Decreased functional connectivity in thalamic-cortex and default mode network in idiopathic generalized epilepsy

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Abstract

Objective: Idiopathic generalized epilepsy (IGE) is a common group of epilepsy syndromes associated with abnormalities in thalamo-cortical circuits and default mode network (DMN) connectivity. The thalamus and the DMN are key brain regions critical for sustaining normal cognitive functions. Alterations in the functionality of these regions may contribute indirectly to the cognitive impairments observed in IGE.

Methods: In this study, we performed functional connectivity analysis to calculate the functional connectivity of the thalamo-cortical circuitry, intra-network of the DMN, and between the DMN and other brain networks. We evaluated the neuropsychological performance of patients with IGE and explored the correlation between abnormal network connectivity and neuropsychological assessment scores.

Results: Compared with healthy controls, IGE exhibited reduced functional connectivity between the thalamus and multiple regions including the cerebellum, motor-related cerebral cortex, basal ganglia, and cingulate cortex. Within the DMN, IGE exhibited widespread reductions in functional connectivity relative to healthy controls, predominantly involving the medial superior frontal gyrus, posterior cingulate cortex, anterior cingulate cortex, angular gyrus and precuneus. Regarding inter-network connectivity between the DMN and other brain networks, IGE showed enhanced functional connectivity of the DMN with the visual network, ventral attention network and sensorimotor network. By contrast, DMN connectivity was reduced with the cerebellar network, limbic network and dorsal attention network. Functional connectivity strength among key nodes of the DMN was negatively correlated with global cognitive level.

Conclusion: This study identified reduced functional connectivity in both the DMN and thalamus, with pronounced reductions in functional connectivity between the cerebellum and each of these two brain structures. Such alterations may constitute an important feature of brain functional impairment in IGE. The role played by the cerebellum also warrants further attention. These findings contribute to a deeper understanding of the pathophysiological mechanisms of IGE.

Keywords: Idiopathic generalized epilepsy; Functional magnetic resonance imaging; Functional connectivity; Thalamus; Default mode network

1. Introduction

Idiopathic generalized epilepsy (IGE) is a common group of epileptic syndromes characterized by typical electroencephalogram (EEG) features, including generalized spike and/or polyspike discharges (2.5–6 Hz), and accounts for approximately one-fifth of epilepsy cases in children and adults.[1] IGE encompasses generalized tonic-clonic seizures, juvenile myoclonic epilepsy, childhood absence epilepsy, and juvenile absence epilepsy. These syndromes share a common genetic background and overlapping EEG features.[2]

In recent years, noninvasive imaging techniques such as functional magnetic resonance imaging (fMRI) have provided new insights into the underlying mechanisms of IGE. Studies have shown that generalized spike-wave discharge (GSWD)-related activation occurs in multiple regions, including the bilateral thalamus and cerebral cortex.[3] The thalamus, a crucial relay station, plays a central role in coordinating synchronous activities between the cerebral cortex and other brain regions.[4,5] Neuroimaging studies in epilepsy have revealed thalamic atrophy across various epilepsy syndromes, which may be a consequence of seizure activity.[6] For instance, compared to drug-sensitive IGE, those with refractory IGE exhibit thalamic atrophy and hyperconnectivity between the ventrolateral nucleus of the thalamus and the cerebral cortex, suggesting a remodeling of thalamo-cortical connections.[7] These findings indicate that structural and functional alterations in the thalamus play a significant role in epilepsy. Furthermore, resting-state functional connectivity (FC) studies have demonstrated that drug-naïve IGE children exhibit reductions in whole-brain FC, particularly within the default mode network (DMN).[8] This suggests that DMN impairment is present in IGE even in the early stages of the disease. Functional alterations in the DMN occur earlier than those in the thalamus.[9] Similar disruptions within the DMN have been observed in patients with drug-resistant epilepsy and are associated with cognitive deficits.[10,11] The DMN is also implicated in sustaining consciousness.[12] EEG-fMRI studies have reported that during absence seizures, cortical regions associated with GSWDs exhibit deactivation, with these deactivated areas overlapping with the DMN.[3] The concurrent occurrence of transient loss of consciousness during absence seizures and DMN deactivation is not coincidental. Abnormal DMN connectivity during seizures may represent a common mechanism across various epilepsy types, potentially leading to cognitive impairments and altered states of consciousness during seizures. IGE often experience multiple cognitive impairments, including deficits in attention, memory, and language function.[13,14] In patients with JME, abnormal thalamo-cortical connectivity alterations were observed during language fluency tasks.[15] Therefore, this study focuses on the thalamus and DMN regions, utilizing

FC analysis to evaluate changes in neural functional activity between brain regions and networks in IGE. Additionally, we assessed the neuropsychological performance of IGE and explored correlations between altered network connectivity and neuropsychological assessment scores.

2. Material and methods

2.1 Participants

A total of 27 patients with IGE were consecutively recruited from the Neurology Outpatient Clinic of Hainan Medical University between April 2022 and December 2023. All patients were diagnosed with IGE according to the 2017 criteria of the International League Against Epilepsy (ILAE)[16]. Additionally, 28 healthy controls matched for gender and age were recruited. All subjects signed informed consent before the study, and the study protocol was approved by the Medical Ethics Committee of Hainan Medical University. Inclusion criteria for IGE: 1) the diagnosis of epilepsy according to the ILAE criteria includes generalized tonic-clonic seizures, juvenile myoclonic epilepsy, childhood absence epilepsy, and juvenile absence epilepsy. 2) Absence of severe central nervous system (CNS) or psychiatric disorders. 3) No contraindications for MRI examination. Exclusion criteria for IGE: 1) patients with mental or cognitive impairments. 2) Patients with progressive CNS diseases or other severe chronic conditions affecting other systems. 3) History of drug abuse, substance use disorder, or alcoholism. Inclusion criteria for healthy controls: 1) no history of progressive CNS diseases or other severe chronic conditions in other systems. 2) absence of obvious structural abnormalities identified by visual inspection of MRI. 3) No history of drug abuse, drug use or alcohol abuse.

2.2 MRI data acquisition

During scanning, participants were instructed to relax, keep their eyes closed, remain awake, and refrain from engaging in specific cognitive tasks. Multimodal data were acquired using a GE Discovery MR750 3.0T MRI scanner. For rs-fMRI, a gradient-recalled echo-planar imaging (GRE-EPI) sequence was used with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, matrix size = 64 × 64, slice thickness = 4 mm, field of view (FOV) = 240 mm × 240 mm, and a total of 255 whole-brain volumes were acquired. For structural MRI, a three-dimensional fast spoiled gradient recalled acquisition (3D FSPGR) sequence was employed with the following parameters: TR = 6.012 ms, TE = 1.968 ms, flip angle = 9°, matrix size = 256 × 256, slice thickness = 1 mm, FOV = 256 mm × 256 mm, and 152 contiguous axial slices covering the entire brain without gaps were obtained.

2.3 Data preprocessing

Analyses of fMRI data were performed using CONN (RRID:SCR_009550) release 25.b and SPM (RRID:SCR_007037) release 12.7771. After removing the first 5 unstable time points, the remaining 250 time points were preprocessed using the default preprocessing pipeline of the CONN toolbox[17], including functional realignment and unwarp, slice-timing correction, outlier detection, direct functional normalization to MNI space (3 mm isotropic voxels), and spatial smoothing with a 6 mm FWHM Gaussian kernel. Global Signal Change (GSC) and Framewise Displacement (FD) were computed during outlier detection, with outlier scans identified as FD > 0.5 mm and/or GSC > 3 SD, summarized as the scrubbing timeseries. Functional data were denoised using the CONN default denoising pipeline. Functional data were denoised following the default denoising pipeline implemented in CONN. Nuisance regressors included the first five principal components from white matter signals, the first five principal components from cerebrospinal fluid signals, 12 motion parameters, outlier scans (scrubbing), session effects convolved with the canonical HRF, and constant and linear session effects. Ordinary least-squares regression was used to remove confounding signals derived from these regressors, followed by temporal band-pass filtering between 0.008 Hz and 0.09 Hz. Five participants were excluded from further analyses due to extreme values in meanmotion and/or maxmotion. The remaining 22 IGE and 28 HC were included in the final analysis. The mean head motion was 0.07 ± 0.01 mm for the IGE and 0.04 ± 0.01 mm for the HC. After denoising, the correlation between functional connectivity and mean head motion was 0.01 ± 0.36 for the IGE and 0.01 ± 0.19 for the HC.

2.4 Thalamo-cortical functional connectivity analysis

After preprocessing of fMRI data, custom-written code was used to calculate the mean time series for all voxels in the bilateral thalamus. Pearson correlation coefficients between the thalamic time series and those of all other voxels across the whole brain were then computed to reflect the synchronization of functional activity across different brain regions. The resulting correlation maps were converted to z-values using Fisher's r-to-z transformation to improve normality. For each group, a one-sample t-test was performed to analyze the functional connectivity maps. A two-sample t-test was subsequently conducted between the two groups, with age, gender, and head motion included as covariates, to compare intergroup differences in functional connectivity. All statistical tests were two-tailed. The threshold we set is $p < 0.01$ after false discovery rate (FDR) correction, and the minimum area of each cluster needs to be larger than 50 consecutive voxels.

2.5 Network-based functional connectivity analysis

The DPABI toolbox was used to compute the functional connectivity

within the DMN and between the DMN and other brain networks. Brain regions were defined according to the Automated Anatomical Labeling (AAL) atlas. Specifically, the mean time series of all voxels within a given brain region was calculated and used as the representative time series for that region. Pearson correlation coefficients were calculated between the mean time series of region pairs within the DMN and between regions within the DMN and regions of other networks to reflect the strength of functional connectivity of the DMN. The resulting correlation matrices were subjected to Fisher's Z-transformation to normalize the distribution of correlation coefficients. One-sample t-tests were performed on the individual functional connectivity maps. Two-sample t-tests were conducted between groups, with age and gender included as covariates, to identify significant differences in functional connectivity. All statistical tests were two-tailed. We adopted the threshold of $p < 0.01$ after correction by FDR.

2.6 Correlation analysis

Neuropsychological cognitive assessment was performed on participants using the Mini-Mental State Examination (MMSE) by trained physicians to evaluate their cognitive function. Cognitive assessment was performed in only 17 healthy controls. Therefore, correlation analyses were conducted across all IGE and these 17 healthy controls. Correlation analyses were performed with regression controlling for covariates (gender, age, and education) to investigate relationships between variables.

3. Results

3.1 Clinical characteristics

There were no statistically significant differences in gender or age between IGE and HC (Table 1). We calculated the total number of seizures in IGE, which represented the cumulative number of seizures each patient had experienced prior to participating in the study. IGE participants had lower MMSE scores compared to HC ($Z = 2.78$, $p = 0.006$). See Table 1 for details. Detailed clinical information for each patient with IGE is provided in Supplementary Table 1.

Table 1. Clinical characteristics of IGE and HC

Characteristics	IGE（n = 22）	HC（n = 28）	*p* value
Gender (male/female)	12/10	13/15	$p = 0.57$[a]

Age (years）	26.50 (18.75, 33.00)	24 .00(21.25, 29.00)	p = 0.83[b]
Duration (years)	8.27±1.30	-	-
Total number of epileptic seizures	<10（n = 12） ≥10（n = 10）	-	-
	IGE (n = 22)	HC（n = 17）	
Education (years)	13.50 (9.00, 16.00)	17 .00(16.00, 19.00)	p < 0.001[b]
MMSE	28.00 (24.75, 29.00)	29.00 (29.00, 30.00)	p = 0.006[b]

Notes: IGE: idiopathic generalized epilepsy; HC: health control; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; a: Pearson's Chi-square test; b: Mann–Whitney U test.

3.2 Seed-based functional connectivity analysis

As shown in Figure 1, compared with HC, IGE exhibited decreased functional connectivity between the bilateral thalamus and the posterior cerebellar cortex, middle vermis and lateral hemispheres, as well as bilateral motor-related cortices, cingulate gyrus, basal ganglia, insula, hippocampus, temporal pole, multiple subregions of the prefrontal cortex, and precuneus. Functional connectivity between the bilateral thalamus and the right orbital superior frontal gyrus, right orbital middle frontal gyrus, left inferior occipital gyrus, left middle occipital gyrus, as well as the right inferior temporal gyrus and right middle temporal gyrus was increased (Fig. 1).

Table 2. Differences in thalamo-cortical functional connectivity between IGE and HC

ROI	Cluster region	Cluster size	*T*-value	Peak MNI-coordinates

				X	Y	Z
Cluster 1	Cerebelum_8_L	238	-5.24	-10	-61	-49
	Cerebelum_8_R	171	-5.25	21	-51	-49
	Cerebelum_9_L	150	-6.07	-13	-51	-48
	Cerebelum_9_R	150	-4.49	8	-56	-49
	Cerebelum_Crus2_L	128	-6.09	1	-80	-27
	Vermis_4_5	88	-4.43	2	-57	-11
	Vermis_6	86	-6.94	1	-68	-10
	Cerebelum_Crus1_L	86	-5.86	-17	-74	-32
	Cerebelum_Crus1_R	57	-4.84	17	-72	-34
	Vermis_8	49	-4.90	6	-67	-35
	Vermis_3	49	-5.36	3	-42	-10
	Cerebelum_6_L	41	-3.87	-7	-70	-21
	Cerebelum_4_5_L	31	-3.60	-6	-49	-14
	Cerebelum_Crus2_R	26	-4.22	12	-73	-32
Cluster 2	Putamen_L	131	-6.77	-16	11	-2
	Caudate_L	111	-5.10	-14	0	19
	Amygdala_L	47	-5.04	-29	-5	-14
	Pallidum_L	39	-5.93	-15	3	3
	Hippocampus_L	29	-5.38	-16	-4	-18
	Temporal_Pole_Sup_L	28	-5.22	-21	8	-20
	Insula_L	27	-5.37	-27	12	-12

	Frontal_Inf_Orb_L	27	-5.22	-22	10	-21
Cluster 3	Putamen_R	136	-7.37	20	10	-3
	Caudate_R	125	-6.08	12	11	5
	Pallidum_R	44	-7.64	18	8	-3
	Amygdala_R	39	-5.13	21	7	-17
Cluster 4	Frontal_Sup_Orb_R	35	5.25	15	49	-16
Cluster 5	Occipital_Inf_L	58	5.01	-30	-78	-1
	Occipital_Mid_L	46	4.12	-33	-74	4
Cluster 7	Rolandic_Oper_L	33	-4.58	-51	3	11
Cluster 8	Frontal_Inf_Tri_R	73	-4.43	44	33	9
Cluster 9	Precuneus_L	44	4.89	-13	-42	6
Cluster 10	Frontal_Inf_Tri_L	50	-4.63	-48	21	27
Cluster 11	Supp_Motor_Area_L	177	-5.28	-5	16	52
	Frontal_Sup_Medial_L	121	-4.18	-2	25	39
	Cingulum_Mid_L	99	-5.42	-6	12	40
	Supp_Motor_Area_R	70	-4.41	1	-1	58
	Frontal_Sup_Medial_R	57	-4.40	3	44	43

Cingulum_Mid_R	34	-4.49	3	12	40
Cingulum_Ant_L	27	-4.45	-5	24	27

Notes: statistical significance was determined by two-tailed, two-sample t-test (FDR-corrected voxel-level $p < 0.01$, minimum cluster size > 50 consecutive voxels). ROI: region of interest; MNI: Montreal Neurological Institute; Mid: middle; Inf: inferior; Orb: orbital; Oper: opercular; Sup: superior; Supp: supplementary; L, left; R, right.

Figure 1. Differences in thalamo-cortical functional connectivity between IGE and HC. Blue areas indicate decreased functional connectivity, while red areas indicate increased functional connectivity. Statistical significance was determined by two-tailed, two-sample t-test (FDR-corrected voxel-level $p < 0.01$, minimum cluster size > 50 consecutive voxels). L, left; R, right

3.3 Default mode network functional connectivity analysis

Within the DMN, IGE exhibited widespread reductions in functional connectivity relative to healthy controls, predominantly involving the medial superior frontal gyrus, posterior cingulate cortex, anterior cingulate cortex, angular gyrus and precuneus. Increased functional connectivity was observed only in the left posterior cingulate cortex and left precuneus (Fig. 2A). Regarding inter-network connectivity between the DMN and other brain networks, IGE showed enhanced functional connectivity of the DMN with the visual network, ventral attention network and sensorimotor network. By contrast, DMN connectivity was reduced with the cerebellar network, limbic network and dorsal attention network. Within the frontoparietal network, DMN connectivity was elevated with ventral prefrontal regions but decreased with the dorsolateral prefrontal cortex and parietal lobe. In addition, functional connectivity between the medial superior frontal gyrus and the thalamus was diminished, whereas connectivity linking the posterior cingulate cortex to the thalamus increased (Fig. 2B).

Figure 2. Functional connectivity changes within the DMN and between networks in IGE and HC. Blue areas indicate decreased functional connectivity, while red areas indicate increased functional connectivity. Statistical significance was determined by two-tailed, two-sample t-test (FDR-corrected $p < 0.01$). IGE: idiopathic generalized epilepsy; HC: health control; DMN: default mode network; LN: limbic network; VAN:

ventral attention network; SCN: subcortical network; VN: visual network; SMN: sensorimotor network; CN: cerebellar network; DAN: dorsal attention network; FPN: frontoparietal network

Table 3. Functional connectivity changes within the DMN and between networks in IGE and HC

ROI	ROI	Network	*T*-value
Intra-DMN			
Frontal_Sup_R	Angular_R		-3.99
Frontal_Sup_Medial_L	Cingulum_Ant_L		-4.27
	Cingulum_Ant_R		-4.10
Frontal_Sup_Medial_R	Cingulum_Ant_L		-3.68
	Cingulum_Ant_R		-4.47
Cingulum_Post_L	Angular_L		-5.91
	Angular_R		-3.90
	Precuneus_L	DMN	4.93
Cingulum_Post_R	Angular_L		-4.36
	Angular_R		-4.86
Angular_L	Angular_R		-6.00
	Temporal_Inf_L		-5.91
Angular_R	Precuneus_R		-4.13
Precuneus_L	Temporal_Mid_R		-3.56
Precuneus_R			-3.96
Inter-network			

Precuneus_L	Calcarine_L	VN	4.01
Precuneus_R			3.83
Angular_R	Occipital_Inf_R		4.88
SFGdor.L	Temporal_Sup_L		4.81
Frontal_Inf_Orb_L			4.38
Frontal_Inf_Orb_R	Rolandic_Oper_R		5.37
	Postcentral_R		7.52
	Heschl_R		4.8
Frontal_Sup_Medial_L	Temporal_Sup_L	SMN	5.00
Cingulum_Ant_R	Rolandic_Oper_R		4.22
	Postcentral_R		5.20
Temporal_Mid_L	Temporal_Sup_L		4.64
Temporal_Inf_L	Precentral_L		-4.54
	Temporal_Sup_L		5.34
	Temporal_Sup_R		3.92
Precuneus_L	Parietal_Sup_L	DAN	-5.41
Frontal_Med_Orb_L	SupraMarginal_R	VAN	4.29
Frontal_Sup_Medial_R	ParaHippocampal_R		-4.03
Cingulum_Ant_L	Frontal_Sup_Orb_L	LN	3.94
Angular_L			-4.04
Angular_R	Frontal_Sup_Orb_R		-4.27
Frontal_Sup_R	Frontal_Inf_Oper_R	FPN	-4.38

Frontal_Inf_Orb_R			-4.52
Frontal_Sup_Medial_L	Frontal_Inf_Tri_L		4.12
Frontal_Sup_Medial_R	Parietal_Inf_L		4.09
Cingulum_Ant_L	Frontal_Mid_Orb_L		7.33
	Frontal_Mid_Orb_R		4.92
Cingulum_Ant_R	Frontal_Mid_Orb_L		5.90
	Frontal_Mid_Orb_R		4.62
Angular_L	Frontal_Inf_Oper_L		-4.77
Angular_R	Frontal_Mid_Orb_R		-4.02
	Parietal_Inf_L		-4.82
	Parietal_Inf_R		-4.73
Frontal_Sup_Medial_L	Thalamus_R	SCN	-4.59
Frontal_Sup_Medial_R			-4.04
Cingulum_Post_L			4.09
Cingulum_Post_R			4.08
Temporal_Mid_L	Putamen_L		-3.81
Frontal_Sup_Medial_L	Cerebelum_6_R	CN	4.57
	Cerebelum_8_L		4.32
	Cerebelum_8_R		7.02
Frontal_Sup_Medial_R	Cerebelum_3_L		-4.68
	Vermis_3		-4.44
Cingulum_Post_L	Cerebelum_7b_L		-4.14

	Cerebelum_8_L	-4.39
	Cerebelum_9_R	-4.51
Cingulum_Post_R	Cerebelum_7b_L	-4.44
	Cerebelum_8_L	-3.84
	Cerebelum_8_R	-4.28
	Cerebelum_9_R	-4.60
Angular_R	Cerebelum_7b_L	-4.04
Precuneus_L	Cerebelum_9_L	-4.16
	Cerebelum_10_R	-3.96
Precuneus_R	Cerebelum_9_R	-4.37
Temporal_Mid_L	Cerebelum_3_L	-3.97
	Vermis_1_2	-3.81
	Vermis_3	-4.14
Temporal_Mid_R	Cerebelum_4_5_L	-3.97
Temporal_Inf_L	Cerebelum_3_L	-4.58

Notes: Statistical significance was determined by two-tailed, two-sample t-test (FDR-corrected $p < 0.01$). ROI: region of interest; DMN: default mode network; LN: limbic network; VAN: ventral attention network; SCN: subcortical network; VN: visual network; SMN: sensorimotor network; CN: cerebellar network; FPN: frontoparietal network; Inf: inferior; Orb: orbital; Med: medial; Ant: anterior; Sup: superior; Mid: middle; Post: posterior; Supp: supplementary; L: left; R: right.

3.4 Correlation analysis

In IGE, the functional connectivity strength of the bilateral angular gyri was negatively correlated with MMSE scores (r = -0.55, p = 0.007). The connectivity strength between the left precuneus and the left superior parietal gyrus was negatively correlated with MMSE scores (r = -0.47, p =

0.026). The connectivity strength between the left posterior cingulate gyrus and the right cerebellum_9 was negatively correlated with MMSE scores (r = -0.43, p = 0.040). The connectivity strength between the right posterior cingulate gyrus and the right cerebellum_9 was negatively correlated with MMSE scores (r = -0.44, p = 0.360) (Fig. 3).

Figure 3. Correlation analyses between functional connectivity and MMSE scores. IGE: idiopathic generalized epilepsy; HC: health control; MMSE: Mini-Mental State Examination; FC: functional connectivity; ANG: angular; PCUN: precuneus; SPG: superior parietal gyrus; PCG: posterior cingulate gyrus; Cere9: cerebelum_9; L, left; R, right.

4. Discussion

Resting-state functional magnetic resonance imaging was utilized in the present study to investigate aberrant functional connectivity of brain networks in IGE. The results demonstrated widespread reductions in thalamic functional connectivity across the whole brain, alongside decreased functional connectivity both within the DMN and between the DMN and other brain networks in IGE. The most prominent reductions were detected in functional connectivity linking the thalamus to the cerebellum and the DMN to the cerebellum. In addition, reduced DMN–cerebellar functional connectivity was negatively correlated with global cognitive performance in individuals with IGE.

Functional connectivity analysis of the thalamic seed in this study revealed decreased functional connectivity between the thalamus and the cerebellum, bilateral basal ganglia, and sensorimotor cortex. Epilepsy is considered a brain network disorder, typically exhibiting widespread functional and structural alterations involving the epileptic focus. A recent study[18], by integrating IGE brain abnormality coordinates with the functional connectome, identified an IGE network centered on the centromedian nucleus of the thalamus, with the IGE network including multiple key brain regions such as the supplementary motor area, sensorimotor cortex, thalamus, anterior cingulate cortex, cerebellum, and basal ganglia. The global ENIGMA multi-center study[19] also found that IGE exhibited reduced right thalamic volume and decreased cortical thickness in the right precentral gyrus. The involvement of these regions in the generation of generalized epileptic discharges has been confirmed by previous studies in animal models.[20,21] The abnormal functional connectivity between the thalamus and the above-mentioned regions observed in this study indicates a thalamus-centered whole-brain network disturbance in IGE.

The DMN is active during rest but is suppressed during the performance

of various cognitive tasks. This network is closely associated with spontaneous activity and represents the baseline state of human brain function.[22] Under normal physiological conditions, functional changes in the DMN are relatively small, and the connectivity strength within the network is strong. However, our study observed reduced functional connectivity within the DMN. This phenomenon has also been confirmed in other related studies.[11,23] Previous research has suggested that the reduction in functional connectivity may be caused by neural substrate damage resulting from prolonged epileptic seizures.[24] All patients included in this study had generalized tonic-clonic seizures, typically characterized by limb stiffness, clonic convulsions, and loss of consciousness. The brain's consciousness system is composed of higher-order association cortices and subcortical structures, specifically including the medial prefrontal cortex, anterior cingulate cortex, posterior cingulate cortex, medial parietal cortex, and their corresponding subcortical core structures.[25] Studies have shown that during epileptic seizures, abnormalities in thalamo-cortical synchrony lead to a temporary cessation of DMN activity and trigger widespread cortical deactivation, ultimately resulting in an abnormal state of consciousness in patients.[3] Electroencephalography and magnetoencephalography-based studies have found that the maximum amplitude of 3–4 Hz spike-and-wave discharges in absence epilepsy typically appears in the midline frontal region.[26] Meanwhile, lesions in the fronto-parietal-cingulate regions have also been confirmed in cases where reduced or loss of consciousness occurs.[27,28] Therefore, abnormal epileptic discharges may damage the structural integrity of DMN-related brain regions, disrupt functional synergy within the network, and lead to a decreased functional integration capacity of the DMN.

We observed decreased functional connectivity between the thalamus, DMN, and multiple cerebellar subregions. The cerebellum transmits integrated motor and cognitive information to the cerebral cortex via the dentate nucleus–thalamus–cortex pathway.[29,30] An increasing number of studies suggest that the cerebellum also plays an important role in epilepsy.[31] In terms of seizure mechanisms, the cerebellum may be involved in seizure generation. Previous studies have shown that during generalized tonic-clonic seizures, the increase in cerebral blood flow begins in the midline cerebellum and then spreads bilaterally to the cerebral hemispheres, indicating that the cerebellum can be activated during seizures.[32] Jiang et al. also found decreased efferent fibers from the cerebellum to the frontoparietal cortex in IGE, and observed reduced interactions between the cerebellum and motor-related regions, suggesting that the cerebellum may play a coordinating role in motor abnormalities[33].

Meanwhile, the cerebellum is also an important site for epilepsy regulation. Purkinje fibers within the cerebellar cortex can provide inhibitory output to the thalamo-cortical circuitry to reduce seizure activity.[34] The decreased functional connectivity between the cerebellum and the thalamus as well as the DMN observed in this study may explain why reduced cerebellar inhibitory signals create favorable conditions for epileptic discharge and the propagation of electrical activity, ultimately leading to motor symptoms during seizures.

The DMN plays a key role in the overall network structure, integrating information from major functional and cognitive domains.[35,36] Human cognitive control processes depend on balanced dynamic interactions among brain networks. However, epileptic discharges cause functional disturbances in brain networks. Lopes et al., using sliding window dynamic analysis, found that IGE exhibited reduced DMN connectivity at baseline, increased global connectivity preceding interictal-like discharges, and a post-discharge pattern of initially increased DMN connectivity followed by a return to baseline.[37] Jiang et al., based on EEG-fMRI, observed increased interactions between the DMN, the salience network, and the sensorimotor network during interictal-like discharges in IGE.[38] This suggests that even during the interictal phase without clinical seizures, abnormal electrical activity can dynamically reshape the topological structure of the whole-brain functional network. Dysfunction of the DMN can affect its information exchange with other brain networks, ultimately leading to impaired brain functional integration.[39] Furthermore, several studies have suggested that reduced DMN connectivity and interictal-like discharges may play a role in cognitive decline in epilepsy.[40,41] This is consistent with our observations. This notion has been confirmed by other studies showing that the extent of DMN impairment is related to the severity of cognitive impairment.[42,43] Petrella et al. found that the DMN connectivity strength was highest in healthy individuals, intermediate in patients with mild cognitive impairment, and lowest in patients with Alzheimer's disease.[44] This indicates that a gradient decrease in DMN connectivity strength is correlated with disease severity. Taken together, these findings suggest that abnormal connectivity of DMN function, including reduced intra-network connectivity and impaired communication with other brain networks, is a key pathological feature of epilepsy. This DMN dysfunction is not only involved in the regulation of epileptic seizures but is also associated with cognitive decline in patients.

Long-term and recurrent generalized spike-wave discharges may affect the DMN and lead to sustained impairment of the structural integrity and function of brain networks. However, antiepileptic drugs (AEDs) may have a potential impact on our findings. Studies have shown that AEDs such as

sodium valproate can normalize pathological connectivity or task-induced abnormal activation.[45,46] A confounding factor in our study is the diversity of AED regimens taken by the patients. Different types of AEDs have different effects on brain networks. Pang et al. observed that both patients taking levetiracetam (LEV) and those not taking LEV exhibited reduced functional connectivity within the DMN.[47] There was no significant difference in DMN functional connectivity between the two groups. This suggests that LEV has little effect on the DMN. Although this diversity in medication use limits our ability to distinguish between disease-induced alterations and drug-induced functional reorganization, our findings reflect the clinical situation of IGE.

Limitations

The present study has several limitations. First, the sample size is relatively small, which may affect the generalizability of the findings. Second, this study employed resting-state fMRI, which cannot monitor the dynamic changes of brain networks during actual epileptic seizures. Third, significant group differences in meanmotion were observed between the two groups ($t = 5.45$, $p < 0.001$). However, correlation analysis demonstrated that head motion exhibited no significant association with functional connectivity alterations in the current study. Finally, medication effects represent an important confounding factor. The antiepileptic drug regimens taken by patients in this study were diverse, and different drugs may have varying effects on brain networks. Future studies should further investigate these aspects to better understand the alterations in inter-network information flow in patients with idiopathic generalized epilepsy.

5. Conclusion

Using resting-state functional magnetic resonance imaging (rs-fMRI), the present study assessed functional connectivity patterns of the thalamus and DMN in patients with IGE and examined relationships between altered functional connectivity and global cognitive performance. We identified reduced functional connectivity for both the thalamus and DMN, with relatively substantial connectivity reductions between each of these two regions and the cerebellum. These findings suggest that aberrant thalamic functional connectivity and disrupted intra- and inter-network connectivity

of the DMN constitute an important feature of brain functional impairment in idiopathic generalized epilepsy. The cerebellar contribution to these changes merits further attention. Such abnormalities in functional connectivity are closely associated with alterations in patients' cognitive performance, and these results facilitate an improved understanding of the pathophysiological mechanisms of IGE.

Author contributions

Huixia Lin, Ting Liu and Junxia Chen designed the study. Yu Wang, Sisi Jiang, Eduardo Martínez-Montes, Lin Ma and Fei Li were responsible for data collection and preparation. Huixia Lin, Ting Liu, Junxia Chen, Shaochun Li, Cheng Luo and Qifu Li analyzed and interpreted the data. Huixia Lin, Ting Liu and Junxia Chen drafted the manuscript. All authors critically reviewed and revised the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

Data availability

The data supporting the findings of this study are available from the corresponding authors upon reasonable request. They are not publicly available due to privacy and ethical restrictions.

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Competing interests

The authors declare that there are no conflicts of interest regarding the publication of this paper.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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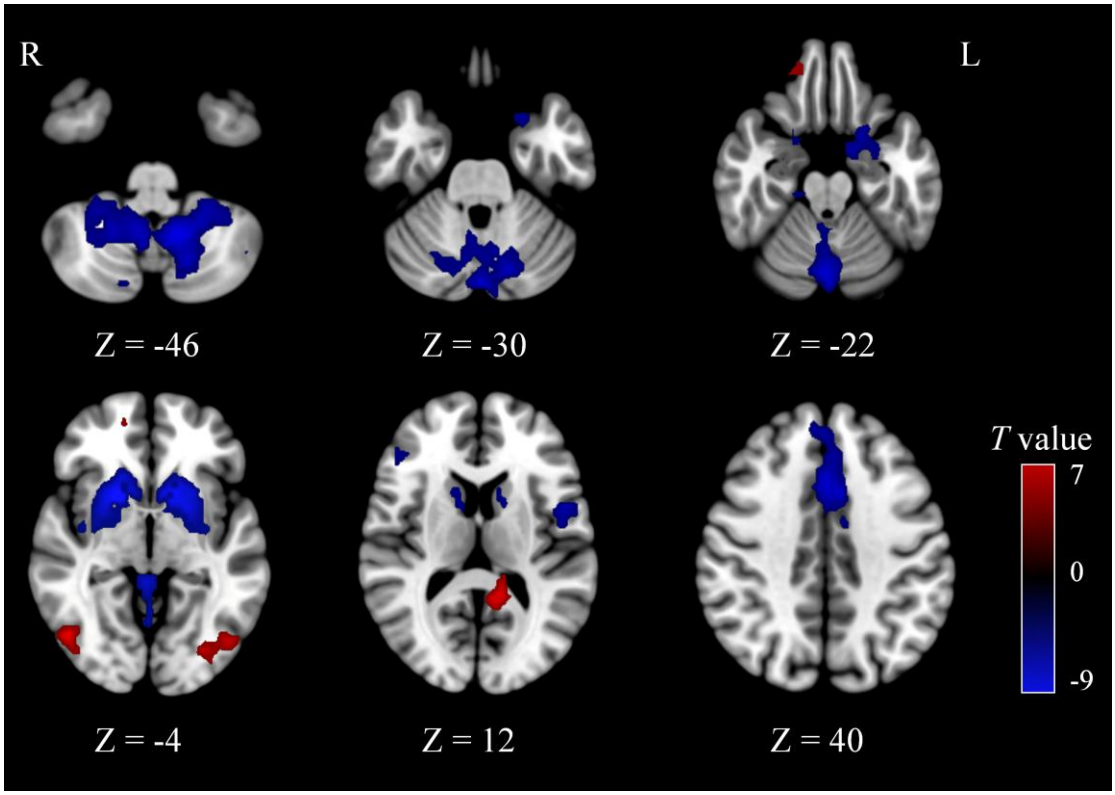
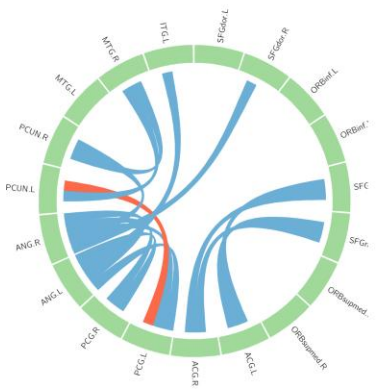
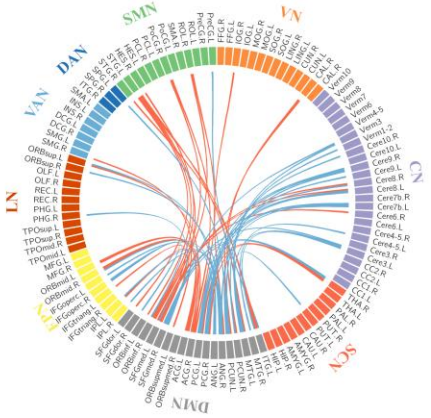


(A) Intra-Network Functional Connectivity

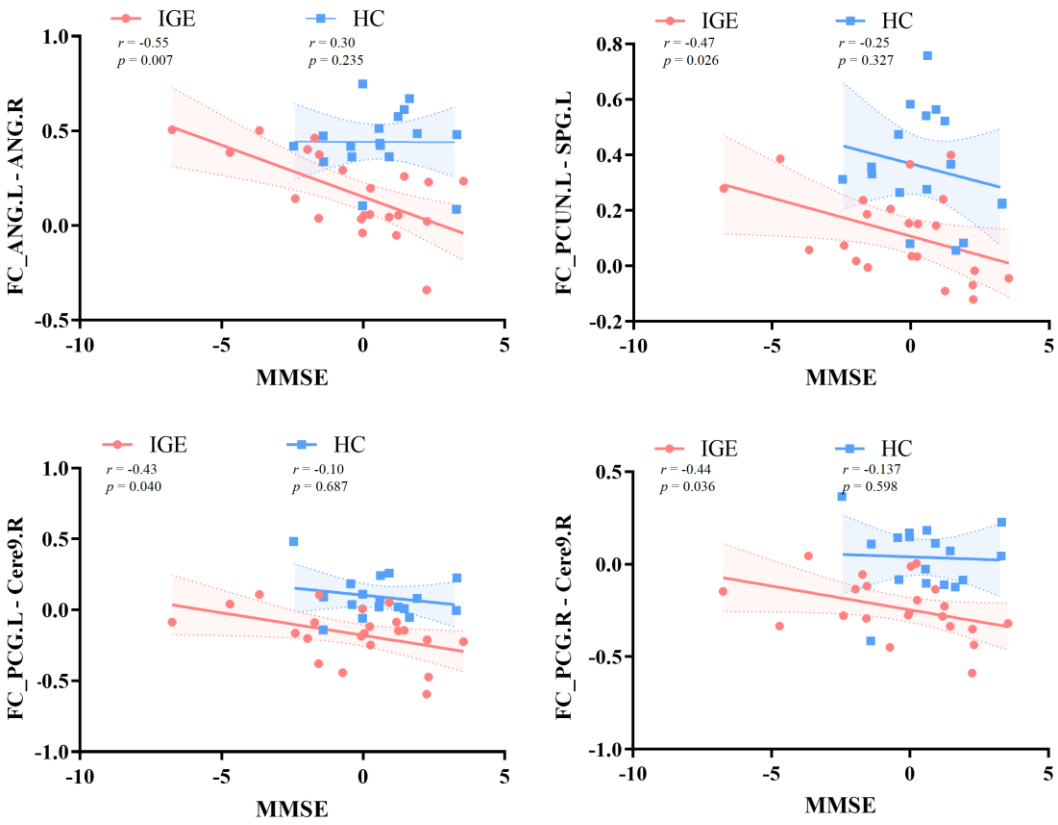


IGE vs HC

(B) Inter-Network Functional Connectivity



IGE vs HC


IGE
HC
r = -0.55
p = 0.007
r = 0.30
p = 0.235
FC_ANG.L - ANG.R
MMSE
r = -0.47
p = 0.026
r = -0.25
p = 0.327
FC_PCUN.L - SPG.L
r = -0.43
p = 0.040
r = -0.10
p = 0.687
FC_PCG.L - Cere9.R
r = -0.44
p = 0.036
r = -0.137
p = 0.598
FC_PCG.R - Cere9.R