

Aberrant long-range functional connectivity density in generalized tonic-clonic seizures

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Abstract

Studies in generalized tonic-clonic seizures (GTCS) have reported both structural and functional alterations in the brain. However, changes in spontaneous neuronal functional organization in GTCS remain largely unknown.

In this study, 70 patients with idiopathic generalized epilepsy characterized by tonic-clonic seizures and 70 age- and sex-matched healthy controls were recruited. Here, functional connectivity density (FCD) mapping, an ultrafast data-driven method based on functional magnetic resonance imaging (fMRI), was applied for the first time to investigate the changes of spontaneous functional brain activity caused by epilepsy.

The results showed significantly decreased long-range FCD in the middle and inferior temporal, prefrontal, and inferior parietal cortices as well as increased long-range FCD in the cerebellum anterior lobe and sensorimotor areas. Negative correlation between duration of disease and reduced long-range FCD was found. In addition, most regions with reduced long-range FCD showed decreased resting-state functional connectivity (rsFC) within default mode network.

Negative correlation between duration of disease and long-range FCD may reflect an adverse consequence eventually from original. Furthermore, the observed FCD and rsFC alterations have been speculated to be associated with the social-cognitive impairments as well as motor control. Our study provided novel evidences to look into neuro-pathophysiological mechanisms underlying GTCS.

Abbreviations: EPI = echo planar imaging, FC = functional connectivity, FCD = functional connectivity density, FD = frame-wise displacement, fMRI = functional magnetic resonance imaging, FOV = field of view, FWHM = full-width at half-maximum, GTCS = generalized tonic-clonic seizures, HCs = healthy controls, IDL = Interactive Data Language, IGE = idiopathic generalized epilepsy, MNI = Montreal Neurological Institute, rsFC = resting-state functional connectivity.

Keywords: fMRI, functional connectivity density, generalized tonic-clonic seizures, resting-state functional connectivity

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1. Introduction

Idiopathic generalized epilepsy (IGE) is characterized by the widespread generalized spike-and-waves or polyspike-waves and undetectable focal anatomical brain abnormalities, and encompasses a group of epileptic disorders.^[1] Generalized tonic-clonic seizures (GTCS), as the most common subtype of IGE, presents typical seizures symptom of dramatic and dangerous convulsions that are responsible for much of the social stigma and mortality associated with epilepsy.^[2] Meanwhile, there are some cognitive impairments in the seizures, such as attention, memory, and language dysfunctions.^[3,4] Although substantial efforts have been made in the past decade, the pathophysiological mechanisms of GTCS remain largely unclear.

Recent advances in neuroimaging techniques have provided an efficient and noninvasive way for better understanding of GTCS. On the one hand, morphometric studies based on structural, magnetic resonance imaging (MRI) have documented significant reduction in cortical thickness,^[5] gray matter density^[6] in IGE patients. In addition, the diffusion tensor imaging revealed the functional integrations among subcortical and cortical areas.^[7,8] On the other hand, the spontaneous functional organization can be investigated via functional connectivity (FC), which measures the temporal correlation of spontaneous fluctuations in brain activity between spatially distinct regions. Some studies revealed disrupted FC between anterior cingulate cortex and cuneus, between frontal cortex and putamen as well as in the thalamocortical functional network involving the bilateral medial prefrontal cortex and precuneus/posterior cingulate

cortex.^[7,9] However, all of these researches adopted seed-based FC analyses that may miss important unpredictable findings. Whole-brain FC analyses are needed to investigate the spontaneous neuronal functional organization in GTCS patients.

FC density (FCD) mapping has been developed to measure the numbers of functional connections of a given voxel with others.^[10] A greater FCD value for a particular voxel indicates that the voxel is functionally connected to a large number of other brain voxels and suggests that this voxel plays more crucial roles in information processing than those voxels with lower FCD values. On the basis of the neighboring relationships among brain voxels, FCD can be further divided into short- and long-range FCD,^[11] which has been used to investigate the abnormal functional integrations in children,^[12] blind subjects,^[13] and psychogenic nonepileptic seizures.^[14]

The aim of our study was to identify the differences in spontaneous functional organization using whole-brain FCD analyses, which are based on large-cohort GTCS patients and healthy controls (HCs). We further tested the functional integrations on the basis of seeds with abnormal FCD. In addition, within the GTCS group, correlation analysis was conducted to evaluate the relationship between duration of disease and FCD in the obtained abnormal region.

2. Methods

2.1. Participants

Seventy patients with GTCS were recruited from Jinling Hospital, Nanjing University School of Medicine. On the basis of the International League Against Epilepsy, all patients match the following criteria: clinical features of GTCS were detected, such as twitching limbs, out of consciousness, and generalized seizures; generalized polyspike-waves were observed in their scalp EEG; no psychiatric or neurological etiology history; and no focal lesions in anatomical MRI.^[15] In addition, 70 matched healthy volunteers who had no history of neurological or psychiatric disorders were recruited from the staff of Jinling Hospital as HCs.

The demographic and clinical information for all patients and HCs are summarized in Table 1. The study was approved by the Medical Ethics Committee of Jinling Hospital and Clinical School of Medical College at Nanjing University, and all participants were given written informed consent before experiment.

Table 1
Characteristics of the GTCS patients and HCs.

Characteristics	GTCS	HC	P
	(n = 70)	(n = 70)	
	Mean ± SD	Mean ± SD	
Age range, yrs	18-47	20-40	—
Age, yrs	24.91 ± 7.00	24.75 ± 5.52	0.88*
Handedness (right/left)	70/0	70/0	0.99†
Gender (male/female)	47/23	42/28	0.38†
Frame-wise displacement (FD)	0.14 ± 0.05	0.13 ± 0.06	0.21*
Duration (year)	8.62 ± 8.63	—	—

Values are mean ± SD.

FD = frame-wise displacement, GTCS = generalized tonic-clonic seizures, HCs = healthy controls.

* The P value was obtained by 2-tailed 2-sample t test.

† The P value was obtained by χ^2 2-tailed test.

2.2. Data acquisition

All resting-state functional MRI (fMRI) images were obtained on a 3.0-T (Siemens, Trio, Germany) magnetic resonance (MR) scanner. To reduce head motion artifacts and scanner noise, the head was immobilized using foam pads and headphones. Subjects were clearly asked to close their eyes and remain motionless, and be sure not to fall asleep. An echo planar imaging (EPI) sequence was applied to collect the functional images [3.75 mm × 3.75 mm × 4 mm voxel size; 30 slices; 64 × 64 matrix; TR = 2000 ms and TE = 30 ms; flip angle = 90°; field of view (FOV) = 24 cm]. For each subject, each functional run contained 250 image volumes.

2.3. Data preprocessing

Data preprocessing was performed using the SPM8 package (<http://www.fil.ion.ucl.ac.uk/spm>). For each participant, the first 5 volumes were discarded during data acquisition to ensure steady-state longitudinal magnetization. The remaining 245 consecutive images were corrected for the acquisition delay between slices and for the head movement. There were no subjects with movement greater than 2 mm translation or 2° rotation. Because some recent studies have shown that FC analysis is sensitive to gross head motion effects,^[16-18] the frame-wise displacement (FD), which represents the scalar quantity of instantaneous head motion of each volume relative to its earlier neighboring volume, was also calculated on the basis of the head motion parameters.^[16] The largest mean FD of all subjects was less than 0.3 mm, and there was no significant difference in mean FD between patients with GTCS and HCs using a 2-sample 2-tailed t test. After realignment, the corrected images were further spatially normalized to the Montreal Neurological Institute (MNI) template and resampled to 3 mm cubic voxels. Then, the data underwent separate and additional preprocessing for the calculation of FCD and rsFC. For the preprocessing to FCD calculation, no spatial smoothing was performed, as a previous study suggested to avoid artificially introducing local spatial correlation.^[19,20] The 6-head motion parameters, white matter signal, and cerebrospinal fluid signal as nuisance covariates were regressed out to reduce the effects of head motion. The resulting images were band-pass filtered (0.01–0.08 Hz) and linear detrended subsequently to remove low-frequency drift^[21] and minimize high-frequency physiological noises.^[22] For the preprocessing of rsFC data, all spatially normalized data were smoothed by convolution with a full-width at half-maximum Gaussian kernel (FWHM) of 6 mm, and nuisance signals were regressed out as the preprocessing for FCD. Finally, band-pass filtering (0.01–0.08 Hz) and linear detrending were also conducted on the time series of each voxel.

2.4. FCD map

The FCD was generated by computing the number of functional connections of each voxel with the rest voxels in human brain.^[10] In our study, we limited the procedure within a gray matter mask that was created on the basis of the automated anatomical labeling atlas.^[23] Pearson correlation was used to calculate the FC. The pair of 2 voxels with a correlation coefficient $r > 0.6$ was considered functionally connected. This threshold was proposed to be the optimal threshold for calculating FCD in a previous study.^[10]

The detailed procedure of the computing of local and global FCD is given in^[10]. Briefly, the gFCD at a given voxel x_0 was computed as the numbers of functional connections above

threshold between voxel x_0 and all other voxels with the brain mask. This calculation was repeated for all voxels within the mask. The computation of IFCD at voxel x_0 was similar with the gFCD calculation, but restricted within its local cluster. To determine the local cluster of x_0 , 3-dimensional searching algorithm developed in Interactive Data Language (IDL) was employed. Specifically, let us consider voxel x_i , which is adjacent to voxel that belongs to the list of neighbors of x_0 . The voxel x_i was included into the list of neighbors of x_0 if correlation value of x_{0i} exceeded the correlation threshold ($r=0.6$). This calculation was repeated for next voxel that belongs to the list of neighbors. And, the local cluster of x_0 was obtained when no voxel was included in the list of neighbors. The IFCD of x_0 was then computed as the numbers of functional connections within the local cluster. This procedure was applied to all other voxels within the brain mask iteratively. Thus, the gFCD maps and IFCD maps of all subjects were obtained.

The IFCD that referred to the voxels that functionally connected to the local cluster was equivalent to short-range FCD.^[24] Given the relationships between brain voxels, the long-range FCD is computed as gFCD-IFCD.^[11,24]

All the short- and long-range FCD values were further standardized by converting into z -scores.^[25,26] Then, the z -scored FCD maps were spatially smoothed with a full-width at half-maximum Gaussian kernel of 6mm to minimize the differences in the functional anatomy of brain across subjects.^[27] To explore the effects of the selection of correlation thresholds on our FCD analysis, we repeated the analysis on 3 additional correlation thresholds ($r=0.4, 0.5, \text{ and } 0.7$).

The calculation of FCD map was processed using self-compiled Matlab script. And, we have published several articles using the in-house software.^[28,29]

2.5. Seed-based resting-state functional connectivity analysis

After applying statistical analysis on FCD maps, significant group differences of FCD between GTCS patients and HCs were observed. These group differences were selected as seed regions to the following analysis. To give a further explanation of FCD abnormalities, seed-based rsFC analysis was conducted in REST

(<http://www.restfmri.net>) based upon those seed regions. For each subject, the mean time course of the seed regions was extracted. The correlation coefficient between the mean time series of each seed region and that of each voxel in the whole brain was computed and converted to z -scores to improve normality like the FCD maps.

2.6. Statistical analysis

One-sample t -test was used to evaluate the distribution of both the short- and long-range FCD maps ($P < 0.05$, FDR corrected). Then, a 2-tailed 2-sample t test within the gray matter mask was implemented in SPM8 to map group differences of FCD between GTCS patients and HCs. The significance level was set at a corrected $P < 0.05$, with a cluster size of at least 224 voxels above an uncorrected $P < 0.01$, with estimated FWHM (13.09, 13.49, 14.06), performed by the AlphaSim program with the REST software (<http://www.restfmri.net>). In addition, Pearson correlation analysis was performed between FCD and the duration of disease in brain regions with significant group differences, with age, gender as covariates to be regressed out. Values of $P < 0.05$ (FDR corrected) were considered to indicate statistical significance.

Group differences of rsFC maps between the patients with GTCS and HC were evaluated using 2-tailed 2-sample t test within the gray matter mask. The significance level was set at a corrected $P < 0.05$, with a cluster size of at least 80 voxels above an uncorrected $P < 0.001$, with estimated FWHM (14.43, 16.01, 15.96), performed by the AlphaSim program with the REST software. The detail of program Alphasim is shown in Supplementary Materials, <http://links.lww.com/MD/B32>.

3. Results

3.1. Spatial distribution of short-range FCD

Figure 1 identifies the spatial distribution of short-range FCD in HC group and GTCS group, respectively. Both groups showed similar distributions of high short-range FCD hub regions, including the bilateral precuneus/posterior cingulate gyrus (PCu/PCC), occipital cortex, parietal cortex, frontal gyrus, and

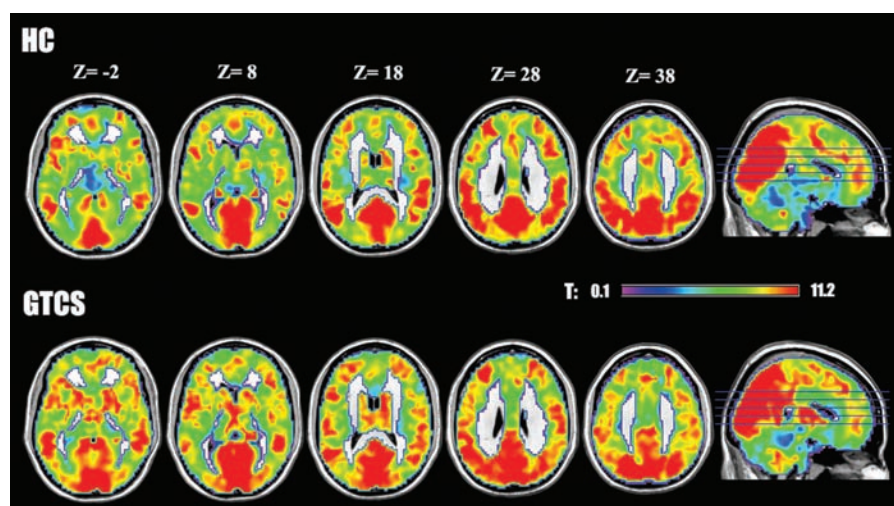


Figure 1. Spatial distribution of short-range FCD in patients with GTCS and HCs. There is no significant statistical difference between the 2 groups.

temporal gyrus. We did not find statistical difference of short-range FCD between 2 groups. No significant intergroup differences in local FCD on other additional correlation thresholds ($r=0.4, 0.5, \text{ and } 0.7$) were found.

3.2. Differences in long-range FCD

The high long-range FCD hubs were also bilaterally distributed in both groups, including the bilateral PCC/PCu, precentral gyri (PreCG), temporal gyrus, and frontal gyrus, which were shown in Fig. 2A and B. Regions with high FCD values indicate that they might play important roles in brain networks, namely hubs. The FCD hubs found in our study are consistent with previous studies.^[24,25]

Group comparisons showed significantly increased long-range FCD in patients with GTCS in the bilateral cerebellum, postcentral gyri (PoCG), and precentral gyri (PreCG). Meanwhile, reduced long-range FCD was shown in the left middle and inferior temporal gyrus (MTG/ITG), supramarginal gyrus (SMG), angular gyrus (ANG), superior frontal gyrus (SFG), and medial prefrontal cortex (MPFC), compared with HCs (Table 2; Fig. 2C, $P<0.05$, AlphaSim corrected, with a cluster size of 224 voxels). Almost all of the significant brain regions at the threshold of $r=0.6$ were included in the maps using thresholds of $r=0.4$ and 0.5 ; however, the significant brain areas were rapidly decreased at the threshold of $r=0.7$ than that at the threshold of $r=0.6$. Significant differences in long-range

FCD at these 3 thresholds are shown in Supplementary Figure S1, <http://links.lww.com/MD/B32>.

3.3. The seed-based rsFC analysis

We further examined the seed-based FC in 2 groups of participants. As discussed earlier, a significant change in long-range FCD measurements of GTCS was detected (Table 2). The regions with significant different long-range FCD between 2 groups were defined as seeds for FC analyses. Specifically, the left MPFC and SFG exhibited decreased rsFCs with the left MTG; the left MTG and ITG displayed subdued rsFCs with the left PCu, ANG, and MPFC (Table 3; Fig. 3).

3.4. Correlation analysis

As seen in Fig. 4, duration of disease was correlated negatively with long-range FCD in the left MPFC, MTG, ITG, and ANG. We also computed the correlation between age and FCD in patients and HCs separately, and no significant correlation was found (minimum P values are 0.06 and 0.08, respectively).

4. Discussion

The present rs-fMRI study investigated disrupted FC patterns in GTCS patients using FCD method combined with seed-based rsFC. Our primary finding was that the GTCS patients not only

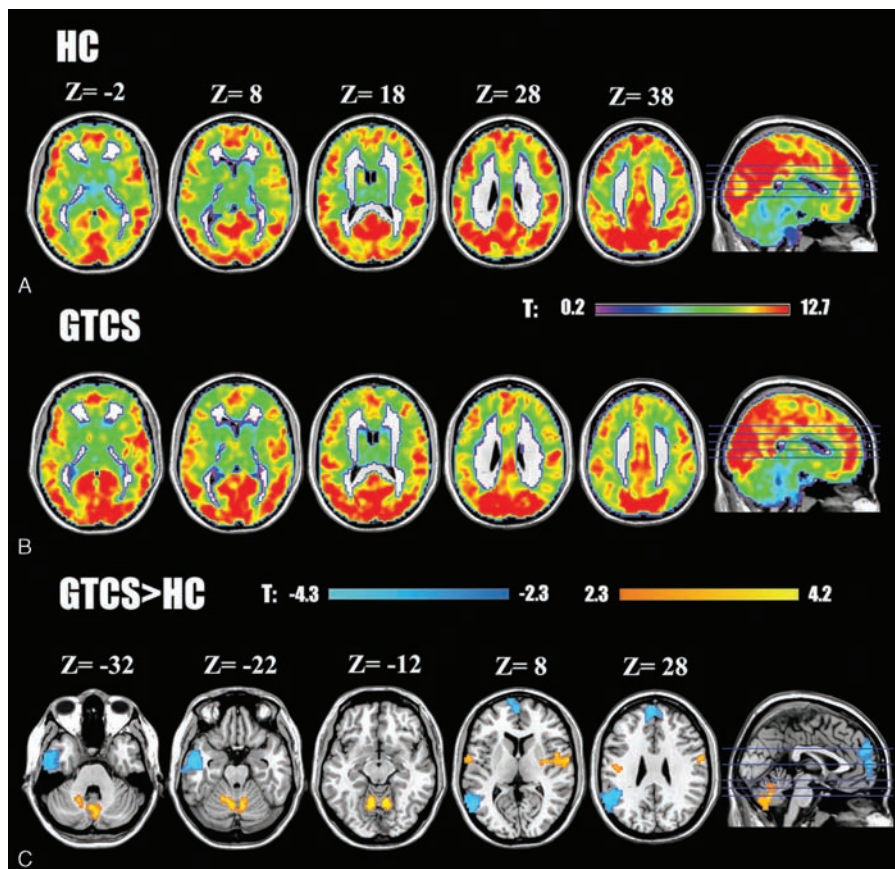


Figure 2. Spatial distribution of long-range FCD in patients with GTCS and HCs and the statistical differences between the 2 groups. The statistical significance of group differences was corrected by AlphaSim ($P<0.05$, a combined threshold of $P<0.01$ with a minimum cluster size of 224 voxels). The left hemisphere is on the left.

Table 2**Differences in the long-range FCD between patients with GTCS and HCs.**

	Anatomical regions	BA	Cluster size	MNI coordinates			Peak T-scores
				X	Y	Z	
GTCS>HC							
Cluster 1	Cerebellum_4_5_L	\	285	30	-42	-36	3.59
	Cerebellum_4_5_R	\		-18	-54	-27	3.50
Cluster 2	PoCG_R	48	254	60	-9	18	3.22
	PreCG_R	6		42	-9	42	3.09
Cluster 3	PreCG_L	6	282	-36	-15	45	3.43
	PoCG_L	6		-36	-12	42	3.17
HC>GTCS							
Cluster 1	MTG_L	21	279	-54	-3	-21	-5.49
	ITG_L	20		-48	-6	-24	-4.29
Cluster 2	MPFC_L	9	277	-9	48	51	-3.91
	SFG_L	9		-12	48	48	-3.52
Cluster 3	MTG_L	21	372	-60	-54	12	-4.44
	SMG_L	40		-57	-51	27	-3.60
	ANG_L	22		-57	-54	27	-3.44

Peak T-scores, statistical value of peak voxel showing long-range FCD differences between the groups.

ANG=angular gyrus, BA=Brodman's area, FCD=functional connectivity density, GTCS=generalized tonic-clonic seizures, HCs=healthy controls, ITG=inferior temporal gyrus, MNI=Montreal Neurologic Institute, MPFC=medial prefrontal cortex, MTG=middle temporal gyrus, PoCG=postcentral gyri, PreCG=precentral gyri, SFG=superior frontal gyrus, SMG=supramarginal gyrus.

had significantly increased long-range FCD mainly distributed in sensorimotor areas but also had decreased long-range FCD in the temporal, prefrontal, and inferior parietal cortices. Some regions in which the GTCS showed reduced long-range FCD also showed significantly decreased rsFC. Furthermore, significant negative correlations between the duration of disease and reduced long-range FCD were found that may provide new insights into our understanding of the pathophysiological mechanisms underlying GTCS.

The GTCS patients showed a significant increment of long-range FCD in the motor areas (Table 2). The cerebellum plays an important role in motor control, such as coordination, precision, and accurate timing.^[8] Specially, there are neural pathways linking the cerebellum with the motor cortex and other movement-generating brain areas.^[8] Gotman et al^[30] also found a higher activation in the cerebellum in IGE patients in a

combined EEG-fMRI study. The authors suggested that the positive activity in the cerebellum indicates an intense involvement of it in response to epileptic discharges and is responsible for the complex motor manifestation seen in the epileptic seizures. Meanwhile, the PreCG and PoCG, known as the motor strip or primary motor and somatosensory cortices, displayed increased long-range FCD in GTCS patients. Spike and wave-related activation was also observed in the precentral gyri by spike-triggered fMRI.^[31] As the part of the brain's neocortex, it is likely to reflect the direct involvement of both areas in motor control and is responsible for executing voluntary movements.^[32]

In the current study, we noted decreased long-range FCD in the GTCS, which covered the left MTG, ITG, SFG, MPFC, SMG, and ANG. Our study did not measure the scale of cognitive abnormalities, but according to previous studies can make a reasonable prediction. Prior studies have demonstrated that

Table 3**Significant differences in rsFC of seed regions of long-range FCD between GTCS and HCs.**

Brain regions	BA	Cluster size	MNI coordinates			Peak T-scores
			X	Y	Z	
Seed from						
MTG_L	BA (21)					
MPFC_L	32	599	-6	45	18	-4.91
PCu_L	20	503	-60	-33	-24	-5.01
ANG_L	39	173	-51	-57	30	-4.93
Seed from						
ITG_L	BA (20)					
PCu_L	23	132	-12	-54	24	-4.27
MPFC_L	32	103	-6	45	21	-4.98
ANG_L	39	172	-48	-63	33	-5.67
Seed from						
MPFC_L	BA (9)					
MTG_L	21	114	-48	9	-30	-4.53
Seed from						
SFG_L	BA (9)					
MTG_L	20	93	-51	3	-33	-4.38

ANG=angular gyrus, BA=Brodman's area, FCD=functional connectivity density, GTCS=generalized tonic-clonic seizures, HCs=healthy controls, ITG=inferior temporal gyrus, MNI=Montreal Neurologic Institute, MPFC=medial prefrontal cortex, MTG=middle temporal gyrus, Pcu=precuneus, rsFC=resting-state functional connectivity, SFG=superior frontal gyrus, SMG=supramarginal gyrus.

Peak T-scores, statistical value of peak voxel showing rsFC differences between the groups.

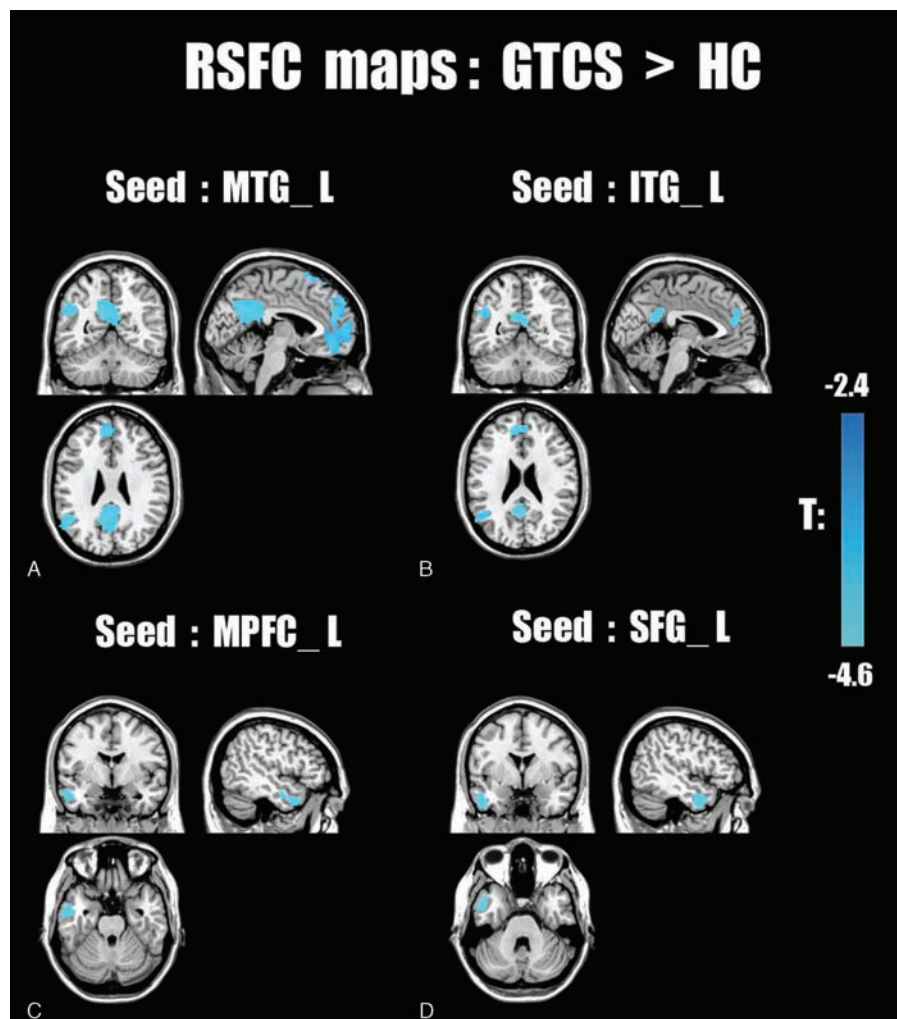


Figure 3. Statistical significance of rsFC patterns for each seed region (middle and inferior temporal gyrus (MTG and ITG), medial prefrontal cortex (MPFC), and superior frontal gyrus (SFG)) with significant group differences in long-range FCD between GTCS and HCs. Each result is displayed on 3 “brains” shown from the right (top left image of each group), from behind (top right image of each group), and from above (bottom left image of each group). Warm and cool colors indicate that rsFC increases and decreases, respectively, in patients with GTCS.

patients with GTCS have cognitive impairments, such as memory and language dysfunctions between the seizures.^[3,41] Gauffin et al^[33] reported subtle language deficits with a test battery in generalized epilepsy. By using California Verbal Learning Test, poor memory efficiency was also observed in IGE patients.^[34] Furthermore, social cognitive deficits were also observed in previous work,^[35] which adds to the literature on social cognition in patients with epilepsy. Functional neuroimaging studies have suggested that MTG and ITG are involved in several cognitive processes, including language, semantic memory processing, as well as visual perception.^[36,37] Moreover, prefrontal association cortex, including SFG and MPFC, has been implicated in planning complex cognitive processing, decision making, and moderating social behavior.^[38] Together, these studies all demonstrated that GTCS patients suffered from impairment of cognitive functions. These may suggest that the dysfunction of MTG, ITG, and prefrontal cortices could result from long-term existence of various epileptic risks and was related to the impairment of cognitive function of GTCS patients.

More interestingly, seed-voxel correlation analysis showed hypo-connectivity between MTG and prefrontal cortices, as well

as between MTG, ITG and PCu, ANG. Collectively, the participants with GTCS showed abnormal FC within the default mode network (DMN). These areas serve various cognitive and emotional functions, including “mentalizing” (i.e., understanding the mental states of one’s self and others).^[39,40] IGE patients showed poorly in social processing such as limited self-control, attention deficit, and response inhibition.^[41] Such difficulties might result from impaired mentalization, for instance, abstract induction, concept formation, psychological stress ability, cognitive processing speed, and planning.^[42,43] These works have shown that DMN is essential for social cognition, especially in the interaction between the self and the social environment in GTCS patients. Further studies may be inclined to discuss whether the aberrant rsFC observed is related to these social processing impairments.

In addition, we observed diminished long-range FCD in the left inferior parietal lobe (IPL), including the left ANG and SMG. It is suggested that the IPL played a central role in action recognition, grasping, and manipulation.^[44] Our findings are in line with the perspective that the left IPL may help the brain to classify and label things, which is a prerequisite for forming concepts and

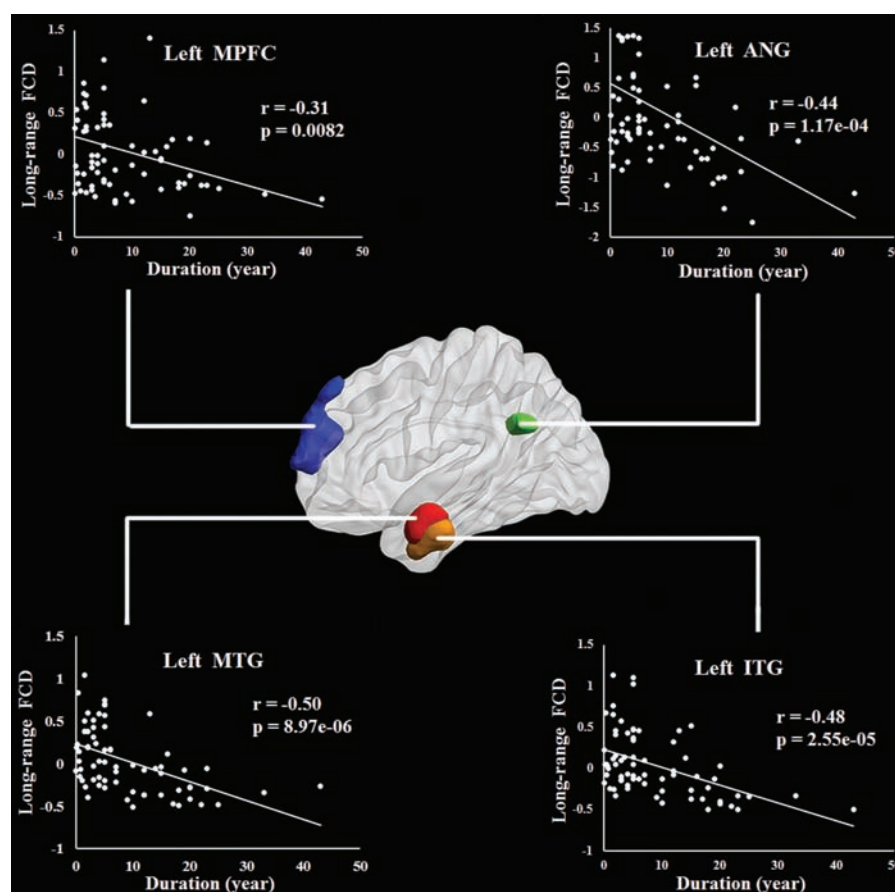


Figure 4. Correlations between duration of disease (years) and long-range FCD in the left medial prefrontal cortex (MPFC), middle and inferior temporal gyrus (MTG and ITG), as well as angular gyrus (ANG). The long-range FCD values in the figure were extracted from the significant clusters after age, gender, and frame-wise displacement of each subject were regressed out. More details of these regions are described in Table 2.

thinking abstractly, and damage to the left IPL is associated with limb apraxia (a syndrome involving difficulty in producing gestures and movements to command).^[45] Moreover, in fMRI experiments, IGE patients perform poorly on a sustained attention task, the deficit being worse as a function of disease duration,^[46] which is consistent with the negative correlation results between long-range FCD and duration of disease in the present study.

Finally, the negative correlation between long-range FCD and duration of disease represented in the left MTG, ITG, MPFC, and ANG may reflect an adverse consequence eventually as a response to slightly impaired cognition from original.

Several technical and biological limitations in the present research must be acknowledged. First, a relatively weak correction (AlphaSim program) was used for multiple comparisons in our study. Next, we used a relatively low sampling rate (TR=2 s) for multiple (30 slices) acquisitions. Although a band-pass filtering in the range (0.01–0.08 Hz) is used to minimize respiratory and cardiac fluctuations, the influence of sampling rate may still be a problem for fMRI time series. Finally, we only selected a single threshold to calculate FCD maps; a range of thresholds can be tried to test the stability of the results in future study.

5. Conclusions

We obtained selective impairments of the brain FC in GTCS patients using FCD mapping. The abnormal FCD regions and FC

based on these regions in GTCS were mainly associated with the relationship between self and the social environment as well as motor control. Furthermore, some alterations of FCD correlated with duration of disease in altered regions, which might reflect an adaptation in GTCS for long-term the loss of consciousness and cognition deficits. This study improves our understanding of the pathophysiological mechanisms underlying GTCS.

References

- [1] Engel J. A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia* 2001;42:796–803.
- [2] Danielson NB, Guo JN, Blumenfeld H. The default mode network and altered consciousness in epilepsy. *Behav Neurol* 2011;24:55–65.
- [3] Baillet LL, Turk WR. The impact of childhood epilepsy on neurocognitive and behavioral performance: a prospective longitudinal study. *Epilepsia* 2000;41:426–31.
- [4] Hommet C, Sauerwein HC, De Toffol B, Lassonde M. Idiopathic epileptic syndromes and cognition. *Neurosci Biobehav Rev* 2006;30:85–96.
- [5] Bernhardt BC, Rozen DA, Worsley KJ, Evans AC, et al. Thalamo-cortical network pathology in idiopathic generalized epilepsy: insights from MRI-based morphometric correlation analysis. *Neuroimage* 2009;46:373–81.
- [6] Wang Z, Zhang Z, Jiao Q, et al. Impairments of thalamic nuclei in idiopathic generalized epilepsy revealed by a study combining morphological and functional connectivity MRI. *PLoS One* 2012;7:e39701.
- [7] Ji G-J, Zhang Z, Xu Q, et al. Generalized tonic-clonic seizures: aberrant interhemispheric functional and anatomical connectivity. *Radiology* 2014;271:839–47.

- [8] 2010;Li Y, Du H, Xie B, et al. Cerebellum abnormalities in idiopathic generalized epilepsy with generalized tonic-clonic seizures revealed by diffusion tensor imaging. *5:e15219*.
- [9] Kim JB, Suh Si, Seo WK, et al. Altered thalamocortical functional connectivity in idiopathic generalized epilepsy. *Epilepsia* 2014;55:592–600.
- [10] Tomasi D, Volkow ND. Functional connectivity density mapping. *Proc Natl Acad Sci U S A* 2010;107:9885–0.
- [11] Tomasi D, Volkow ND. Aging and functional brain networks. *Mol Psychiatry* 2012;17:549–8.
- [12] Wang T, Li Q, Guo M, et al. Abnormal functional connectivity density in children with anisometropic amblyopia at resting-state. *Brain Res* 2014;1563:41–51.
- [13] Qin W, Xuan Y, Liu Y, et al. Functional connectivity density in congenitally and late blind subjects. *Cereb Cortex* 2015;25:2507–16.
- [14] Ding J, An D, Liao W, et al. Abnormal functional connectivity density in psychogenic non-epileptic seizures. *Epilepsy Res* 2014;108:1184–94.
- [15] Zhang Z, Liao W, Chen H, et al. Altered functional–structural coupling of large-scale brain networks in idiopathic generalized epilepsy. *Brain* 2011;134:2912–8.
- [16] Power JD, Barnes KA, Snyder AZ, et al. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 2012;59:2142–54.
- [17] Satterthwaite TD, Wolf DH, Loughhead J, et al. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. *Neuroimage* 2012;60:623.
- [18] Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage* 2012;59:431–8.
- [19] Achard S, Salvador R, Whitcher B, et al. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J Neurosci* 2006;26:63–72.
- [20] Liao W, Zhang Z, Pan Z, et al. Altered functional connectivity and small-world in mesial temporal lobe epilepsy. *PLoS One* 2010;5:e8525.
- [21] Foerster BU, Tomasi D, Caparelli EC. Magnetic field shift due to mechanical vibration in functional magnetic resonance imaging. *Magn Reson Med* 2005;54:1261–7.
- [22] Cordes D, Houghton VM, Arfanakis K, et al. Frequencies contributing to functional connectivity in the cerebral cortex in “resting-state” data. *Am J Neuroradiol* 2001;22:1326.
- [23] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 2002;15:273–89.
- [24] Tomasi D, Volkow ND. Abnormal functional connectivity in children with attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2012;71:443–50.
- [25] Buckner RL, Sepulcre J, Talukdar T, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer’s disease. *J Neurosci* 2009;29:1860–73.
- [26] Liao X-H, Xia M-R, Xu T, et al. Functional brain hubs and their test–retest reliability: a multiband resting-state functional MRI study. *Neuroimage* 2013;83:969–82.
- [27] Tomasi D, Volkow ND. Functional connectivity hubs in the human brain. *Neuroimage* 2011;57:908–17.
- [28] Ding J, An D, Liao W, et al. Abnormal functional connectivity density in psychogenic non-epileptic seizures. *Epilepsy Res* 2014;108:1184–94.
- [29] Zhang Y, Xie B, Chen H, et al. Abnormal functional connectivity density in post-traumatic stress disorder. *Brain Topogr* 2016;29:405–11.
- [30] Gotman J, Grova C, Bagshaw A, et al. Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain. *Proc Natl Acad Sci U S A* 2005;102:15236–40.
- [31] Archer JS, Abbott DF, Waites AB, et al. fMRI “deactivation” of the posterior cingulate during generalized spike and wave. *Neuroimage* 2003;20:1915–22.
- [32] Porro CA, Francescato MP, Cettolo V, et al. Primary motor and sensory cortex activation during motor performance and motor imagery: a functional magnetic resonance imaging study. *J Neurosci* 1996;16:7688–98.
- [33] Gauffin H, van Ettinger-Veenstra H, Landtblom A-M, et al. Impaired language function in generalized epilepsy: inadequate suppression of the default mode network. *Epilepsy Behav* 2013;28:26–35.
- [34] Henkin Y, Sadeh M, Kivity S, et al. Cognitive function in idiopathic generalized epilepsy of childhood. *Develop Med Child Neurol* 2005;47:2126–32.
- [35] Fournier N, Calverley K, Wagner J, et al. Impaired social cognition 30 years after hemispherectomy for intractable epilepsy: the importance of the right hemisphere in complex social functioning. *Epilepsy Behav* 2008;12:460–71.
- [36] Cabeza R, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 2000;12:1–47.
- [37] Herath P, Kinomura S, Roland PE. Visual recognition: evidence for two distinctive mechanisms from a PET study. *Hum Brain Mapp* 2001;12:110–9.
- [38] Yang Y, Raine A. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. *Psychiatry Res* 2009;174:81.
- [39] Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nat Rev Neurosci* 2006;7:268–77.
- [40] Gusnard DA, Akbudak E, Shulman GL, et al. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci* 2001;98:4259–64.
- [41] de Araújo Filho GM, Jackowski AP, Lin K, et al. Personality traits related to juvenile myoclonic epilepsy: MRI reveals prefrontal abnormalities through a voxel-based morphometry study. *Epilepsy Behav* 2009;15:202–7.
- [42] Devinsky O, Gershengorn J, Brown E, et al. Frontal functions in juvenile myoclonic epilepsy. *Cogn Behav Neurol* 1997;10:243–6.
- [43] McGill ML, Devinsky O, Kelly C, et al. Default mode network abnormalities in idiopathic generalized epilepsy. *Epilepsy Behav* 2012;23:353–9.
- [44] Rizzolatti G, Matelli M. Two different streams form the dorsal visual system: anatomy and functions. *Exp Brain Res* 2003;153:146–57.
- [45] Singh-Curry V, Husain M. The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy. *Neuropsychologia* 2009;47:1434–8.
- [46] Maneshi M, Moeller F, Fahoum F, et al. Resting-state connectivity of the sustained attention network correlates with disease duration in idiopathic generalized epilepsy. *PLoS One* 2012;7:e50359.