Research article

To explore the potential mechanisms of cognitive impairment in children with MRI-negative pharmacoresistant epilepsy due to focal cortical dysplasia: A pilot study from gray matter structure view

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ABSTRACT

Objectives: To investigate the characteristics of brain structure in children with focal cortical dysplasia (FCD)-induced pharmacoresistant epilepsy, and explore the potential mechanisms of cognitive impairment from the view of gray matter alteration.

Methods: 25 pharmacoresistant pediatric patients with pathologically confirmed focal cortical dysplasia (FCD), and 25 gender-matched healthy controls were included in this study. 3.0T MRI data and intelligence tests using the Wechsler Intelligence Scale for Children-Forth Edition (WISC-IV) were generated for all subjects. Voxel-based morphometry (VBM)-diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) and surface-based morphometry (SBM) analyses were performed to analyze gray matter volume and cortical structure. Two-sample t-tests were used to compare the differences in gray matter volume ($P < 0.05$, FWE) and cortical thickness ($P < 0.001$, FWE) between the two groups. Also, the Spearman rank correlation analyses were employed to determine the relationship between structural alterations and neuropsychological results.

Results: The WISC-IV scores of the FCD group were significantly lower than those of the HC group in terms of full-scale intelligence quotient (FSIQ), verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI) (all $P < 0.01$). Compared with the HC group, in the FCD group, the gray matter volume (GMV) reduced significantly in the left cerebellum_8, cerebellum_Crus2, and bilateral thalamus ($P < 0.05$, FWE); the GMV increased in the bilateral medial frontal gyrus, right precuneus, and left inferior temporal gyrus ($P < 0.05$, FWE), and the cortical thickness increased in the bilateral frontal, parietal, and temporal areas ($P < 0.001$, FWE). Correlation analyses showed that the age of seizure onset had positive correlations with the WISC-IV scores significantly. Meanwhile, the cortex thicknesses of the left pars opercularis gyrus, left middle temporal gyrus, and right inferior temporal gyrus had negative correlations with the WISC-IV scores significantly.

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Conclusion: FCD patients showed subtle structural abnormalities in multiple brain regions, with significant involvement of the primary visual cortex and language function cortex. And we also demonstrated a crucial correlation between gray matter structural alteration and cognitive impairment.

1. Introduction Background

Focal cortical dysplasia (FCD) is a type of malformation of cortical development characterized by disorders of cortical structure with or without abnormal cell patterns, and it is one of the most common etiologies of pharmacoresistant epilepsy requiring surgery [1,2]. The International League Against Epilepsy (ILAE) classifies FCD into three types based on pathological features: FCD type I, characterized by abnormal laminae and disorganization, FCD type II, characterized by the presence of deformed neurons (IIa) or globular cells (IIb), and FCD type III, which is combined with other brain lesions [3]. According to the literature, children with FCD have a younger age of onset, with a median age of 5 years for the first episode of FCD type I and 3 years for the first episode of FCD type II [4]. Pharmacoresistant epilepsy is usually caused by FCD, however, approximately 17% of patients will show a transient response (≥1-year seizure-free) to antiepileptic drugs after initial treatment (50%) or in the later part of the disease course (50%) [5].

Abnormal discharges caused by epileptogenic foci, both ictal and inter-ictal phase, may interfere with the normal development of the nervous system, leading to impaired advanced cognitive function [6]. Some quantitative neuroimaging studies have discovered essential relations between intelligence and structural variation in specific gray matter regions, such as the prefrontal regions [7], the anterior cingulate cortices [8], the orbitofrontal [9], and the fusiform gyrus in the temporal cortex [10]. Tosun et al. [11] have discovered that the childhood absence epilepsy (CAE) patients use different brain regions to perform cognitive functions compared to healthy controls. Similar investigations have also found that executive function, attention, and working memory problems are connected with altered gray matter structures in the thalamus and frontoparietal-temporal lobes in children with juvenile myoclonic epilepsy [12].

According to studies, 22%–50% of FCD patients who underwent surgery had cognitive impairments or developmental delays in the adult group [13], while up to 70%–80% of children experienced growth delays [14]. According to earlier studies, smaller FCD lesions frequently had substantial cognitive impairment and behavioral abnormalities [15]. Recent studies have revealed that aberrant intercortical connection patterns in FCD patients without visible intracranial lesions have distinct consequences on entire brain network architecture as research and neurological function have evolved [16]. Quantitative neuroimaging studies of temporal lobe epilepsy, have shown neuroanatomic abnormalities to extend far outside the zone of seizure onset, affecting temporal and extra-temporal regions of the cortical mantle, also affecting a diversity of subcortical regions, cerebellum, and white matter diffusely [17].

More studies have found that the severity of cognitive impairment was correlated with seizure frequency, seizure type, disease duration, and age of onset [15,18–20]. However, the underlying causes of impaired cognitive function in children with FCD are still unclear, and it is also unknown how structural changes in the nervous system affect central gray matter nuclei and significant functional areas of gray matter.

Therefore, we conducted this study to investigate the gray matter volume and cortical structure in children with FCD using VBM-DARTEL and SBM. This study was aiming to examine the relationship between advanced cognitive function alteration and its corresponding regions' gray matter structural changes. Furthermore, to explore neuroimaging markers and potential pathogenic mechanisms associated with impaired intelligence.

2. Methods

2.1. Subjects

Twenty-five pharmacoresistant pediatric patients with pathologically diagnosed focal cortical dysplasia (FCD) and 25 gender-matched healthy controls were recruited. All subjects underwent MRI scanning to get high-resolution MRI data and conducted the Wechsler Intelligence Scale for Children-Forth Edition (WISC-IV) to evaluate their presurgical IQ. This study was a retrospective study, approved by the Ethics Committee of Shenzhen Children's Hospital (No. 202208602).

Inclusion criteria for the FCD group were: (1) Children with pharmacoresistant epilepsy who fulfill the International League Against Epilepsy (ILAE) standard of two antiseizure medications (alone or in combination) correctly and logically selected and tolerated but who have not yet attained prolonged seizure independence. (2) Postoperative pathology confirmed focal cortical dysplasia, patients with dual pathology (Type IIIs) are included (except III b/c); (3) Routine head MRI examinations were negative at admission, which were diagnosed by two senior neuroradiologists; (4) Preoperative clinical information was full; there was no history of any organic abnormalities of essential organs or other neuropsychiatric illnesses.

Inclusion criteria for the HC group were: (1) Health assessment and intelligence evaluation showed normal; (2) No abnormalities in brain structure and no MRI contraindications; (3) Past medical history without neuropsychiatric illnesses and organic lesions of essential organs.

Exclusion criteria for both groups were: (1) Children with psychiatric disorders, visual or hearing impairment; (2) children who need long-term medication for chronic conditions, such as bronchial asthma, hyperthyroidism, or diabetes; (3) children whose routine magnetic resonance imaging reveals positive lesions.

2.2. Neuropsychological evaluation

A psychologist with at least five years of professional experience conducted cognition assessment using the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) at the Child Health Department of our hospital. The verbal comprehension, perceptual reasoning, working memory, and processing speed domains of the Wechsler Intellect Scale for Children were used to measure the intelligence of children between the ages of 6–16. The verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (WMI) are four composite scores produced by the WISC-IV software, which is also used to calculate the full-scale IQ (FSIQ).

2.3. MRI acquisition

MRI data was collected using a 3T scanner (Siemens Magnetom Skyra) with a 32-channel standard head coil. The T1-weighted magnetization prepared gradient-echo (MP-RAGE) image was obtained with the following parameters: repetition time (TR) = 2000 ms , echo time (TE) = 2.44 ms , inversion time (TI) = 90 ms, flip angle = $10°$, slice thickness = 1 mm , gap = 0 , FOV = 256mm × 256 mm, voxel size = $0.9 × 0.9 × 1.0$ mm^3, and slice number = 176.

2.4. Image analysis

2.4.1. Voxel-based morphometry (VBM)

T1-MPRAGE images were preprocessed using the VBM-DARTEL toolkit of statistical parametric map SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and computational anatomical toolbox CAT12 (http://www.neuro.ubi-jena.de/cat/). Matlab R2017a (http://www.mathworks.cn/products/matlab/) was the platform for these programs. The major processing steps included: NIFTI format conversion and AC-PC correction of the original images; standardization of the unified segmentation template, segmentation of the images into gray matter, white matter, cerebrospinal fluid and other structures according to the signal probability; averaging of the images to generate the subject's self-constructed template, alignment using the DARTEL algorithm, modulation of all images, nonlinear alignment to the Montreal Neurological Institute (MNI) standard coordinate space, and images were smoothed with an isotropic Gaussian kernel with a sigma of 8 mm.

2.4.2. Surface-based morphometry (SBM)

The extraction of surface parameters was implemented by the computational anatomy toolbox CAT12 (http://www.neuro.ubi-jena.de/cat/) in the statistical parametric mapping software SPM12 (http://www.fil.iom.ucl.ac.uk/spm). Image processing steps to

Table 1
Demographic and clinical information of the FCD patients and healthy controls.

	FCD (n = 25)	HCs (n = 25)	*P*-value
Age, months (mean ± SD)	127.9 ± 36.6	128.8 ± 17.5	0.910
Gender (M/F)	15/10	15/10	1.000
Education, months (mean ± SD)	56.8 ± 34.9	56.8 ± 17.5	1.000
Age of seizure onset, months (mean ± SD)	49.8 ± 7.5	–	
Disease duration, month (mean ± SD)	79.9 ± 9.2	–	
Number of AEds (mean ± SD)	3.38 ± 0.2	–	
Pathological typing, n(%)			
FCD Ia	10 (40)	–	
FCD Ib	1 (4)	–	
FCD IIa	4 (16)	–	
FCD IIb	7 (28)	–	
FCD IIIa	2 (8)	–	
FCD IIId	1 (4)	–	
Resected/disconnected lobe, n(%)			
Frontal/central	11 (44)		
Parietal	1 (4)		
Occipital	1 (4)		
Temporal	3 (12)		
Multilobar	7 (28)		
Hemisphere	2 (8)		
WISC-IV scores			
FSIQ	63.4 ± 19.3	103.3 ± 8.5	< 0.001*
VCI	68.6 ± 19.3	97.8 ± 9.8	< 0.001*
PRI	70.0 ± 20.1	108.2 ± 11.9	< 0.001*
WMI	64.9 ± 17.5	95.1 ± 8.2	< 0.001*
PSI	66.2 ± 19.2	107.0 ± 9.5	< 0.001*

FCD, focal cortical dysplasia; HCs, healthy controls; M, male; F, female; R, right; AEds, anti-epileptic drugs; FSIQ, full scale intelligence quotient; VCI, verbal comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index.

evaluate cortical thickness: skull stripping, inflation of folded surface tessellation patterns, normalization of intensity, white matter and gray matter segmentation, and final gray matter/white matter boundary subdivision and automatic correction. After that, grayscale/white matter and grayscale/cerebrospinal fluid (CSF) surfaces are acquired by using the deformable surface algorithm. The intensity and information from the surface during deformation are used to calculate cortical parameters, and cortical thickness will be calculated based on the closest distance from the gray/cerebrospinal fluid boundary to the gray/white matter boundary at each vertex on the subdivision surface. Finally, thickness measurements can be mapped on the inflatable surface of each subject's brain reconstruction. Cortical surface segmentation was performed with CAT12, and the DK40 atlas was applied to generate 3D reconstruction maps of each brain region to extract cortical parameters.

2.5. Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, NY, USA) was used to process the statistical data. For continuous and categorical variables, independent samples t-tests and chi-square analyses were used to test for between-group differences in demographic measures, respectively. SPM12 was used to process the magnetic resonance data. ANOVA was used for the analysis of partial regional differences in gray matter volume and cortical thickness, taking age, sex and total intracranial volume (TIV) as covariates. To correct for multiple comparisons, the gray matter volume and cortical thickness results in family-wise error (FWE) correction. Correlations between structural parameters with disease duration、age at onset and WISC-IV scores were analyzed using Spearman rank correlation coefficients. P-values <0.05 were considered statistically significant.

3. Results

3.1. Demographic and clinical data

A total of 25 patients with FCD (15 males, mean age = 127.9 ± 36.6 months) and 25 control subjects (15 males, mean age = 128.8 ± 17.5 months) were recruited for the analysis (Table 1) . Patients and HCs did not differ in age, gender, and education years. Mean age of seizure onset were 49.8 ± 7.5 months and epilepsy duration were 79.9 ± 9.2 months. Postoperative pathological results showed that there were 10 cases of FCD type Ia and 1 case of type Ib; 4 cases of type IIa and 7 cases of type IIb; 2 cases of type IIIa and 1 case of type IIId. FSIQ、VCI、PRI、WMI and PSI scores were all lower in the FCD group compared to the HC group (all P values <0.001) (Fig. 1)

3.2. VBM

Compared with HCs, the FCD group showed reduced gray matter volume in the bilateral thalamus, cerebellum_8 and cerebellum_Crus2, and increased gray matter volume in the right precuneus, the bilateral superior middle frontal gyrus, the middle frontal gyrus and the left inferior temporal gyrus (FWE $P < 0.05$, k > 50voxels; Table 2; Fig. 2) .
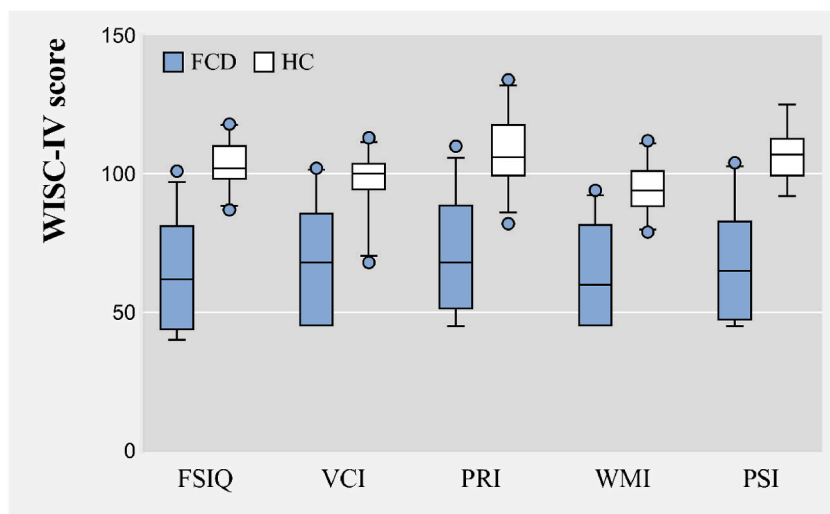

Fig. 1. Box plots of raw data for control and epilepsy patient groups' Wechsler Intelligence Scale for Children-Forth Edition (WISC-IV) score. Data are median (central line), interquartile range (box margins), adjacent values (whiskers), and outliers (dots).

Table 2
The difference of gray matter volume between FCD and HCs.

| Brain region Cluster max (AAL)	Hemisphere (L/R)	Cluster size	MNI coordinates			Z scores
			x	y	z	
FCD patients < controls						
Thalamus	L	807	−4.5	−25.5	−3	−7.638
Thalamus	R	666				
Cerebellum_8	L	804	−31.5	−39	−54	−7.1991
Cerebellum_Crus2	R	153	49.5	−72	−40.5	−5.8713
FCD patients > controls						
Precuneus	R	15571	12	−72	55.5	16.8605
Superior Medial Frontal Gyrus	L	2033	−4.5	46.5	48	10.3624
Superior Medial Frontal Gyrus	R	2027	5	41	51	
Middle Frontal Gyrus	L	411	−36	31.5	46.5	6.7159
Middle Frontal Gyrus	R	67	39	31.5	28.5	5.8518
Inferior Temporal Gyrus	L	57	−57	−48	−24	5.9877
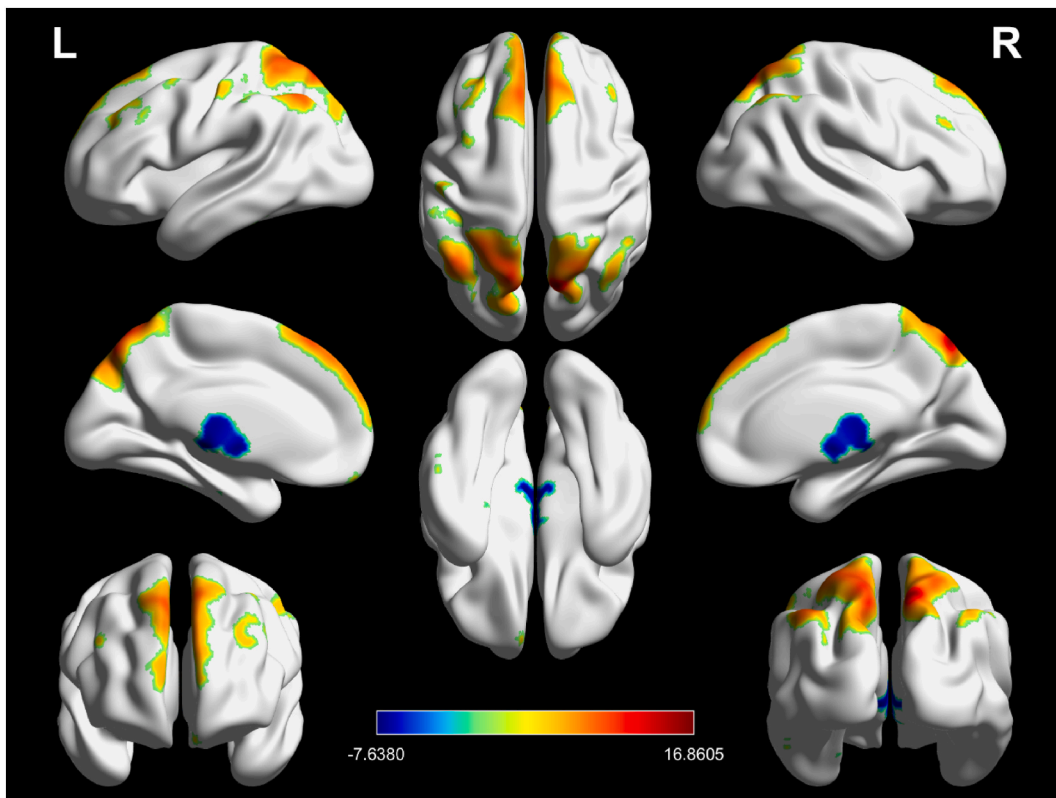
Fig. 2. The difference of gray matter volume between FCD and HCs ($P < 0.05$, FWE corrected). Representative views are shown with a color-coded depiction of abnormalities. Regions of reduced volume are shown in blue to yellow and regions of increased volume are shown in yellow to red (color-coded according to z value). FCD, focal cortical dysplasia; HCs, healthy controls; FWE, family-wise error. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.3. SBM

Compared with HCs, the FCD group showed increased cortical thickness in the bilateral superior parietal gyrus, the bilateral superior frontal gyrus, the bilateral supramarginal gyrus, the bilateral rostral middle frontal gyrus, the bilateral precentral gyrus, the left superior temporal gyrus, the left parsopercularis gyrus, the left middle temporal gyrus, the right superior parietal gyrus, the right lateralorbitofrontal gyrus, the right inferior temporal gyrus and the right postcentral (FWE *P* < 0.001, k > 50voxels; Fig. 3) .
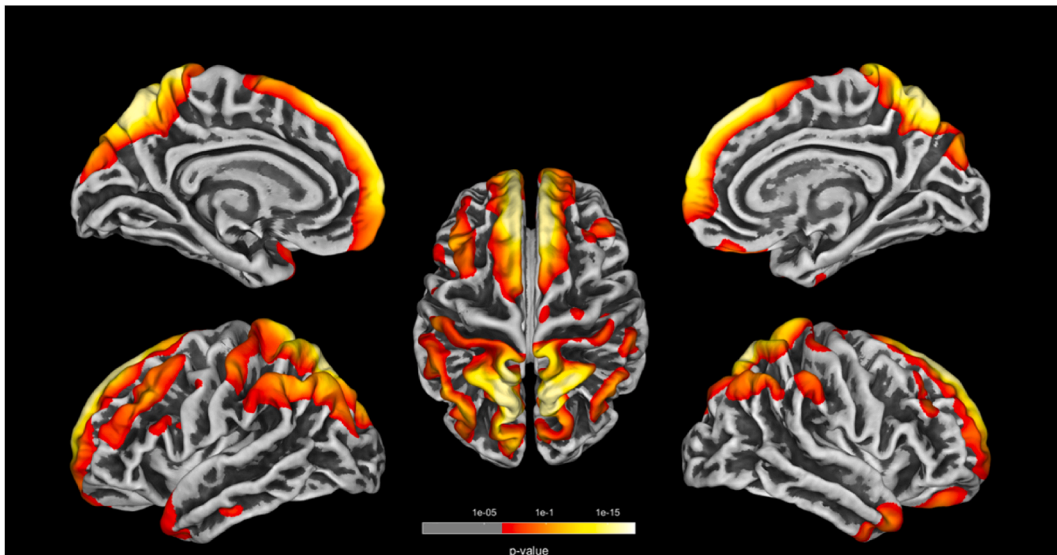
Fig. 3. Regions of increased cortical thickness between FCD and HCs ($P < 0.001$, FWE corrected) represent views with a color-coded depiction of abnormalities. Regions of increased volume are shown in yellow to red (color-coded according to *p-value*). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

3.4. Correlation of cortical thickness and clinical variables

Positive partial correlations emerged between the age of seizure onset and WISC-IV scores ($P < 0.01$; Fig. 4), but no correlation between disease duration and WISC-IV scores. While the thicknesses of the left parsopercularis gyrus and middle temporal gyrus presented negative correlations with the PRI and PSI, the thicknesses of the left middle temporal gyrus presented negative correlations with the WMI, the thicknesses of the right inferior temporal gyrus presented negative correlations with the PRI, only when considering all FCD subjects in one group (Table 3, Figs. 5 and 6).

4. Discussion

4.1. Overview

In this study, the decrease of gray matter volume in the bilateral thalamus and cerebellar hemispheres and the increase of gray matter volume and cortical thickness in partial brain regions of the bilateral frontal, parietal and temporal lobes in children with FCD were shown. The left middle temporal gyrus, the posterior inferior frontal gyrus and the right inferior temporal gyrus, which were considered the higher visual- and language-related centers, may be associated with the intelligence decrease in children with FCD. Our study indicates the quantitative MRI's importance to detect the subtle secondary abnormalities in FCD-related epilepsy and highlight
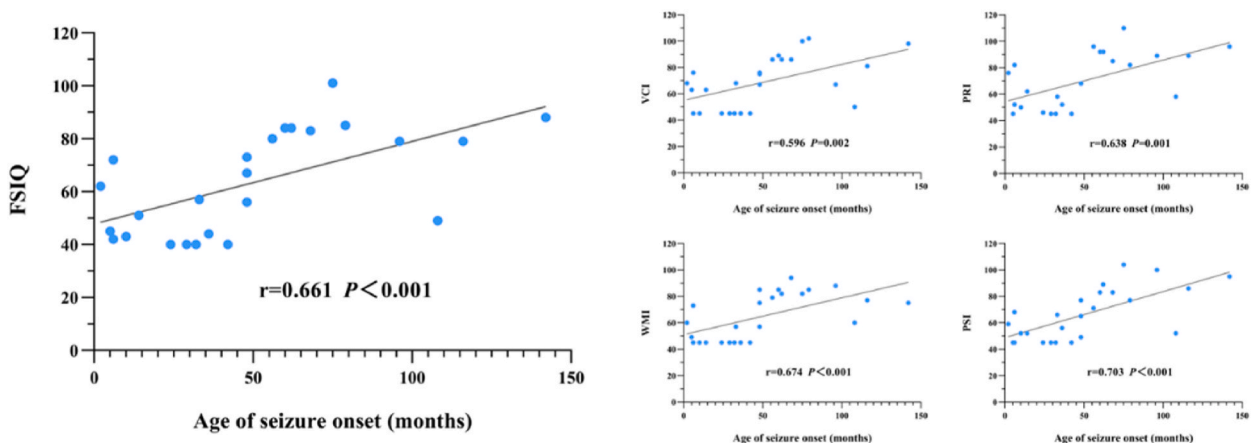

Fig. 4. Scatter plots of FSIQ, VCI, PRI, WMI, PSI positively correlated with the age of seizure onset in FCD patients.

Table 3
Spearman Rank Correlation Analysis; CT, cortical thickness; **为$p < 0.01$, *为$p < 0.05$, two-tailed test.

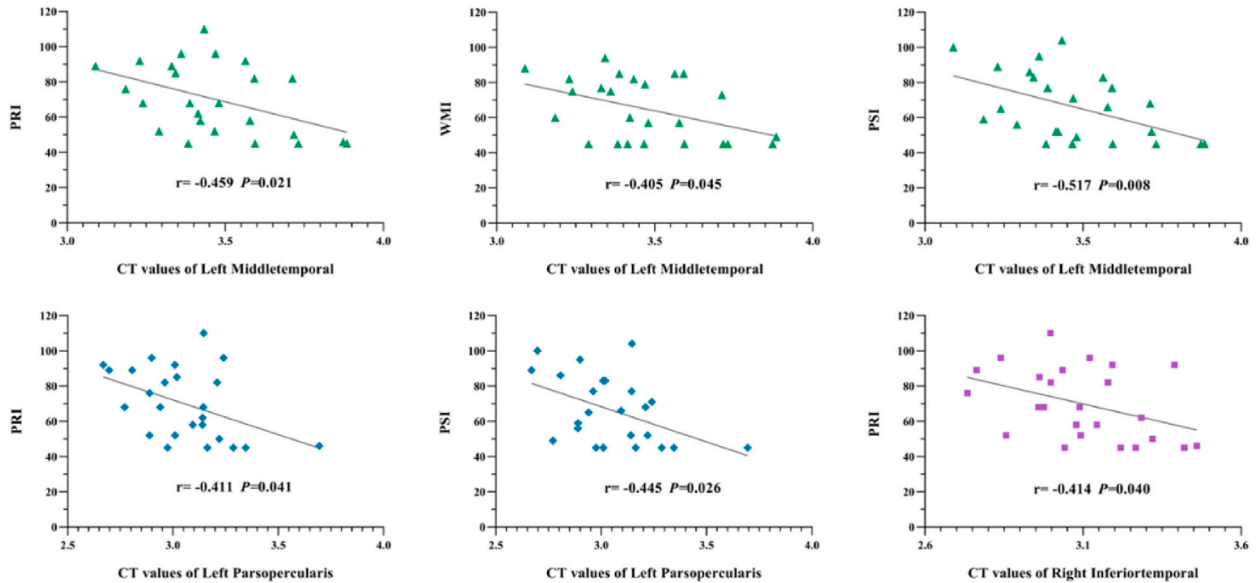|	r				
	FSIQ	VCI	PRI	WMI	PSI
Age of seizure onset	0.661**	0.596**	0.638**	0.674**	0.703**
Disease duration	−0.374	−0.384	−0.277	−0.239	−0.361
CT of left pars opercularis	−0.382	−0.277	−0.411*	−0.348	−445*
CT of left middle temporal	−0.385	−0.256	−0.459*	−0.405*	−0.517**
CT of right inferior temporal	−0.392	−0.366	−0.414*	−0.369	−0.357

Fig. 5. Scatter plots of the mean cortical thickness in the left pars opercularis, the left middle temporal, the right inferior temporal gyrus negatively correlated with WISC-IV scores in FCD patients.

the importance of early seizure treatment in children with pharmacoresistant epilepsy.

4.2. Seizure onset age associated with cognitive function

The central nervous system of children is immature or is tending to mature during the early phases of growth and development, and its development (increasing neuronal cell volume, enlarged dendrites, and construction of neural networks) is susceptible to illness and environmental variables. It may result in a progressive increase in the risk of cognitive dysfunction in children. Animal studies have found that early seizures will change the balance of neural excitation and inhibition, network connectivity, and temporal coding, which is frequently accompanied by concurrent impairments in cognitive function [21]. Up to 84% of children with FCD are at high risk of neurocognitive impairments and developmental delays, making them more likely to experience cognitive impairment than children with focal intracranial occupancies (such as gliomas or deformities) [22,23]. Some studies have found a positive correlation between the age of onset and intelligence or developmental level in children with pharmacoresistant epilepsy [24,25]. Vendrame et al. [26] have discovered that the younger age of onset, the more significant impairment of cognition, and the more severe of prognosis. Cohen et al. [27] have demonstrated that FCD co-localization to distributed functional cortical networks was associated with age of epilepsy onset: sensory neural networks (somatomotor and visual) with earlier onset, and limbic latest onset, which may reflect developmental differences in network activation. According to our research, children with FCD have poorer cognitive function, as the younger of onset age, and this is in line with the other findings [28]. Verbal intelligence, reading comprehension, and spelling abilities play a significant role in the development of this network, which steadily becomes better and matures with age, according to research on healthy youngsters [29]. Cognitive networks linked to executive function, language, and working memory become dysfunctional as a direct result of decreased or lost connection between network segments following seizures and decreased neuronal activation during particular activities [30]. This dysregulation of network activity and connectivity may lead to reduced neuronal activation and ultimately cortical volume loss [31]. Bechtel et al. [32] discovered that patients with epilepsy and attentional concerns recruited substantially less cortical regions required for working memory performance (frontal and parietal lobes) compared with healthy controls, including the insular region and cingulate. Therefore, the earlier the seizure, the more damage to developing neurocognitive networks it will cause, and the more likely it will result in cognitive impairment.
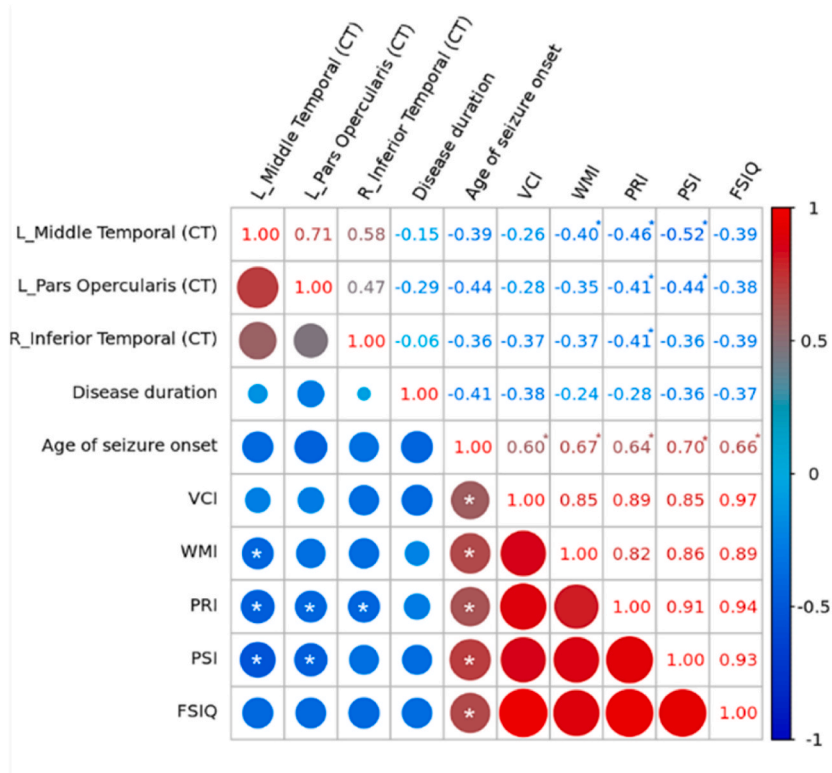
Fig. 6. Spearman's rank correlation matrix between brain regions and WISC-IV scores in FCD patients (adjusted $P < 0.05$).

4.3. Volume loss in FCD

Voxel-based Morphometry (VBM) is a quantitative neuroimaging analytic technique that is used to quantify gray and white matter volumes in distinct subject brain areas and identify morphological variations between different brain structures. In this study, we used the VBM to evaluate the volume alteration of gray matter in the bilateral thalamus and cerebellum of children with FCD. The thalamus, as the largest gray matter nucleus in the mesencephalon, is also an important relay station for subcortical centers and sensory transmission. Types of sensory transmission pathways (except olfaction) project to the cerebral cortex after replacing neurons in the thalamus [33]. Children with epilepsy exhibit thalamic atrophy in a variety of seizure types, and uncontrollable aberrant discharge rhythms may be mediated via thalamocortical pathways [33–36]. Resting-state MRI studies have also shown that local cortical abnormal discharges can be transmitted to the ipsilateral thalamus and then to contralateral cortical areas via the contralateral thalamus, resulting in a generalization of abnormal discharges [37,38].

Previous studies confirm that the cerebellum is primarily associated with motor functions. Additionally, the cerebellum is also a crucial element involved in cognitive networks, including memory, language, and emotion, and these processes are mediated through the cerebro-cerebellar circuit [39–41]. The cerebellum interacts with the cerebral cortex mainly through two pathways (cerebello-thalamo-cortical (CTC) pathway and the cortico-ponto-cerebellar (CPC) pathway) [41]. Cerebellum atrophy volume is frequently observed in patients with epilepsy, and Carrie discovered decreased gray matter volume in both cerebellar hemispheres of patients with medial temporal lobe epilepsy, pointing to a connection with seizure-mediated seizure cell loss or antiseizure medication phenytoin [42]. It has been hypothesized that the cause of cerebellar volume reduction in epileptic patients may be related to the reduction of Purkinje cells [43]. Similarly, some studies have demonstrated that seizures might result in a reduction in Purkinje cell density [44]. Researchers also discovered that non-motor functions were primarily related to lobule VII (including hemispheric extensions of lobule VIIA, i.e. crus I and crus II, and lobule VIIB) and lobule IX, while motor processing functions were primarily associated with lobules IV-VI and VIII of the cerebellar hemispheres [45]. In this work, we discovered that children with FCD had significantly lower Crus II volumes in the right cerebellar hemisphere, which showed that structural abnormalities of the cerebellum may be related to early cognitive impairment in children with FCD.

4.4. The increased volume in FCD

In this study, analysis results revealed that children with FCD had an increased gray matter volume in the right precuneus, bilateral medial superior frontal gyrus, bilateral middle frontal gyrus, and left inferior temporal gyrus. According to the previous study and knowledge, the potential mechanisms for the increased gray matter volume might be: (1) There are self-regulating mechanisms in the

cortex that only keep the best connection configuration while cortical networks are forming throughout brain growth and development. Delays in the self-regulatory system can result in an overabundance of gray matter. Patients with FCD type II are most likely to experience this anomaly [46]; (2) The brain's adaptive reactions to damage include compensatory growth of other brain regions to replace the function of the injured brain parts [47]; (3) The pro-inflammatory cytokines that have been reported to activate astrocytes in cortical tissue and drive their cell proliferation in individuals with post-traumatic stress disorder may be responsible for the early increase in gray matter volume [48]. The precuneus is a central node of the "default attention network" (DMN), which is considered to be a key brain network for maintaining the baseline state of the nervous system. The DMN is inhibited during working states or in response to significant external stimuli, and recovering and remaining active during resting states [49]. In our study, increased gray matter volume in brain regions involves several component nodes of the DMN, with the precuneus being a key structure of the DMN. Additional studies have found abnormal DMN in children with BECT [50]. The other study confirmed DMN plays a significant role in the onset and development of cognitive and behavioral impairments [51]. Our study did not find the correlation between gray matter volume and cognitive function, similar study has suggested that gray matter volumes may have limited explanatory value for cognitive function in childhood epilepsy [52].

4.5. Cortical thickness increase associated with cognitive function

For the structural examination of the brain, surface-based morphometry (SBM) can also offer more information, and it can also acquire some features that VBM is unable to. In this study, we observed that utilizing the SBM, FCD group had bilaterally increased cortical thickness in the frontal, parietal, and temporal lobes to varying degrees. The basic principle for brain development is that as age grows, a gradual decrease in its cortical gray matter volume and cortical thickness [53], which is essentially a decrease in selective neurons and an increase in myelin sheathing [54]. This process of neurodevelopment in children is evident from research on children who are normally developing. Cortical thickness often decreases in adult patients with epilepsy [55–58], but aberrant cortical thickening is observed in children with epilepsy. Hong et al. performed morphological measurements at the brain-wide level in patients with FCD and found increased cortical thickness in the temporal lobe and postcentral gyrus in patients with FCD type II, suggesting an association with delayed neuronal pruning [46]. A longitudinal SBM study found that cortical thickness in the Rolandic region increased bilaterally before drug treatment in children with central temporal lobe spike-wave epilepsy (CECTS) and was negatively correlated with seizure-free duration; cortical thickness in the Rolandic region thinned bilaterally and cognition improved after drug treatment [59], suggesting that antiepileptic drug treatment is associated with a reduction in the thickness of the abnormally thickened cortices in the Rolandic region bilaterally in patients and that changes in gray matter structure may be an important mediator of seizure control and cognitive improvement with drugs.

Further correlation analysis showed a strong negative correlation between the PRI, WMI, or PSI and the thickness of the left middle temporal gyrus, right inferior temporal gyrus, and posterior left inferior frontal gyrus brain. As transfer points between perception of language based on sounds and conceptual expression during language development, the middle temporal gyrus and inferior temporal gyrus function as conduction endpoints in the ventral pathway of language [60]. The middle temporal gyrus, a joint auditory-linguistic processing cortex, is crucial for language comprehension and is continuously active during speech perception, and this functional area is associated with the level of the sound-semantic handoff system [61]. The inferior temporal gyrus, as the starting point of the visual ventral pathway, is connected to the primary visual cortex and the temporal lobe, and is directly involved in the construction of perception and perception, which is necessary for the development of vision [62]. In addition to being associated with the development of vision, the inferior temporal gyrus is also involved in the processes of lexical-semantic association (linking words to visual perception) and auditory information-linguistic integration, and is an important "contact area" in language processing [63]. The posterior left inferior frontal gyrus, also known as Broca's area, serves as a motor language center and is an important brain region involved in language expression; Shaw et al. [64] demonstrated that the acquisition of higher cognitive functions such as language is associated with rapid cortical thinning, and Qi et al. [65] further found that thinner left inferior frontal gyrus cortical thickness was associated with higher sentence comprehension compared to the right cerebral cortex. Similar study also found that disruption in normal age-related cortical thickness expression is related to IQ in pediatric epilepsy patients both with average and below average IQ scores [66].

Damage to the middle temporal gyrus, inferior temporal gyrus, and posterior inferior frontal gyrus may cause problems with language and visual information processing as well as the integration and transformation of outside information, which may aggravate the damage to functional structures and induce cognitive dysfunction in children with FCD to develop.

4.6. Limitation

There are still some limitations to our study. Firstly, a larger sample size and longitudinal follow-up are required in order to fully understand the dynamic changes in cortical volume and morphology, the effects of various treatment modalities, and the causal relationships with cognitive function because this study was cross-sectional and had a small sample size. Second, although neuropsychological tests were administered to kids with FCD, dedicating assessments for cognitive abilities including language, attention, and memory will enhance the study. Due to reality, FCD patients received several antiepileptic treatment measures, which may have effects on cognition and developing cognitive networks and these may confound findings.

5. Conclusion

This study found cortical structural differences in patients with FCD-related epilepsy compared to controls using quantitative morphometric analyses, abnormalities in the visual-language association of the middle temporal gyrus, inferior temporal gyrus, and posterior inferior frontal gyrus may be the neuropathological basis of cognitive impairment in children with FCD. These differences may flag FCD patients at higher risk of neurocognitive impairments. Future studies should focus on validating these findings in larger populations, and integrating structural and functional network findings with multimodal techniques.

Data availability statement

Data will be made available on request.

Funding

Ethics approval and consent to participate

This study was a retrospective study, approved by the Ethics Committee of Shenzhen Children's Hospital (No. 202208602). This study complied with all relevant national regulations and institutional policies. The informed consent was obtained from all participants.

CRediT authorship contribution statement

Yilin Zhao: Writing – review & editing, Writing – original draft, Conceptualization. **Jieqiong Lin:** Data curation. **Xinxin Qi:** Formal analysis. **Dezhi Cao:** Investigation. **Fengjun Zhu:** Project administration. **Li Chen:** Resources. **Zeshi Tan:** Validation. **Tong Mo:** Visualization. **Hongwu Zeng:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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