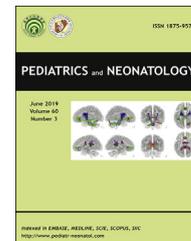




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Original Article

Specifying the diffusion MRI connectome in Chinese-speaking children with developmental dyslexia and auditory processing deficits



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Keywords

auditory frequency-modulation processing;
Chinese developmental dyslexia;
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diffusion MRI;
lexical tone awareness

Background: Lexical tone identification has a unique role in the perceptual processes of Chinese readers. Reduced lexical tone awareness, along with poor word-decoding abilities, is frequently observed in Chinese-speaking children with developmental dyslexia. However, whether this deficit is linked to reduced auditory processing and interrupted structural connectivity in the brain requires further investigation. This study therefore explores the white matter pathways associated with Chinese character recognition and auditory processing of pitch variations, with the objective of to identify the most representative neural correlates for Chinese developmental dyslexia.

Methods: Diffusion magnetic resonance imaging and several behavior measures related to reading attainment and phonological awareness were acquired in twenty-four Chinese-speaking children with developmental dyslexia and twenty-two age-matched controls. We used diffusion magnetic resonance imaging connectometry to explore the relationships between behavior performance and specific white matter tracts.

Results: The results revealed significant correlations of the left inferior fronto-occipital fasciculus, cerebellar pathways, and thalamopontine tracts with Chinese character recognition (FDR = 0.03235). In addition, the posterior isthmus and anterior splenium of the corpus callosum correlated with auditory processing (FDR = 0.03980).

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Conclusion: The study provides evidence that the dysconnectivity on white matter pathways correlated with developmental dyslexia in Chinese-speaking children. Furthermore, the impairments of auditory temporal timing processing presented in poor readers with significant phonological deficits are likely to be a result of impoverished myelination in sub-cortical tracts. Such findings may assist in the clinical identification of Chinese developmental dyslexia. Copyright © 2018, Taiwan Pediatric Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Developmental dyslexia (DD) is a neurodevelopmental disorder affecting approximately 5–17.5% of the population, regardless of culture or language backgrounds.¹ According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),² dyslexia is a learning disability that affects word recognition, decoding, and spelling abilities. Interrupted neural mechanisms, such as auditory perception and language processing, are reflected by profound reading difficulties. Phonological deficits, including impaired phonological representation and speech sound processing, are presented in the majority of the dyslexic population.³ The difficulties in basic auditory processing have been further suggested as a characteristic of DD and adversely affect the formation of high-quality phonological representations. However, the phonology of tonal languages, such as Chinese, contains a unique suprasegmental feature—lexical tone—that is a crucial language-specific factor to be considered in Chinese dyslexia.

Many studies have demonstrated that lexical tone plays an important role in reading development.⁴ Reduced lexical tone awareness has frequently been reported among Chinese-speaking children with dyslexia.^{5,6} Chinese Mandarin has four lexical tones, each with a different internal pattern of rising and falling pitch, that is, a change of fundamental frequency. Because frequency modulation (FM) is one of the most vital physical aspects of making lexical distinctions, a neurophysiological investigation of the sensitivity of the human auditory system to FM signals may help elucidate the processing difficulties of lexical tones in Chinese-speaking children. However, literature on the neural mechanism of lexical tone awareness and FM sensitivity in Chinese dyslexia is scarce.

Functional magnetic resonance imaging (fMRI) studies have shown that reading involves a widespread left-hemisphere network, which includes the frontal, temporoparietal, and occipito-temporal cortical regions.^{7,8} In children with DD, altered activation patterns have been reported during task performance. For instance, under-activation of the left posterior areas, including the dorsal temporoparietal and ventral occipitotemporal cortexes, has been observed in reading-related tasks.⁹ The integrity of the white matter pathways, which are the anatomical counterparts of functional connectivity, may account for these functional disruptions. Building on the fMRI evidence, many structural investigations using diffusion MRI have

focused on the left arcuate fasciculus, which connects two regions of the reading network: the left temporoparietal and the left inferior frontal gyrus.¹⁰ This particular white matter tract is closely associated with phoneme awareness and speech perception. Reduced integrity of the left arcuate fasciculus has been commonly reported in children with DD.^{10,11} Some studies have demonstrated positive correlations between various reading components (word naming, decoding, and reading fluency) and the integrity of white matter tracts in the thalamus and parietal and temporal areas.¹²

In addition to the change of activation within the putative reading network in the left hemisphere, altered right-hemisphere activations have been observed and are considered as a compensatory mechanism.^{13–15} The involvement of the right hemisphere during various reading tasks draws attention to the white matter structure, namely the corpus callosum that bridges the two hemispheres.¹⁶ For instance, Farris et al. noted that the integrity of the corpus callosum plays a role in DD treatment response.¹⁵ Farris et al. demonstrated that while performing a phoneme–grapheme task, treatment responders exhibited greater activation in the right-hemisphere regions, including the right inferior frontal gyrus, triangularis, precentral gyrus, and opercularis, than treatment non-responders and controls. Correlation analyses incorporating fMRI and diffusion MRI data further revealed an association between the anterior corpus callosum and the right-hemisphere activations; that is, when performing a challenging task, the treatment responders activated the right-hemisphere regions to compensate processing, and this compensation process was mediated by the anterior corpus callosum.

Functional and structural imaging evidences support the multidimensional deficit theory, which argues that DD is under the effect of multiple cognitive and neural deficits.¹⁷ However, consensus is lacking regarding which behavioral characteristic and corresponding white matter tract provide the most accurate reflection of Chinese DD and, therefore, may be used as neural correlates to assist clinical diagnosis. This study aims to identify the neural correlates that reflect the underlying deficits in Chinese DD. In particular, because auditory FM sensitivity has typically been overlooked, this study investigates the extent to which it accounts for reduced phonological and reading functions. In addition, this study identifies the most representative behavioral characteristic and its white matter counterpart(s).

2. Methods

2.1. Participants

Forty-six children aged nine to eleven from primary schools in Taipei City, Taiwan, participated in the study. All children were monolingual Mandarin Chinese speakers. Twenty-four children with DD (DD group) were screened from the database of the Special Education Division, Department of Education of Taipei City Government, and recruited. Children with DD were required to demonstrate sufficient reading failure in Chinese character recognition, assessed by the Chinese Character Recognition Test, and to have been behind typically developing reading skills for two years.¹⁸ The diagnostic features met the criteria suggested by the DSM-5. Moreover, the children in this study exhibited severe literacy and phonological deficits in our assessment. Twenty-two age-matched volunteers (control group) participated in the study as controls.

The children's intelligence quotient (IQ) was assessed using the Abbreviated Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) to ensure that all participants recruited had a regular IQ (full scale IQ > 80).¹⁹ All the participants exhibited no other neurological or psychiatric disorders. A consent form was given to the children and their parents to ensure their understanding of the study. This study was approved by the Research Ethics Committee at National Taiwan University (NTU-REC, No. 201310EM016).

2.2. Behavioral measures

All participants completed three sessions, allocated on different days, at their school. Each session lasted for approximately 40 min and included three tests: Chinese character recognition, tone awareness, and auditory FM identification. The order of the tests was randomized among the participants.

2.2.1. Chinese character recognition

Character recognition ability was measured with the Chinese Character Recognition Test, developed by Huang.¹⁸ In the test, the children were instructed to read aloud a series of 200 characters with progressively lowered printed-word frequency. All characters were semantically irrelevant and contained orthographic correspondences (real characters). One point was assigned to each correct response; thus, the maximum score was 200. Each participant's accuracy was recorded. The split-test reliability coefficient of this test was 0.99.

2.2.2. Chinese lexical tone awareness test

This test contained four practice trials and twenty test trials. Each trial comprised three distinct monosyllables. Nonsense syllables were used in ten out of twenty test trials. Children were asked to identify the syllable with the odd tone after a trial was presented by the administrator. A correct response earned one point and the maximum score was 20. The coefficient of internal consistency for this test was 0.81 (Cronbach's α).

2.2.3. Auditory identification of FM test

The auditory stimuli were created using LabVIEW 2013 Service Pack 1 to generate linear frequency-modulated tone slides with 16 bits of resolution and a sampling rate of 44.1 kHz. The FM slides comprised upward and downward directions. For each direction, two frequency ranges (600–900 Hz & 85–200 Hz) at seven FM rates (5, 10, 20, 30, 40, 50, & 80 ms) were presented. Linear rise and fall times of 2 ms were included in all the FM slides to minimize spectral splatter. Fourteen complex tone slides were created for the task. In total, 140 items were divided into seven runs, each of which lasted 15–20 min.

This task was presented as a computer-based game run on Matlab. Children listened to three complex FM slides of the same duration. Each FM slide had a cartoon character counterpart. Once all three slides were presented, the children were to identify which cartoon character sounded different; that is, the task was to identify the odd FM slide with a direction that was different from the others. The response accuracy was recorded for each child, and the maximum score for the test was 140.

2.3. MRI acquisition

The data of the 44 participants were included in the connectometry database. The diffusion images were acquired on a Siemens Prisma scanner as a 2D EPI diffusion sequence. The echo time was 97 ms, and the repetition time was 6700 ms. A diffusion spectrum imaging scheme with a total of 128 diffusion samplings was acquired. The maximum b -value was 5000 s/mm². The in-plane resolution was 2.7 mm, and the slice thickness was 2.7 mm. The diffusion data were reconstructed in the MNI space using q-space diffeomorphic reconstruction to obtain the spin distribution function (SDF).^{20,21} With the default settings, a diffusion sampling length ratio of 1.25 was used, and the output resolution was 2 mm.

2.4. Connectogram

We constructed group average templates by averaging the SDF for the DD and control groups. The average templates (control and dyslexic) allowed us to study the representative brain connections and their differences. To generate a connectogram for the group template, a deterministic fiber tracking algorithm was applied respectively to generate whole-brain tractography.²² The anisotropy threshold, angular threshold, and step size were randomly selected using the default setting in DSI Studio, and 1,000,000 tracts were calculated for the connectivity matrix based on an automated anatomical labeling atlas, allowing us to visualize the connectogram for each group.²³ To further analyze the group difference, we calculated the between-group connectivity difference for each entry and plotted the connectogram to facilitate inspection. A dysconnectivity network was obtained by filtering the matrix entries with fewer fibers in the template of DD.

2.5. Diffusion MRI connectometry

Diffusion MRI connectometry enabled us to further investigate the specific pathways associated with the decrease

of behavioral scores.²⁴ Because most of the behavioral scores were highly correlated with each other, we first conducted a principal component analysis to isolate the principal components that explained the overall score variability. This avoided overfitting in the regression model. Diffusion MRI connectometry was used to study the effect of the selected components on the white matter structure in the whole brain. A multiple regression model was used to adjust for sex and age, and the following default parameters were used. Different t thresholds (2, 2.5, and 3) were used to study the correlation at different significance levels. The local connectomes were tracked using a deterministic fiber tracking algorithm.²² Track trimming was conducted with 1 iteration. All tracks generated from bootstrap resampling were included. A length threshold of 40 mm was used to select tracks. The seeding density was 20 seeds per mm³. To estimate the false discovery rate, 2000 randomized permutations were applied to the group label to obtain the null distribution of the track length.

3. Results

3.1. Group comparisons of behavioral assessment

The data distribution and outliers were checked to ensure the statistical analyses were appropriate. Table 1 presents the mean score and standard deviation of each variable. A t -test was conducted to examine the group effect upon the individual tests. Alpha level for all tests was 0.05. No significant difference existed between the control and DD groups in age. However, significant group differences were found in Chinese character recognition (t [46] = 4.042, p < 0.001). The results also showed that the DD group was significantly poorer at lexical tone awareness (t [46] = 4.645, p < 0.006) compared with the controls. For the auditory identification of the FM task, the DD group scored significantly lower than the controls (t [46] = 3.168, p = 0.004).

3.2. Group average connectogram

The group average connectograms for the two groups are illustrated in Fig. 1A and B. The left part of the connectogram corresponds to the left hemisphere, whereas the right corresponds to the right hemisphere. The upper part corresponds to the frontal lobes, whereas the lower part corresponds to the occipital lobe. Colors are used to separate different cortical parcellations and their corresponding brain connections. The overall group average connectogram does not reveal an obvious discrepancy, though minor differences can be noted. That is, no significant difference

is present in the gross structure between groups, but some fragmental connectivity differences appear and widespread the whole brain. The connectogram of the dysconnectivity (control > dyslexic) in Fig. 2A explores the dysconnectivity in the DD group, which can be further separated into interhemisphere connections (Fig. 2B) and intrahemisphere connections (Fig. 2C). A substantial amount of intrahemisphere dysconnectivity can be seen in the figure. To examine this qualitative observation, we used connectometry analysis to identify the fiber pathways responsible for the dysconnectivity.

3.3. Principle component analysis

To avoid overfitting in the connectometry analysis, we first used principle component analysis (PCA) to isolate variables that explained most of the data variation. The PCA indicated that only two components were sufficient to explain 96.65% of the score variance (Table 2). The first component was Chinese character recognition, with a coefficient of 0.95, which explained 69.00% of the behavioral data. The second component was FM, with a coefficient of 0.96, which explained the other 27.65%.

This result suggested that in the subsequent connectometry analysis, only the two variables were required to examine 96.65% of the group variance. In the connectometry analysis, we used the first component and second component as the regressors to explore the correlating fiber pathways in the whole brain.

3.4. Tracks correlated with Chinese character recognition

We first used connectometry to map fiber pathways correlated with the first PCA component, which was predominantly weighted by the Chinese character recognition score. Fig. 3 shows the tracks positively correlated with Chinese character recognition. The false discovery rate (FDR) was 0.03235. The analysis indicated that the pathways that correlated with Chinese character recognition were the left inferior fronto-occipital fasciculus (IFOF), anterior corpus callosum, and cerebellar and thalamo-pontine pathways.

3.5. Tracks correlated with auditory identification of FM

We used connectometry to map the fiber pathways correlated with the second PCA component, which was predominantly weighted by the FM score. Fig. 4 shows the

Table 1 Mean participant characteristics.

	Controls <i>n</i> = 22	Developmental dyslexia <i>n</i> = 24	Two-sample t -test (t)
Mean age (month)	113.95 (10.00)	114.25 (11.52)	0.093 NS
Chinese character recognition	92.82 (23.43)	62.38 (22.16)	4.042***
Tone awareness	15.86 (2.53)	11.08 (4.29)	4.645***
Auditory identification of FM test	133.00 (8.73)	115.38 (25.68)	3.168**

** stands for p < 0.01; *** stands for p = 0.000.

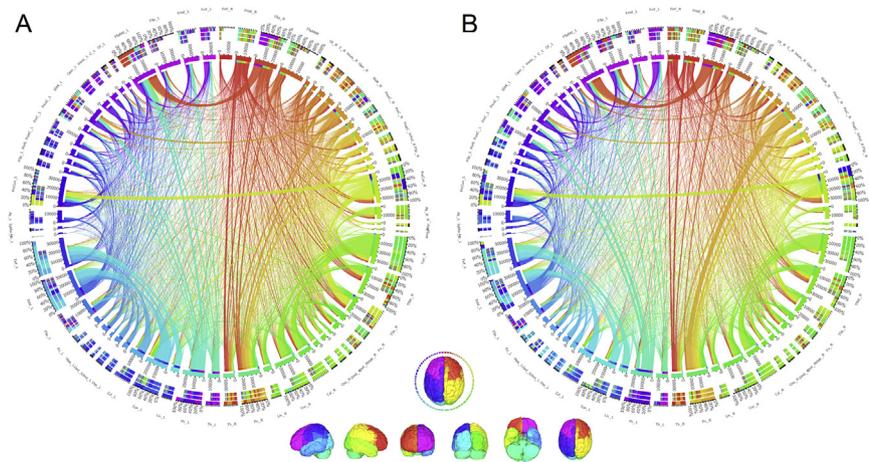


Figure 1 Group-average connectogram of (A) control and (B) dyslexic subjects.

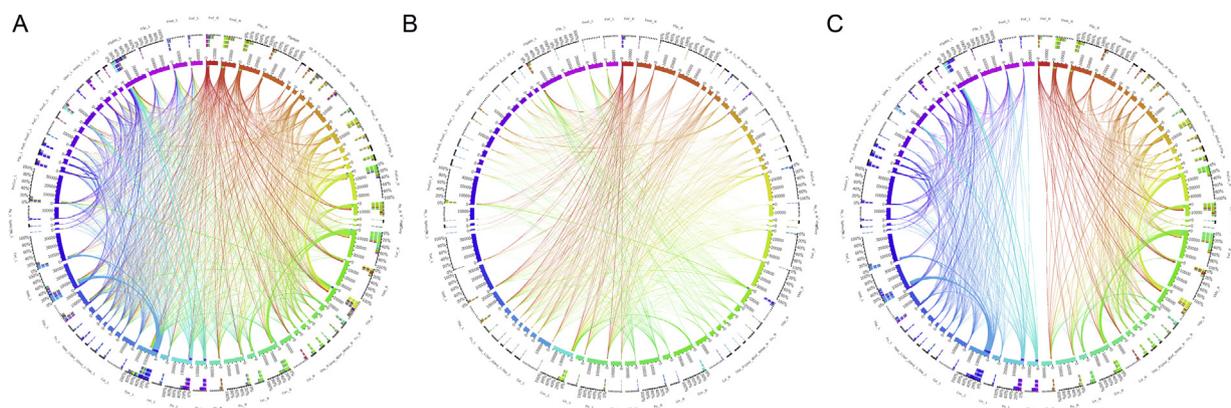


Figure 2 (A) Connectogram of dysconnectivity (control > dyslexic) between group-average templates shows that the dysconnectivity involves multiples pathways, including (B) inter-hemispheric connections, and (C) intra-hemispheric connections.

Table 2 Principle component analysis of the behavior scores.

	First component	Second component
Variance explained	69.00%	27.65%
	First component coefficient	Second component coefficient
Character recognition	0.95	-0.26
Auditory identification of FM test	0.24	0.96
Tone awareness	0.09	0.074

tracks positively correlated with FM. The FDR was 0.03980. The analysis revealed that the pathways correlated with FM were predominately located at the corpus callosum, particularly the posterior isthmus and anterior splenium, which connect the bilateral superior and inferior temporal lobes, and the anterior portion of the corpus callosum.

4. Discussion

The present study is the first to provide evidence for the association between white matter structure and Chinese character recognition and auditory FM processing in

Chinese-speaking children with DD. The results revealed that character recognition and auditory FM processing are highly representative characteristics of DD. Anatomically, the left IFOF and cerebellar and thalamopontine tracts were significantly correlated with Chinese character recognition, whereas the posterior isthmus and anterior splenium within the posterior corpus callosum were significantly associated with auditory FM processing. In addition, the anterior corpus callosum was associated with Chinese character recognition and FM processing. The findings implicate the possible pathophysiology of Chinese DD that is of a phonological type.

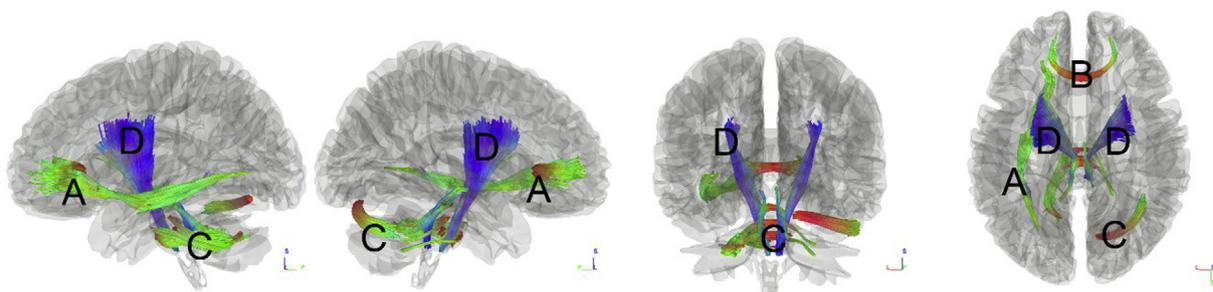


Figure 3 Diffusion MRI connectometry analysis shows significant correlation ($FDR = 0.03235$) between Chinese character recognition and pathways including (A) left inferior fronto-occipital fasciculus, (B) anterior corpus callosum, (C) cerebellar and (D) thalamopontine pathways.

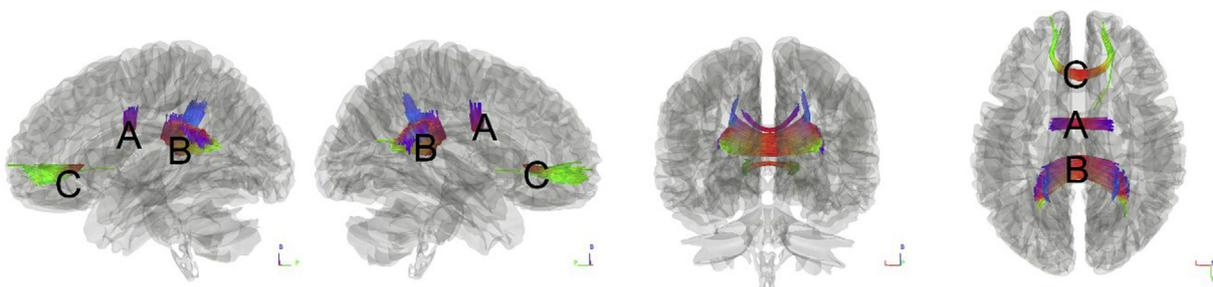


Figure 4 Diffusion MRI connectometry analysis shows significant correlation ($FDR = 0.03980$) between auditory frequency discrimination and predominately inter-hemispheric pathways including (A) the posterior isthmus of the corpus callosum, (B) the anterior splenium of the corpus callosum, and (C) the anterior of corpus callosum.

The data may be linked to the cerebellar-deficit hypothesis (CDH).²⁵ The CDH also supported the automatization deficit hypothesis by revealing an impaired ability to multitask in children with DD; balance was not automatic for them. According to Fawcett and Nicolson, deficits in phonological and balancing skills did not improve through maturation, with the oldest children with DD barely achieving the same level of performance as the youngest controls in the study.²⁵ Thus, along with poor automaticity, cerebellum dysfunctions could account for these deficits. Not only was the CDH supported, it expanded upon the automatization deficit hypothesis and was implicated in the phonological core deficit and double deficit hypotheses. In terms of the phonological impairments found in DD, the involvement of the cerebellum in formulating the difference between actual and intended phonological rehearsal was identified. Activation of the right cerebellum has also been reported to be involved in the process of silent word generation and verbal working memory.^{26–28}

Because the cerebellum engages in various linguistic functions, it might also be a natural contributor to poor Chinese word recognition in children with DD.²⁹ Yang, Bi, Long, and Tao identified atypical activation among Chinese children with DD during the performance on a single-handed version of serial reaction time task.³⁰ Significantly increased functional activation, particularly in the left cerebellum, left, middle, and medial temporal lobes, and the right thalamus, was found in children with DD. Notably, when investigating anatomical structure, Yang, Yang, Chen, Zhang, and Bi observed reduced gray matter volume in the left cerebellum of Chinese-speaking children with DD

relative to controls.³¹ Feng et al. further explored cerebro-cerebellar functional connectivity and suggested atypical connectivity patterns existed between the left cerebellum and the left fusiform gyrus during orthographic processing, whereas increased connectivity between the right cerebellum and the left supramarginal gyrus was found during phonological processing.³² However, in the present study, the integrity of the right cerebellar tracts was significantly associated with the children's performance of character recognition. The findings were similar to research that investigated English-speaking children with DD, indicating that the right cerebellum was an anatomical area that could be used to discriminate DD with strong phonological differences from typically developing readers.³³ This area has been suggested to be related to the perception of the temporal organization between syllables as well as the production of single-word utterance and syllable repetition.^{34,35} As in Chinese, each orthographic character represents a phonetic syllable in speech. The involvement of the right cerebellar tracts may demonstrate certain phonological recoding processes during Chinese character recognition.

Thalamopontine tracts were also found to be related to character recognition. We suspected that this was due to the cerebello-ponto-thalamo-cortical pathways. As suggested by the anatomical findings, the cerebellum receives information from all cortical and subcortical structures involved in the organization (via the cerebro-ponto-cerebellar pathways) and processes (via the cerebellar-thalamo-cortical pathways) of language. A decreased connectivity in the cerebello-ponto-thalamo-cortical pathways

may therefore suppress the functional performance of the supratentorial regions that intrinsically subserve linguistic processing in the language dominant hemisphere, such as the left supramarginal area.

Per the PCA, auditory processing of FM could explain 27.65% of the behavioral data. The diffusion MRI connectometry indicated a strong link between auditory FM processing and the posterior area of the corpus callosum (posterior curvature topography) in Chinese-speaking children. The findings are in line with previous research that has reported that proficient readers activate the posterior systems, whereas in individuals with DD, the activation shifted toward the anterior systems.³⁶ A developmental study suggested that the posterior corpus callosum may undergo an intensive myelination in typically developing readers in the early years of language acquisition.³⁷ Castro-Caldas et al. investigated the morphology of the corpus callosum between illiterate and literate adults and reported that the illiterate group exhibited reduced volume in the posterior section.³⁸ Therefore, a possible physiological explanation for our data could be that lower-level temporal auditory processing is associated with the corpus callosum at the posterior segment and supports the establishment of phonological representations in the brain. Poor performance on auditory FM processing among Chinese-speaking children with DD resulted in a dysfunction of lexical tone decoding for Chinese reading. Existing evidence supports the view that profound phonological processing difficulties result from auditory processing deficits.³⁹

The current study employed a novel approach of diffusion connectometry to identify the most representative behavioral characteristics and the corresponding white matter structures that could be used as neural correlates for clinical diagnosis. Although the research is at a preliminary stage, our results support theories that suggest impoverished myelination and connection in subcortical tracts are the potential causes of impaired sensory temporal timing processing observed in dyslexic people with phonological deficits. These features might be valuable for identifying children who at risk of developing DD and might make early intervention feasible. The limitation of this study was the lack of concurrent functional MRI data and longitudinal traces. Therefore, we cannot provide evidence on the potential structural and functional associations that reflect the developmental changes of the brain. Because neuroplasticity is evident in the developmental brain, further research should carefully examine whether reading attainment is sensitive to experiential and environmental factors and use multimodal imaging techniques to examine the related cortical function and neural substrates. Clinically, the identification of white matter tracts associated with the two major behavioral characteristics of Chinese DD may contribute to early diagnosis for pediatric psychiatry. With early diagnosis, interventions that improve reading development may begin at the earliest possible opportunity.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

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