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RESEARCH ARTICLE

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Distinct effects of the basal ganglia and cerebellum on the thalamocortical pathway in idiopathic generalized epilepsy

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Abstract

The aberrant thalamocortical pathways of epilepsy have been detected recently, while its underlying effects on epilepsy are still not well understood. Exploring pathoglytic changes in two important thalamocortical pathways, that is, the basal ganglia (BG)-thalamocortical and the cerebellum-thalamocortical pathways, in people with idiopathic generalized epilepsy (IGE), could deepen our understanding on the pathological mechanism of this disease. These two pathways were reconstructed and investigated in this study by combining diffusion and functional MRI. Both pathways showed connectivity changes with the perception and cognition systems in patients. Consistent functional connectivity (FC) changes were observed mainly in perception regions, revealing the aberrant integration of sensorimotor and visual information in IGE. The pathway-specific FC alterations in high-order regions give neuroimaging evidence of the neural mechanisms of cognitive impairment and epileptic activities in IGE. Abnormal functional and structural integration of cerebellum, basal ganglia and thalamus could result in an imbalance of inhibition and excitability in brain systems of IGE. This study located the regulated cortical regions of BG and cerebellum which been affected in IGE, established possible links between the neuroimaging findings and epileptic symptoms, and enriched the understanding of the regulatory effects of BG and cerebellum on epilepsy.

KEYWORDS
basal ganglia, cerebellum, epilepsy, MRI, thalamocortical pathway

1 | INTRODUCTION

Idiopathic generalized epilepsy (IGE) is a group of epileptic syndromes that characterized by widespread generalized spike wave discharges (GSWDs). Typically, imbalance of local excitation and inhibition causes seizures generation and the epileptic activity propagated to a brain

Abbreviations: ACC, cingulate gyrus, anterior division; BGN, basal ganglia network; Cun, cuneal cortex; Ins, insular; ITG, inferior temporal gyrus; ITG_TO, inferior temporal gyrus, temporooccipital part; LinG, lingual gyrus; LOC_i, lateral occipital cortex, inferior division; LOC_S, lateral occipital cortex, superior division; M1, precentral gyrus; MTG_TO, middle temporal gyrus, temporooccipital part; OP, occipital pole; PreCun, precuneous; SPL, superior parietal lobule; TFC_p, temporal fusiform cortex, posterior division; Tha, thalamus.

network through thalamus in IGE, causing abnormal activity in wide brain regions (Hwang, Bertolero, Liu, & D'Esposito, 2017). Specifically, the GABA-mediated inhibition in thalamus has been suggested to play a crucial role in synchronizing electrical activity (Huguenard & McCormick, 2007; Snead, 1995). It has been identified that abnormal oscillatory neuronal firing throughout thalamocortical loop contributes to the generation and propagation of epileptic activities in the patients with IGE (Blumenfeld & McCormick, 2000; Gotman et al., 2005; Jiang et al., 2017). These studies also suggest that the aberrant discharging of cortex may be induced by the thalamus. In fact, except for directly thalamic intervening, alterations of cortical activities and thalamocortical oscillations may also be potentially regulated by changed afferent synapsis to the thalamus.

Thalamus relays information from cerebellar interposed nucleus and dentate nuclei to cerebral cortex composing the cerebellum related thalamocortical (CTC) pathway which is mainly involved in motor function as well as cognitive and affective function (Martin, 2012). A potential modulation effect of cerebellum on epileptic activity has been suggested. Previous evidence from animal model has indicated the high effectiveness of electrical stimulation on the dentate nucleus for stopping the GSWDs (Kros, Rooda, Spanke, et al., 2015). Besides, the ventral-anterior thalamic nucleus and the ventrolateral nucleus receives information from globus pallidus, the primary output nucleus of basal ganglia (BG), forming the BG related thalamocortical (BTC) pathway, which plays a decisive role in motor initiation. The BTC pathway plays a decisive role in motor initiation and learning (Grillner & Robertson, 2016). Basal ganglia also demonstrated modulation effect on epileptic discharges (Chen et al., 2014). Simultaneously EEG-fMRI studies revealed a coordinated effect of the basal ganglia and the thalamus on the generation and propagation of epileptic activities (Badawy, Lai, Vogrin, & Cook, 2013; Kros, Eelkman Rooda, De Zeeuw, & Hoebeek, 2015). Moreover, physical connections among cerebellum, basal ganglia and thalamus has been identified through virus injection in animal studies which can regulate the excitation-inhibition balance, contributing to epileptic activity (Bostan, Dum, & Strick, 2010; Norden & Blumenfeld, 2002). The above findings indicated that the cerebellum and basal ganglia have modulation effects on the thalamocortical loop, which were responsible for the epileptic activities and dysfunctions.

Up to now, the modulation effects of cerebellum and basal ganglia on the thalamocortical loop in the patients with IGE has been recognized. However, it is less clear which specific cortical areas the cerebellum and basal ganglia regulate through thalamus. The present study aims to address this issue using fusion data of function and structure. First, cerebellum and basal ganglia connectivity-weighted sub-regions of thalamus was acquired by projecting cerebellum and basal ganglia into the thalamus based on their structural connectivity (SC) (Pelzer, Melzer, Timmermann, von Cramon, & Tittgemeyer, 2017). Therefore, the thalamocortical loop was fall into two distinct circuits labeled as BTC and CTC pathway correspondingly. And then, functional and SC in the two pathways were further investigated in the patients with IGE. We hypothesis that the cerebellum and basal ganglia would demonstrate modulation effects on common and distinct cortical regions in the patients with IGE. And the interaction between thalamus, basal ganglia and cerebellum might also be disrupted. We hope this study can provide further insights into the modulation effects of cerebellum and basal ganglia in the patients with IGE.

2 | METHODS

2.1 | Subjects

A total of 127 participants (65 IGE patients with 62 healthy controls) were recruited in this study. The patients with IGE were diagnosed based on clinical and seizure semiology information consistent with the International League Against Epilepsy (ILAE) guidelines. None of the participants had any other neurologic or psychiatric disorders or exhibited detectable structural abnormalities by routine MRI. This study was permitted by the ethics committee of the University of Electronic Science and Technology of China (UESTC).

2.2 | MRI acquisition

For each participant, high resolution structural images, diffusion MRI (dMRI) data, and resting-states functional MRI (rs-fMRI) data were acquired for each subject using a GE 3.0 Tesla Discovery 750 MR scanner in the Center for Information in Medicine of UESTC. The structural images were acquired using a fast-spoiled gradient-recalled echo sequence (TR = 6,000 ms; TE = 2 ms; flip angle = 9°; voxel size $1 \times 1 \times 1$ mm^3). The dMRI data was composed by three b0 images following with 64 diffusion-weighted images, and was acquired by using a single-shot, spin-echo, echo-planar sequence (TR = 8,500 ms; TE = 70 ms; voxel size is isotropic 2 mm; FOV = 256×256 mm^2; 76 axial slices; 64 diffusion directions; b = 1,000 s/mm^2). The fMRI data was acquired with axial slices parallel to the anterior–posterior commissure using a standard T2*-weighted Echo Planar Imaging pulse sequence (TR/TE = 2000 ms/30 ms, flip angle = 90°, field of view = 24×24 cm, acquisition matrix = 64×64, slice number = 35, scanned interleaved and slice thickness = 4 mm with no gap) covering the whole brain. Before scanning of fMRI, subjects were told to close eyes and stay awake.

2.3 | SC of the cerebellum-thalamocortical and BG-thalamocortical pathways

Here, structural cerebellum/BG-thalamocortical pathway was constructed among three "nodes" (dentate/pallidum, thalamus, and cortex) using dMRI. In order to label dentate and pallidum more accurately, their templates were registered to individual dMRI by using individual high resolution T1 image as the intermediate image. Two structural features including microstructural measurements and the connectivity strength of white matter(WM) were calculated to investigate structural pathway alterations in patients with epilepsy.

First, briefly, the microstructural measurements were extracted from two tracts constructed using deterministic tractography (see Supporting Information for details): one connects the thalamus and dentate, and the other connects the thalamus and pallidum. Then, the mean microstructural measurements, including fractional anisotropy (FA) and mean diffusivity (MD), on the two tracts were compared between groups using the Mann–Whitney *U* test. After that, an along-tract statistics pipeline was also used to detect more local changes in FA/MD along these two tracts (Colby et al., 2012). Multivariate analysis of variance was used to measure the differences in FA/MD between groups along these two tracts with age and gender as confounding variables. The significance of the differences was quantified by a permutation-based null-distribution method.

Second, to examine the potential SC matched with the FC pattern, the WM connectivity of the BTC and CTC pathways were reconstructed using probabilistic tractography. In this step, the bilateral dentate and pallidum were set as seed regions, and the cerebral cortex was set as the target with the corresponding ipsilateral thalamic projection as the waypoint. The nonparametric permutation test (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) with threshold-free cluster enhancement correction was used to investigate the intergroup differences with age and gender controlled. Spearman's rank correlation coefficient was used to describe the association between SC and clinical measures including the duration and onset of illness.

2.4 | Functional connectivity of the cerebellum-thalamocortical and BG-thalamocortical pathways

Functional cerebellum-thalamocortical pathway was acquired using two steps. The first: dentate-specific thalamic mapping was determined using probabilistic tractography of dMRI. Cerebellum-constrained thalamic BOLD timecourse was acquired by a regression analysis between whole thalamic BOLD signals (Y) and the dentate-specific thalamic mapping (X). The second: functional connectivity was calculated between cerebellum-constrained thalamic BOLD timecourse and that of each cortical voxel. Similarly, functional BG-thalamocortical pathways was also defined. The detailed was shown as following.

2.4.1 | First step: Region-specific thalamic signals constrained by dMRI

After preprocessing and quality control of dMRI data (see Supporting Information for details), white matter connectivity was used to define the spatial pattern of dentate (or pallidum) projections to the ipsilateral thalamus. The thalamic mapping that structurally connect to the dentate or pallidum were identified analogous to Pelzer's work (Pelzer et al., 2017). Take the dentate-thalamic mapping as an example. First, probabilistic tractography was performed for each participant using FMRIB's Diffusion Toolbox in MNI space. Tractograms were acquired using unilateral thalamus as the seed mask and the ipsilateral dentate as the target. A total of 10,000 iterations were performed for each seed voxel in individual diffusion space with pathway distance corrected (other tracking parameters: curvature threshold = 0.2, maximum number of steps = 2000, step length = 0.5 mm). Thus, the resulting maps inside the thalamus indicate the spatial pattern of the white matter connections from the dentate projecting to the thalamus, reflecting the effect of the cerebellum on each voxel of the thalamus.

After preprocessing of functional images (see Supporting Information for details), the BOLD signal of dentate-thalamic mapping were acquired by a regression analysis (O'Muircheartaigh, Keller, Barker, & Richardson, 2015). Individual high-resolution T1 image was used to make the registration between dMRI and fMRI more accurate. In order to extract thalamic BOLD signal constrained by dentate-thalamus white matter pathways, a spatial regression was done by using dentate projections inside thalamus (dentate-thalamic mapping) as the spatial predictors of the preprocessed individual fMRI volumes, and resulted in a time series. Similarly, BOLD signal of pallidum-thalamic mapping was also defined.

2.4.2 | Second step: Thalamocortical FC constrained by dentate/pallidum-thalamic mapping

Then, individual FC were obtained by regressing this time series into individual fMRI data to get a spatial map. Here, the FC of dentate/pallidum projection map represents the effects of the cerebellum/BG on the thalamocortical circuit. Subsequently, these FC maps were spatially smoothed with an 8-mm FWHM Gaussian kernel and then Fisher's Z-shifted. The intergroup difference of the FCs was calculated using two-sample *t* tests under a significance level of $p < .05$ with family-wise error (FWE) correction. To investigate the clinical relevance, the altered FC in IGE was correlated with the duration and onset of illness. Spearman's rank correlation coefficient was used to describe the association.

2.5 | Validation analysis

Two validation analyses were introduced in the study.

First, a relatively traditional modulation model was used to validate the results of the present study which used a new method to construct brain circuits. This model (the following formula) aimed to investigate the modulatory role of the basal ganglia and cerebellum on the thalamocortical circuit for cortical regions that showed intergroup differences:

$$Y_{roi} = \beta_0 + \beta_1 X_{Th} + \beta_2 X_{DoP} + \beta_3 X_{inter} + \epsilon$$

where Y_{roi} represents the time series of cortical regions that showed intergroup differences in both pathways, X_{Th} represents the average time series of the bilateral thalamus (the whole thalamus, not only the above-mentioned mapping), X_{DoP} represents the average time series of the modulator (the bilateral dentate or pallidum), and $X_{inter} = X_{Th} \times X_{DoP}$ represents the interaction of the thalamus and the

modulators. Thus, β_3 reflects the thalamocortical FC under the modulation of the basal ganglia/dentate. Then, intergroup differences in β_3 were detected using a two-sample *t* test.

Second, to investigate the coupling effects of functional and structural connection, the structural-weighted FC were calculated using the product of FC and SC (FC × SC). A permutation-based statistic (iterated 10,000 times) was used to test the intergroup differences of the structure-modulated FC.

TABLE 1 Demography information

	Subjects					
	HC *N* = 59		IGE *N* = 58		Stats	
					t/χ^2	*p*
Gender (male: Female)	35:24		28:30		0.01	.92
Type (GTCS:JME)	–		31:27		–	–
	Mean	*SD*	Mean	*SD*		
Age	25.6	5.6	25.5	10.1	0.86	.39
Duration of illness (years)	–	–	11.1	8.3	–	–
Onset of illness (years)	–	–	13.1	6.8	–	–

Abbreviation: IGE, idiopathic generalized epilepsy.

3 | RESULTS

After quality control (see Supporting Information), ten subjects were excluded from the subsequent analysis because of the large head motion during their scanning. Fifty-eight patients with IGE (28 males, mean age: 25.5 ± 10.1 years) and 59 age-matched healthy controls (35 males, 25.6 ± 5.6 years) were reserved (Table 1).

3.1 | Alterations of SC

Microstructural measurements were extracted from the cerebellum-thalamus and BG-thalamus pathways, which were defined by deterministic tractography (Figure S5). Relative to the healthy control (HC) group, the mean FA value in the ipsilateral pallidum-thalamus connection decreased in patients with IGE (Figure S6, $p < .001$). There was no intergroup difference in the MD in either pathway.

However, an increased FA was detected in the cerebellar section of the dentate-thalamus WM connection in IGE (Figure 1). There was no significant MD alteration in this pathway.

3.2 | Alterations of functional connectivity

According to the results of the white matter mapping analysis, the thalamus was segmented into two projected parts: pallido-thalamic

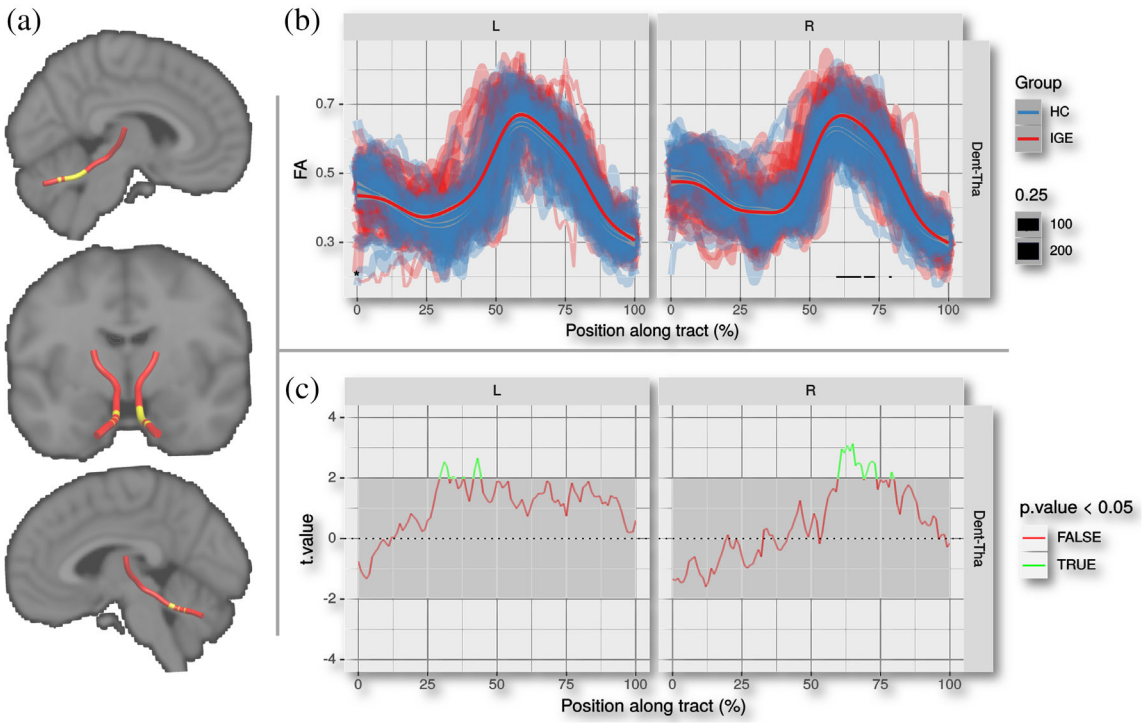

FIGURE 1 The fractional anisotropy (FA) changes along the dentate-thalamus WM pathway. (a) The increased FA in the cerebellar section of the dentate-thalamus WM connection in idiopathic generalized epilepsy (IGE). (b) The FA is plotted versus position from tract origin, with plots faceted by tract name and hemisphere, and colored according to group membership (HC or IGE). (c) Statistical result was plotted versus position from tract origin. Significant regions were plotted in green line

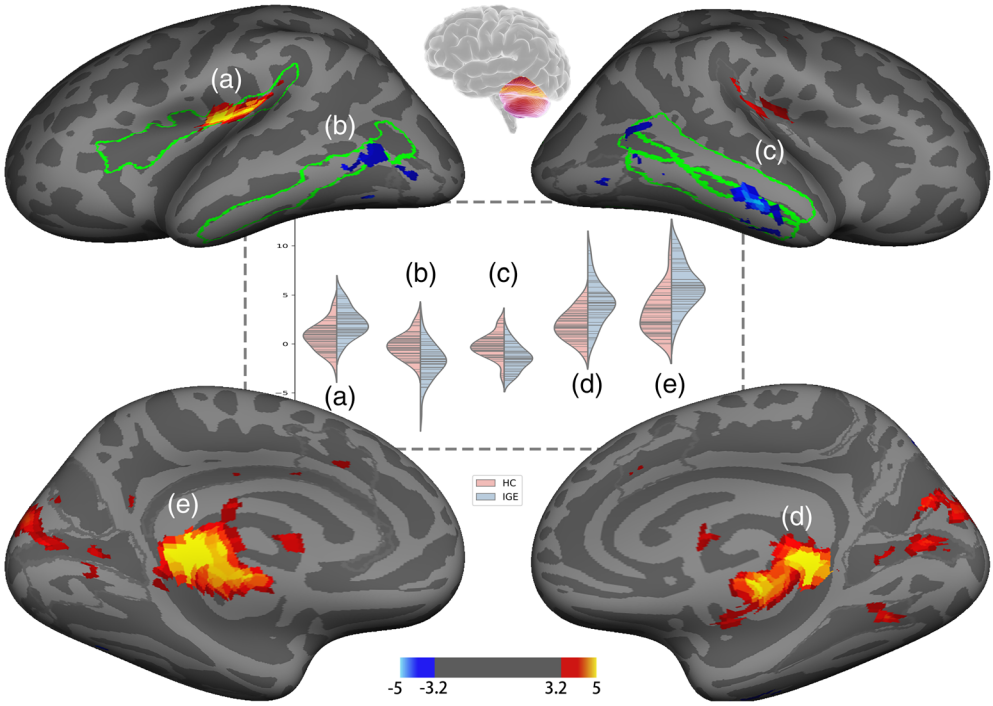

FIGURE 2 The aberrant cerebellum-thalamocortical functional pathway in idiopathic generalized epilepsy (IGE). The crucial cortical regions were outlined in green. Significant functional connectivity (FC) changes ($p < .05$ family-wise error [FWE] corrected) were found in posterior insula (a), temporal gyri (b and c), and subcortical nuclei (d and e). The violinplots in the center illustrate the functional connectivity distribution (vertical coordinates) of significant FC changed regions across subjects in the two groups

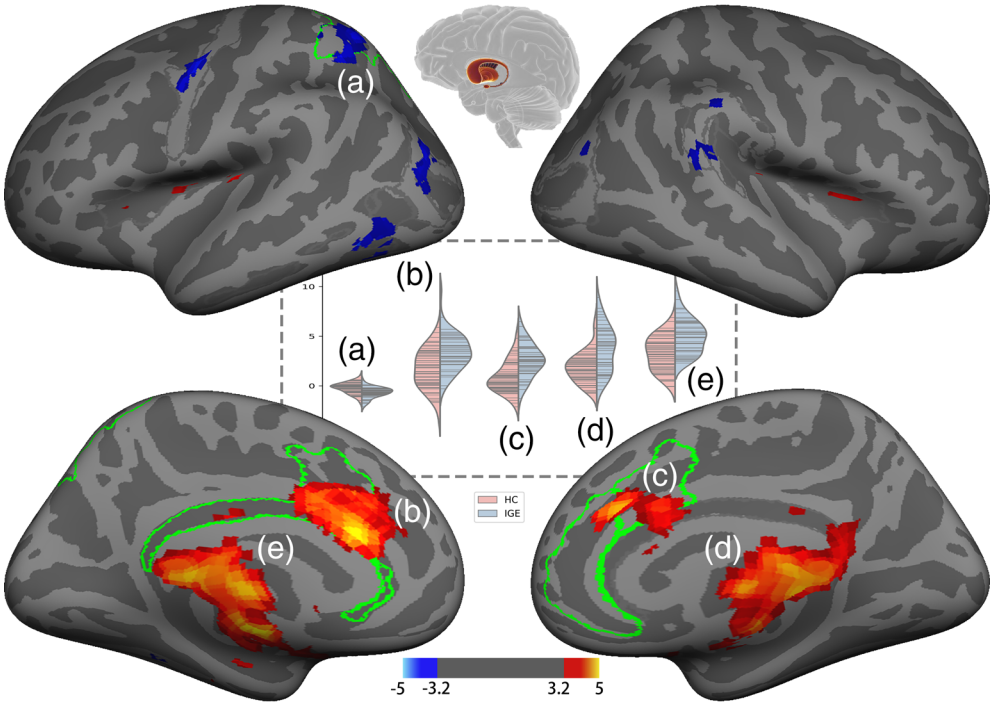

FIGURE 3 The aberrant basal ganglia (BG)-thalamocortical functional connectivity in idiopathic generalized epilepsy (IGE). The crucial cortical regions were outlined in green. Significant functional connectivity (FC) changes ($p < .05$ family-wise error [FWE] corrected) were found in superior parietal lobe (region a), anterior cingulate area (region b and c) and subcortical regions (region d and e). The violinplots in the center illustrate the functional connectivity distribution (vertical coordinates) of significant FC changed regions across subjects in the two groups

projections and dentate-thalamic projections. The mapping results demonstrated a decreasing posterior-to-anterior gradient for the dentate-thalamic projection and an increasing posterior-to-anterior gradient for the pallido-thalamic projection (see Figures S3 and S4 for details). These mapping results were consistent with previous works (Pelzer et al., 2017; Worbe, Yelnik, & Lehéricy, 2010). Then cerebellum/BG specific thalamic timecourses were acquired according to their projected thalamic part.

In the patients with IGE, the FC in the CTC pathway was found to be significantly increased in the thalamus (region e and d in Figure 2, $p < .05$ FWE corrected), BGN, Cun, Ling and posterior Ins (region a, FWE corrected). In addition, decreased FC connections mainly found in the temporal lobe (region b and c, FWE corrected) and the occipital lobe in the CTC pathway by comparing with controls (Figure 2).

The altered FC in the BG-thalamocortical pathway was illustrated in Figure 3. In detail, M1, SPL (region a in Figure 3, $p < .05$ FWE

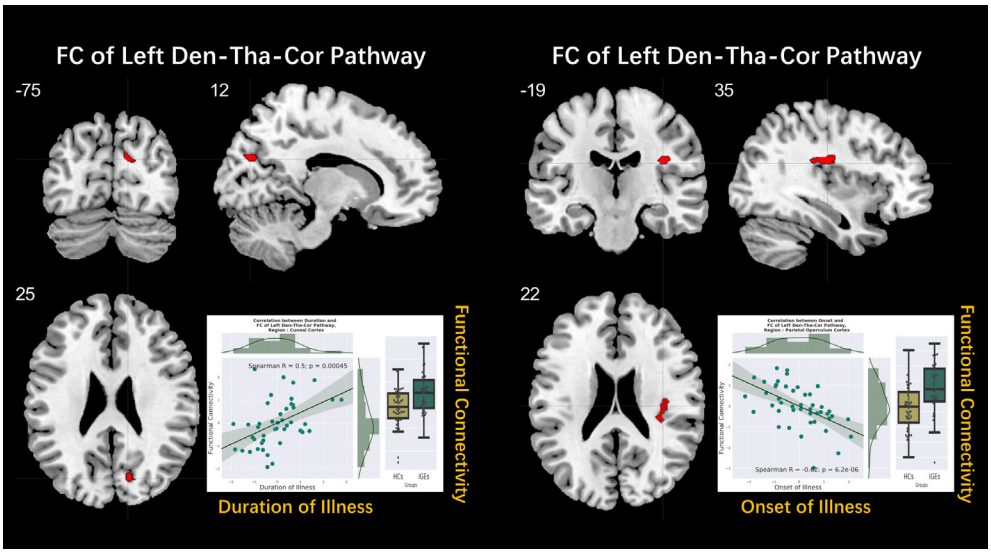

FIGURE 4 The correlation between functional connectivity (FC) and clinical measurements

TABLE 2 Changed cerebellar/BG regulation on TC in IGE

	p value			*T* value
	β_{Th}	$\beta_{dentate}$	β_{inter}	β_{inter}
Changed cerebellar regulation on TC in IGE				
LOC-s	.019	.983	.029	2.212
SPL	.019	.133	.031	−2.1 90
Changed BG regulation on TC in IGE				
SPL	.249	.002	.046	−2.018

Note: β indicates the effects effecs of dentate, thalamus and their interaction on cortex. *T* value <0 indicates a decreased effect in IGE, vice versa.
Abbreviations: BG, basal ganglia; IGE, idiopathic generalized epilepsy; TC, thalamocortical loop.

corrected), temporo-occipital junction and temporo-parietal junction showed a decreased FC with the BG-thalamic projection. The increased FC in the BTC pathway was located in the ACC (region b and c, FWE corrected), thalamus and BGN (region d and e, FWE corrected).

Besides, the FC of the right cuneal cortex in the CTC pathway was positively correlated with the duration of illness (Figure 4 left panel, $p < .05$, FDR corrected). The FC of the right insular in the CTC pathway was negatively correlated with the onset of illness (Figure 4 right panel, $p < .05$, FDR corrected).

3.3 | Results of validation analysis

GLM analysis revealed the modulation effects of the BG and cerebellum on the FC of bilateral SPL, OP, LOC-s and ITG-to in the thalamocortical loop. Specifically, in terms of the modulation effects of the cerebellum, an increased FC in LOC-s and a decreased FC in SPL in the thalamocortical loop were demonstrated in the patients with IGE (Table 2, row 4–5). In addition, a decreased thalamic FC was found in SPL in IGE with modulation from the BG (Table 2, row 7).

An increased WM-weighted FC of the BTC pathway was found in the SPL and LOC-s in patients with IGE. In the CTC pathway, the ITG-to and LOC-s showed stronger negative WM-weighted FC, while the SPL showed decreased positive WM-weighted FC in the patient group (Figure S13, $p < .05$, uncorrected).

4 | DISCUSSION

In the present study, we applied a full data-driven approach for constructing two crucial components of the thalamocortical loop and then investigated the affected connections of those pathways in patients with IGE in terms of functional and SC. Briefly, some consistent FC changes were detected in these two pathways, mainly in perception regions, and contrariwise, it was also observed that the connection with high-order cognition regions showed pathway-specific FC alterations in the IGE group. In addition, WM connectivity aberrance between thalamus and dentate, between thalamus and pallidum, as well as thalamocortical WM connections, were also detected in the IGE group. Moreover, the combination of functional and SC of these two pathways in association areas were found to be altered in IGE. Alterations in the primary system of the two pathways may reveal the aberrant integration of sensorimotor and visual information in IGE; cognitive impairment and epileptic activities in IGE may come from distinct disease effects of the two pathways on high order cortical systems; moreover, abnormal integration of cerebellum, basal ganglia and thalamus could result in an imbalance of inhibition and excitability in brain systems.

4.1 | Alterations in the primary system in the two pathways

Mounting evidence indicates that the sensorimotor system is impacted in patients with IGE (Vollmar et al., 2011; Vulliemoz et al., 2011). A previous multimodel study provided convincing

evidence for structural abnormalities in the thalamo-motor pathway in IGE (O'Muircheartaigh et al., 2012). According to the model of the cortico-basal ganglia-thalamocortical loop (DeLong & Wichmann, 2007), the thalamus serves as a central integrator in modulating behaviors. Specifically, motor information is processed in the putamen and then sent to the ventrolateral nucleus of the thalamus via the pallidum (Worbe et al., 2010). In the present study, FC enhancement between the thalamic projection of the BG and M1 was found in patients with IGE. This projection covered the ventrolateral nucleus, which has a major role in the coordination and planning of movement. Hence, the present findings indicated that the altered connectivity in the BG-thalamus-M1 loop might be related to motor dysfunction in IGE. The decreased WM connectivity (see Figure S9) of the BG-thalamocortical pathway in the CST suggested impacted sensorimotor information transforming to SM1, which provided anatomic evidence to support this argument. The decreased FC in the SPL in the BTC pathway might implicate a disrupted dorsal stream of the visual system in IGE. In addition, regulation analysis (Table 2) demonstrated that the modulation effects of the pallidum on the FC between its thalamic projection and the SPL was significantly changed in IGE. The dysregulation of the thalamic projection of the basal ganglia in the motor and visual system provided a possible mechanism for the motor abnormalities induced by visual cue errors in patients with epilepsy.

4.2 | Alterations in the cognitive system: The shared and distinct effects in the BTC and CTC pathway

It has been suggested that the mesial thalamus (MT) is involved in modulating limbic regions in epilepsy (Shyu & Chang, 2014). BOLD enhancement in ACC at the beginning of GSWD indicated its potential involvement in the initiation and progression of epileptic oscillations (Benuzzi et al., 2012). The disrupted anatomical and functional connectivity between bilateral ACC was suggested to be critical to the pathophysiology of patients with IGE (Ji et al., 2014). Specifically, previous investigations have emphasized the participation of ACC in thalamic modulation of epileptic activity. The MT reciprocally connected with the ACC and might play an important role in remotely controlling seizure synchronization (Kahane & Depaulis, 2010; Vogt, 2005). Thalamus might cause epileptic activity to wane by strengthening surrounding inhibition of regions involved in seizures (Pinto, Patrick, Huang, & Connors, 2005; Trevelyan, Sussillo, Watson, & Yuste, 2006). More important, animal studies suggested that thalamic stimulation could efficiently inhibit ACC seizure-like activities through the GABAergic system, demonstrating specific desynchronization modulation in the MT-ACC pathway (Chang, Wu, Lee, Vogt, & Shyu, 2011). Here, the basal ganglia was mainly projected into MT using structural profiles and the basal ganglia related thalamus demonstrated specific modulation effect on ACC. Meanwhile, a proposed model of BG circuits (Worbe et al., 2010) stated that the internal segment of the globus pallidus mediates the interaction between medial dorsal thalamus and ACC. Combing with previous hypothesis, the present study further suggested that the modulation effects of basal ganglia on TC loop mainly located in ACC, contributing to the desynchronization of epileptic network. Furthermore, from the brain network view, ACC is a critical node of salience network (SN), responsible for processing activities standing out in the background (Menon, 2015). Disturbance in ACC has been demonstrated to potentially cause conscious impairment (Qin et al., 2010). Moreover, it was demonstrated that the interaction between medial dorsal thalamus and ACC is crucial for normal consciousness state (Delevich, Tucciarone, Huang, & Li, 2015). Abnormal burst of epileptic activities tends to consume resource of SN, which might be related to the insufficiency for maintaining normal conscious state during seizures in IGE. Besides, it was indicated that consciousness impairment is more likely to occur when seizure involves the ACC. The patients with IGE are often accompanied by disturbance of consciousness when suffering seizures. In line with a potential effect of BTC pathway on SN suggested in a previous study (Peters, Dunlop, & Downar, 2016), the present finding might imply a potential modulation effects of basal ganglia on conscious impairment and epileptic activities through specific MT-ACC pathway.

The precuneus is a core node in the well-known default mode network (DMN). Enhanced negative FC in the precuneus of the CTC functional pathway was found in patients with IGE, which might suggest abnormal interaction between the CTC pathway and the DMN. Previous studies have indicated disrupted DMN function in IGE, which might be associated with epileptic activity and cognitive impairment. In addition, a study on intrinsic connectivity networks illustrated that the cerebellum and thalamus were functionally involved in the DMN, which provided evidence to support the regulatory effect of the cerebellum and thalamus on the DMN (Habas et al., 2009). The abnormal interaction between the CTC pathway and the DMN provided further and new clues to understanding the role of the DMN in epilepsy. Neuroimaging evidence has indicated that the SN receives information from the thalamus via the dorsal posterior insular cortex and mid-insula (Uddin, 2015). Moreover, it was known that the SN mediates the activity of the DMN, which plays a key role in cognitive control processes (Bressler & Menon, 2010). An increased FC in insular was observed in the CTC pathway, which might suggest a potential effect on the SN. Moreover, the FC between the insular and the thalamic projection of the dentate was found to be negatively correlated with the onset of illness; that is, the later the onset, the lower the FC changes, which might imply less cognitive impairment with later onset age. Thus, the dysfunction of CTC pathway maybe contributing to the disbalance between DMN and SN, and could be the neuromechanism of cognition disorder in IGE.

Compared with HCs, both pathways demonstrated decreased interaction with temporal lobe cortex (i.e., ITG) in IGE. In addition, the altered FC of cerebellar projections with the middle temporal gyrus was detected. The interaction between the temporal lobe and the cerebellum and BG was found to be involved in memory processes (Andreasen et al., 1999; Kéri, Nagy, Kelemen, Myers, & Gluck, 2005;

Packard & Knowlton, 2002). In a neural model study, the middle temporal gyrus and medial dorsal thalamus were important for memory processes (Ketz, Jensen, & O'Reilly, 2015). A study on semantic dementia and Alzheimer's disease demonstrated that the inferior temporal gyrus might play an important role in semantic memory (Chan et al., 2001). The impairment of memory in IGE has been demonstrated in a previous task-fMRI study (Swartz, Halgren, Simpkins, & Syndulko, 1994).

As can be seen, our findings supported the involvement of the BTC and CTC pathways in memory impairment in IGE. In summary, the BTC and CTC pathways demonstrated abnormal interactions with the cognitive system, including shared alterations in the temporal memory system and distinct effects on the high-level cognitive system (SN and DMN).

4.3 | Hyperinteraction between the cerebellum, basal ganglia and thalamus

Recently, some studies demonstrated that the information from the BG and cerebellum interact and converge with each other in specific nuclei in thalamus (Hintzen, Pelzer, & Tittgemeyer, 2018; Pelzer et al., 2017). A conceivable function of these specific nuclei could be a competitive gating mechanism. The cerebellum and basal ganglia have been said to be associated with motor, cognitive and affective dysfunctions in IGE (Bostan & Strick, 2018). Consistent with our previous studies in JME, an increased FC within the thalamus and basal ganglia was observed in two pathways in the present study (Jiang et al., 2017). In addition, an increased FC in cerebellar Crus 1 was found in the BTC pathway (Figure S14). The enhanced connectivity implicated hyperintegration of information in the thalamus and over-interaction between the thalamus and basal ganglia. This phenomenon was consistent with the notion that both the thalamus and basal ganglia contribute to the generation and propagation of epileptic activities of spike wave discharges (Blumenfeld et al., 2009). Since the direct interaction between the basal ganglia and cerebellum has been identified (Bostan et al., 2010), the increased FC observed in left cerebellum Crus 1 in the BTC pathway suggests a hyperregulation of the cerebellum in the IGE. Moreover, a locally increased WM microstructural connectivity (Figure 1, increased FA along dentate-thalamus WM connection without MD/RD changing) of the dentate-thalamus connection were observed in IGE. This anatomic alteration provided potential evidence to support the dysfunction (increased) of cerebellar regulation in the thalamocortical loop in IGE. Besides, neurotransmitter studies have shown that the output of the cerebellum to the cerebral cortex is mainly inhibitory (Nakayama et al., 2012). Combined with previous findings, we proposed a reasonable speculation that the increased inhibition effect of the cerebellum on the BTC pathway might potentially contribute to the motor symptoms in patients during seizures. In conclusion, abnormal interactions between the thalamus, basal ganglia and cerebellum implicated a disrupted balance between inhibition and excitation IGE (Gotman et al., 2005; Hintzen et al., 2018).

4.4 | Limitations and methodological considerations

Two limitations and methodological considerations of the current study should be noted. First, information about antiepileptic medications, medical intervention and treatments administered to patients was not fully collected. We hope to collect this information and then inspect their effects on the BTC and CTC pathways in patients with IGE. Second, limited by the number of subjects, the IGE group was not subdivided into subtype groups in this study. We will continue collecting participants in the future and explore specific changes in FC of the two pathways in various epilepsy syndromes.

5 | CONCLUSION

To the best of our knowledge, this is the first study to investigate the connectivity of the BTC and CTC pathways in IGE. The present study mapped the source of altered cortical regions of thalamocortical connections, revealed coordinate/competitive effects of the two thalamocortical pathways on the perception and high-order cognitive systems in IGE. Hyperinteraction between the thalamus, basal ganglia and cerebellum was speculated to provide basic support for the disrupted balance between inhibition and excitation in the cortex in IGE. Overall, this study provided new clues to understanding the role of the basal ganglia and cerebellum on the TC loop, strengthening our knowledge on the different effects of disease on specific components of the thalamocortical loop, implying the mutual restraint relationship between the cerebellum, thalamus, which might contribute to the pathological mechanism and clinical manifestations of IGE.

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DATA AVAILABILITY STATEMENT

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

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