

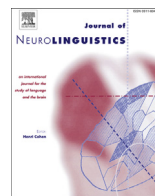


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Atypical lateralization of phonological working memory in developmental dyslexia



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ABSTRACT

Developmental dyslexia is a neurological condition characterized by unexpected low reading performance in people with normal intelligence and typical schooling. One prominent theory posits that dyslexic children fail to establish left-hemispheric dominance of visual representations and visual-phonological/meaning integration of printed words and thus exhibit an atypical lateralization of lexical processing. Behavioral, electrophysiological, histological, and morphological imaging studies examining this hemispheric asymmetry have generated conflicting evidence; however, it remains possible that dyslexics have impaired functional lateralization of language processes without a structural correlate. Here, using functional magnetic resonance imaging (fMRI) and a phonological task with working memory, we found distinct hemispheric asymmetry differences between dyslexic and normal children in brain regions subserving the storage and manipulation of phonological information in phonological working memory.

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Further, the degree of leftward asymmetry correlates positively with reading performance. Thus, the language impairments in dyslexic children appear related to a reduced dominance of the left hemisphere in phonological language functions, which offers clues into the biological dysfunction and possible remediation of developmental dyslexia.

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1. Introduction

Reading is the process of extracting meaning from written symbols that represent speech. It is a crucial skill for children to master, but unfortunately there are a considerable proportion of people who suffer from developmental dyslexia, which manifests as unexpected low reading performance despite normal intelligence and typical schooling (Eden & Moats, 2002; Gabrieli, 2009; Goswami, 2006; Horwitz, Rumsey, & Donohue, 1998; Peterson & Pennington, 2012; Price & Mechelli, 2005; Schlaggar & McCandliss, 2007; S. E. Shaywitz, 1998). The prevalence estimates of dyslexia in English population range from 5% to 17% (Gabrieli, 2009). It is widely recognized as a neurological disorder with dysfunction of the left-hemisphere language network (Eden & Moats, 2002; Gabrieli, 2009; Goswami, 2006; Horwitz et al., 1998; Paulesu et al., 2001; Peterson & Pennington, 2012; Price & Mechelli, 2005; Schlaggar & McCandliss, 2007; S. E. Shaywitz, 1998; Temple et al., 2000). Despite intensive research after it was first reported more than a century ago (Hinshelwood, 1895; Morgan, 1896), the core deficits of dyslexia are still hotly debated.

In the 1920s, Samuel Orton proposed an atypical lateralization theory of dyslexia (Orton, 1925, 1937). According to this idea, learning to read requires children to develop left-hemispheric dominance of visual representations and visual-phonological/meaning integration of printed words. Further, dyslexic children fail to suppress the right-hemisphere representation to establish appropriate hemisphere dominance, leading to improper word identification. A series of post-mortem studies of dyslexics by Geschwind and Galaburda et al. revealed a symmetrical structure in the planum temporale (Galaburda & Kemper, 1979; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Geschwind & Galaburda, 1985; Humphreys, Kaufmann, & Galaburda, 1990), a region important for phonological encoding and speech perception, whereas most normal brains showed marked leftward asymmetry in this region (Geschwind & Levitsky, 1968; Toga & Thompson, 2003). However, many other approaches, such as behavioral, electrophysiological, and morphological imaging, examining hemispheric asymmetry in dyslexics have generated inconsistent evidence (e.g., Green et al., 1999; Habib, 2000; Heiervang et al., 2000; Heim, Eulitz, & Elbert, 2003; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopoulos, 1990; Leonard, Eckert, Given, Virginia, & Eden, 2006). For example, with morphological MRI, some studies failed to find any difference of cortical symmetry between dyslexic and normal subjects (Green et al., 1999), and some even found an exaggerated pattern of leftward cerebral asymmetry in dyslexics (Leonard et al., 2006). Therefore, the question of whether and how dyslexics differ from normal subjects in brain lateralization is still unsolved.

Even if the morphological structure of language cortex in dyslexics is normal, it is still possible that dyslexics have an abnormal lateralization of functionally defined areas. In the present study, we used fMRI to compare the patterns of hemispheric lateralization in dyslexic and control children when they performed a phonological working memory task in an n-back paradigm. Phonological working memory involves the temporary storage and manipulation of phonological information (Baddeley, 2003b). It has been well-established that phonological working memory makes a unique contribution to learning of spoken and written languages (Baddeley, 2003a; Chee, Soon, Lee, & Pallier, 2004; Gathercole & Baddeley, 1993; Leong, Tse, Loh, & Hau, 2008; Mann & Liberman, 1984) and that children with dyslexia exhibit deficits in phonological working memory (de Jong, 1998; Gathercole,

Alloway, Willis, & Adams, 2006; Jeffries & Everatt, 2004; Pickering, 2006; Poblano, Valadéz-Tepec, de Lourdes Arias, & Garcí; a-Pedroza, 2000). Therefore, we investigated how the hemispheric lateralization might differ in dyslexic and normal children in brain systems mediating storage and manipulation of phonological information.

2. Methods

2.1. Subjects

Twenty-four children participated in our experiment, 12 dyslexics (4 girls and 8 boys, mean age = 10 years 7 months, range 9 years 7 months–12 years 2 months), and 12 typically developing controls (4 girls and 8 boys, mean age = 10 years 2 months, range 9 years 0 month–11 years 2 months) (see Table 1 for demographic information). The participants were 4th or 5th graders from a Primary School in Beijing, and were physically healthy and free of neurological disease, head injury and psychiatric disorder. Because there is no standardized reading ability test in Chinese, the classification of children's reading performance was based primarily on their teacher's evaluation and their school performance in the Chinese language course. In addition, a character-reading test measuring their reading ability and the Raven IQ test (Zhang & Wang, 1989) measuring nonverbal intelligence were administered to all children in the 4th and 5th grades ($N = 524$). The reading test comprises 160 Chinese characters, of which 120 characters were selected from textbooks for 3–5 graders (40 characters for each grade) and 40 characters were not from textbooks. Characters were listed in 16 rows with 10 columns in each row and were arranged from easy to difficult based on grade level. The reading test was administered individually and children were instructed to read the characters one by one as quickly and as accurately as possible. They read from left to right and from top to bottom. The time limit is 90 s. The reading scores for dyslexics were 1.5 standard deviations below the average score of each grade and for normal subjects were 1.5 standard deviations above the average (mean reading scores were 38 (SD = 13) for dyslexic children and 117 (SD = 16) for the normal subjects ($t = 13.48, p < 0.001$)). All subjects had normal nonverbal Raven IQ above the 50th percentile (average 76th and 66th percentile for dyslexic and normal children). There were no significant differences in age ($t = 1.53, p > 0.1$) or IQ ($t = 1.52, p > 0.1$) between groups. 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 assessed by an adapted handedness inventory (Oldfield, 1971) and no significant group difference was observed in handedness score ($t = 1.45, p > 0.1$).

2.2. Design and materials

A blocked design was used, with 4 blocks of a 2-back experimental task alternated with 4 blocks of a 0-back control task. In the 2-back task, subjects were asked to judge whether a visually presented Chinese single-character word was pronounced the same as the one presented two words previously in

Table 1
Demographic characteristics and behavioral results.

Characteristic	Normal children mean (SD)	Dyslexic children mean (SD)	<i>t</i> test, <i>p</i>
Age, in months	122.3 (7.4)	127.3 (8.8)	1.53; 0.14
Gender	4 female, 8 male	4 female, 8 male	
Handedness	12 right-handed	12 right-handed	1.45; 0.16
Reading (max = 160)	116.8 (15.7)	37.9 (12.9)	13.48; <0.001
Raven, in percentile	65.8 (14.6)	75.8 (17.4)	1.52; 0.14
2-back RT, ms	1250.3 (243.5)	1393.2 (239.0)	1.45; 0.16
2-back accuracy, %	81.6 (6.6)	69.7 (13.7)	2.71; <0.05
0-back RT, ms	987.3 (113.3)	1090.9 (118.4)	2.19; <0.05
0-back accuracy, %	95.0 (4.3)	86.5 (10.6)	2.57; <0.05

RT, reaction time.

the sequence. In the 0-back task, they judged whether viewed words have the same pronunciation as the one pre-specified at the beginning of the block. Condition order was counterbalanced. N-back blocks were interleaved with fixation block, each for 12 s. There were 8 words per block, with each word displayed for 500 ms, followed by a 2500 ms blank interval. The words were selected from children's textbooks and their frequency and stroke complexity were matched across conditions. The word frequencies are 156 and 153 in 0-back and 2-back conditions, respectively, and stroke number is 10 in both conditions.

2.3. MRI acquisition

Experiment was performed on a 3 T Siemens MRI scanner at the Beijing MRI Imaging Center. A T2*-weighted gradient-echo echo planar imaging (EPI) sequence was used, with TE = 30 ms, TR = 2000 ms, flip angle = 90°, field of view = 200 mm × 200 mm, slice thickness = 4 mm, and the acquisition matrix = 64 × 64. Thirty-two contiguous axial slices were acquired parallel to the AC-PC line to cover the whole brain. Visual stimuli were presented through a projector onto a translucent screen and subjects viewed the screen through a mirror attached to the head coil.

2.4. fMRI data analysis

Statistical Parametric Mapping software package (SPM2) (<http://www.fil.ion.ucl.ac.uk/spm/>) was used for pre-processing and analysis of imaging data. Functional images were realigned to remove movement artifact. They were then spatially normalized to an EPI template based on the ICBM 152 stereotactic space. An isotropic Gaussian kernel (8 mm full width at half-maximum) was applied for spatial smoothing. The first three volumes of each fMRI scan were excluded from further analysis to allow for T1 equilibration. Each time series was high-pass filtered with a cutoff period set at 128 s to remove low-frequency components. For each subject, contrast images were generated by subtracting the 0-back condition from the 2-back condition. They then were used to create group contrast images with the voxel-wise threshold set at $p < 0.05$, FDR corrected for multiple comparisons and the extent threshold of 10 contiguous voxels.

We defined regions of interest (ROIs) based on anatomical areas that correspond to the classically recognized regions associated with phonological working memory, including middle frontal gyrus (MFG) implicated in central executive processes (D'Esposito, 2007; Nee et al., 2013; Smith & Jonides, 1999), inferior parietal lobule (IPL) implicated in maintenance and rehearsal (Cohen et al., 1997; Paulesu, Frith, & Frackowiak, 1993), and superior parietal lobule (SPL) implicated in storage and manipulations of information (Awh et al., 1996; Koenigs, Barbey, Postle, & Grafman, 2009). A global ROI was also defined to include all the three regions to generate a general picture of global lateralization in phonological working memory (for a similar procedure, see Szaflarski, Holland, Schmithorst, & Byars, 2006). ROI masks were generated using the Wake Forest PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). We calculated an asymmetry index (AI) for each ROI by comparing voxels activated in each hemisphere: $AI = (\text{Left} - \text{Right}) / (\text{Left} + \text{Right})$. The AI value ranges from -1 to 1 . We adopted the convention for categorization of language hemisphere dominance (e.g., Gaillard et al., 2002, 2011), in which left hemisphere dominance was defined by $AI \geq 0.2$, right hemisphere dominance $AI \leq -0.2$, and bilateral representation $-0.2 < AI < 0.2$. A bootstrap method in LI-toolbox (Wilke & Lidzba, 2007) was used to calculate AI and the weighted mean of AI values were reported. This method avoids using a fixed threshold to determine AI; instead it allows for thousands of comparisons across thresholds between the two hemispheres by repeatedly sampling with replacement. A two-sample t tests was performed to compare AI values for each ROI between the two groups.

3. Results

3.1. Behavioral data

Table 1 shows the task performance of normal and dyslexic children. Dyslexic children did not differ from normal children on the Raven's Progressive Matrices test. However, they were less

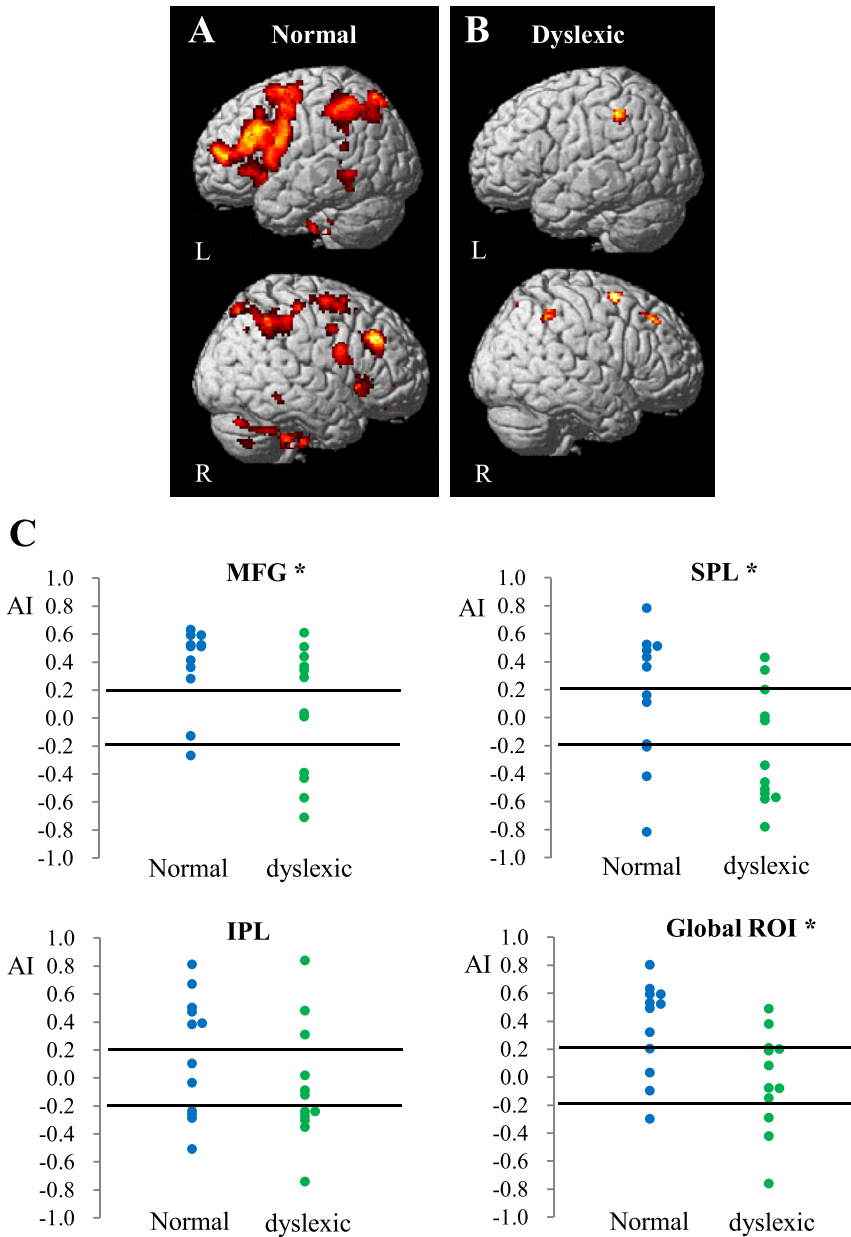


Fig. 1. Cortical activation associated with 2-back task contrasted with 0-back task in (A) normal and (B) dyslexic children. The significant threshold is $p < 0.05$, FDR corrected. (C) Asymmetry indices (AI) in the four ROIs during phonological working memory task in normal and dyslexic children. Left hemisphere dominance was defined by $AI \geq 0.2$, right hemisphere dominance $AI \leq -0.2$, and bilateral representation $-0.2 < AI < 0.2$. L = the left hemisphere; R = the right hemisphere; MFG = middle frontal gyrus; SPL = superior parietal lobule; IPL = inferior parietal lobule; * significant difference between the two groups at $p < 0.05$.

accurate than normal children in both 2-back and 0-back tasks and they also responded significantly more slowly than normal children in the 0-back task, indicating a general phonological deficit and a working memory deficit in dyslexic children. In addition, there was no significant interaction between group (normal vs. dyslexic) and task (2-back vs. 0-back), $F(1, 22) = 1.08$, $p = 0.31$ for reaction time and $F(1, 22) = 0.26$, $p = 0.62$ for accuracy, suggesting that task manipulations have an equal influence on the two groups.

3.2. fMRI data and lateralization

Whole-brain analysis revealed stronger activation during the phonological 2-back task contrasted with the 0-back task in normal children in left prefrontal cortex, left posterior parietal cortex and right cortical regions including middle frontal gyrus as well as inferior and superior parietal cortex (Fig. 1A). For the same contrast, dyslexic children showed stronger activation mainly in right prefrontal and bilateral posterior parietal cortices (Fig. 1B).

T-test of AI values yielded a significant group difference in MFG ($t = 2.14$, $p < 0.05$), SPL ($t = 2.11$, $p < 0.05$) and global ROI ($t = 2.68$, $p < 0.05$), but not in IPL ($t = 1.29$, $p > 0.05$). Fig. 1C shows AIs of the ROIs for individual subjects. The mean AI in MFG was 0.38 in normal children compared to 0.04 in dyslexic children, and 0.14 and -0.24 in SPL, respectively, indicating that activation in MFG and SPL was more bilateral or right-lateralized in dyslexics than in normal readers. The percentages of subjects who exhibited left-, right- and bi-lateralized activation in the four ROIs are shown in Table 2. Across ROIs, 50–83% of normal children presented leftward asymmetry, while only 25–50% of dyslexic children demonstrated leftward asymmetry. Based on previous findings (Bishop, 2013; Groen, Whitehouse, Badcock, & Bishop, 2012), we hypothesize that degree of left-lateralization would positively correlated with reading scores. Results showed significant correlation ($p < 0.05$, one-tailed) between AI values and reading scores in SPL ($r = 0.37$) and global ROI ($r = 0.36$), and a marginally significant correlation in MFG ($r = 0.29$, $p = 0.085$) (Fig. 2).

4. Discussion

Our present study has demonstrated an atypical lateralization pattern in dyslexic children. Unlike normal children, they failed to produce left-hemispheric dominant activation during a phonological working memory task. Direct correlations between degree of leftward asymmetry and reading performance suggest that the variation of lateralization may contribute to individual differences in children's reading ability. These results lend strong support to the idea of abnormal lateralization mechanisms in dyslexia.

Phonological working memory is conceptualized as a multi-component system that includes storage and executive processes (Baddeley, 2003b). Previous studies examining the neural correlates of phonological working memory have consistently found left-lateralized activation in normal subjects (D'Esposito et al., 1998; Paulesu et al., 1993; Smith & Jonides, 1998, 1999; Smith, Jonides, & Koeppe, 1996; Reuter-Lorenz et al., 2000; Thomason et al., 2009). The left posterior parietal region, the inferior prefrontal area, and the premotor cortex, are critically involved in phonological storage (Paulesu et al., 1993; Ravizza, Delgado, Chein, Becker, & Fiez, 2004; Smith & Jonides, 1998, 1999), whereas

Table 2

Percentages of children who showed left-, right- and bi-lateralized activation in the four ROIs in normal and dyslexic groups. MFG = middle frontal gyrus; SPL = superior parietal lobe; IPL = inferior parietal lobe.

ROI	Normal children (%)			Dyslexic children (%)		
	Left	Right	Bilateral	Left	Right	Bilateral
MFG	83.3	8.3	8.3	50	33.3	16.7
SPL	50	25	25	25	58.3	16.7
IPL	50	33.3	16.7	25	50	25
Global ROI	75	8.3	16.7	33.3	25	41.7

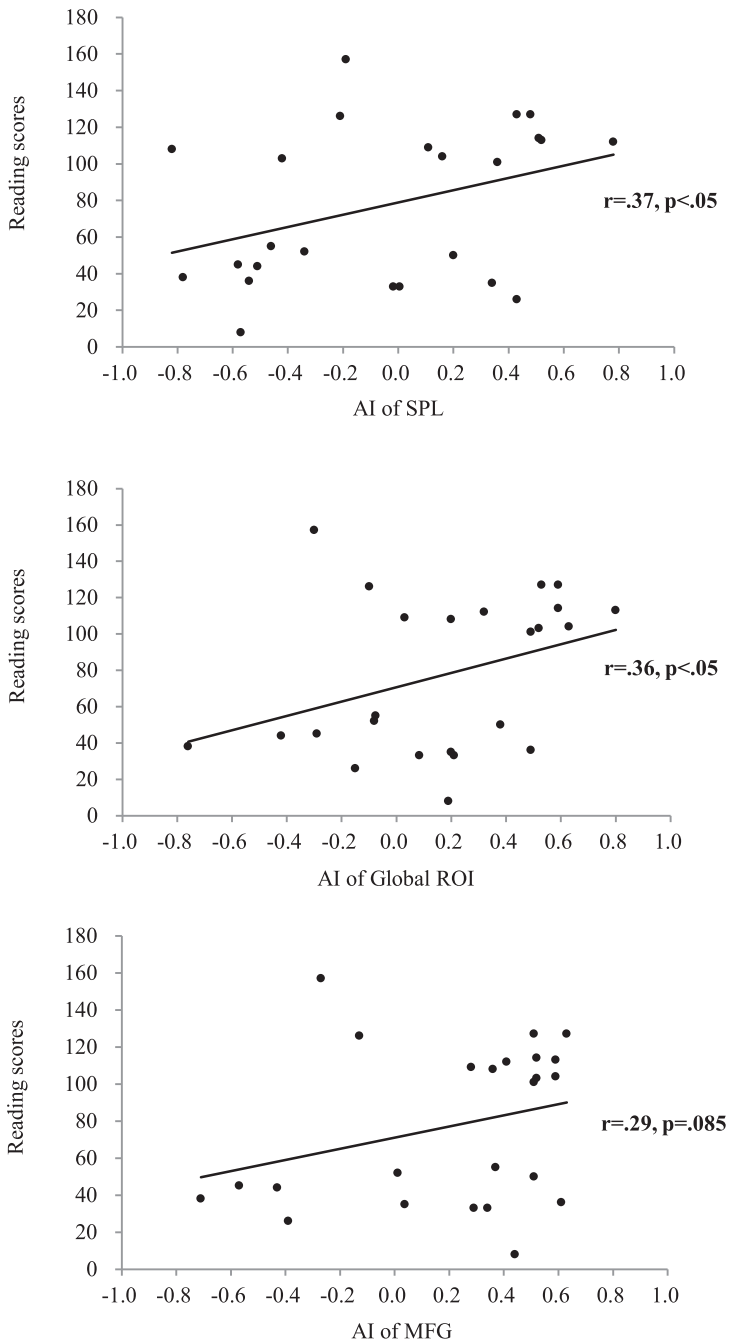


Fig. 2. Correlations between reading scores and AI values in superior parietal lobule (SPL), global ROI and middle frontal gyrus (MFG).

dorsolateral prefrontal cortex subserves central executive processes (D'Esposito, 2007; Nee et al., 2013; Smith & Jonides, 1999). Our study using a phonological n-back task found distinct asymmetry patterns in frontal and parietal regions between good and impaired readers, indicating that children with dyslexia may show abnormal hemispheric specialization in both storage and manipulation of phonological information.

One possible explanation for the irregular functional asymmetry is that the left-hemisphere regions develop atypically in dyslexics, and consequently more neural resources in the right hemisphere homologs are recruited to compensate for the dysfunction of left-hemisphere areas. Previous studies have reported less-than-normal gray matter volume and reduced activation in dyslexics in the left dorsal prefrontal regions (Aylward et al., 2003; Hoeft et al., 2006; Hu et al., 2010; Siok, Niu, Jin, Perfetti, & Tan, 2008; Siok, Perfetti, Jin, & Tan, 2004) and the left superior parietal lobule (Peyrin, Démonet, N'Guyen-Morel, Le Bas, & Valdois, 2011; Vasic, Lohr, Steinbrink, Martin, & Wolf, 2008). Consistent with those studies, our finding indicates that dyslexic children may develop a compensatory mechanism by recruiting more areas in the right hemisphere. Formation of a compensatory mechanism may be due to the restricted availability of the left hemispheric regions (Eden et al., 2004; Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Pugh et al., 2000; B. A. Shaywitz et al., 2002) or the use of different processes when dyslexic readers performed the task. For example, they may rely more on the visual-spatial information of stimuli to perform the task, which could cause the right hemisphere sites for processing visual-spatial information (Reuter-Lorenz et al., 2000; Smith et al., 1996; Thomason et al., 2009) to be more strongly activated.

Alternatively, dyslexic children may fail to suppress the right hemispheric regions to establish proper hemispheric dominance for reading. Transcallosal inhibition is proposed to have an important role in the development of lateralized functions such as language (Bloom & Hynd, 2005; Cook, 1986; Selnes, 2000), and this idea is supported by recent neuroimaging studies of inter-hemispheric coordination (Hervé, Zago, Petit, Mazoyer, & Tzourio-Mazoyer, 2013; Josse, Seghier, Kherif, & Price, 2008; Putnam, Wig, Grafton, Kelley, & Gazzaniga, 2008; Seghier, Josse, Leff, & Price, 2011; Vigneau et al., 2011). One possibility is that dyslexics have functional or morphological defects of the left hemisphere, which increase the excitability in the right hemisphere following the release of transcallosal inhibition. However, this does not necessarily mean that more recruitment of right-hemisphere regions aids the performance of reading task; instead, it may cause confusion in reading processing (Orton, 1937; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003).

One limitation of our results is that the effects of group differences in AI values and correlations coefficients were not robust enough to survive corrections for multiple comparisons. One reason might be that our sample size is relatively small. Future studies with a larger sample size are needed to confirm the results and evaluate the correlations between AI values and behavioral performance in each group.

To conclude, our study found distinct hemispheric asymmetry in dyslexic and normal children in brain regions that mediated the storage and manipulation of phonological information, suggesting that language impairments in dyslexic children may be related to a reduced dominance of the left hemisphere in phonological language functions. The finding has theoretical implications for the cause and remediation of developmental dyslexia and strongly indicate the needs for investigating how brain lateralization for reading arise and what factors contribute to the atypical lateralization in dyslexic readers.

Conflict of interest

The authors declare no conflict of interest.

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