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The brain basis of handwriting deficits in Chinese children with developmental dyslexia

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Abstract

Abundant behavioral studies have demonstrated high comorbidity of reading and handwriting difficulties in developmental dyslexia (DD), a neurological condition characterized by unexpectedly low reading ability despite adequate nonverbal intelligence and typical schooling. The neural correlates of handwriting deficits remain largely unknown; however, as well as the extent that handwriting deficits share common neural bases with reading deficits in DD. The present work used functional magnetic resonance imaging to examine brain activity during handwriting and reading tasks in Chinese dyslexic children ($n = 18$) and age-matched controls ($n = 23$). Compared to controls, dyslexic children exhibited reduced activation during handwriting tasks in brain regions supporting sensory-motor processing (including supplementary motor area and postcentral gyrus) and visual-orthography processing (including bilateral precuneus and right cuneus). Among these regions, the left supplementary motor area and the right precuneus also showed a trend of reduced activation during reading tasks in dyslexics. Moreover, increased activation was found in the left inferior frontal gyrus and anterior cingulate cortex in dyslexics, which may reflect more efforts of executive control to compensate for the impairments of motor and visual-orthographic processing. Finally, dyslexic children exhibited aberrant functional connectivity among brain areas for cognitive control and sensory-motor processes during handwriting tasks. Together, these findings suggest that handwriting deficits in DD are associated with functional abnormalities of multiple brain regions implicated in motor execution, visual-orthographic processing, and cognitive control, providing important implications for the diagnosis and treatment of dyslexia.

KEYWORDS
brain activation, developmental dyslexia, fMRI, functional connectivity, handwriting, reading

1 | INTRODUCTION

Developmental dyslexia (DD) is a neurological learning disability characterized by significantly low reading achievement based on chronological age, despite adequate intelligence and socioeconomic opportunity. It affects approximately 5%—17% of school-aged children (Gabrieli, 2009). Individuals with dyslexia demonstrate difficulties with accurate and/or fluent word recognition and poor spelling abilities. Their problems are persistent and are thought to be specific to the acquisition and development of written language code (Démonet et al., 2004; Habib & Giraud, 2013). Current research generally suggests that dyslexic individuals show weakness in the process of mapping between orthographic and phonological units during reading, which is associated with atypical brain activation (e.g., in the left temporoparietal cortex, inferior frontal gyrus, and occipitotemporal cortex) and atypical connectivity of the reading pathway in the left hemisphere (Finn et al., 2014; Gabrieli, 2009; Olulade et al., 2013; Peterson & Pennington, 2012; van der Mark et al., 2011).

Ample evidence has also shown that handwriting disability is a persistent problem in DD (Graham et al., 2020). With respect to writing products, children with DD exhibited poorer legibility (Martlew, 1992) and greater character size compared to age-matched controls (Lam et al., 2011). Similarly, college students with dyslexia showed more spelling errors than their age-matched peers in handwriting fluency and spelling tests (Connelly et al., 2006). In terms of writing processing, a typical manifestation of handwriting deficit is reduced writing speed, which has been observed in both children (Sumner et al., 2013) and adult dyslexics (Connelly et al., 2006; Hatcher et al., 2002). Further examination revealed that slower handwriting speed in dyslexics was associated with more pauses between words and within words (Sumner et al., 2013, 2014) and longer writing latencies (Afonso et al., 2019). Some studies have attributed the high rate of pause during handwriting to the orthographic spelling difficulties in dyslexia (Sumner et al., 2013, 2014), whereas others have suggested an impairment of motor execution during handwriting in DD (Pagliarini et al., 2015). For example, it was found that children with DD failed to comply with the principles of isochrony and homothety in the motor execution of handwriting (Pagliarini et al., 2015); and compared to age-matched and spelling-matched controls, dyslexics were more impacted by the graphic complexity of words (Gosse & Van Reybroeck, 2020). Thus, problems of visual-orthographic and motor processing are candidate components that may account for handwriting deficits in DD.

Both reading and handwriting involve processing of written symbols: The reading process involves extracting sound and meaning from orthography, and handwriting is a visual-motor process for production of orthographic scripts. Past research has demonstrated that handwriting is a powerful procedure for establishing high-quality representation of written word form knowledge and acquiring reading skills (Cao et al., 2013; Longcamp et al., 2005, 2008; Perfetti & Tan, 2013; Tan, Spinks, et al., 2005). Some researchers have also proposed a gestural component for reading (i.e., reading by hand), which recruits the left premotor region for automatic dynamic motor representations of writing action when recognizing written words (James & Gauthier, 2006; Longcamp et al., 2003; Nakamura et al., 2012). Moreover, whereas reading and writing/spelling problems are pervasive in dyslexics, defective writing and spelling in particular may continue to appear long into adult life, after reading accuracy has developed. This is because writing is more difficult, requiring individuals to reproduce the words, not just recognize them (Bruck, 1993; Leong et al., 2000; Richards et al., 2015).

Thus, previous studies unequivocally demonstrate close connection between reading and writing, and high comorbidity of reading and writing/spelling difficulties in DD. However, the neural correlates of handwriting deficits remain poorly understood, as well as the extent that handwriting deficits share common neural bases with reading deficits in dyslexics. Investigation of this issue will improve the understanding of the challenges that dyslexic children face during literacy development, and will help to identify biological markers that aid diagnosis and treatment of DD. Both fundamental and clinical studies of handwriting in dyslexia are underemphasized in comparison with studies of reading, and examination of the neural bases of handwriting deficits in DD is rare. A prior functional magnetic resonance imaging (fMRI) study (Richards et al., 2015) demonstrated that both dyslexic and dysgraphic children showed more functional connectivity during an alphabet writing task than age-matched controls, and less white matter integrity. Moreover, the authors counted the total number of functionally connected voxels from seed regions and found that dyslexic and dysgraphic groups differed in their patterns of abnormalities: The dyslexic group showed more functionally connected voxels than the dysgraphic group from the left occipital temporal and left supramarginal gyri, whereas the dysgraphic group showed more functional connectivity from the left precuneus than the dyslexic group, suggesting that the neural correlates of writing deficits in dyslexia may be different from those in dysgraphia. However, this study focused on the comparison between dyslexic and dysgraphic groups using a region of interest (ROI)-based functional connectivity analysis. Thus, the nature of writing deficits in dyslexics remained largely unclear, especially regarding the relationships between neural abnormalities associated with handwriting and reading deficits in DD.

The present study uses fMRI to examine brain activation patterns during handwriting and reading tasks in Chinese dyslexic children and age-matched controls.

In written Chinese, the graphic units (characters) correspond to specific morphemes and map onto the whole syllables, in contrast to alphabetic languages such as English and Russian, in which graphic units (letters) are associated with phonemes. Chinese reading requires intensive visual-orthographic analysis and arbitrary association between visual forms and pronunciations, but cannot rely on the letter-sound conversion process that is critical for alphabetic reading. Indeed, functional neuroimaging studies of Chinese dyslexia have demonstrated brain abnormalities in the left inferior and middle frontal cortices during phonological and semantic tasks (Liu et al., 2012; Siok et al., 2004, 2009), and in the intraparietal sulcus and precuneus during visual-orthographic processing (Cao et al., 2018; Siok et al., 2009). These findings are only partly consistent with those from studies of dyslexics in alphabetic languages (Gabrieli, 2009), which suggest that how the graphic units map onto language units may influence the weighting of the various challenges of reading and the neural expression of reading difficulties (Perfetti et al., 2013; Xu et al., 2019).

Reading-writing connections are studied in Chinese DD because previous work has established that handwriting and reading are closely correlated with each other in Chinese due to its linguistic and visual features (Cao et al., 2013; Guan et al., 2011; Tan, Spinks, et al., 2005; Tan & Xu, 2020; Tan et al., 2013; Tso et al., 2011), although there was empirical evidence supporting that writing is not necessarily required for reading in Chinese readers (Bi et al., 2009; Li & Yeh, 2003; Zhai & Fischer-Baum, 2019). Specifically, learning Chinese requires memorization of thousands of distinct characters, and the challenging properties of Chinese characters (no phonemic constituents and visually complex forms) have led to a prevalent strategy for learning to read through repeatedly writing/copying the characters. Handwriting practice is thought to elaborate orthographic representation and to form motor memory of orthographic units (McBride-Chang et al., 2011; Tan, Spinks, et al., 2005). Given the critical role of handwriting in Chinese reading, handwriting problems might be more severe in Chinese dyslexia compared to dyslexia in alphabetic languages. This notion is supported by some behavioral studies demonstrating that compared to age-matched controls, Chinese children with DD exhibited impaired speed and products when handwriting characters (Chan et al., 2006; Lam et al., 2011), and during copying of unfamiliar scripts (nonlinguistic material) (McBride-Chang et al., 2011). Furthermore, copying performance can successfully discriminate Chinese children with dyslexia or with both poor Chinese and English reading skill from children with average reading skill, but copying performance cannot discriminate poor from average readers of English only (Kalindi et al., 2015).

Another important methodological component of the present study is the use of a copying task to probe the neural correlates of handwriting processes. This required the children to reproduce the visual word form and provided better control for variability in high-level cognitive and linguistic processes (such as planning what to write) (Graham et al., 2006). Several linguistic and cognitive variables related to handwriting were also taken into account, including word frequency (by varying word frequency of the words) (Rapp & Dufor, 2011; Yang et al., 2018) and orthographic working memory load (by comparing direct copying and delayed copying conditions) (Han et al., 2007; Rapp et al., 2016). For the reading task, both orthographic and phonological processing tasks were included. Brain activation was hypothesized to occur in regions involving visual-orthographic and motor processing in both handwriting and reading tasks, based on the following reasons: (1) both reading and handwriting tasks involve visual-orthographic processing and (2) previous studies have demonstrated that handwriting contributes to reading by tuning orthographic representation and forming motor memory (Tan, Spinks, et al., 2005), and that motor-related brain regions associated with handwriting are automatically activated in seeing letters or words without motor output requirement (James & Gauthier, 2006; Longcamp et al., 2003; Nakamura et al., 2012). It was also hypothesized that during reading and handwriting tasks, dyslexic children would show neural deficits in brain regions involved in visual-orthographic or/and motor processing.

RESEARCH HIGHLIGHTS

1. Previous studies unequivocally demonstrate high comorbidity of reading and handwriting difficulties in developmental dyslexia, but the neural correlates of handwriting deficits remain largely unknown.
2. Chinese dyslexic children and age-matched controls were scanned using functional magnetic resonance imaging while performing handwriting and reading tasks.
3. Dyslexic children exhibited activation and connectivity abnormalities in brain regions implicated in motor execution, visual-orthographic processing, and cognitive control during handwriting tasks.
4. Dyslexic children showed atypical activation in visual and motor-related regions in both handwriting and reading tasks.

2 | MATERIALS AND METHODS

2.1 | Participants

Forty-one children participated in the study, including 18 DD participants (12 males, mean age = 10.23 years) and 23 age-matched controls (10 males, mean age = 10.14 years). Because there are no standardized tests to screen for dyslexia in Chinese, a large population of 1715 primary school children was tested in Beijing (4th or 5th graders recruited from five primary schools). The dyslexic participants were determined by the following criteria: (1) having a score that was at least 1.25 standard deviations (SD) below the average score of

TABLE 1 Demographic characteristics of participants and behavioral results

	Dyslexic ($n = 18$) Mean (SD)	Control ($n = 23$) Mean (SD)	t/χ^2/U values
Age	10.23 (0.59)	10.14 (0.53)	−0.49
Sex (male/female)	12/6	10/13	0.14
Raven's progressive matrices	105.00 (9.71)	111.43 (13.31)	1.72
Chinese character recognition	1976.66 (306.28)	2826.07 (250.61)	9.77***
Reading-related skill tests			
Reading fluency (number of characters)	65.50 (18.51)	102.57 (19.59)	6.16***
Phonological awareness	25.44 (3.97)	28.00(2.37)	2.41*
Rapid automatized naming			
Objects (s)	21.62 (3.98)	18.11 (2.31)	−3.32**
Numbers (s)	12.11 (2.57)	9.82 (2.49)	−2.87**
Orthographic awareness			
RT (ms)	1050 (178)	893 (141)	−3.14**
ACC (%)	0.70(0.14)	0.82 (0.11)	2.77**
Handwriting skill tests			
Copying time (s)	108.13 (26.32)	98.21 (30.45)	142.50
Copying quality	24.37 (4.41)	24.50(5.51)	0.08
Handwriting fluency (number of digits)	51.67 (8.69)	57.17 (13.89)	1.47
Handwriting fluency (number of characters)	23.56 (6.94)	27.65 (5.31)	2.14*
Visual-motor integration	46.22 (5.48)	50.95 (4.63)	2.99**
Cognitive skill tests			
Phonological working memory span	4.78 (1.00)	5.78 (1.44)	2.51*
Sustained attention	28.56 (7.90)	31.39 (6.11)	1.30

Abbreviations: ACC, accuracy; ms, milliseconds; RT, response time; s, seconds; SD, standard deviation.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

children in the same grade as assessed by the Character Recognition Measures and Assessment Scale (CRM) (Wang & Tao, 1993). The CRM is a standardized vocabulary test that has been widely used for screening dyslexia in Mandarin-speaking children (Amalric & Dehaene, 2016; Feng et al., 2020; Yang et al., 2016; Zhang et al., 2018); (2) having a nonverbal intelligence quotient standardized score above 85 as evaluated by Combined Raven's Progressive Matrices; (3) having normal hearing, normal or corrected-to-normal vision, and no ophthalmological or neurological abnormalities; and (4) not suffering from attention-deficit/hyperactivity disorder based on the Chinese Classification of Mental Disorder 3 (CCMD-3). Similar procedure has been used for diagnosing dyslexia in previous studies in mainland China (e.g., Feng et al., 2020). All the children were native speakers of Mandarin, the official dialect of mainland China and the language of instruction in school, and they were right-handed as assessed by the Handedness Inventory (Snyder & Harris, 1993). The study was approved by the ethics committee of the Institute of Psychology at the Chinese Academy of Sciences. Prior to entering the study, written informed consent was obtained from each participant's guardian. Detailed participant information is listed in Table 1, together with the results of behavioral tests that are described immediately below.

2.2 | Behavioral tests

A series of behavioral tests were administered to examine the reading, handwriting, visual-motor skill, and domain-general cognitive skills of the participants.

2.2.1 | Reading-related skill tests

Reading-related skills were assessed including reading fluency, phonological awareness, rapid automatized naming (RAN), and orthographic awareness. The reading fluency test consisted of 160 Chinese characters of medium to high frequency, which the participants were asked to read aloud as fast and accurately as possible within 1 min. Performance was scored as the number of correctly named characters. In the phonological awareness test, oddity tests were used to examine phonological awareness of consonant, vowel, and tone. For each item, the participants were required to listen carefully to three syllables, one of which was the odd one out by virtue of lacking an initial sound, final sound, or tone shared by the other two syllables. The participants were asked to report the odd syllable. There were 10 items for each of consonant, vowel, and tone awareness tests, and the score was the total number of items correctly answered (maximum score = 30). RAN was used to examine the ability to name familiar stimuli quickly and automatically. Participants were required to name 30 digits and 30 simple drawings of objects in a left-to-right fashion as correctly and rapidly as possible. Each participant performed the RAN task twice, and the mean naming time was taken as the score. In the orthographic awareness test, the participants were required to judge whether the characters presented visually on a computer display screen were real Chinese characters. Forty real Chinese characters, 20 pseudo-characters, and 20 non-characters were included as stimuli, with performance scored in terms of the mean accuracy rate (ACC) and reaction times (RT) for responses to pseudo-characters and non-characters. Responses to real characters were not included to minimize the influence of language experience.

2.2.2 | Handwriting skill tests

Both handwriting accuracy and fluency were assessed. Handwriting accuracy was evaluated using a pen-and-paper copying task, in which the participants were required to write (in their natural style) 48 Chinese characters varying in frequency and visual complexity. The writing time was recorded, and writing quality was evaluated by two independent (one male) examiners using a 7-point Likert scale (1 = very bad and 7 = very good) based on six dimensions, including stroke form, slant, organization of radicals, neatness, average size, and overall appearance (Gimenez et al., 2014; Yang et al., 2020). The score was the sum of the sub-scores across all dimensions. The inter-rater reliability was high (intra-class correlation coefficient [ICC] = 0.91). Handwriting fluency was evaluated using a digit writing task and a character writing task, in which the participants were asked to handwrite digits continuously, ranging from 1 to 10 in Chinese, or a Chinese sentence “妈妈永远爱我” (“Mommy loves me forever”) as fast and as legibly as possible within 1 min. The score was the number of correct digits or characters written.

2.2.3 | Visuo-motor skill tests

A visual-motor integration test was conducted to assess visual-motor skill, in which the participants were asked to copy as accurately as possible 12 geometric symbols varying in visual complexity. The stimuli were derived from the Beery-Buktenica Development Test of Visual Motor Integration (Beery, 2004). Two independent evaluators assessed the degree of similarity between templates and participant responses using a 7-point Likert scale, and the total score was the sum of the ratings for each item. The inter-rater reliability of the assessment was high (ICC = 0.92).

2.2.4 | Cognitive skill tests

Phonological working memory and sustained attention tests were evaluated. A backward digit span task was used to assess phonological working memory, in which participants listened to a sequence of digits and then were asked to repeat the digits in reverse order (i.e., from the end to the beginning). Trials were administered with digit sequences ranging from 3 to 10 digits in length. The test was terminated when the participants failed in two consecutive trials of the same length, and the score was the maximum length of digit span with a correct response. Sustained attention was assessed using a cancellation test, in which participants were instructed to search and mark the target number (chosen as “3”) from a list of numbers as quickly and accurately as possible within 3 min. The score was calculated according to: score = attack − (false alarms + 0.5*omission), where attack was the number of correctly marked items, false alarms was the number of incorrectly marked items, and omission was the number of items missed.

Independent two-sample *t*-tests were applied to examine between-group differences of the behavioral tests. Because the variable of pen-and-paper copying time did not follow a normal distribution as evaluated by the Shapiro–Wilk test [$W = 0.81$, $p < 0.001$], it was analyzed using the Mann–Whitney *U* test.

2.3 | Stimuli and task procedure during fMRI

The participants were instructed to perform tasks of delayed and direct copying of Chinese characters during fMRI (Figure 1a). Forty-eight characters were selected, of which 32 characters were used for the delayed copying condition and 16 were used for the direct copying task. One half of the characters in the delayed condition were of high frequency (mean frequency = 1375 times per million) and the other half were of low frequency (mean frequency = 50 times per million), according to the Modern Chinese Frequency Dictionary (1986). All 16 characters used for the direct copying task were of low frequency (mean frequency = 52 times per million). Motoric complexity, measured by the mean number of strokes, was matched across conditions [average number of strokes (SD): delayed copying of high-frequency characters = 5.56 (0.63), delayed copying of low-frequency characters = 5.35 (0.72), and direct copying of low-frequency characters = 5.23 (0.77)]. In addition, a geometric figure drawing condition was included as a control condition for excluding low-level visual and motor processes, in which participants were asked to draw geometric figures as instructed by presentation of the appropriate Chinese characters. Four types of geometric figures were included (line, dot, circle, and triangle). Participants were instructed to draw the indicated geometric figure repeatedly, four times in each trial. Participants were instructed to start handwritten responses when the cursor appeared (a pencil symbol). Participants were trained to write characters and draw figures with matched duration and size, while minimizing movements of their upper arm and forearm to minimize task-related head motion during fMRI. To approximate real handwriting, immediate visual (“ink”) feedback was provided on the display screen during responses.

Two reading tasks were also implemented (orthographic decision and homophonic decision) together with a control condition (line-pattern judgment) (Figure 1b). The orthographic decision task was

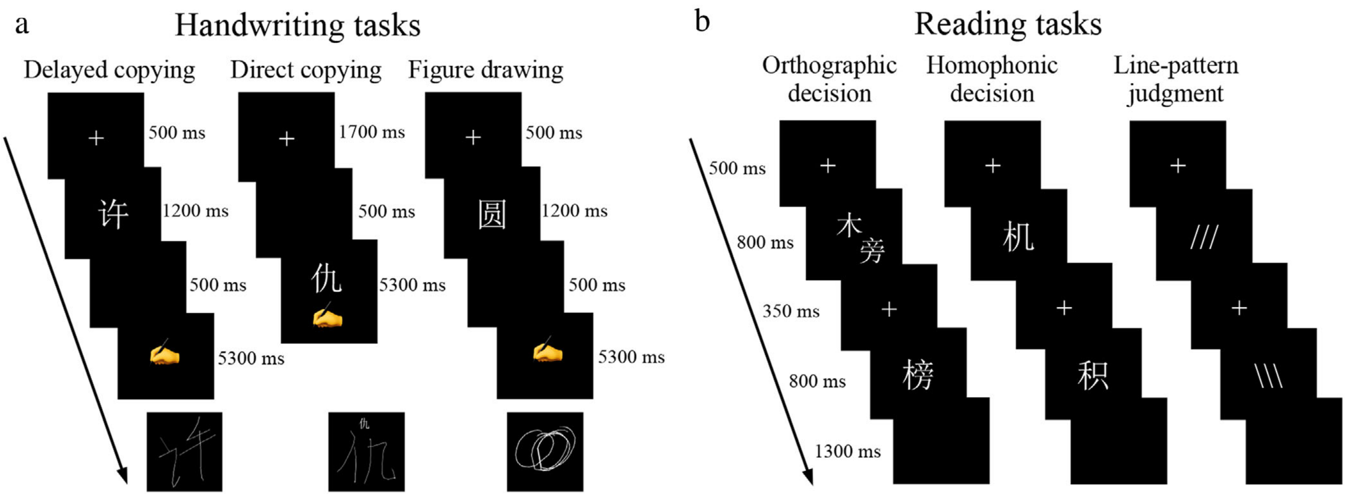

FIGURE 1 Handwriting and reading tasks during fMRI. (a) The handwriting tasks included delayed copying of Chinese characters (high-frequency and low-frequency characters), direct copying of low-frequency characters, and figure drawing. (b) The reading tasks included orthographic decision, homophonic decision, and line-pattern judgment tasks

designed to test awareness and manipulation of the internal structure of Chinese characters. In written Chinese, characters are the basic graphic units, which provide visually salient graphs formed with intricate strokes. Strokes are grouped into identifiable stroke patterns or radicals, which are arranged in appropriate positions relative to one another in the characters. In the orthographic decision task, participants were first presented with two stroke patterns that were spatially separated, followed by a character presented in the center of the screen. They were required to judge whether the two stroke patterns could be combined to form the central character, by pressing a button. The homophonic decision task was designed to examine brain activation for phonological processing. As mentioned previously, the graphemes (characters) in Chinese map to morphemes and syllables. There are approximately 400 different syllables in Mandarin Chinese, and with tone taken into account, the number of syllables increases to about 1300 (Taylor & Taylor, 1995). There are a considerable number of characters that share the same syllables (i.e., homophonic heterographs). In the homophonic decision task, participants were instructed to judge whether two sequentially presented characters were of the same pronunciation, by pressing a button. A line-pattern judgment task was also designed to control for brain activation arising from low-level visual perception and motor response. This task required participants to judge whether two sequentially presented line patterns were the same, by pressing a button.

Each participant underwent two runs for the handwriting tasks and two runs for the reading tasks, using a block design throughout. For the handwriting tasks, each run consisted of eight blocks including four blocks of delayed copying of characters (two for high-frequency characters and two for low-frequency characters), two blocks of direct copying, and two blocks of figure drawing, in pseudo-random order. Each block started with visual presentation of an instruction for 2000 ms, followed by four trials. As shown in Figure 1a, in each trial of the delayed copying condition and the figure drawing condition, a fixation was first presented visually and centrally for 500 ms, followed by the presentation of a character stimulus for 1200 ms (i.e., the character for copying in the delayed copying condition, or the character indicating the shape of the figure in the figure drawing condition). Next, a blank screen was displayed during a delay period of 500 ms, followed by the central appearance of the cursor for writing/drawing at the beginning of a response period of 5300 ms. In the direct copying condition, each trial started with a fixation for 1700 ms, followed by a blank display interval of 500 ms, and finally a response period of 5300 ms, beginning simultaneously with the onset of the character for direct copying presented at the top of the screen and persisting throughout the response period. The task blocks in each run were alternated with eight blocks of an additional rest condition that lasted for 12,000 ms. Therefore, the overall duration of each run was 352 s.

The handwriting data were recorded using a specially developed fMRI-compatible, touch-sensitive tablet system. Including a touch-sensitive surface, a force-sensitive stylus and an adjustable support frame, the system is MRI-safe without significantly degrading fMRI data quality (Karimpoor et al., 2018; Tam et al., 2011). The support frame was adjusted carefully for each participant to ensure that handwriting and drawing could be undertaken comfortably throughout the imaging session, and to enable tablet interaction with the forearm or wrist resting on the support such that there was no fatigue from handwriting against gravity.

For the reading tasks, there were two blocks for each task condition in each run (i.e., orthographic decision, homophonic decision, and line-pattern judgment). A whole-character decision condition was also included as part of a larger study, but was not analyzed in the present study. Each block started with a 4000 ms instruction, followed by eight trials. As shown in Figure 1b, in each trial, a fixation cross was first presented visually and centrally for 500 ms, followed by 800 ms presentation of the first stimulus (separated stroke patterns in the orthographic decision task, the first character in the homophonic task, and the first line-pattern in the line-pattern judgment task). Following the subsequent fixation period of 350 ms, the second stimulus was presented for

800 ms, followed by a blank screen lasting for 1300 ms as the response period. The task blocks were alternated with blocks of the rest condition that lasted for 10,000 ms. Therefore, the overall duration of each run was 352 s.

2.4 | Imaging acquisition

Imaging was performed using a 3T MRI system (MAGNETOM Prisma$^{\text{fit}}$, Siemens, Erlangen, Germany) at the Beijing MRI Center for Brain Research of the Chinese Academy of Sciences. Functional MRI time series data with blood oxygenation level-dependent (BOLD) contrast were acquired using a two-dimensional, T2*-weighted, multiband gradient-echo echo planar imaging sequence (Moeller et al., 2010): four-fold acceleration, repetition time (TR) = 1000 ms, echo time (TE) = 30 ms, slice thickness = 2.2 mm, in-plane resolution = 2.2 × 2.2 mm, flip angle (θ) = 45°, 64 axial slices. High spatial resolution anatomical images were acquired using a three-dimensional, T1-weighted, magnetization-prepared rapid acquisition gradient echo sequence: TR = 2200 ms, TE = 3.49 ms, slice thickness = 1 mm, inversion time (TI) = 1000 ms, in-plane resolution = 1.0 × 1.0 mm, and $\theta = 8°$.

2.5 | Data analysis

2.5.1 | Behavioral data acquired during fMRI

Writing latency and several other kinematic variables were quantified for the handwriting tasks performed during fMRI. Writing latency was defined as the duration from the onset of the trial's response period, signaled by the appearance of the response cue, to the beginning of writing/drawing. The other kinematic variables of handwriting included: (1) the overall writing duration, which was defined from the start of the response (first contact with the tablet) to the end of the last written or drawn stroke of the response; (2) the mean overall speed, which was defined as the ratio between the total distance traversed on the tablet (including non-inked segments) divided by total duration; and (3) the mean time interval between two strokes for each character. A two (group: DD and controls) by four (writing conditions: delayed copying of high-frequency characters vs. delayed copying of low-frequency characters vs. direct copying of low-frequency characters vs. figure drawing) analysis of variance (ANOVA) was conducted for each variable. For the reading tasks performed during fMRI, the accuracy and response time for each condition were compared between DD and control participants using two-sample *t*-tests.

2.5.2 | fMRI data analysis

Preprocessing

Image preprocessing and statistical analyses were conducted using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Department of Cognitive Neurology, University College London, London). The fMRI time series data for each participant were first corrected for head motion, and the corrected images were transformed into Montreal Neurological Institute (MNI) stereotactic space with cubic voxels at 2 × 2 × 2 mm spatial resolution(Calhoun et al., 2017). These images were then spatially smoothed using an isotropic Gaussian kernel template with 6 mm full-width at half-maximum. The handwriting task data for eight participants (three DD and five controls) were excluded from further analysis due to strong head motion during fMRI (exclusion criteria > 3 mm translation, or >3.5° rotation; note that a strict limit on head motion was not applied because the participants were children and handwriting is a motor task). The reading task data for eight participants were excluded due to strong head motion (five participants) or failure to complete a given task (three participants). Therefore, there remained 33 participants (15 DD and 18 controls) with usable handwriting task data and 33 participants (15 DD, 18 controls) with usable reading task data. Among these participants, 30 (14 DD and 16 controls) had fMRI data for both handwriting and reading tasks. In addition, the head motion in the handwriting and reading tasks was quantified by calculating the mean framewise displacement (FD) based on estimates of the six head movement parameters. The independent two-sample *t*-test indicated that dyslexics and controls did not differ in FD during handwriting [$t(31) = 0.902$, $p = 0.37$] or reading tasks [$t(31) = 0.93$, $p = 0.36$].

2.5.3 | Whole-brain activation analysis of handwriting and reading tasks

Brain activation analysis of handwriting and reading tasks.The preprocessed images were passed to a first level general linear model (GLM), which was used to obtain parameter estimate (beta) images associated with each stimulus condition. For the handwriting tasks, the design matrix included three character-writing regressors (delayed copying of high-frequency characters, delayed copying of low-frequency characters, direct copying of low-frequency characters), a figure-drawing regressor, and a rest regressor. In addition, head movement parameters (estimated with six parameters during the motion correction step) were included in the design matrix as nuisance covariates to minimize residual motion artifacts. For the reading tasks, the design matrix included three character-reading regressors (orthographic decision, homophonic decision, and whole-character decision) and a regressor for the line-pattern judgment condition. Six head movement parameters were also used as nuisance covariates. The GLM design matrix including the block design time series were convolved with a canonical hemodynamic response function. The data were high-pass filtered at 0.008 Hz to remove low-frequency drifts.

Parameter estimate images generated at the first level of analysis for each participant were then used to create group contrast images at the second level. For the handwriting tasks, the parameter maps were entered into a two (group: DD vs. control) by four (conditions: delayed copying of high-frequency vs. low-frequency characters vs. direct copying of low-frequency character vs. figure drawing) ANOVA to examine the effects of group and condition, and their interaction. Post hoc one-sample *t*-tests were then used to identify brain activation associated with handwriting separately for each group and for each task, as informed by the ANOVA results. For the reading tasks, one-sample *t*-tests were used to test the effect of orthographic decision (as well as homophonic decision) versus line-pattern judgment, and two-sample *t*-tests were used to examine group differences in orthographic and phonological processing. The statistical threshold was set to $p < 0.001$ at the voxel level, followed by a cluster size correction for multiple comparisons with a family-wise error (FWE) of $p < 0.05$.

Moreover, to explore the extent to which handwriting deficits and reading deficits share common brain activation patterns in dyslexic children, two-sample *t*-tests were used to compare the fMRI results during reading tasks between the two groups (DD and controls) based on seven spherical ROIs, which were created with a 6-mm radius centered at the activation peaks of the regions showing significant group differences in the handwriting tasks, including the supplementary motor area (SMA, MNI central x, y, z coordinates: −2, −12, 50), left postcentral gyrus (−24, −36, 68), left precuneus (−24, −84, 36), right precuneus (16, −82, 42), right cuneus (24, −82, 8), cingulate gyrus (−8, 24, 42), and the left inferior frontal gyrus (−46, 10, 20).

2.5.4 | Brain activation-behavior correlation analysis during handwriting tasks

Next, we tested whether brain activation during handwriting tasks was correlated with participants' handwriting skill behavioral score. Linear regression analyses were performed across the two groups of participants. The pen-and-paper handwriting fluency performance was used to index handwriting skill performance and served as a dependent variable in this analysis. During this task, the participants used more familiar, natural gestures during the task and this enabled better assessment of their writing skills than the in-scanner handwriting task. The mean contrast estimates (linear combination of β estimates) of delayed and direct copying conditions were extracted from ROIs, which were taken as independent variables. The ROIs were selected from the regions showing significant group differences, including SMA, left postcentral gyrus, left precuneus, right precuneus, right cuneus, cingulate gyrus, and the left inferior frontal gyrus. In addition, sex and age were also included in the analysis as predictors. The significance level was set at $p < 0.05$ after correction for multiple comparisons using the false discovery rate (FDR).

2.5.5 | Functional connectivity analysis of the handwriting task

A generalized psychophysiological interaction (gPPI) analysis (McLaren et al., 2012) was applied to investigate the potential abnormality of functional brain interactions underlying handwriting in DD. The gPPI analysis illustrates task-dependent interaction between a seed region defined a priori and all voxels in the rest of the brain, based on multiple regression models (Friston et al., 1997). Focusing on the character-handwriting conditions, seed ROIs were selected based on the results of between-group comparisons in the brain activation analysis. All selected ROIs were also required to be located within the brain networks of handwriting reported in previous literature (Purcell et al., 2011). Accordingly, the SMA (−2, −12, 50 in MNI coordinates), left postcentral gyrus (−24, −36, 68), bilateral precuneus (−24, −84, 36; 16, −82, 42), cingulate gyrus (−8, 24, 42), and the left inferior frontal gyrus (−46, 10, 20) were selected and used to create spherical ROIs with 6-mm radius. For each ROI, a regression model was built using the following regressors: the task effects (delayed copying of high-frequency characters, delayed copying of low-frequency characters, direct copying of low-frequency characters, figure drawing, and rest), the seed time course, and the task by seed interaction terms. At the first level, gPPI parameter maps were generated for each ROI for handwriting and figure drawing, with each of the four tasks contrasted to the resting condition. These maps were then input to a two (group: DD vs. control) by four (conditions: delayed copying high-frequency vs. delayed copying low-frequency vs. direct copying low-frequency characters vs. figure drawing) ANOVA to examine the group differences in functional connectivity. The statistical threshold was set to $p < 0.001$ at the voxel level, followed by a cluster size correction for multiple comparisons with an FWE of $p < 0.05$.

Moreover, regression analyses were also applied to examine the relationship between functional connectivity and performance in the out-of-scanner handwriting fluency task, with behavioral performance scores as dependent variables, and functional connectivity parameters, sex, and age as predictors. The significance level was set at $p < 0.05$ after correction for multiple comparisons using the FDR.

3 | RESULTS

3.1 | Behavioral performance outside and inside the MRI system

As shown in Table 1, dyslexic children performed worse than controls in the reading-related and handwriting tasks, including those assessing reading fluency, orthographic awareness, phonological awareness, RAN, phonological working memory, pen-and-paper handwriting, and visual-motor integration.

The behavioral results for handwriting tasks during fMRI were based on 33 participants (15 DD and 18 controls) (Figure 2a), after screening for fMRI data quality issues as described in the Methods. For writing latency, the effect of condition [$F(3,93) = 133.43$, $p < 0.001$] was significant, while the effect of group [$F(1,31) = 0$, $p = 0.99$] and the interaction of group by condition [$F(3,93) = 2.75$, $p = 0.06$] were not statistically significant. For total writing duration, the effect of condition [$F(3,93) = 18.90$, $p < 0.001$] was significant, but the effect of group [$F(1,31) = 0.01$, $p = 0.92$] and the interaction of group by condition [$F(3,93) = 2.42$, $p = 0.07$] were not significant. For mean writing speed, the effect of condition [$F(3,93) = 80.26$, $p < 0.001$] and the interaction of group by condition [$F(3,93) = 5.19$, $p = 0.02$] were significant, while the effect of group [$F(1,31) = 0.02$, $p = 0.88$] was not significant. For mean stroke interval, the effect of condition [$F(3,93) = 5.55$, $p = 0.004$]

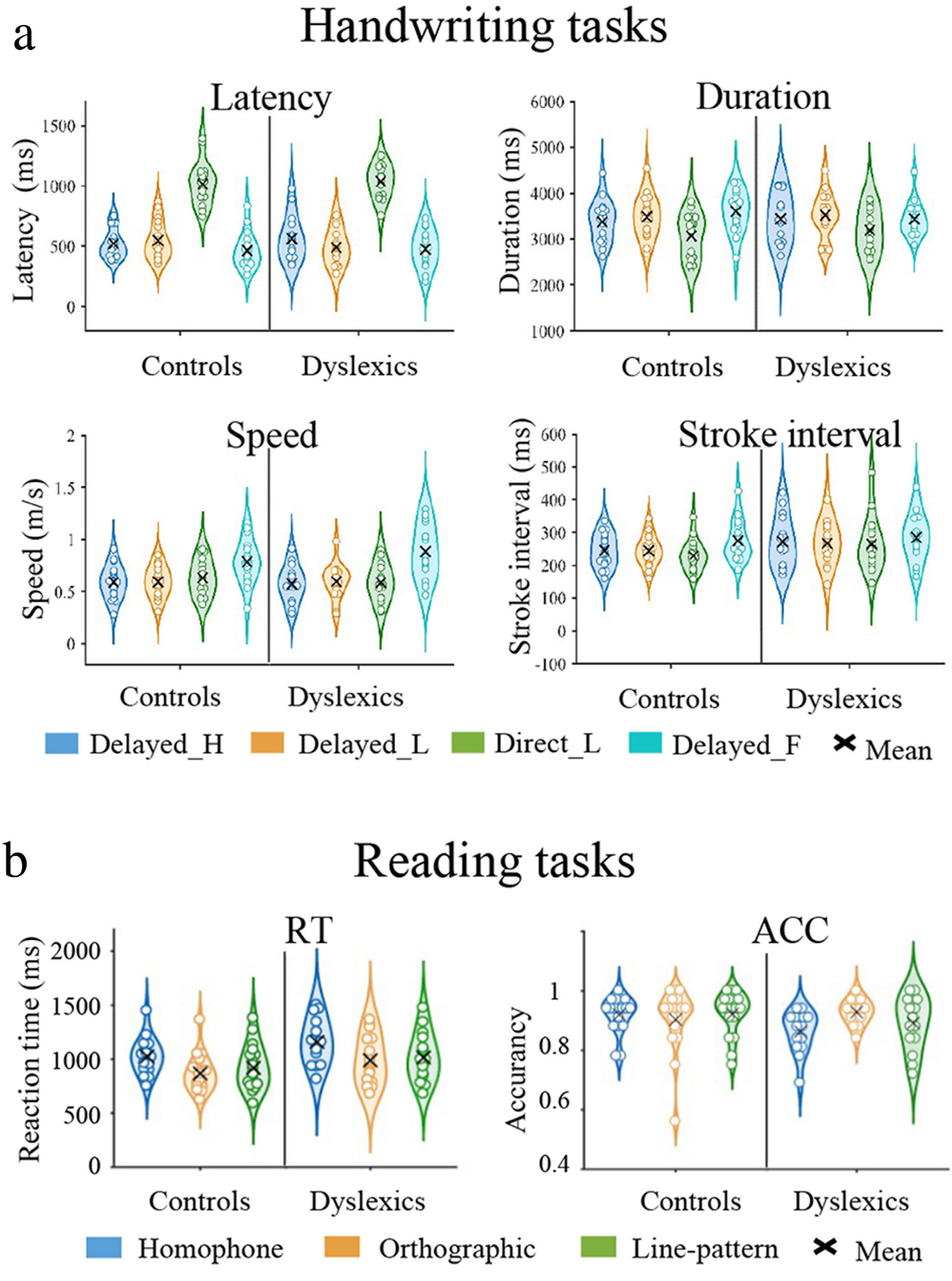

FIGURE 2 Behavioral results of handwriting and reading tasks during fMRI. (a) Violin plots of writing latency, total writing duration, mean writing speed, and mean stroke interval in handwriting tasks. (b) Violin plots of reaction time and accuracy in reading tasks
Abbreviations: ACC, accuracy; Delayed_F, delayed drawing of figures; Delayed_H, delayed copying of high-frequency Chinese characters; Delayed_L, delayed copying of low-frequency Chinese characters; Direct_L, direct copying of low-frequency Chinese characters; m, meters; ms, milliseconds; RT, reaction time; s, seconds.

TABLE 2 Brain regions showing group differences in the character handwriting conditions

Brain region	BA	MNI coordinates x	y	z	z score	Voxels
Controls > dyslexics						
R cuneus	17	24	−82	8	6.45	239
	18	18	−92	18	4.64	
L precuneus	19	−24	−84	36	6.30	245
		−15	−85	40	5.76	
		−8	−80	50	3.18	
R precuneus	19	16	−82	42	4.81	
	7	12	−78	54	4.77	
	7	22	−88	38	4.26	
L medial frontal gyrus	24	0	−8	50	5.11	426
	6	−2	−12	50	4.65	
	6	−8	−12	70	4.29	
L postcentral gyrus	3	−24	−36	68	4.42	277
	3	−22	−34	50	4.08	
		−15	−34	45	3.68	
R medial frontal gyrus	6	18	−16	52	5.72	247
R superior frontal gyrus	6	15	−4	70	4.11	
		24	−8	58	4.06	
Dyslexics > controls						
L inferior frontal gyrus	44	−46	10	20	4.90	238
L middle frontal gyrus	9	−45	5	34	4.07	
	9	−40	15	30	4.06	
L anterior cingulate gyrus	32	−8	24	42	4.38	233
L superior frontal gyrus	8	−18	26	44	3.42	

Abbreviations: BA, Brodmann area; L, left; MNI, Montreal Neurological Institute; R, right.

was significant, but the effect of group [F(1,31) = 1.41, $p = 0.24$] and the interaction of group by condition [F(3,93) = 0.90, $p = 0.43$] were not significant. These results suggest that dyslexics and controls had comparable performance in the handwriting tasks during fMRI.

Behavioral results of the reading tasks during fMRI were based on 33 participants (15 DD and 18 controls) (Figure 2b). The DD participants were less accurate than controls in performing the homophonic decision task (U = 62.50, $p = 0.01$, Mann–Whitney *U* test). Trends were also observed that DD participants performed slower in the homophonic decision task [$t(31) = 2.03$, $p = 0.05$] and the orthographic decision task [$t(31) = 1.73$, $p = 0.09$]. No significant group differences were found for accuracy in the orthographic decision task [ACC: U = 138.50, $p = 0.90$] and for performance in the line-pattern judgment task [ACC: U = 110, $p = 0.38$; RT: $t(31) = 1.26$, $p = 0.22$].

3.2 | Brain activation of handwriting tasks

In the ANOVA analysis involving the factors group (dyslexics vs. controls) and condition (delayed copying high-frequency characters vs. delayed copying low-frequency characters vs. direct copying low-frequency characters vs. figure drawing), a significant main effect of group was found in several brain regions including the bilateral precentral gyrus, left postcentral gyrus, left superior parietal lobule, bilateral precuneus, left inferior temporal gyrus, and the lateral occipital gyrus. In addition, a significant main effect of condition was found for the cuneus. Group by condition interaction effects were not statistically significant. We then used one-sample *t*-tests to examine the activation pattern during handwriting in each group of participants. Results revealed a similar and widespread brain activation pattern during handwriting under different conditions in controls (Figure 3a) and DD participants (Figure 3b, Table 2), involving the bilateral precentral gyrus, superior/middle/inferior frontal gyrus, postcentral gyrus, superior and inferior parietal lobule, superior and middle temporal gyrus, fusiform gyrus, and cerebellum. These regions were consistent with previous findings of the neural correlates of handwriting (Planton et al., 2013, 2017; Purcell et al., 2011).

The group differences for the three handwriting character conditions were investigated next. Dyslexic children showed reduced activation in comparison to controls in the left medial frontal gyrus

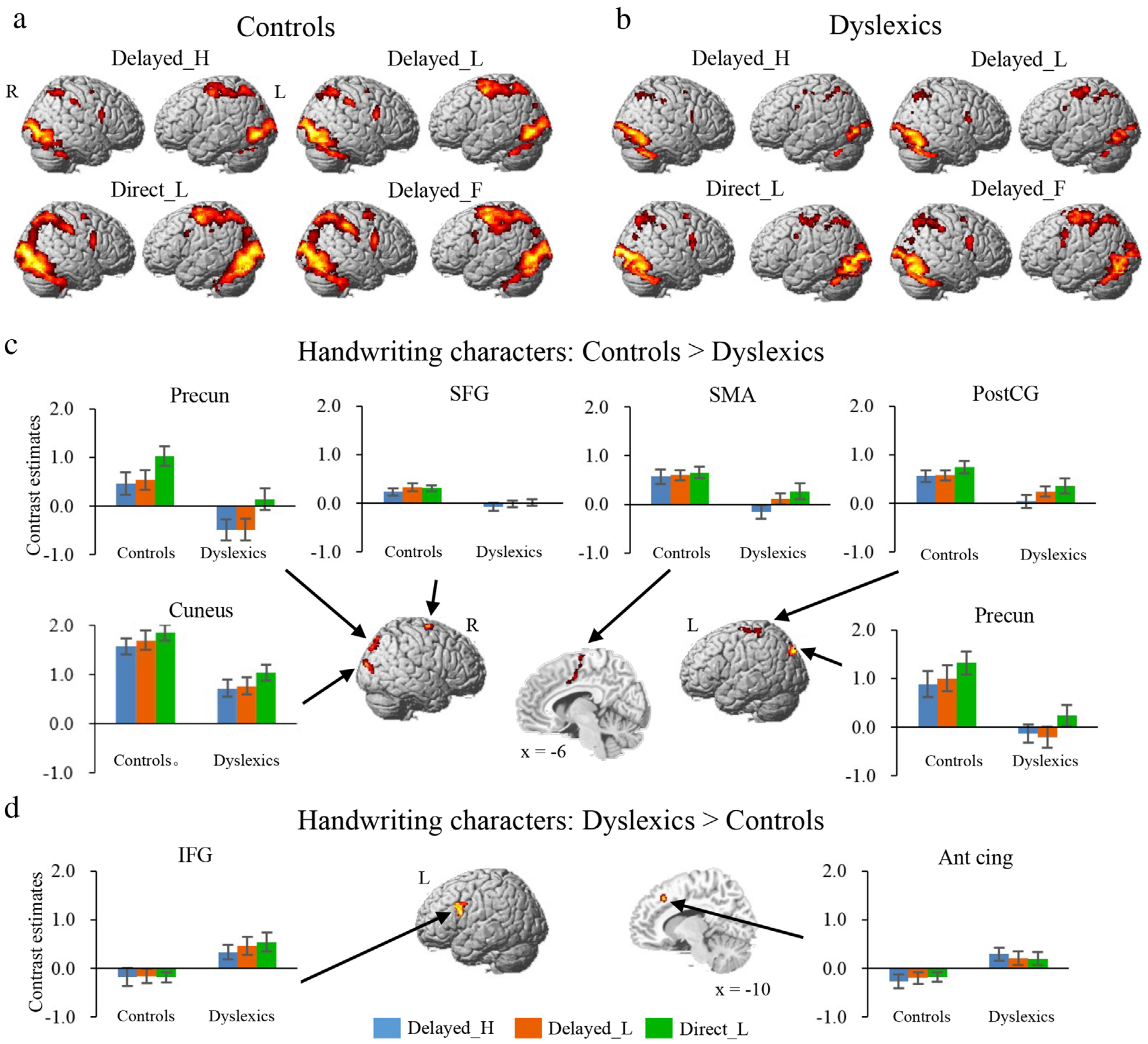

FIGURE 3 Brain activation results in the handwriting tasks. Lateral surface-rendered views of brain activation during handwriting and drawing in controls (a) and in dyslexics (b). Lateral surface-rendered views of brain regions showing reduced activation (c) and increased activation (d) during handwriting characters in dyslexics compared to controls
Abbreviations: ant cing, anterior cingulate gyrus; Delayed_F, delayed drawing of figures; Delayed_H, delayed copying of high-frequency characters; Delayed_L, delayed copying of low-frequency characters; Direct_L, direct copying of low-frequency characters; IFG, inferior frontal gyrus; L, left; postCG, postcentral gyrus; precun, precuneus; R, right; SFG, superior frontal gyrus; SMA, supplementary motor area.

including the SMA, left postcentral gyrus, right superior frontal gyrus, bilateral precuneus, and right cuneus (Figure 3c). Dyslexic children also showed increased activation in comparison to controls in the left inferior/middle frontal gyrus and anterior cingulate cortex (extending to the superior medial frontal gyrus) (Figure 3d, Table 2).

Regression analysis revealed that performance in the out-of-scanner handwriting fluency task was positively correlated with brain activation level in the left postcentral gyrus [$t(29) = 2.97$, FDR-corrected $p = 0.048$]. There was also a trend of correlation between handwriting fluency and activation in the left SMA, but the correlation did not survive the correction for multiple comparisons [$t(29) = 2.15$, uncorrected $p = 0.040$].

3.3 | Brain activation of reading tasks

The reading task yielded significant brain activation mainly in the left inferior and middle frontal gyrus, bilateral inferior temporal gyrus,

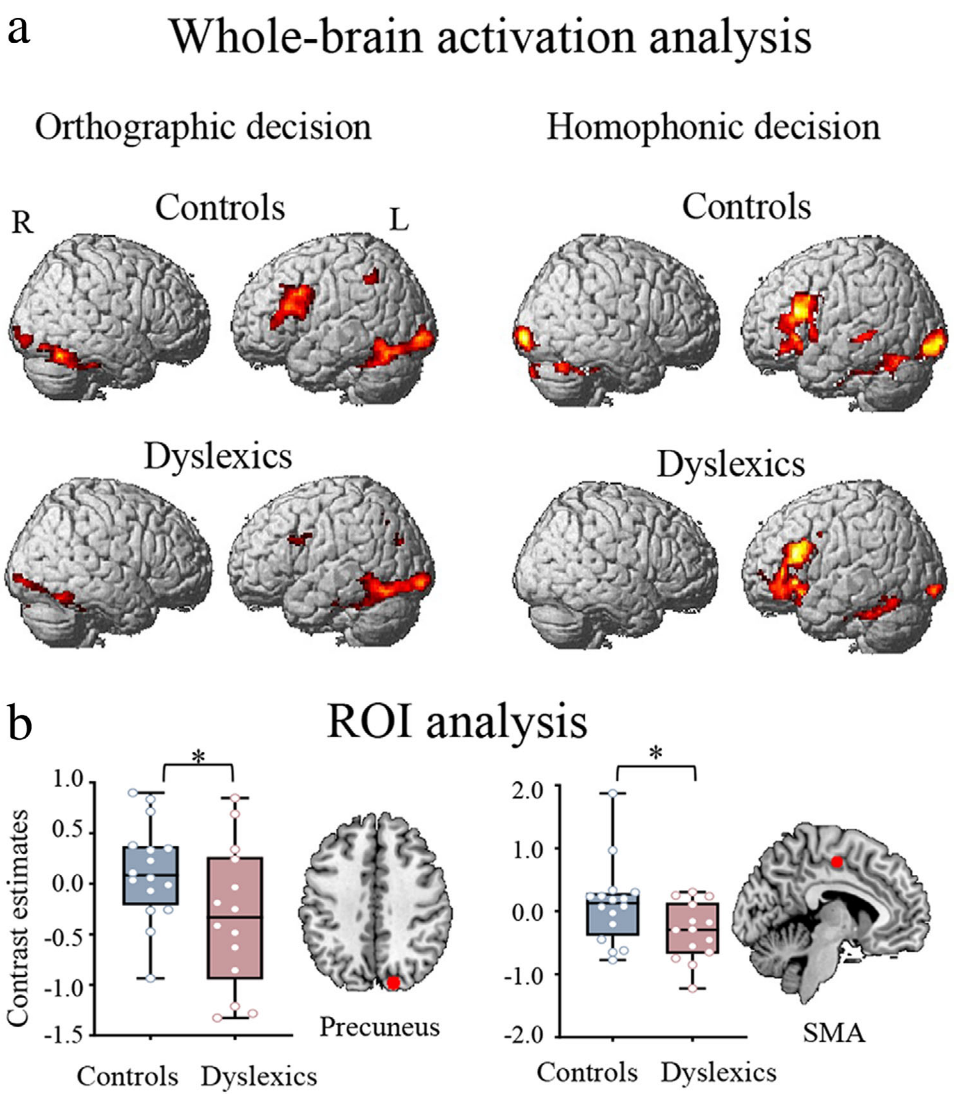

FIGURE 4 Brain activation for reading tasks. (a) Lateral surface-rendered views of whole-brain analyses for the orthographic decision and homophonic decision tasks in controls and dyslexics. (b) ROI-analysis showing significant group differences in the right precuneus during the orthographic decision task and in the SMA during the homophonic decision task. The horizontal lines in the middle represent medians, the edges of boxes represent quartiles, and the whiskers represent maximum and minimum values. Abbreviations: ROI, region of interest; SMA, supplementary motor area. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

inferior/middle occipital gyrus, and fusiform gyrus in both orthographic decision and homophonic decision conditions. More wide-spread activation was observed for controls than dyslexics in prefrontal and parietal cortices during the orthographic decision task, and in middle/superior temporal cortex and the right occipitotemporal cortex during the homophonic decision task, but the direct contrast between the two groups was not statistically significant (Figure 4a).

Brain activity during reading tasks was then compared between the two groups, focusing on the ROIs that showed significant group differences in handwriting tasks (as shown in Figure 3c,d, and described in the Materials and Methods section). Dyslexic participants showed reduced activation in the right precuneus during the orthographic decision task [$t(28) = 2.06$, uncorrected $p = 0.049$] and in the SMA during the homophonic decision task [$t(28) = 2.08$, uncorrected $p = 0.047$], but neither result survived correction for multiple comparisons (Figure 4b).

3.4 | Functional connectivity results of handwriting tasks

To further examine whether the two groups differed in functional connectivity during handwriting, gPPI analysis was performed using seed regions consisting of the ROIs that showed significant group activation differences for the handwriting tasks. We found no interaction between group and condition for functional connectivity, and we then focused on the main effect of group across the three handwriting tasks. Compared to controls, dyslexic participants exhibited weaker

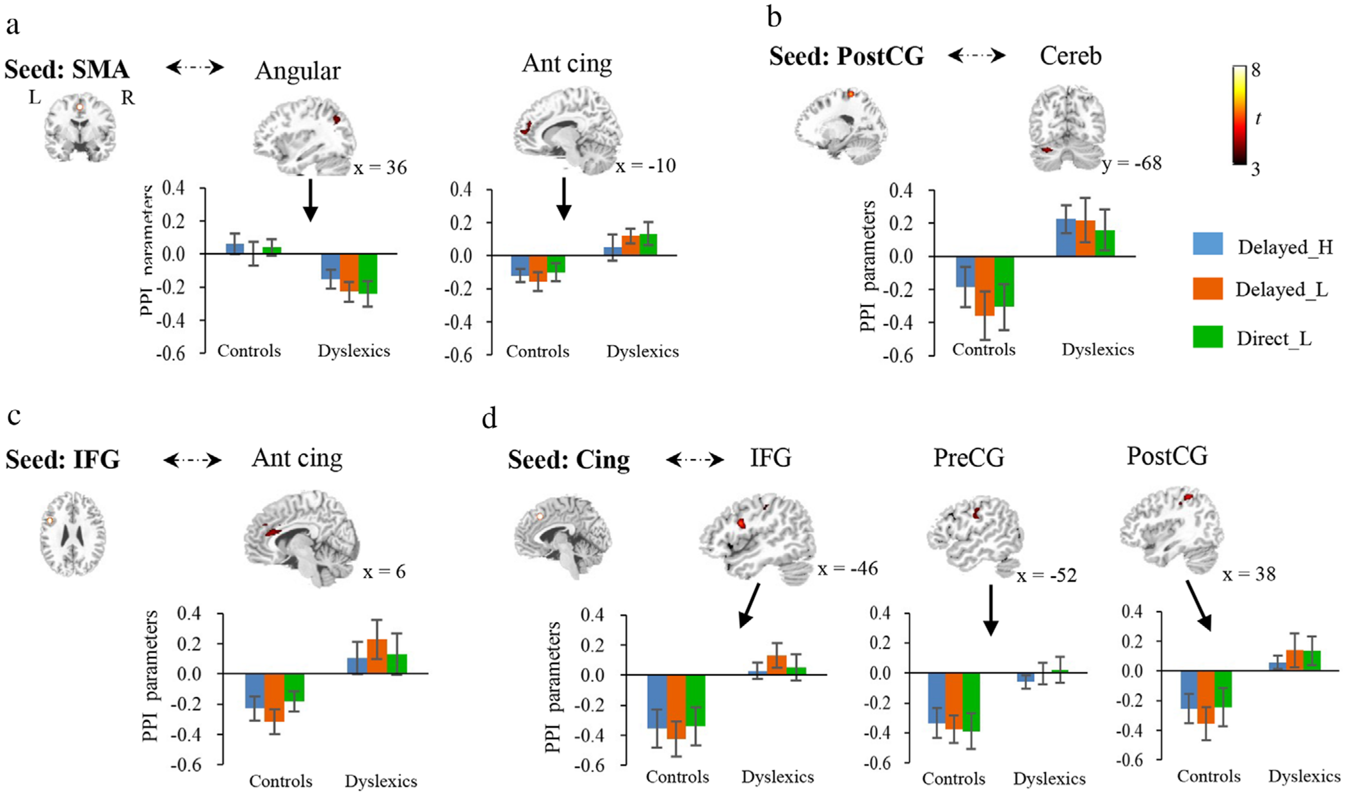

FIGURE 5 The results of generalized psychophysiological interaction (gPPI) analysis for the handwriting tasks. Sagittal, coronal, or axial views of implicated regions and PPI parameters showing group differences based on connectivity analysis of the following seed regions: (a) the SMA, (b) left postcentral gyrus, (c) left inferior frontal gyrus, and (d) anterior cingulate cortex

Abbreviations: ant cing, anterior cingulate gyrus; Delayed_L, delayed copying of low-frequency characters; Direct_L, direct copying of low-frequency characters; IFG, inferior frontal gyrus; L, left; postCG, postcentral gyrus; precun, precuneus; R, right; SFG, superior frontal gyrus; SMA, supplementary motor area.

connectivity between SMA and the angular gyrus. As illustrated by plots of connectivity strength, this effect was largely driven by negative connection between SMA and the angular gyrus in children with dyslexia and an absence of connectivity in controls (Figure 5a, Table 3). Conversely, DD showed hyperconnectivity in a larger scale functional network, including the connectivity between the SMA and the left cingulate gyrus, between the left postcentral gyrus and left cerebellum, between the left inferior frontal gyrus and the right anterior cingulate cortex, and between the left cingulate cortex and left inferior frontal gyrus, left precentral gyrus, and right postcentral gyrus. Visualizing the connectivity strength of these clusters showed that these effects were mainly driven by negative connectivity in controls but either positive or no connectivity in the dyslexic group (Figure 5b–d, Table 3).

Finally, we examined whether the functional connectivity showing significant group differences was related to handwriting performance. We found that handwriting fluency of characters was negatively correlated with strength of functional connections among brain areas for motor and cognitive control, including connections between the left SMA and the left cingulate gyrus [$t(29) = -3.38$, $p = 0.003$], the left postcentral gyrus and the left cerebellum [$t(29) = -3.43$, $p = 0.003$], the left inferior frontal gyrus and the right anterior cingulate gyrus [$t(29) = -2.22$, $p = 0.040$], and between the left cingulate and three other brain regions, including the left inferior frontal gyrus [$t(29) = -4.13$, $p < 0.001$], the left precentral gyrus [$t(29) = -4.12$, $p < 0.001$], and the right postcentral gyrus [$t(29) = -3.69$, $p = 0.002$].

4 | DISCUSSION

This study examined the neural correlates of handwriting deficits and the connection between reading and handwriting deficits in DD participants. The findings suggest that the handwriting problem in dyslexics is not a pure motor deficit, but instead is associated with functional abnormalities of multiple brain regions implicated in motor execution, visual-orthographic processing, and cognitive control. Compared to controls, DD participants were found to exhibit reduced activation in multiple brain regions supporting sensory-motor processing (such as the SMA and the postcentral gyrus) and visual-orthographic processing (such as the bilateral precuneus and the right cuneus) during handwriting. Among these regions, the SMA and the right precuneus also showed reduced activation during reading tasks in DD participants.

TABLE 3 Group differences in functional connectivity between controls and dyslexic participants, associated with handwriting of Chinese characters

Brain regions	BA	MNI coordinate x	y	z	z score	Voxels
Seed: L SMA (0, −8, 50)						
Controls > dyslexics						
R angular gyrus	39	32	−64	36	4.23	282
	39	50	−72	34	3.81	
R middle temporal gyrus	39	40	−58	24	3.57	
Dyslexics > controls						
L anterior cingulate gyrus	32	−18	46	12	4.59	285
L medial frontal gyrus	10	−12	54	8	4.33	
	9	−12	44	22	4.27	
Seed: L inferior frontal gyrus (−46, 10, 22)						
Dyslexics > controls						
R anterior cingulate	24	2	14	26	4.91	964
	32	5	32	34	4.70	
	24	−10	30	18	4.29	
Seed: L postcentral gyrus (−24, −36, 68)						
Dyslexics > controls						
L postcentral gyrus	40	−53	−32	54	4.84	609
L inferior parietal lobule	40	−46	−52	54	4.04	
	40	−40	−46	54	3.86	
L cerebellar declive	−44	−60	−30	4.30	280	
		−28	−68	−28	4.15	
		−26	−75	−24	3.90	
Seed: L cingulate gyrus (−8, 24, 42)						
Dyslexics > controls						
L inferior frontal gyrus	44	−50	7	24	5.56	236
L precentral gyrus	4	−57	−16	39	4.56	552
L inferior parietal lobule	40	−38	−38	52	4.51	
	40	−63	−27	38	3.82	
R postcentral gyrus	43	63	−14	21	4.53	517
	4	57	−18	38	4.43	
	2	53	−18	27	4.41	

Abbreviations: BA, Brodmann area; L, left; MNI, Montreal Neurological Institute; R, right; SMA, supplementary motor area.

Conversely, increased activation was observed in the left inferior frontal gyrus and anterior cingulate cortex in dyslexics during handwriting, which may reflect more efforts of executive control due to low level of handwriting automatization.

4.1 | Behavioral correlates of handwriting deficit in dyslexic children

Considering behavioral performance, DD participants showed slower handwriting speed in handwriting fluency tasks than controls, consistent with previous behavioral studies of dyslexia (Connelly et al., 2006; Hatcher et al., 2002; Kalindi et al., 2015; Kalindi et al., 2015; Lam & McBride, 2018; Sumner et al., 2013). However, significant group differences were not observed in pen-and-paper copying tasks that assessed handwriting quality outside of the MRI system, or in the handwriting tasks performed during fMRI. Different from the handwriting fluency task, these two sets of tasks did not explicitly require the participants to write fast. Thus, the results suggest a handwriting fluency deficit in dyslexic children. Notably, both groups showed comparable behavioral performance in the handwriting tasks during fMRI, but group differences were revealed in brain activation and functional connectivity during the task, suggesting that there may be group differences in the cognitive processes during handwriting, which are captured by brain functional patterns but not by behavioral performance.

4.2 | Brain activation for peripheral motor processing during handwriting

Contemporary models consider handwriting as a complex neuromotor skill involving cognitive and motor processes that are controlled by a hierarchic architecture of both central components (such as the store of the orthographic lexicon, and orthographic working memory) and peripheral components (such as letter-shape conversion, graphic motor planning and execution) (Kandel et al., 2011; Purcell et al., 2011; Van Galen, 1991). The present study found that DD participants had reduced brain activation in the medial frontal gyrus corresponding to the SMA, and the postcentral gyrus extending to the superior parietal lobule in the handwriting tasks. These regions are typically associated with peripheral motor processing, as revealed by previous neuroimaging studies (for a review, see Purcell et al., 2011).

The SMA plays a vital role in handwriting and it is activated in a variety of handwriting tasks (Planton et al., 2013; Purcell et al., 2011). Functionally, it has been implicated to support the organization and execution of motor sequences (Gerloff et al., 1997; Nachev et al., 2008; Nakamura et al., 1998). For example, Gerloff et al. demonstrated that stimulation of the SMA using high-frequency repetitive transcranial magnetic stimulation interfered with the organization of subsequent elements in the complex motor sequence (Gerloff et al., 1997). A previous study has also reported that dyslexics showed reduced activation in the SMA during motor sequence learning (Menghini et al., 2006). Consequently, the results of the present study and the existing literature support that the SMA may be recruited for motor sequence memory during handwriting of written words, and that the impaired function of the SMA in dyslexics may interfere with the retrieval and execution of the motor sequence during handwriting.

The DD participants also exhibited reduced activation in the SMA during reading tasks, which may be due to a disruption of motor sequence memory for visual word recognition. This explanation is supported by the previous finding that activation of the SMA was sensitive to the stroke sequence of Chinese characters in visual word recognition (Yu et al., 2011; Zhang et al., 2021). During reading acquisition, Chinese children spend much time learning by writing characters following conventional rules of stroke sequences. Through repetitive practice of handwriting, children learn how to deconstruct characters into strokes and stroke patterns, then regroup these stroke patterns into square units, which helps to establish elaborated representations of written word forms (Cao et al., 2013; Tan, Spinks, et al., 2005; Tan et al., 2013). The gestural and sequence information concerning how the written symbols are produced could be represented in specific brain regions and recruited during both writing and reading (Nakamura et al., 2012; Zhang et al., 2021). Therefore, the SMA may be an important neural locus where dyslexic children showed a deficit in automatic dynamic motor representations of written words. However, future studies are needed to further elucidate whether the neural deficit in this region is caused by insufficient writing practice in dyslexic children as compared to normal children, as well as whether it represents a language-specific neural deficit in Chinese dyslexia. For example, studies with dyslexic participants of alphabetic languages would help inform the universal and language-specific neural mechanisms for reading and handwriting in DD.

The present study also found that DD participants had reduced activation during handwriting in a cluster of voxels with its peak at the left postcentral gyrus and extending posteriorly into the superior parietal lobule. Convergent evidence from patient studies (Alexander et al., 1992; Sakurai et al., 2007) and neuroimaging studies of normal people (Planton et al., 2013; Purcell et al., 2011) has shown that the postcentral gyrus and the posterior parietal lobule are critically involved in the peripheral motor component of handwriting processing. The left postcentral gyrus is thought to be engaged in the somatosensory feedback that is important for handwriting motor execution (Sakurai et al., 2007). For example, postcentral gyrus lesions can yield graphemic distortion (somesthetic dysgraphia) and reduced writing speed in brain-damaged patients, probably due to insufficient sensory and kinesthetic feedback during writing (Sakurai et al., 2007).These observations are consistent with our finding of significant correlation between the activation level in the postcentral gyrus area and handwriting fluency. Furthermore, the superior parietal lobule receives a great deal of visual and sensory input, and it has been suggested to house the kinesthetic and sequential motor engrams of letters that support serial production of letter shapes during writing (Planton et al., 2013; Sakurai et al., 2007).

4.3 | Brain regions for visual-orthographic processing during handwriting and reading

The present study found that DD participants had reduced activation in the occipital-parietal regions relative to controls in handwriting tasks, including bilateral precuneus (BA 7/19) and the right cuneus extending to the extrastriate area (BA 17/18). The DD participants also exhibited reduced activation in the right precuneus during reading tasks. Whereas the cuneus subserves basic visual processing, the precuneus is involved in more complex functions such as visual attention, integration of information, and visuo-spatial imagery (Cavanna & Trimble, 2006). Reduced activation in the precuneus in dyslexic children may reflect less efficient or less complete processing of visual-spatial and orthographic information during reading and handwriting. Furthermore, previous studies have consistently found reduced brain activation (Cao et al., 2018; Maisog et al., 2008) and structural alterations (Menghini et al., 2008) in the precuneus in dyslexics. The present study extends previous findings by demonstrating that reduced activation of these brain regions for visual-orthographic processing is also associated with handwriting processing in dyslexics. The left precuneus has been reported to serve a key role in handwriting processing (Cao & Perfetti, 2016; Purcell et al., 2011), as well as the spatial location (Thompson et al., 2009) and visuo-spatial imagery of letters (Raij, 1999). The impaired activation of the precuneus, as found in both handwriting and reading tasks in the present study, suggest that this dysfunction may not be specific to reading or handwriting and instead represents a more general deficit in visuo-spatial processing of written language.

Moreover, due to the complex visuo-spatial configurations of Chinese characters, reading and writing Chinese characters demand greater visuo-spatial analysis relative to other languages such as English (Bolger et al., 2005; Tan, Laird, et al., 2005; Wu et al., 2012). It has been suggested that the precuneus and surrounding areas are more involved in the processing of written Chinese, and these regions are consistently deactivated in Chinese dyslexics (Cao et al., 2018; Siok et al., 2009). Therefore, whereas the visual-orthographic deficit is found to be related to dyslexia across languages, it may be more pronounced in Chinese dyslexics.

4.4 | Increased brain activation and aberrant connectivity in dyslexics during handwriting

The present study showed hyperactivity in the anterior cingulate cortex and the left dorsal inferior frontal gyrus in DD participants compared to controls. The anterior cingulate cortex is a multifunctional brain region involved in cognitive, motor, and affective processes (Bush et al., 2000; Paus, 2001). It plays an important role in response inhibition (Bush et al., 2000; Hung et al., 2018; Kerns, 2004), and provides a continuous updated prediction of ongoing cognitive processing to optimize performance (Sheth et al., 2012). During handwriting, the correct orthographic units have to be retrieved in the correct order and put into a tuned motor system for stroke-by-stroke execution, processes that require ongoing monitoring to inhibit erroneous responses. Consequently, the increased brain activation in the anterior cingulate cortex may reflect that dyslexics incur greater demands on cognitive control.

Increased activation of the left inferior frontal gyrus in dyslexia has been previously reported during reading (Pugh et al., 2000; Siok et al., 2004). Some propose that this region may support fine-grained articulatory recoding and serve as a compensatory mechanism for the problematic phonological analysis of printed words in the posterior reading circuits during the reading process (Pugh et al., 2001; Shaywitz & Shaywitz, 2008). With respect to handwriting, the left inferior frontal gyrus has been found to be sensitive to word frequency effect during writing to dictation, suggesting a role for this region in orthographic representation in long-term memory (Rapp & Dufor, 2011). Alternatively, the left inferior frontal gyrus has also been posited to be responsible for general control processing, such as the selection of a response among competing responses (Thompson-Schill et al., 1998). The present study did not observe an effect of word frequency or an interaction effect of group and a linguistic factor (such as word frequency) related to activation of this region during handwriting. One explanation for the increased activation of the left inferior frontal gyrus in DD participants compared to controls is that it may reflect a greater reliance on this circuit to support domain-general executive control.

Analysis of connectivity revealed aberrant functional connectivity in children with DD compared to controls. In control children, we found negative connectivity among brain areas for cognitive control and sensory-motor processes during handwriting tasks, but this pattern was not observed in children with DD. For example, we observed negative connectivity between the anterior cingulate cortex and SMA, precentral gyrus, and postcentral gyrus in controls, but the connections were absent in DD participants. Evidence from primate and human studies has indicated close connectivity of the cingulate cortex with the prefrontal motor regions including the premotor area, primary motor area, and the SMA (Paus, 2001). Anatomically, the SMA is extensively connected with the anterior cingulate cortex via cingulum fibers (Jones et al., 2013). Previous work has shown that motor skill learning induces an autonomy of the sensorimotor system, which is associated with discontinued coordinated activity in cognitive control hubs in frontal and cingulate cortices (Bassett et al., 2015; Mohr et al., 2016). In addition, increased connectivity in dyslexic children compared to controls was found in previous studies, and it was interpreted as reduced segregation between different functional networks (Cao et al., 2017). Thus, the negative functional connectivity during handwriting in control participants may reflect functional segregation between brain regions for cognitive control and motor regions, whereas an increase or absence of connectivity in dyslexic children may suggest a reduced segregation of cognitive control and sensory-motor networks, which affects the automatization of handwriting. This interpretation was further supported by the connectivity-performance correlational results showing that the greater connectivity strength (e.g., between cingulate cortex and precentral gyrus) was associated with lower writing speed in the handwriting fluency task.

4.5 | Conclusion and limitations

It was found that handwriting deficits in dyslexia are associated with abnormal brain activation and functional connectivity involving brain regions with roles in motor, visual orthographic, and executive control processes. Thus, it is proposed that the handwriting deficit in DD is not a pure language or motor problem, but instead a systematic cognitive and motor dysfunction. The present study advances understanding of the neurological basis associated with handwriting deficits in dyslexia. In the future, this new information may help to improve diagnostic and training strategies for dyslexia.

The present study has some limitations. First, the sample size is relatively small, although the statistical power of the main results is acceptable. The study findings nevertheless will require replication in future studies by other investigators. In addition, the control participants were only matched with the DD participants by mean age and sex, and thus it is still unclear whether the observed between-group differences are the origin of the handwriting problem in dyslexia, or the consequence of delayed development of reading and writing skills (which also could be sex-dependent). Further studies with a reading/writing performance-matched control group, and with additional consideration for sex, are needed to examine the causal relationship between brain dysfunction and handwriting deficits in dyslexia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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