at $x = -58$, $y = -47$, $z = 45$ within the left posterior temporoparietal region (1), one at $x = -56$, $y = -51$, $z = 2$ within the left middle temporal region (26), and the other at $x = -30$, $y = -56$, $z = -2$ within the left inferior occipito-temporal cortex region (25). Two-sample *t* tests were conducted to determine group differences in gray matter volume in these regions.

In determining the relationship between brain activation and regional gray matter volume, we performed a correlation analysis between BOLD-contrast activity and gray matter volume in the left middle frontal cortex in the 24 children who participated in both the structural and functional study. A functional ROI in the left middle frontal region was defined in which dyslexic readers exhibited significantly less activation than normal readers during rhyme judgment at $P < 0.005$ uncorrected. Following an established procedure (1), mean contrast estimates (linear combination of β estimates) from this functional ROI were extracted for each individual's rhyme > font size contrast images (at $P < 0.005$ uncorrected) and subject to correlation analysis with gray matter volume measures extracted from the VBM ROI in the left middle frontal cortex.

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1. Hoeft F, *et al.* (2007) Functional and morphometric brain dissociation between dyslexia and reading ability. *Proc Natl Acad Sci USA* 104:4234–4239.
2. Horwitz B, Rumsey JM, Donohue BC (1998) Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proc Natl Acad Sci USA* 95:8939–8944.
3. Eden G, Moats L (2002) The role of neuroscience in the remediation of students with dyslexia. *Nat Neurosci* 5:1080–1084.
4. Goswami U (2006) Neuroscience and education: From research to practice? *Nat Rev Neurosci* 7:406–413.
5. Schlaggar BL, McCandliss BD (2007) Development of neural systems for reading. *Annu Rev Neurosci* 30:475–503.
6. Eden GF, *et al.* (2004) Neural changes following remediation in adult developmental dyslexia. *Neuron* 44:411–422.
7. Price CJ, Mechelli A (2005) Reading and reading disturbance. *Curr Opin Neurobiol* 15:231–238.
8. Johansson BB (2006) Cultural and linguistic influence on brain organization for language and possible consequences for dyslexia: A review. *Ann Dyslexia* 56:13–50.
9. Shaywitz SE, Escobar MD, Shaywitz BA, Fletcher JM, Makuch R (1992) Evidence that dyslexia may represent the lower tail of a normal distribution of reading ability. *N Engl J Med* 326:145–150.
10. Tallal P (2000) The science of literacy: From the laboratory to the classroom. *Proc Natl Acad Sci USA* 97:2402–2404.
11. Galaburda AM, Kemper TL (1979) Cytoarchitectonic abnormalities in developmental dyslexia: A case study. *Ann Neurol* 6:94–100.
12. Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N (1985) Developmental dyslexia: Four consecutive patients with cortical anomalies. *Ann Neurol* 18:222–233.
13. Flowers DL, Wood FB, Naylor CE (1991) Regional cerebral blood-flow correlates of language processes in reading disability. *Arch Neurol* 48:637–643.
14. Hoeft F, *et al.* (2006) Neural basis of dyslexia: A comparison between dyslexic and nondyslexic children equated for reading ability. *J Neurosci* 26:10700–10708.
15. Temple E, *et al.* (2003) Neural deficits in children with dyslexia ameliorated by behavioral remediation: Evidence from functional MRI. *Proc Natl Acad Sci USA* 100:2860–2865.
16. Klingberg T, *et al.* (2000) Microstructure of temporo-parietal white matter as a basis for reading ability: Evidence from diffusion tensor magnetic resonance imaging. *Neuron* 25:493–500.
17. Aylward EH, *et al.* (2003) Instructional treatment associated with changes in brain activation in children with dyslexia. *Neurology* 61:212–219.
18. Brown WE, *et al.* (2001) Preliminary evidence of widespread morphological variations of the brain in dyslexia. *Neurology* 56:781–783.
19. Paulesu E, *et al.* (2001) Dyslexia: Cultural diversity and biological unity. *Science* 291:2165–2167.
20. Brambati SM, *et al.* (2004) Regional reductions of gray matter volume in familial dyslexia. *Neurology* 63:742–745.
21. Eckert M (2004) Neuroanatomical markers for dyslexia: A review of dyslexia structural imaging studies. *Neuroscientist* 10:362–371.
22. Horwitz B, Braun AR (2004) Brain network interactions in auditory, visual, and linguistic processing. *Brain Lang* 89:377–384.
23. Shaywitz BA, *et al.* (2002) Disruption of posterior brain systems for reading in children with developmental dyslexia *Biol Psychiatry* 52:101–110.
24. Pugh KR, Sandak R, Frost SJ, Moore D, Mencl WE (2005) Examining reading development and reading disability in English language learners: Potential contributions from functional neuroimaging. *Learn Disabilities Res Practice* 20:24–30.
25. Kronbichler M, *et al.* (2008) Developmental dyslexia: Gray matter abnormalities in the occipitotemporal cortex. *Hum Brain Mapp*, in press.
26. Silani G, *et al.* (2005) Brain abnormalities underlying altered activation in dyslexia: A voxel-based morphometry study. *Brain* 128:2453–2461.
27. Simos PG, *et al.* (2002) Dyslexia-specific brain activation profile becomes normal following successful remedial training. *Neurology* 58:1203–1213.
28. Siok WT, Perfetti CA, Jin Z, Tan LH (2004) Biological abnormality of impaired reading is constrained by culture. *Nature* 431:71–76.
29. Goswami U (2002) Phonology, reading development, and dyslexia: A cross-linguistic perspective. *Ann Dyslexia* 52:1–23.
30. Perfetti CA, Liu Y, Tan LH (2005) The lexical constituency model: Some implications of research on Chinese for general theories of reading. *Psychol Rev* 112:43–59.
31. Tan LH, Laird A, Li K, Fox PT (2005) Neuroanatomical correlates of phonological processing of Chinese characters and alphabetic words: A meta-analysis. *Hum Brain Mapp* 25:83–91.
32. Booth JR, *et al.* (2006) Specialization of phonological and semantic processing in Chinese word reading. *Brain Res* 1071:197–207.
33. Liu CL, *et al.* (2006) Dissociated roles of the middle frontal gyri in the processing of Chinese characters. *NeuroReport* 17:1397–1401.
34. Chen HC, Vaid J, Bortfeld H, Boas DA (2008) Optical imaging of phonological processing in two distinct orthographies. *Exp Brain Res* 184:427–433.

35. Liu Y, Dunlap S, Fiez J, Perfetti CA (2007) Evidence for neural accommodation to a writing system following learning. *Hum Brain Mapp* 28:1223–1234.
36. Petrides M, Alivisatos B, Meyer E, Evans AC (1993) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc Natl Acad Sci USA* 90:878–882.
37. Deco G, Rolls ET, Horwitz B (2004) ''What'' and ''where'' in visual working memory: A computational neurodynamical perspective for integrating FMRI and single-neuron data. *J Cognit Neurosci* 16:683–701.
38. Leong CK, Hau KT, Tse SK, Loh KY (2007) Component skills of text comprehension in less competent Chinese comprehenders. *Ann Dyslexia* 57:75–97.
39. Tan LH, Spinks JA, Eden G, Perfetti CA, Siok WT (2005) Reading depends on writing in Chinese. *Proc Natl Acad Sci USA* 102:8781–8785.
40. Tang YY, *et al.* (2006) Arithmetic processing in the brain shaped by cultures. *Proc Natl Acad Sci USA* 103:10775–10780.
41. Siok WT, Fletcher P (2001) The role of phonological awareness and visual-orthographic skills in Chinese reading acquisition. *Dev Psychol* 37:886–899.
42. Snyder PJ, Harris LJ (1993) Handedness, sex, and familiar sinistrality effects on spatial tasks. *Cortex* 29:115–134.
43. Good CD, *et al.* (2001) A voxel-based morphometric study of aging in 465 normal adult human brains. *NeuroImage* 14:21–36.
44. Ashburner J, Friston KJ (2000) Voxel-based morphometry: The methods. *NeuroImage* 11:805–821.
45. Talairach J, Tournoux P (1988) *Coplanar Stereotactic Atlas of the Human Brain* (Theime Medical, New York).