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MAGNETIC RESONANCE

Cerebello-cerebral connectivity in idiopathic generalized epilepsy

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Abstract

Purpose The present study aims to investigate structural and functional connectivity (SC and FC) in cerebello-cerebral circuit in idiopathic generalized epilepsy (IGE).

Methods Diffusion tensor imaging and resting-state imaging data were collected from 57 patients with IGE and 66 controls in the present study. First, we performed bidirectional probabilistic fiber tracking between cerebellum and cerebral cortex, consisting of cerebellar efferent and afferent fibers. Then, strength of structural connectivity (SCS), fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) were extracted and compared between groups. Finally, cerebellar FC with cerebral cortex was evaluated with seeding at dentate nucleus. Between-group comparisons were performed using *t* tests with a significant level setting at $p < 0.05$ with threshold-free cluster enhancement correction.

Results The patients with IGE showed decreased SCS in cerebellar efferent fibers to sensorimotor cortex in anterior corona radiate and increased SCS in efferent fibers to occipital cortex in posterior corona radiata. The SCS in cerebellar afferent fibers in corticospinal tract from frontal and in retrolenticular part of the internal capsule from occipital cortices were increased in IGE, and SCS in afferent fibers in posterior limb of internal capsule from parietal cortex was decreased. Decreased FA and increased MD and RD were observed in cerebello-cerebral tracts. Besides, decreased cerebellar FC with putamen and motor cortex was observed in IGE.

Conclusion The patients with IGE demonstrated distinct alterations in efferent and afferent pathways between cerebellum and different cerebral cortices, which might be the pathological anatomical basis for cerebellar modulation effect on epileptic activities and contribute to motor deficits.

Key Points

- *IGE showed decreased SCS in cerebellar efferent fibers to the sensorimotor cortex and increased SCS in efferent fibers to the occipital cortex.*
- *Patients demonstrated increased SCS in cerebellar afferent fibers from the frontal and the occipital cortex and decreased SCS in afferent fibers from parietal cortex.*
- *Decreased FC between motor-related regions and dentate nucleus was observed in IGE.*

Keywords Structural connectivity · Functional connectivity · Cerebellum · Idiopathic generalized epilepsy

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Abbreviations

AEDs	Antiepileptic drugs
DlCl	Pathway from left dentate nucleus to left cerebral cortex
DlCr	Pathway from left dentate nucleus to right cerebral cortex
DrCl	Pathway from right dentate nucleus to left cerebral cortex
DrCr	Pathway from right dentate nucleus to right cerebral cortex
DTI	Diffusion tensor image
FA	Fractional anisotropy
FC	Functional connectivity

FlCBr	Pathway from left frontal lobe to right cerebellum
GTCS	Generalized tonic-clonic seizures
HCs	Healthy controls
IBLS	Interval between scanning and last seizure
IGE	Idiopathic generalized epilepsy
JME	Juvenile myoclonic epilepsy
MCP	Middle cerebellar peduncle
MD	Mean diffusivity
OrCBl	Pathway from right occipital lobe to left cerebellum
PrCBl	Pathway from right parietal lobe to left cerebellum
SC	Structural connectivity
SCP	Superior cerebellar peduncle
SCS	Strength of structural connectivity
TFCE	Threshold-free cluster enhancement

Introduction

Through communication with the cerebral cortex, the cerebellum participates not only in motor control but also in higher cognitive functions [1]. It is known that the superior cerebellar peduncle (SCP) gathers the primary efferent fibers of the cerebellum, and the middle cerebellar peduncle (MCP) collects the main afferent fibers from the cerebral cortex. Major efferent fibers of the cerebellum originate in the dentate nucleus, pass through the SCP, and then ascend to the thalamus, projecting finally to the wide cerebral cortex [2]. Meanwhile, the dentate nucleus has been suggested to play a role in motor and cognitive modulations [3]. The cerebral cortex projects back to the cerebellum mainly via the cortico-ponto-cerebellar pathway through the MCP [1]. In recent years, the cerebellum has been divided into various subdivisions according to the patterns of functional connectivity (FC) with the cerebral cortex, which could be roughly described as motor and nonmotor parts [4, 5]. The specific functional interaction between cerebellar subregions and cerebral functional networks has provided accumulated evidence to support the participation of the cerebellum in motor and cognitive processes [6]. Furthermore, it has been demonstrated that separated cerebellar regions communicate with distinct cerebral areas through a complex topography [5, 7]. Chronic and appropriate cerebellar stimulation has been shown to potentially improve microstructural plasticity and compensate for functional damage [8].

Recently, accumulated evidence has been gathered in support of the important role of the cerebellum in epilepsy [9, 10]. Since the activation of the cerebellum has been observed during spike-wave discharges (SWDs), the cerebellum has been speculated to contribute to the generation and propagation of epileptic activities [11]. In addition, evidence from animal studies has suggested a crucial role of the cerebellum in the termination of epileptic discharges [12]. The potential treatment effects of the cerebellum on epileptic activities have been widely recognized by neuroimaging studies in recent years [13, 14]. The most probable mechanism underlying the cerebellar therapeutic effect on epilepsy originates from the inhibitory role of Purkinje cells and their wide projections to the cortical regions [15]. In addition, a potential effect of the cerebellum on the thalamocortical circuit has also been proposed in patients with idiopathic generalized epilepsy (IGE), which has been suggested to contribute to the abnormal organization of brain networks [16]. A cerebral blood flow study further indicated that the cerebellum and thalamus were consistently involved in generalized epileptic activities and impaired consciousness [17]. The disrupted functional interaction in the cerebello-cerebral circuit was demonstrated to be associated with the underlying pathomechanism of epilepsy [18]. In all, the cerebellum has been suggested to be closely related to the disturbed inhibition and excitation in epilepsy and to further contribute to the clinical manifestations of this disorder in patients.

Cerebellar structural alterations have also been observed in previous studies. For example, decreased fractional anisotropy (FA) was demonstrated in generalized tonic-clonic seizures (GTCS) [19]. Patients with juvenile myoclonic epilepsy (JME) showed reduced cerebellar gray volume [20, 21]. Moreover, the participation of the cerebellum in a hyperconnected structural network was proposed to contribute to the motor and cognitive manifestations in JME [22]. Even so, structural evidence was relatively less than functional findings for the understanding of the pathomechanism of epilepsy. Considering that the cerebellum plays an important role in epilepsy by interacting with the extensive cortex of the brain, we speculate that the structural connectivity (SC) between the cerebellum and cerebral cortex might also have potential abnormalities. We also want to see if the cerebellum had distinct effects on different cerebral regions in epilepsy. Additionally, we deemed that SC abnormalities might not be the same in the bidirectional pathways of the cerebello-cerebral circuit, which is likely to provide more valuable information for exploring the structural basis underlying the pathology of patients with epilepsy. Using probabilistic tracking, the present study first investigated efferent and afferent SC between the cerebellum and cerebral cortex in patients with IGE. Notably, it must be stated here that even though the fibers acquired through probability tracking do not suggest particular directions in nature, specific waypoints of cerebellar anatomic pathways could assist in distinguishing between the bundles of efferent and afferent tracts. Between-group comparisons were performed to investigate alterations of structural connectivity strength (SCS) in all tracking fibers. In addition, the FC between the bilateral dentate nucleus and the whole brain was calculated to study cerebello-cerebral functional interactions, which would provide complementary evidence to further support the structural findings.

Materials and methods

Participants and data acquisition

We obtained data from 57 patients with IGE who were diagnosed based on the classification scheme proposed by International League Against Epilepsy (ILAE) guidelines [23]. Among the 57 patients, 31 patients were further classified into the subgroup of epilepsy with GTCS only and 26 were diagnosed with JME. All patients underwent electroencephalography monitoring, revealing a normal background and interictal generalized (poly)spike-waves. Those patients suffering from GTCS only but with any clue of secondary GTCS were excluded, including an abnormal background EEG, interictal slow or irregular generalized spike-waves, ictal semiology suggesting of focal onset, and ictal focal electrographic onset if available. Eight patients were drug-naive, 29 patients received monotherapy and 20 patients were multidrug therapy. In the present study, 36 patients responded to antiepileptic drugs, showing significantly decreased seizure frequency with drug treatment. All patients in this study still suffered epileptic seizures, but 36 of the 49 drug-treated patients responded well to antiepileptic drugs (AED), showing significantly decreased seizure frequency. Sixty-six matched healthy controls (HCs) free of neurological and psychiatric disorders were recruited in this study. The present study excluded subjects who exhibited any radiologic abnormalities with routine brain neuroimaging examination (MRI and CT). The clinical data of all subjects are summarized in Table 1. Written informed consent was obtained from all subjects. This study was approved by the ethical committee of the University of Science and Technology of China in accordance with the standards of the Declaration of Helsinki.

All subjects underwent MRI scanning in a 3-T GE scanner (MR750; GE Discovery) at the Center for Information in Medicine, University of Electronic Science and Technology of China. Axial anatomical T1-weighted images were acquired using a 3-dimensional fast spoiled gradient echo (T1-3D FSPGR) sequence with repetition time (TR) = 6.012 ms, echo time (TE) = 1.968 ms, flip angle = 9°, matrix = 256 × 256, field of view (FOV) = 25.6 × 25.6 cm^2, and slice thickness = 1 mm to generate 170 slices without gap. The diffusion tensor image (DTI) data were acquired using a single-shot, spin-echo, echo-planar sequence (75 slices, voxel size 2 × 2 × 2 mm^3, 128 × 128 base resolution, diffusion weighting isotopically distributed along 64 directions, *b*-value 1000 s/mm^2). Resting-state functional data was collected using an echo-planar imaging sequence with the following parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 24 × 24 cm^2, matrix = 64 × 64, slice thickness = 4 mm with a 0.4 mm gap, and 255 volumes in each run. All subjects were required to remain awake and to be relaxed with their eyes closed during the scanning.

Data preprocessing

Preprocessing of the DTI data was conducted using the FSL software package (FMRIB Software Library, available at http://fsl.fmrib.ox.ac.uk/fsl). Individual T1 images were registered to a standard T1 image in MNI space. DTI images were registered to the average of the B0 images. First, nonbrain tissues were deleted from the diffusion MRI data using the brain extraction tool (BET) of the FSL. Then, distortion effects originating from eddy currents, head motion, and the susceptibility of the diffusion data were corrected using the eddy tool of the FSL. Markov chain Monte Carlo sampling was used to estimate diffusion parameters in every voxel. Preprocessing of the fMRI data was conducted using the NIT software package (Neuroscience Information Toolbox, available at http://www.neuro.uestc.edu.cn/NIT.html) [24]. First, the first five volumes were discarded to eliminate magnetic field instability. Then, slice-timing,

Table 1 Clinical characteristics in IGE and HC

Characteristic	IGE ($n = 57$)	HC ($n = 66$)	p_1 value	GTCS ($n = 31$)	JME ($n = 26$)	p_2 value
Age (year)	25.3 ± 10.1	24.5 ± 5.3	0.53[a]	26.9 ± 11.5	23.5 ± 7.9	0.22[a]
Gender (M:F)	26:31	34:32	0.51[b]	14:17	12:14	0.94[b]
AED (with: without)	49:8	–	–	27:4	22:4	0.79[b]
Therapy (single: multiple)	29:20	–	–	16:11	13:9	0.99[b]
Age at onset (year)	17.6 ± 10.3	–	–	21.1 ± 11.8	13.38 ± 5.7	0.004[a]
Duration (year)	8.3 ± 6.9	–	–	5.8 ± 7.9	10.15 ± 7.2	0.04[a]
Seizure frequency (time/month)	0.41 ± 0.35	–	–	0.46 ± 0.38	0.34 ± 0.31	0.18[a]
IBSL (month)	1.37 ± 1.01	–	–	1.38 ± 1.13	1.36 ± 1.00	0.94[a]

The p_1 value indicates the comparison between IGE and HC, and the p_2 value indicates the comparison between GTCS and JME. [a] The p value was obtained by a two-sample two-tailed t test. [b] The p value was obtained by a χ^2 test. *M*: male; *F*: female; *AED*: antiepileptic drug; *IBLS*: the interval between scanning and last seizure

realignment, normalization to MNI space with a voxel size of 3 mm × 3 mm × 3 mm, and smoothing with a Gaussian kernel (full width at half maximum = 8 mm) were performed in the remaining 250 volumes successively. The present study excluded subjects with translational head motion greater than 2 mm or/and rotational motion greater than 2 degrees. In addition, nuisance signals, including head-motion signals, white matter signals, and cerebrospinal fluid signals, were regressed out from normalized data. Finally, resting-state data were temporally filtered in the 0.01–0.08-Hz band.

Probabilistic fiber tracking between cerebellum and cerebral cortex

To assess the SC from the cerebellum to the cerebral cortex, the bilateral dentate nuclei were selected as two seed regions and the whole cerebral cortex as the target with waypoints at the superior cerebellar peduncle and thalamus. The bilateral frontal, temporal, parietal, and occipital lobes were used as seed regions, and the whole cerebellum served as the targets to evaluate white matter tracts from the cerebral cortex to the cerebellum with a waypoint at the middle cerebellar peduncle. All seed regions in the present study were defined according to the JHU-MNI (Johns Hopkins University-Montreal Neurologic Institute) atlas. In the present study, probabilistic tractography was obtained using FSL's probtrackxs tool. In general, an individual T1-weighted image was first coregistered to its B0 image in the DTI native space and then registered to the MNI space, generating a warp image. The inverse warp image was utilized to warp the seed regions in MNI space back to DTI native space. For each voxel in the seed region, 5000 iterations of tracking were performed in individual native spaces with the following parameters: curvature threshold = 0.2, a maximum number of steps = 2000, step length = 0.5 mm. Finally, 20 white matter tracts were generated for each subject. Then, these tractograms were nonlinearly transformed to MNI space according to the previously mentioned warp images. For each tract, a two-sample *t* test was performed to detect alterations of SCS in IGE with a significant level setting at $p < 0.05$ with threshold-free cluster enhancement (TFCE) correction. Present probabilistic fiber tracking was mainly based on the anatomic basis of cerebellar efferent and afferent fibers, which was described in Fig. 1.

To further study microstructural alterations in specific tracts in cerebello-cerebral pathway in IGE, the FA, mean diffusivity (MD), and radial diffusivity (RD) indicators were extracted and compared between groups. Specifically, we adopted an ICBM DTI-81 Atlas-based spatial statistical method. First, a mean FA map of all subjects was generated in the MNI space. Next, the mean FA map was skeletonized with a threshold of 0.2, generating a white matter skeleton. For each subject, the FA, mean diffusivity (MD), and radial diffusivity (RD) maps were projected onto the skeleton. The present

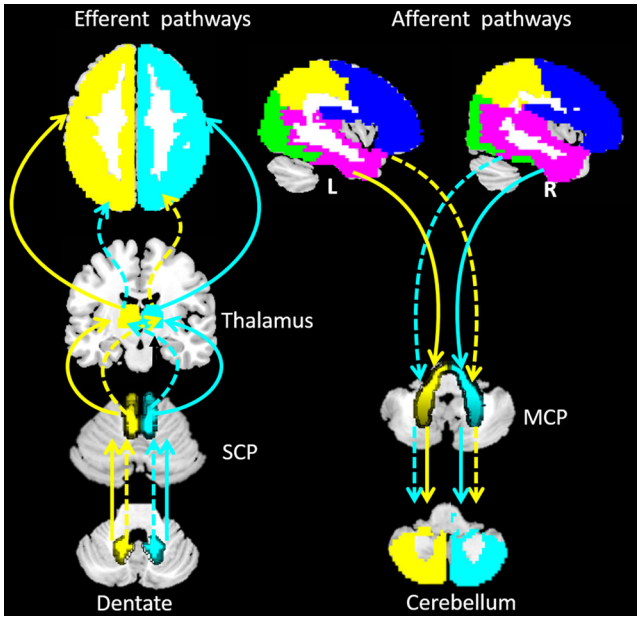

Fig. 1 Illustration probabilistic tracking between cerebellum and cerebrum. The directions of the arrows represent the cerebral afferent and efferent pathways from an anatomical basis rather than the direction of the reconstructed white matter from probabilistic tracking. SCP: superior cerebellar peduncle; MCP: middle cerebellar peduncle

study mainly focused on alteration in cerebello-cerebral circuit; thus, we selected 26 sub-tracts locating in the cerebello-cerebral pathway based on ICBM DTI-81 Atlas, including bilateral SCP; MCP; inferior cerebellar peduncle (ICP); pontine crossing tract (PCT); corticospinal tract (CST); cerebral peduncle (CP); anterior and posterior limb of internal capsule (ALIC and PLIC); retrolenticular part of internal capsule (RLIC); anterior, superior, and posterior corona radiata (ACR, SCR, and PCR); posterior thalamic radiation (PTR); and external capsule (EC). Finally, for a given tract, the microstructural characters were extracted by averaging values of all voxels within the intersection area of the skeleton and atlas. Between-group differences of above microstructural measurements were investigated using a two-sample *t* test ($p < 0.05$, corrected).

Functional connectivity between dentate and cortical cortex

For the FC analysis, the JHU-MNI atlas was used to define the bilateral dentate nucleus. The averaged time series of the dentate nucleus was extracted and correlated with every voxel in the whole brain. The correlations were assessed by Pearson's correlation coefficients and followed by a Fisher-Z transformation. A two-sample *t* test was used to investigate the between-group differences with a significance level setting of $p < 0.05$ with TFCE correction.

Results

For tracking from the dentate nucleus to the cerebral cortex, the between-group comparison is shown in Fig. 2. Compared with the HCs, a decreased SCS was observed in the efferent fibers of the left dentate nucleus in the ACR, which links the thalamus to bilateral sensorimotor areas in the patients with IGE ($p < 0.05$, TFCE corrected). Meanwhile, the right dentate nucleus also demonstrated a deceased SCS in the ACR in the efferent fibers to contralateral sensorimotor areas. Moreover, the increased SCS was observed in the PCR in the efferent fibers from the cerebellum to the occipital cortex in the IGE patients ($p < 0.05$, TFCE corrected).

For tracking from the cerebral cortex to the cerebellum, the between-group comparison is shown in Fig. 3 ($p < 0.05$, TFCE corrected). Compared with the HCs, the increased SCS was observed in the CST in the left cerebellar afferent fibers from the right frontal lobe in the IGE patients. Notably, the alterations of the SCS in the efferent and afferent fibers between the frontal lobe and cerebellum were opposite (increased in afferent and decreased in efferent fibers). In addition, in the patients with IGE, a decreased SCS in the PLIC was observed in the afferent fibers from the right parietal lobe to the ipsilateral cerebellum. In the cerebellar afferent fibers from the right occipital lobe, the patients with IGE demonstrated increased SCS in the ipsilateral RLIC.

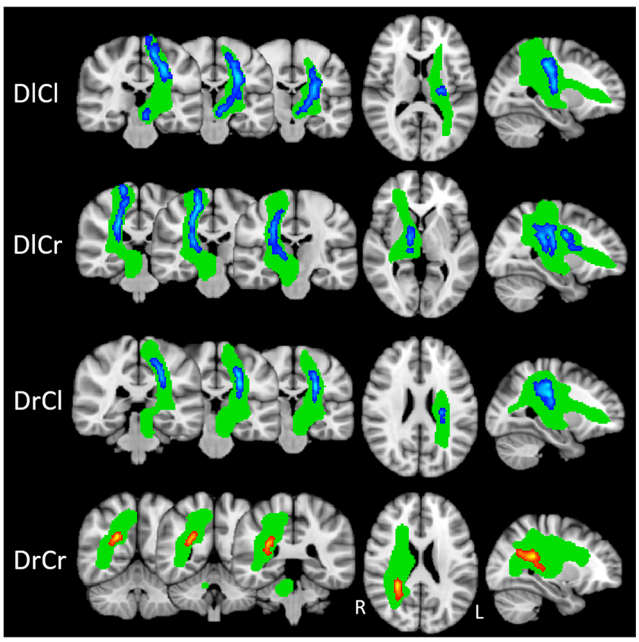

Fig. 2 Between-group comparison of SCS from the dentate nucleus to the cerebral cortex ($p < 0.05$, TFCE corrected). Green represents the group-level tractography in HC, blue represents the decreased SCS, and red represents the increased SCS in the patients with IGE. The abbreviation DrCr represents SC from the right dentate nucleus to the right cerebral cortex. The same naming rule was followed for DrCl, DlCl, and DlCr: D: dentate nucleus; C: cerebral cortex; l: left; r: right

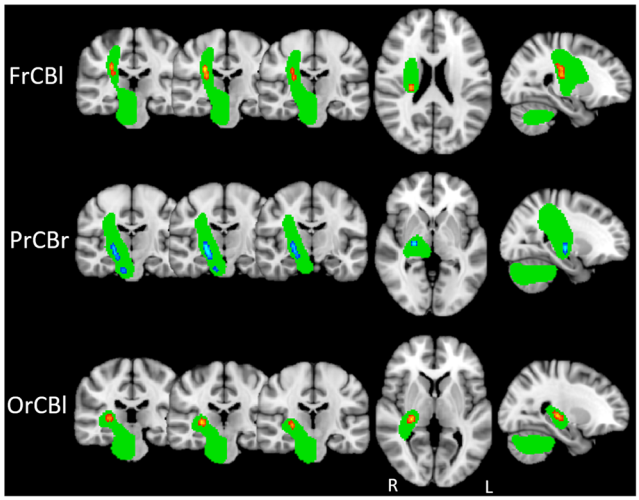

Fig. 3 Altered SCS from frontal, occipital, and parietal cortex to the cerebellum in IGE ($p < 0.05$, TFCE corrected). Green represents the group-level tractography in HC, the blue represents the decreased SCS, and the red represents increased SCS in the patients with IGE. The abbreviation FlCBr represents SC from left frontal lobe to right cerebellum. The same naming rule was followed for OrCBl and PrCBl. F: frontal; O: occipital; P: parietal; CB: cerebellum; l: left; r: right

The patients with IGE demonstrated microstructure alterations in white matter fibers in the cerebello-cerebral pathway. In IGE, decreased FA and increased MD were observed in MCP, CST, RLIC, PCR, PTR, and EC. Besides, the patients also showed decreased FA in PCT and SCR. Moreover, increased MD was also observed in SCP, ICP, CP, PLIC, and ALIC (Fig. 4). Meanwhile, the present study demonstrated increased RD of many sub-tracts in the patients with IGE, which had a high coincidence with the tracts with increased MD (Supplementary Fig. 1).

Compared with the HCs, the bilateral dentate nucleus demonstrated almost the same FC alterations in the patients with IGE. The bilateral dentate nucleus showed decreased FC with the bilateral putamen and left precentral cortex. Additionally, an increased FC between the vermis and bilateral dentate nucleus was also observed in IGE (Fig. 5). Detailed information of the altered regions in the IGE is shown in Table 2. Moreover, the synthetical results of the altered SCS and FC in the cerebello-cerebral circuit are shown in Fig. 6, which concisely illustrates the SC alterations in the cerebellar afferent fibers and the cerebellar efferent fibers and the FC alterations between the bilateral dentate nucleus and whole-brain voxels.

For the comparisons between GTCS and JME, no difference was found in the structural and functional features (SCS, FA, MD, RD, and FC).

Discussion

The SC and FC patterns between the cerebellum and cerebral cortex were investigated in patients with IGE. Compared with

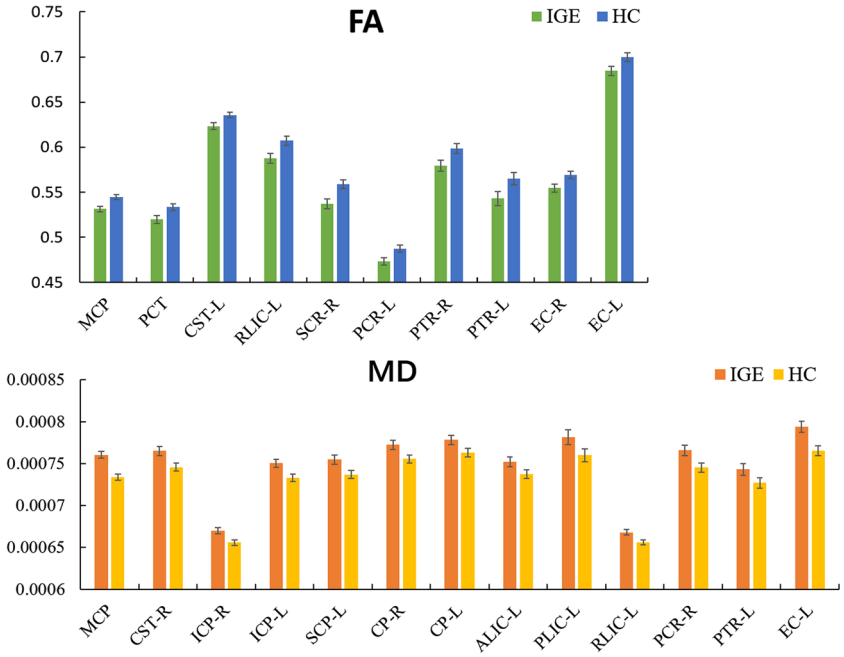

Fig. 4 Comparisons of FA and MD in cerebello-cerebral tracts. Based on ICBM DTI-81 Atlas, the present study demonstrated decreased FA and increased MD in specific cerebello-cerebral subtracts in the patients with IGE, mainly including cerebellar and BG-related tracts

HCs, a consistently decreased SCS in the cerebellar efferent fibers to the frontoparietal cortex and an inconsistently altered SCS in the afferent fibers from the frontoparietal cortex were observed in the patients with IGE; specifically, these consisted of increased SCS in the cerebellar afferent fibers from the frontal cortex and decreased SCS in the afferent fibers from the parietal cortex. In addition, the SCS in the efferent and afferent fibers between the cerebellum and occipital cortex was increased in the patients relative to the HCs. The FC analysis revealed a decreased interaction between the cerebellum and motion-related regions in the patients with IGE. The patients demonstrated distinct alterations in the efferent and afferent pathways between the cerebellum and different parts of the cerebral cortices, which might be the pathological anatomical basis for the cerebellar modulation effect on epileptic activities. The present findings suggest that the cerebellum plays a coordinated role in motion abnormalities and might be associated with cognitive impairment in IGE. The FC results further suggest cerebellar involvement in motor dysfunction. Interestingly, contrary alterations of SCS in the efferent and afferent fibers between the frontal cortex and cerebellum are presumed to indicate unbalanced communication, which might be a specific feature in patients with IGE. In all, the present study revealed connectivity alterations in the cerebello-cerebral circuit and provided new clues to understanding the role of cerebellum in IGE.

Previous functional studies have identified that the cerebellum is associated with the regulation of epileptic activities [25, 26]. Evidence from animal studies has demonstrated that the cerebellum could stop the occurrence of generalized spike-and-wave discharges or inhibit epileptic activities [25, 27, 28]. Epilepsy is caused by disturbed levels of brain excitation and inhibition. The cerebellar neurons exhibited epilepsy-related activity changes, which were inferred to be caused by the abnormally increased excitatory input from the cerebral cortex [29, 30]. The present findings revealed disturbed anatomical connectivity from the cerebral cortex to the cerebellum, which might be the structural basis for the abnormal

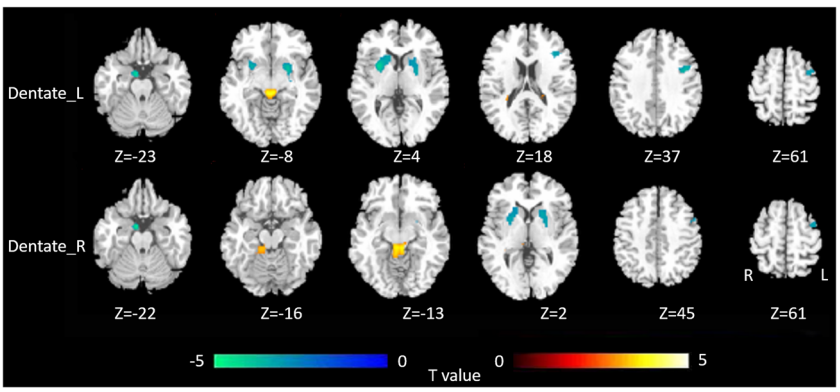

Fig. 5 Altered FC between the dentate nucleus and cerebral cortex in IGE. The bilateral dentate nucleus demonstrated a decreased FC with the bilateral putamen and left precentral gyrus and an increased FC with the vermis. Warm colors represent increased FC, and cold colors represent decreased FC in patients with IGE

Table 2 Results of FC differences between groups

Regions	MNI coordinates	Peak *T* value	Number of voxels
Dentate_L			
Putamen_R	27 6 0	− 4.26	226
Putamen_L	27 0 − 6	− 3.89	152
Precentral_L	− 42 0 36	− 3.71	53
Vermis_3	0 − 33 − 9	4.24	57
Dentate_R			
Vermis_3	3 − 33 − 9	4.12	107
Putamen_R	24 6 3	− 3.35	51
Putamen_L	− 24 0 3	− 3.29	96

R: right; *L*: left

information input. In addition, previous studies have demonstrated that Purkinje cells and cerebellar nuclei usually generate action potential during epileptic seizures [25, 27]. It has been demonstrated that stimulating the cerebellum has a glutamatergic impact on thalamic neurons, which subsequently prevents excessive hyperpolarization of the thalamic membrane and avoid evoking bursts of action potentials [31]. Our findings also revealed disrupted structural connectivity in the pathways from the cerebellum to different cerebral regions, especially in the cerebellum-thalamocortical pathway, providing anatomical evidence to help understand the modulatory role of the cerebellum in epileptic activities. For example, the sensorimotor cortex has been suggested to be one of the regions of epileptic origin; thus, its abnormal connectivity with the cerebellum implies a potential modulatory effect of the cerebellum on the generation and propagation of epileptic activities. Furthermore, in the present study, different SCS alterations were observed in different efferent pathways, which suggests that the cerebellum exerts different effects on different cerebral regions. Therefore, we boldly and reasonably speculate that the distinct connectivity alteration patterns between the cerebellum and cerebral regions might partially contribute to the abnormal interactions between cerebral regions, especially regions within epileptogenic and propagation networks, which thereby facilitate the propagation of epileptic activities.

Motor abnormalities are a common clinical manifestation in IGE, and the involvement of motion-related regions, including sensorimotor regions, the basal ganglia (BG), and the cerebellum, has been widely reported in previous studies. It has been demonstrated that hyper-excitability in the cerebral cortex is associated with clinical manifestations in patients with epilepsy [32]. Consistently, the present study demonstrated a decreased SCS from the cerebellum to sensorimotor regions, which was inferred to imply a subdued inhibitory effect of the cerebellum on the cerebral cortex in IGE [33]. Meanwhile, a decreased FC between the dentate nucleus and the primary motor cortex was also observed in the patients. These findings provide evidence to understand the contribution of the cerebellum to motor abnormalities in patients with IGE from structural and functional connectivity viewpoints. Notably, the decreased SCS was mainly located in the thalamus and the pathway across the internal capsule. The thalamus is a key relaying point in the pathway between the cerebellum and cerebral cortex and has been demonstrated to abnormally connect with the cerebellum and cerebral cortex in IGE [13, 34, 35]. In addition, as major tracts across the BG, the internal capsule contains ascending fibers from the thalamus to the cerebral cortex and descending fibers from the frontoparietal cortex to subcortical areas [36]. It has been noted that disrupted connections of the BG are involved in motor abnormalities in several clinical syndromes [37]. Our results further provided structural evidence to support the involvement of the BG and thalamus in motor abnormalities in patients with IGE. In line with the structural alterations, the patients with IGE also showed decreased FC between the dentate nucleus and BG. The present results suggested that the cerebellum and BG showed coordinated effects on motion abnormalities in

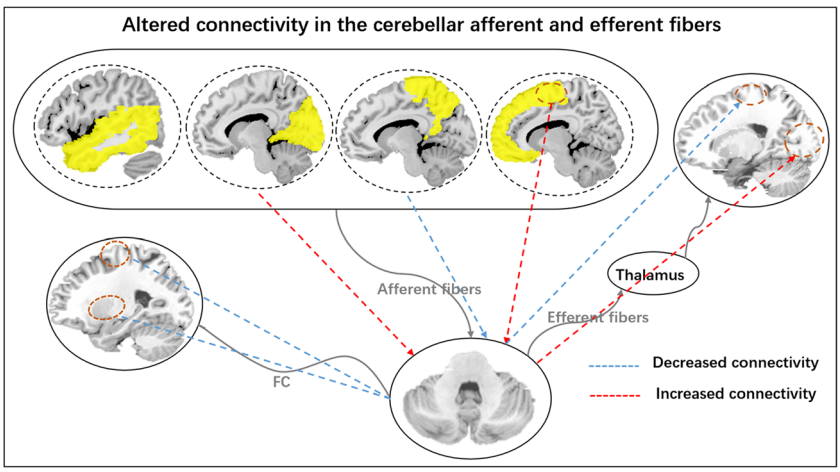

Fig. 6 Synthetical results of altered SCS and FC in cerebello-cerebral circuit in patients with IGE

patients with IGE. In all, the present study revealed disrupted SC from the cerebellum to the sensorimotor cortex in the pathway through the thalamus and internal capsule and abnormal FC between the cerebellum and motion-related regions, which provides powerful evidence for understanding the abnormal motor functioning in patients with IGE.

Accumulated evidence has suggested various cognitive dysfunctions in patients with epilepsy and revealed a potential association with brain network dysfunction [38]. Although the mechanisms have not been made completely clear, increasing evidence has demonstrated that chronic recurrent seizures could cause and aggravate cognitive impairment [39, 40]. Previous studies have demonstrated an important role of the frontoparietal cortex in cognitive dysfunction in patients with IGE [41, 42]. In addition, hyperconnectivity between the frontoparietal area and cortical motor regions is presumed to be a potential mechanism for the seizures induced by cognition [43]. Moreover, in recent years, it has been widely demonstrated that the cerebellum is involved in cognitive functions in addition to motor functions [44, 45]. And different neurological disorders have demonstrated a potential association with abnormal cerebellar dysfunction [46]. In this study, altered SCS from the frontal and parietal cortices to the cerebellum might contribute to cognitive impairment in patients with IGE. The present findings provide structural evidence to indicate a possible contribution of the cerebellum to abnormal frontoparietal function in IGE.

Except for the strength of SC, the WM microstructural diffusion features (FA, MD, and RD) related to the subtracts in cerebello-cerebral pathway were also investigated, which are directly affected by the membrane and myelin integrity and fiber density [47, 48]. In the present study, decreased FA and increased MD and RD were mainly observed in cerebellar and BG-related tracts. Previous researches suggested that reduced FA and increased MD might be related to the degradations of microstructural organization of white matter fiber in JME [49, 50]. Specifically, it further indicated that the microstructural damage of fiber tracts in thalamofrontal circuit and interhemispheric connections played an important role in the epileptogenesis. Besides, increased RD in IGE was also inferred to potentially reduced myelination or demyelination [51]. We took these microstructural metrics for a cautious inference of histopathological proof of myelin loss, which might contribute to the structural and functional underlying IGE.

The present study does carry a limitation. Notwithstanding that white matter has no predefined direction, the present study attempted to investigate the SC in efferent and afferent pathways. However, the existing analytical technology of DTI does not allow for easy differentiation between the two types of fibers. Here, combining evidence from anatomical characteristics, we used a probabilistic fiber tracking approach to make a pioneer search to distinguish between the two types of fibers to a large extent.

Conclusions

Efferent and afferent SC between the cerebellum and cerebral cortex was first compared between patients with IGE and HCs. Distinct efferent and afferent connectivity alterations between the cerebellum and various cerebral regions provided further evidence to understand the cerebellar modulatory effect on epileptic activities, which was inferred to partially contribute to abnormal interactions between cerebral regions. The decreased SCS and FC between the cerebellum and regions of the frontoparietal cortex observed in the patients were inferred to be associated with motor abnormalities and cognitive impairment. Distributed microstructural alterations in the patients implied a potential contribution to the pathomechanism of IGE. In summary, different anatomical alterations in the cerebellar efferent and afferent pathways implied a disrupted communication pattern between the cerebellum and cerebral regions, which provided additional clues to understanding the role of the cerebellum in IGE from both structural and functional viewpoints.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Cheng Luo.

Conflict of interest The authors declare that they have no conflicts of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects in this study.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- Prospective
- Cross-sectional study
- Performed at one institution

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