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Aberrant Thalamocortical Connectivity in Juvenile Myoclonic Epilepsy

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The purpose of this study was to investigate the functional connectivity (FC) of thalamic subdivisions in patients with juvenile myoclonic epilepsy (JME). Resting state functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) data were acquired from 22 JME and 25 healthy controls. We first divided the thalamus into eight subdivisions by performing independent component analysis on tracking fibers and clustering thalamus-related FC maps. We then analyzed abnormal FC in each subdivision in JME compared with healthy controls, and we investigated their associations with clinical features. Eight thalamic sub-regions identified in the current study showed unbalanced thalamic FC in JME: decreased FC with the superior frontal gyrus and enhanced FC with the supplementary motor area in the posterior thalamus increased thalamic FC with the salience network (SN) and reduced FC with the default mode network (DMN). Abnormalities in thalamo-prefrontocortical networks might be related to the propagation of generalized spikes with frontocentral predominance in JME, and the network connectivity differences with the SN and DMN might be implicated in emotional and cognitive defects in JME. JME was also associated with enhanced FC among thalamic sub-regions and with the basal ganglia and cerebellum, suggesting the regulatory role of subcortical nuclei and the cerebellum on the thalamo-cortical circuit. Additionally, increased FC with the pallidum was positive related with the duration of disease. The present study provides emerging evidence of FC to understand that specific thalamic subdivisions contribute to the abnormalities of thalamic-cortical networks in JME. Moreover, the posterior thalamus could play a crucial role in generalized epileptic activity in JME.

Keywords: Juvenile myoclonic epilepsy; functional connectivity; thalamus; resting-state fMRI.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a subtype of idiopathic generalized epilepsy (IGE) characterized by myoclonic jerks, generalized tonic–clonic seizures and less frequent absence seizures,[1] with age-related onset of seizures. The typical EEG features of JME include 2–6 Hz generalized spike-wave or polyspike-wave discharges (GSWD) with high amplitudes in

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frontocentral regions. Accompaned with the development of methodology,[2–4] EEG would provide valuable information to uncover the potential pathophysiology in neurologic disorders.[5–7] A series of methods have been also applied to EEG data to detect seizures.[8,9] In general, no significant structural abnormalities have been found in JME. However, functional magnetic resonance imaging (fMRI) has been widely used to investigate the mechanisms underlying GSWD,[10–13] and abnormalities in thalamo-cortical and/or thalamo-subcortical links have been accepted to be related to the generation and propagation of GSWD in IGE.[14–17] The thalamus appears to play a key role in the propagation of generalized seizures by amplifying and synchronizing epileptic activity deriving from cortical structures.[18,19] In addition, accumulating evidence also suggests structural and functional abnormalities of the frontal lobes[20,21] and thalamus[22] in JME. Decreased gray matter volumes in the bilateral thalamus have been reported in some studies of childhood absence epilepsy[23] and JME,[24] and thalamic gray matter concentration reductions and negative correlations between thalamic gray matter and disease duration have been observed in JME, which suggest that there might be progressive thalamic neuronal loss with time.[22] Using diffusion tensor imaging (DTI), reduced fractional anisotropy (FA) has been observed in white matter fibers associated with the anterior thalamus and prefrontal cortex in JME.[25] Functional connectivity (FC) has shown great potential for identifying abnormalities in brain networks,[26] and it has been widely used in research on neuropsychological diseases such as epilepsy, Alzheimer's disease and schizophrenia. For example, altered FC patterns across the whole brain have been observed in temporal lobe epilepsy (TLE)[27]; and hippocampal FC in TLE is related to working memory performance.[28] Interestingly, the thalamic FC has been used to predict seizure laterality in individuals with TLE.[29] In IGE, Ji and colleagues showed that the strength of increased thalamic FC with several regions of cerebral cortex[30] could reflect underlying epileptic pathology mechanisms.

It is clear that thalamus is a crucial relay for sensory information projecting to the cerebral cortex.[31] Many studies have ascribed different roles and connectivity patterns to thalamic subunits due to its intrinsic anatomy and widely demonstrated distinct FC and structural connectivity profiles for different thalamic nuclei. For example, DTI-based segmentations have been regarded as a direct method for classifying these nuclei.[32] Yuan *et al.* identified multiple thalamus-related networks by performing independent component analysis (ICA) on voxel-based thalamic FC maps and located thalamic sub-regions for each network.[33] Zhang *et al.* calculated FC and structural connectivity between ROIs and each thalamic voxel to identify thalamic sub-regions and to demonstrate the relationship between FC and structural connectivity.[34] In patients with JME, Jonathan and colleagues detected altered anterior thalamocortical structural connectivity in JME, and they found that impaired phonemic verbal fluency was task-modulated by FC from the anterior thalamic subunit compared with healthy controls.[35] FC would be a potential way to reveal FC patterns of subregions of thalamus by segmenting the thalamus.

In this study, we used an approach combining resting-state thalamic FC and DTI-based structural connectivity profiles to obtain sub-regions of the thalamus, which differed from the approach of thalamic parcellation based upon DTI tractography in Jonathan's study.[35] We investigated FC patterns across different thalamic sub-regions between JME and healthy controls and we identified different FC patterns between groups. We detailed the variety and similarities among thalamic sub-regions. Furthermore, we detected altered thalamic functional networks which were significantly related with epilepsy duration and age of onset.

2. Methods

2.1. *Participants*

Twenty-two patients (12 females, age: 24.0 ± 6.9 years; disease duration: 11.5 ± 3.34 years) with JME were recruited in this study. All patients were diagnosed with JME based upon clinical and seizure semiology information consistent with International League Against Epilepsy (ILAE) guidelines[36] by neurologists (S. Tan and S. Ma). No structural abnormalities were observed during routine brain imaging. Twenty-five healthy controls were recruited as sex- and age-matched controls (11 females, age: 24.7 ± 6.2 years). All controls were free of neurological and psychiatric disorders. 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. Written informed consent was obtained from each subject.

2.2. *Data acquisition*

All subjects underwent MRI scanning in a 3T GE scanner (MR750; GE Discovery, Milwaukee, WI) at the Center for Information in Medicine, University of Electronic Science and Technology of China. Resting-state functional data were collected using an echo-planar imaging sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°, field of view (FOV) = 24 × 24 cm^2, matric = 64 × 64, and slice thickness = 4 mm with 0.4 mm gap, and 255 volumes in each run. Axial anatomical T1-weighted images were acquired using a 3-dimensional fast spoiled gradient echo (T1-3D FSPGR) sequence [TR = 6.012 ms, TE = 1.968 ms, FA = 9°, matrix = 256 × 256, FOV = 25.6 × 25.6 cm^2, slice thickness = 1 mm] to generate 152 slices without gap. DTI images were acquired using a diffusion weighted spin-echo EPI sequence (TR = 8500 ms, TE = 63 ms, flip angle = 90°, NEX = 1, matrix = 128 × 128, FOV = 25.6 cm × 25.6 cm, thickness = 2 mm without gap, 77 slices covered the whole brain). Three diffusion-unweighted volumes were acquired with $b = 0\,\mathrm{s/mm^2}$ and 64 diffusion-weighted directions with $b = 1000\,\mathrm{s/mm^2}$. All subjects were instructed to remain "relaxed, with eyes closed" and keep awake during the scanning.

2.3. *Data preprocessing*

Preprocessing of the fMRI dataset was conducted using the SPM8 software package (statistical parametric mapping available at: http://www.fil.ion.ucl.ac.uk/spm). The first five volumes of each run were discarded to ensure magnetic field stabilization. The remaining 250 volumes were slice-time corrected and realigned. Any subject whose head motion exceeded 2 mm or/and 2 degrees was excluded. The realigned images were spatially normalized to the Montreal Neurological Institute (MNI) template using a 12-parameter affine transformation and resliced with a voxel size of 3 mm × 3 mm × 3 mm. Finally, resting-state data were also temporally filtered in the 0.01–0.08 Hz band.

Diffusion-weighted data were analyzed using the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/ fsl). These data were corrected for eddy currents and subject inter-scan motion by affine registration to a reference volume. Using dtifit (FSL), fractional anisotropy images were created by adjusting diffusion tensor data to eddy-corrected data. Nonlinear model warp between individual FA images and the FMRIB58_FA template in 2 mm isotropic resolution MNI standard image was obtained using the FNIRT toolbox in FSL.

2.4. *Parcellation of the thalamus*

Probabilistic tractography was done in native space from bilateral thalamic seed regions extracted from the Harvard–Oxford atlas (including 449 voxels with 2 mm isotropic cubes in the left thalamus, and 444 voxels in the right thalamus). For each subject, probabilistic tractography from each voxel in the bilateral thalamus seed regions was acquired with 5000 iterations, resulting in 449 volumes for voxels for the left thalamus and 444 volumes for right thalamic voxels. These 3D images were then registered to MNI space using the nonlinear model warp obtained in preprocessing. 3D images of the unilateral thalamus were concatenated into 4D volumes. Finally, these bilateral 4D images were smoothed using a weighted average 6 mm FWHM Gaussian kernel of tractograms initiating from surrounding thalamic seeds.

For bilateral thalamic-4D images, we performed ICA separately by group.[37] We then used the FSL MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) toolkit to decompose these 4D data into spatially independent components (ICs), representing tractography-defined connectivity which was consistent in thalamic origins. The number of independent components was estimated automatically. Using the output from MELODIC, weighted thalamic maps were obtained in accordance with each IC. For each subject, weighted thalamic maps were used in a spatial regression on the unsmoothed fMRI data to obtain time courses for each weighted thalamic map.

Then, Pearson's correlations between each time series of weighted thalamic origin maps and all other brain voxels were calculated. These correlation coefficients were transformed to Z-scores. A one sample

t-test was performed for each weighted thalamic origin map, thus producing a FC t-map. A correlation matrix was produced using cross-correlations among all FC t-maps. Then, the correlation matrix was clustered using affinity propagation. Every thalamic voxel was assigned to the cluster that generated the highest FC value, resulting in a set of thalamic origins with the same assignment.

2.5. *Functional connectivity with seed at thalamic subdivisions*

To define the FC of the thalamus, we calculated Pearson correlation coefficients between the average time series of each thalamic subdivision and the time course from all other brain voxels. These correlation maps were then submitted to Fisher's r-to-z transformation, and one-sample t-tests for each correlation map were performed to assess the statistical significance. The statistical threshold of FDR was corrected at $p < 0.05$. Then, two sample t-tests were utilized to obtain differences in FC between JME and controls for each thalamic sub-region. The significance threshold was set at $p < 0.005$ with cluster-level FDR correction. Moreover, leave-one-out cross validation was performed to verify our statistical results.

Furthermore, for each thalamic sub-region, we investigated correlations between the FC values of regions showed significant differences and clinical features (duration and age of onset) in the JME group, controlling for the effects of gender, at $p < 0.05$ (FDR corrected).

3. Results

No excessive head motion was observed in any subject. There were no significant differences between the two groups in head motion and rotation (two-sample two-tailed t-test, $t = 0.81$, $p = 0.42$ for translational motion, and $t = 0.92$, $p = 0.36$ for rotational motion). Detailed demographic data of patients is shown in Table 1.

Table 1. Demographic data of JME patients.

No.	Gender	Age (year)	Age at seizure onset (year)	Frequency of GSWDs (Hz)	Seizure semiology	Family history	Photosensitivity	AEDs
1	F	16	12	3–3.5	MS, AS	Brother with JME	—	VPA
2	F	17	3	2	MS	—	—	VPA
3	M	17	13	6	MS, GTCS	—	Yes	VPA
4	M	23	13	2	MS	—	—	VPA
5	F	23	16	4	MS	Mother with GTCS	—	VPA
6	F	34	14	3	MS, GTCS	—	Yes	LTG
7	F	26	15	3	MS, GTCS	—	—	VPA
8	F	16	13	5	MS	—	—	VPA
9	M	33	13	3–3.5	MS, AS	—	—	VPA
10	M	22	14	4–4.5	MS	—	—	VPA
11	F	28	17	3–3.5	MS	—	—	VPA
12	F	37	12	6.5–7	MS, AS	—	—	VPA
13	M	23	7	5	MS	—	—	VPA
14	F	17	10	4	MS	—	—	VPA
15	F	28	9	2	MS	—	Yes	VPA
16	F	33	12	2	MS, AS	—	—	VPA
17	M	18	14	3	MS, GTCS	—	—	VPA
18	M	18	7	3–3.5	MS	Uncle with GTCS	—	VPA
19	M	38	8	3.5–4	MS, GTCS	—	—	TOP
20	M	21	7	4	MS	—	—	LTG
21	F	22	12	3.5	MS, GTCS	—	—	VPA
22	M	19	12	3	MS	—	—	VPA

Notes: Abbreviation: MS, myoclonic seizure; GTCS, generalized tonic–clonic seizure; AS, absence seizure; VPA, valproate; LTG, lamotrigine; TOP, topiram.

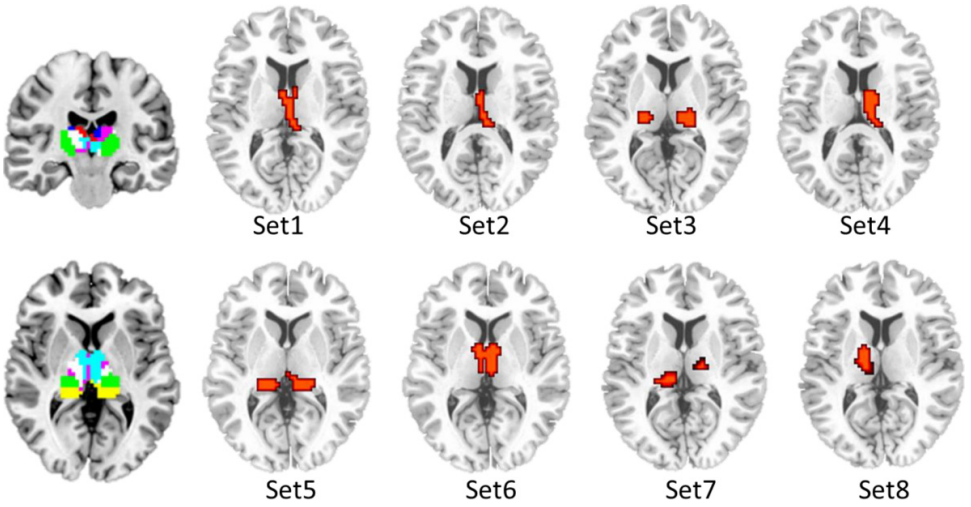

Fig. 1. The parcellation of bilateral thalamus. Eight thalamic subunits were shown. In the first column, eight thalamic subunits were overlaid in a volume.

3.1. *Thalamic parcellation analysis*

Combining thalamic voxel-level fiber tracking with group ICA yielded eight thalamic sub-regions. Set 1 (right dorsal medial thalamus) and Set 2 (left dorsal medial thalamus) overlapped primarily with the anterior nuclei, midline nuclei, and medial pulvinar. Set 3 (ventral middle thalamus) was mainly located in the bilateral symmetric ventral posterior and ventral lateral nucleus groups. Set 4 (left dorsal lateral thalamus) overlapped with the lateral and posterior nuclei groups. Set 5 (posterior thalamus) showed overlap with the bilaterally symmetrical ventrolateral posterior nucleus group. Set 6 (ventral medial thalamus) appeared to overlap the medial nucleus group and anterior regions. Thalamic regions contributing to Set 7 (dorsal mid-posterior thalamus) were predominantly located in the lateral and medial nucleus and right posterior nuclei. Set 8 (right lateral anterior thalamus) showed a rightward asymmetry and was more anterior and inferior than Set 7 Parcellation results are shown in Fig. 1.

3.2. *Functional connectivity analyses*

A series of two-sample t-tests were performed to identify significant ($p < 0.005$, FDR corrected) between-group differences in FC emerging from thalamic sub-regions. Summary information for these regions are shown in Table 2 and Figs. 2 and 3.

Compared with the healthy controls, JME patients showed significantly increased FC at the insula and middle occipital gyrus across all thalamic sub-regions. Connections between the putamen and seven thalamic subdivisions, except the right lateral anterior subdivision (Set 8), and connections between the pallidum and six thalamic subdivisions except the ventral middle and right lateral anterior subdivisions (Sets 3 and 8) were stronger in JME. More than half of the thalamic parcellations (Set 1, Set 3, Set 4, Set 5, Set 6 and Set 7) demonstrated increased connectivity with the dorsal anterior cingulate cortex. Increased FC with the bilateral anterior cerebellum and amygdala occurred in three thalamic sub-regions (Set 1, Set 2 and Set 5 for cerebellum; Set 2, Set 3 and Set 6 for amygdala, respectively). Two thalamic subdivisions (Set 1 and Set 2) showed increased FC with the caudate in the JME group.

Significantly decreased connectivity was observed between the precuneus and all thalamic subdivisions. Decreased FC was also found for five thalamic sub-regions (Set 3, Set 4, Set 5, Set 6, Set 7 and Set 8) with the frontal lobe, as well as for four sub-regions (Set 1, Set 3, Set 5 and Set 6) with temporal lobe. The left angular gyrus showed decreased connectivity with two thalamic sub-regions: the left dorsal lateral thalamus (Set 4) and the dorsal mid-posterior thalamus (Set 7). The right dorsal medial thalamus (Set 1) and posterior thalamus (Set 5) showed decreased FC with the hippocampus and parahippocampus, respectively. For each thalamic subdivision, a distinct set of regions was observed, which showed significant differences between groups.

Table 2. The conclusion of results of each thalamic sub-region.

	Tha	Insula	Putamen	Pallidum	ACC	MOC	Cuneus	Precuneus
S1	B	B	R	R	B	L	R	L
S2	B	B	R	R	—	R	—	L
S3	B	B	L	—	B	B	L	R
S4	B	B	B	B	B	L	R	L
S5	B	B	B	R	B	R	—	B
S6	B	B	R	R	B	R	—	L
S7	B	B	B	L	L	B	R	L
S8	B	L	—	—	—	B	R	L

Note: Samples containing the regions which demonstrated abnormal FC with more than four thalamic subunits. Abbreviation: Tha, within thalamus; ACC, anterior cingulate cortex; MOC, middle occipital cortex.

As an example, detailed brain regions demonstrating abnormal FC with the posterior thalamus (Set 5) in JME are shown in Table 3. Validation analyses showed consistent results for comparison between groups.

3.3. *Correlation analyses*

For each thalamic subdivision, FC values were extracted from regions which showed significant between-group differences and correlated with epilepsy duration and age at onset, controlling the effect of gender. Connections between the ventral middle thalamus and bilateral lingual gyrus and right fusiform showed significant negative correlations with duration and connections between the posterior thalamus and right pallidum were positively correlated with epilepsy duration (Fig. 4). There were no significant correlations observed between FC and age of onset of epilepsy.

4. Discussion

Thalamo-cortical connectivity plays an important role in the regulation and propagation of GSWD in IGE.[15,38] JME, as a specific type of IGE, is associated with specific thalamo-cortical circuits. In a previous study, it has been demonstrated that the thalamo-cortical dysrhythmia is encountered in epilepsy and that the different thalamocortical cellular pathways produce different cortical oscillations,[39] which is consistent with this study and help to understand the underlying mechanism of the altered FC in patients with JME. In the present study, we first parcellated the thalamus into eight different subdivisions using an approach combining thalamic voxel-level white-matter connectivity and resting-state FC profiles with the whole brain. Then, seed-based FC analyses were performed for each subdivision. Compared with healthy controls, three main findings were observed. First, consistent with previous studies, patients with JME showed decreased FC between the posterior thalamus and the SFG; additionally, the posterior thalamus also showed increased FC with the SMA. Second, increased FC was observed among all of the thalamic sub-regions, and these sub-regions also demonstrated increased FC with the putamen and pallidum in JME. Increased FC with the pallidum was positively correlated with disease duration. Interestingly, the dorsal medial thalamus showed increased positive FC with the contralateral cerebellum hemisphere (lobules VIII). Relating our results to previous studies,[40] we presumed that increased FC between subcortical nuclei and the cerebellum or specific thalamocortical circuits might be implicated in JME. Finally, many thalamic sub-regions showed higher positive FC with the anterior insula and dorsal anterior cingulate cortex (key regions in the salience network), and with smaller FC with regions in the DMN (precuneus and angular gyrus) in patients. This unbalance in thalamic connectivity with the DMN and SN (salience network) implicates that specific thalamic nuclei might contribute to understanding emotional and cognitive defects of JME patients, which are related to disrupted interaction between SN and DMN.

A clear frontocentral predominance of ictal EEG is observed in JME. In addition, the myoclonic jerks are assumed to relate to hyper-excitability at motor-related regions in the frontal lobe. JME

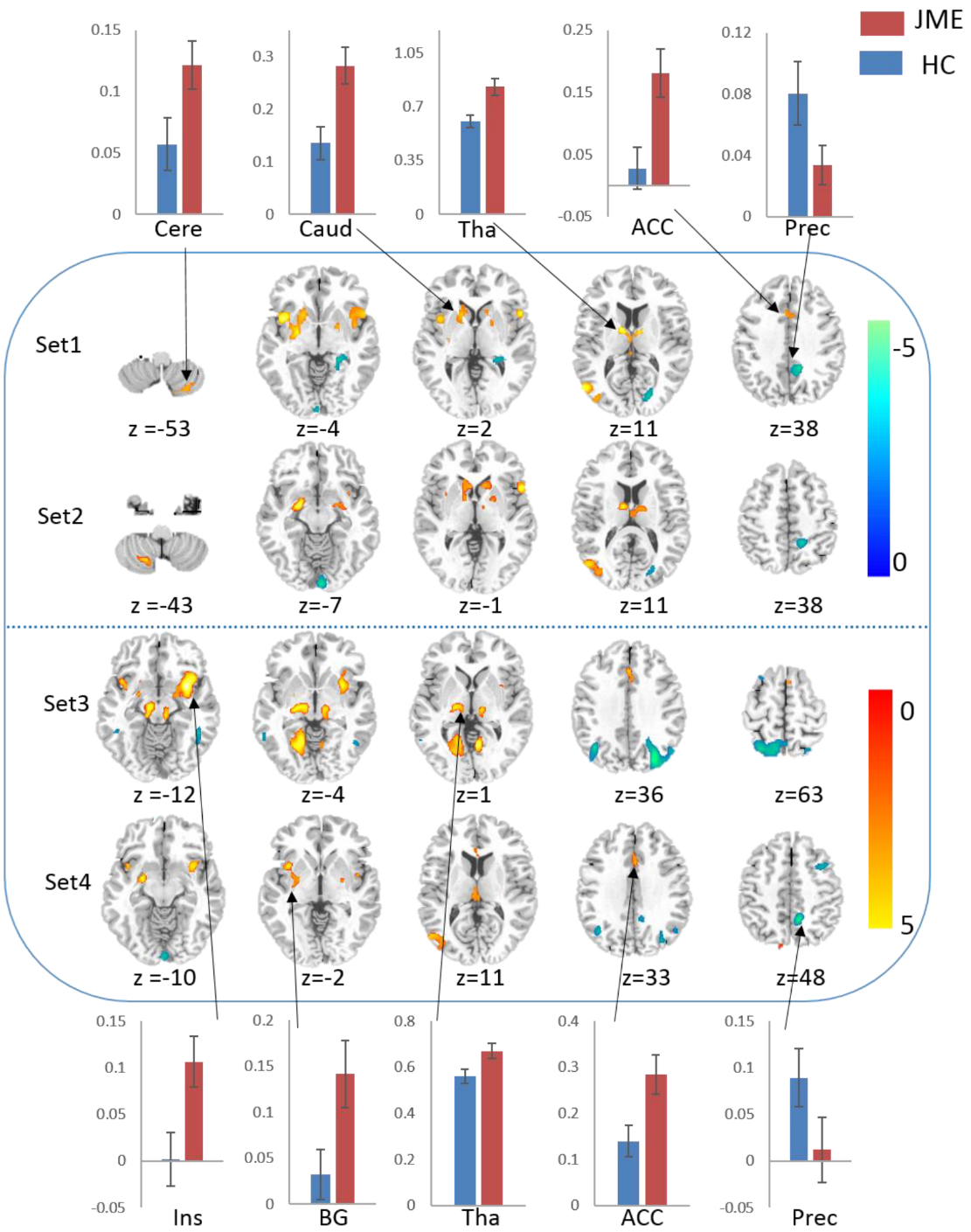

Fig. 2. The results of two sample t-test in thalamic Set 1 to Set 4 Histograms of the crucial regions were illustrated. Abbreviation: Cere, cerebellum; Caud, caudate; Tha, thalamus; ACC, anterior cingulate cortex; Prec, precuneus; Ins, insular; BG, basal ganglia; SFG, superior frontal gyrus; Ang, angular.

patients have been reported to show structural and functional abnormalities of the frontal lobes, including the mesial frontal region, SMA, and primary motor cortex,[41] which were considered as the important regions associated with the generation or propagation of bursts of GSWD. Moreover, abnormality in these regions might cause motor abnormalities in JME such as jerk. Consistent with previous

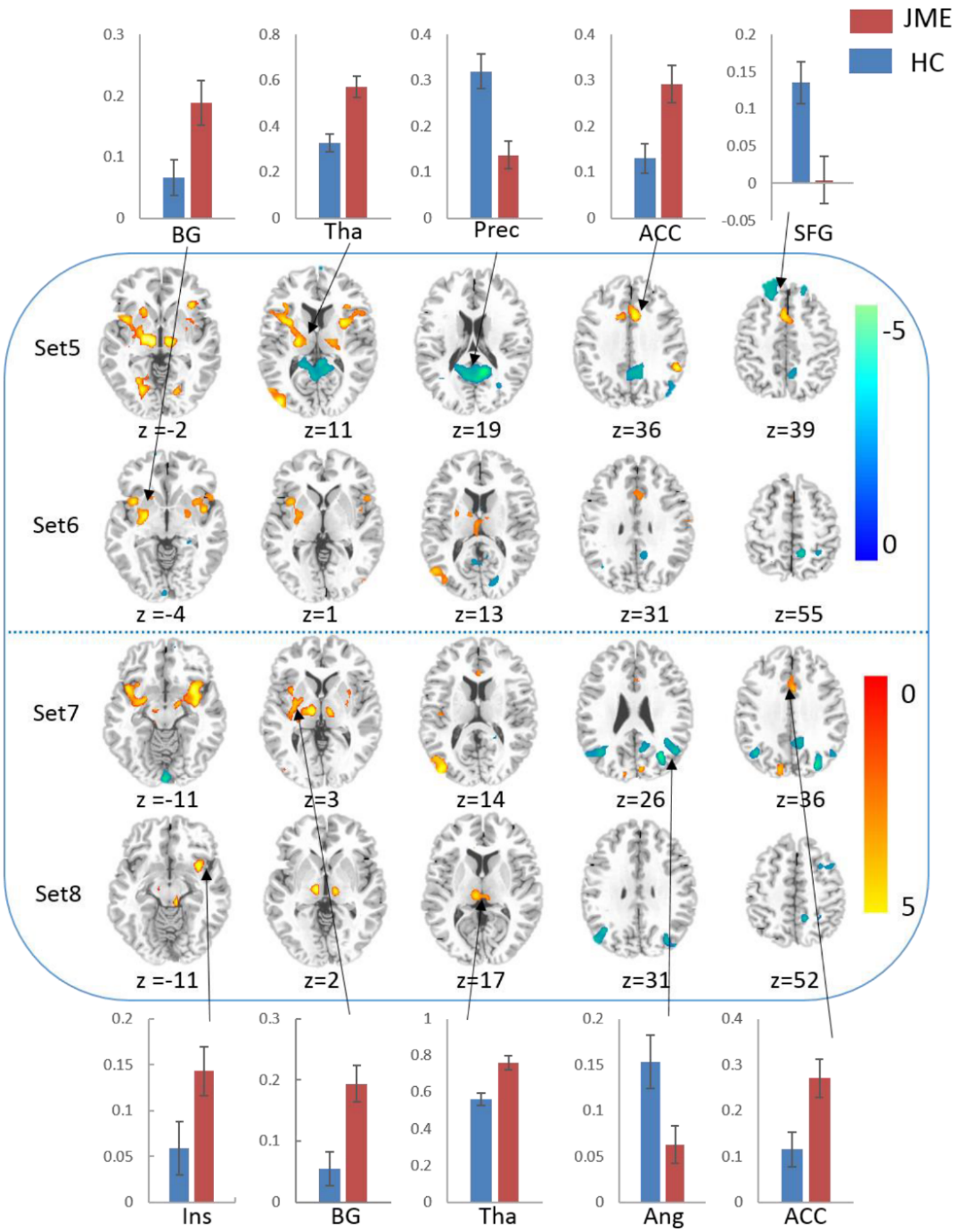

Fig. 3. (Color online) The results of two sample t-test in thalamic Sets 5 to 8. Histograms of the crucial regions were illustrated, representing the FC in two groups (blue bar represents FC in control, red bar represents JME). Abbreviation: Cere, cerebellum; Caud, caudate; Tha, thalamus; ACC, anterior cingulate cortex; Prec, precuneus; Ins, insular; BG, basal ganglia; SFG, superior frontal gyrus; Ang, angular.

studies, we also found altered FC between the thalamus (posterior) and frontal cortex. Previous studies have found that the posterior thalamus connects to prefrontal and motor networks including the SMA, primary and pre-motor areas in healthy controls.[33,42] To the best of our knowledge, this is the first study to identify that the posterior thalamus may play a key role in disturbed thalamo-cortical circuity in

Table 3. The brain regions showing abnormal FC with posterior thalamus (Set 5) in JMEs.

Brain region	MNI coordinates			BA	T value	Voxel number
	X	Y	Z			
JME>HC						
Thalamus_R	9	−17	0	—	4.45	462
Thalamus_L	−8	−19	0	—	4.00	
Putamen_R	32	6	9	48	3.65	
Insula_R	38	9	9	48	3.58	
Pallidum_R	24	−10	1	—	3.16	
Cingulum_Ant_L	−5	12	32	24	3.92	129
Cingulum_Ant_R	7	12	30	24	3.82	
Supp_Motor_Area_L	2	12	47	32	3.53	
Supp_Motor_Area_R	4	13	47	32	3.53	
Insula_L	−36	5	10	48	3.52	105
Putamen_L	−31	4	4	48	3.30	
JME<HC						
Precuneus_L	−13	−51	15	30	5.16	361
Precuneus_R	6	−53	15	30	3.69	
Frontal_Sup_R	16	40	49	9	3.67	134
ParaHippocampal_L	−29	−26	−21	30	3.85	165
Fusiform_L	−29	−34	−20	37	3.53	
ParaHippocampal_R	26	−15	−27	36	3.74	173
Cerebelum_Crus2_R	45	−73	−42	—	3.72	75

Note: MNI, Montreal Neurological Institute; BA, Brodmann area; L, left; R, right.

JME and to implicate imbalanced functional links of thalamus between the prefrontal lobe and SMA. Interestingly, two main frontal regions, the SMA and the prefrontal lobe, showed decreased FC with the posterior thalamus in the current study. Consistent with this finding, a previous study also identified a reduction of thalamo-cortical FC in the bilateral prefrontal cortex in IGE patients compared with healthy controls.[43] In contrast, increased thalamic FC strength with the SMA has also been observed in IGE patients.[30] In JME, altered white matter connectivity between the SMA and various cortical areas has been observed, and connectivity between the SMA and central region is correlated with the interval since the last seizure.[44] In addition, microstructural abnormalities have been widely demonstrated, suggesting that SMA is a crucial hub in the thalamo-prefrontocortical network in JME.[45] Thus, the enhanced FC between SMA and posterior thalamus might implicate the abnormal synchronization between them, which might facilitate the burst of GSWD in JME. Together, the abnormal FC of posterior thalamus with the frontal lobe should be considered a major alteration of typical thalamo-cortical circuits in JME, which might contribute to the generation and propagation of GSWD with frontocentral predominance in JME patients.

In healthy individuals, the significant FC between the right ventro-anterior and ventro-posterior thalamus, left ventral-anterior and pulvinar thalamus was reported by Dae-Jin Kim,[46] suggesting intrinsically different FC within the thalamic subunits. The present study showed significantly increased functional interactions among thalamic subunits, suggesting excessive cooperation within thalamic nuclei in JME. Considering the crucial modulator role of the thalamus in cortico-thalamo-cortical information flow,[47] it is reasonable to infer that this hyper-connectivity within thalamus might be related to abnormal cortical activity in patients with generalized epilepsy such as JME. Additionally, many studies have identified that GSWD implicates abnormal thalamo-cortical network activities.[48–50] In general, the nuclei in the thalamus link to diverse cerebral cortex, which has been observed in several neuroimaging studies. The significant FC alteration within thalamus demonstrated here might suggest

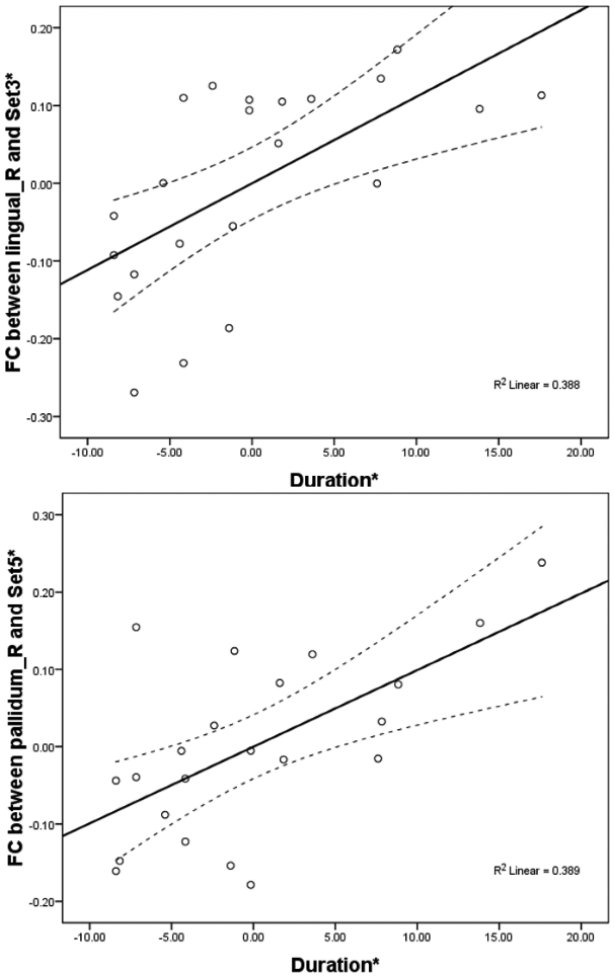

Fig. 4. The FDR corrected correlation between FC and disease duration.

Note: Controlling the effect of gender.

its potential effects on abnormal interaction between thalamus and cerebral cortex.

Some evidence indicates that an intact basal ganglia may be necessary for the propagation of seizure activity,[51] and the basal ganglia is widely considered to play a vital role in the regulation of epileptiform spikes (see review Ref. 40). It has been reported that the myoclonic expression of rat predominantly requires NMDA activity at pallidal level.[52] In our previous study using simultaneous EEG and fMRI in IGE, significant deactivation associated with interictal GSWD was observed in the basal ganglia[53]; additionally, the basal ganglia as a network is recognized in the modulation of epileptic spikes, which supports our findings that patients in the discharge period demonstrate increased FC in the bilateral putamen compared with the nondischarge period.[54] Deep brain stimulation of the basal ganglia (*substantia nigra pars reticulata*) have suggested an effective treatment for myoclonic epilepsy patients.[55] In the current study, all thalamic subdivisions except for the right lateral anterior thalamus showed hyperconnectivity with the putamen and pallidum. Thus, we extended the regular view of the basal ganglia to also implicate that the extensive thalamic nuclei linked to the putamen and pallidum may be potential abnormal pathways in JME. Moreover, disturbances of the basal ganglia in JME have also been supported by structural studies. Subcortical structural alterations have been reported in JME or absence epilepsy.[25,56,57] Altered diffusion features (increased FA) have been observed in the bilateral putamen and is correlated with reduced putamen volume in patients with JME.[58,59] Basal ganglia are

generally considered to be associated with motor movements.[60,61] The disruption of the basal ganglia-thalamo-cortical loop might also be linked with alterations in executive function in JME.[24] Thus, our findings could also be interpreted in light of the abnormal hyper-motor function in JME to some extent, characterizing JME specific syndrome different from other types of IGE.

In the present study, we found that the dorsal medial thalamus (Sets 1 and 2) showed increased FC with the contralateral cerebellar hemisphere (lobules VIII) in JME. The best known role of the cerebellum is related to motor control,[62] and its involvement in some cognitive functions, such as attention and language, has also been reported.[63] Typical clinical manifestations of JME include movement-related abnormalities. In this study, thalamic dorsal medial sub-regions showed increased FC with lobule VIII of cerebellum, which are primarily linked with motor cortex,[64,65] suggesting abnormal functional interactions between specific thalamic regions and the cerebellum in JME. This altered information communication between cerebellum and thalamus might be related to abnormal behavioral expressions in JME patients. Recently, Kros and colleagues demonstrated that cerebellar nuclei are potent modulators of abnormal oscillations in thalamo-cortical linkages during generalized seizures,[66] and the possibility of treating epilepsy by stimulating these cerebellar nuclei was proposed.[67,68] The cerebellar origin projected to cerebral cortex is often considered at the dentate nuclei.[69] The cerebellum connects to the thalamus through the deep nuclei. Thus, FC alterations between the cerebellum and specific thalamic neurons might reflect the regulation on epileptic activity in the thalamo-cortical network. Further study is needed to illustrate these potential underlying mechanisms in JME.

All thalamic sub-regions showed reduced FC with the precuneus. The precuneus is an important node in the known resting-state brain network (DMN). The DMN activity is active when people are not focused on the external environment.[70] Evidence has emerged indicating the disturbance of the DMN in epilepsy. For example, deactivation related to GSWD was found by using simultaneous EEG and fMRI. In addition, Greicius *et al.* reported decreased FC in the DMN during slight sedation.[71] Decreased FC has been found in absence epilepsy[72] and TLE,[73] suggesting abnormal consciousness during seizures. In this study, we also observed that all thalamic sub-regions demonstrated increased FC with the insula. In a previous study, we demonstrated increased regional homogeneity in the bilateral insula in JME.[74] Reduced gray matter volume in the bilateral insula has been found in IGE patients.[75] Moreover, converging evidence implicates the insula in emotion and cognition process. Findings in the current study inferred that emotional and affective deficits in JME might result from abnormal insular connectivity with the thalamus.[76] The anterior insula is also thought to be a key node in the salience network (SN). The SN plays a key and causal role in switching between the central executive network and the DMN.[77] Dysregulation among these three networks has been reported in other sub-types of IGE in previous studies.[78,79] Cognitive and mental deficits are commonly observed in patients with JME.[76,80] Although psychiatric test was not conducted in our current study, the specific thalamic nuclei demonstrated that abnormal FC with SN and DMN in JME might indicate underlying mechanism of the dysregulations between the SN and DMN in JME patients.

There are several limitations to this study. First, the sample sizes were relatively small. In a further study, more JME patients will be recruited. Second, our study did not rule out the confounding effects of AED (antiepileptic drug) treatment. Although all patients were asked not to take their medicine on the day of scanning, we were unable to rule out possible contributions of AED medications to thalamic connectivity in resting state. The duration and dose of taking medicine were not equal, thus the effects of AED differed across patients, which might confuse the FC findings. In our further study, drug-naïve epilepsy patients would be collected to avoid interference of AED. Finally, we did not take cognitive measurements in this study, which might lead to deficient interpretation for cognitive dysfunction in JME. In summary, a prospective study is planned taking these limitations into consideration.

In conclusion, this study provided two major understanding for JME. First, patients showed an imbalanced functional links of posterior thalamic sub-regions with the prefrontal lobe and SMA. Thus the posterior thalamus was identified as a key role in disturbed thalamo-cortical circuity in JME. Second,

patients also demonstrated the unbalance in thalamic connectivity with the DMN and SN, which would implicate that specific thalamic nuclei might contribute to understand emotional and cognitive defects. In addition, JME patients showed enhanced FC among thalamic sub-regions with the basal ganglia and cerebellum, suggesting the crucial role of subcortical nuclei and the cerebellum in the thalamocortical circuit in JME. The present study provides converging evidence confirming the contributions of FC in specific thalamic subdivisions to the abnormal of thalamic-cortical networks in JME, especially the posterior thalamus involvement in the generation and propagation of GSWD with frontocentral predominance in JME.

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