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Author(s):	Sisi Jiang, Haonan Pei, Yang Huang, Yan Chen, Linli Liu, Jianfu Li, Hui He, Dezhong Yao, Cheng Luo
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DYNAMIC TEMPOROSPATIAL PATTERNS OF FUNCTIONAL CONNECTIVITY AND ALTERATIONS IN IDIOPATHIC GENERALIZED EPILEPSY

SISI JIANG[*], HAONAN PEI[*], YANG HUANG[*], YAN CHEN[*], LINLI LIU[*], JIANFU LI[*], HUI HE[*], DEZHONG YAO[*,Ψ,‡], CHENG LUO[*,‡,Ψ,ζ]

**The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, Center for Information in Medicine School of Life Science and Technology, University of Electronic Science and Technology of China, Chengdu 611731, P. R. China*

[‡]High-Field Magnetic Resonance Brain Imaging Key Laboratory of Sichuan Province, University of Electronic Science and Technology of China, Chengdu, China

[Ψ]Research Unit of NeuroInformation, Chinese Academy of Medical Sciences, 2019RU035, Chengdu, China

[ζ]chengluo@uest.edu.cn

The dynamic profile of brain function has received much attention in recent years and is also a focus in the study of epilepsy. The present study aims to integrate the dynamics of temporal and spatial characteristics to provide comprehensive and novel understandingofepileptic dynamics.Resting state fMRI data werecollected from eighty-three patients withidiopathic generalized epilepsy(IGE) and eighty-seven healthy controls(HC). Specifically, we explored the temporal and spatial variationoffunctional connectivity density(tvFCD and svFCD) in the whole brain. Usinga sliding-window approach, for a given region, the standard variation of the FCD series was calculated as thetvFCD and the variation of voxel-wise spatial distribution was calculated as the svFCD. We found primary, high-level, and sub-cortical networks demonstrated distinct tvFCD and svFCD patterns in HC. In general, the high-level networks showed the highest variation, the subcortical and primary networks showed moderate variation, and the limbic system showed the lowest variation.Relative to HC, the patients with IGE showed weaken temporal and enhanced spatial variation in the default mode networkand weakentemporospatialvariationinthe subcortical network. Besides, enhanced temporospatial variation in sensorimotor and high-level networks was also observed in patients. The hyper-synchronization of specific brain networks was inferred to be associated with the phenomenon responsible for the intrinsic propensityof generation and propagation of epileptic activities. The disrupted dynamic characteristics of sensorimotor and high-level networks might potentially contribute to the driven motion and cognition phenotypes in patients.In all, presently provided evidence from thetemporospatial variation of functional interaction shed light on the dynamics underlying neuropathological profiles of epilepsy.

Keywords：Generalized epilepsy;functional connectivity; dynamic; temporal variability; spatial variability

[ζ] Corresponding author

1. Introduction

Dynamic functional integration and separation across brain networks make the brain to be flexible in responding to both internal and external stimuli[1, 2].A previous fMRIstudy has investigated the variability of local spontaneous activity throughout the brain, suggesting a distinct distribution of variability in different brain regions[3].Functional connectivity(FC)reflectsthe synchronization of spontaneous neuronal activity between brain regions and has been investigated in various disorders of neural systems and provided significant evidence for understanding the pathological mechanism of diseases[4-7].Over the years, accumulatedfMRIstudies have revealed temporallyvariation of intrinsic FC responding to distinct brain states[8-11]. A region with high variability tends to be involved in complex and integrated cognitive activities.Temporal variability ofbrain activity is viewed to representthe adaptabilityof the brain and high temporal variability is proposed to be associated with learning plasticity[12]. The significance of studying brain dynamic characteristics lies not only in the cognition of normal brain function but also in the study of neuropsychiatric diseases[12, 13].

Generalized epilepsy is a clinical syndrome typically characterized by paroxysmal generalized spike-wave discharges(GSWD) and emerging evidence has suggested it to be a network disorder[14-16]. Bistability between epileptic and normal brain states makes the dynamic investigation especially important in epilepsy[17].A series of studiesfocused on detecting crucial features of brain activity to predict seizures[18, 19].The seizure process is usually divided into preictal, ictal and postictal in most researches investigating the evolutionof epileptic activities[20, 21].Simultaneous EEG-fMRI studies revealed thespatiotemporal dynamics of an active pattern of wide-spread regions at different periods[22, 23].

The deactivation of thedefault mode network(DMN) and activation of the thalamus are consistently reported to be responsible for the generation and propagation of epileptic activities[24]. Temporally desynchronized and synchronized networks over the discharge period provided remarkable evidence to understand the potential pathomechanism underlying epilepsy[25]. Previousresearches of dynamic functional connectivity in epilepsy predominantly focused on the delineation of epileptogenic foci, seizure prediction, and discriminating patients with epilepsy from healthy controls[26, 27].By studying the variability of local brain activity in resting state, hyper-and hypo-variability in different networks were revealed in patients with generalized tonic-clonic seizures[28, 29].Besides,a recentfMRI studyconcerned the dynamics of functional connectivity profile and revealed enhanced temporal variability in patients with generalized epilepsy, suggesting a dynamic reconfiguration of large-scale brain networks[30].Moreover, the investigations of spatial characteristics havealso been proven to be of significance in revealing normal and pathological brain function[31-35]. At present, however, the study of the dynamicsof spatial features is relatively limited.

Themetastability of the brain state remains in spontaneous activity for most of the time and autonomously bursts into GSWD periods[36].Thus, it is imperative to study the temporal and spatial characteristics of dynamic brain function in patients with epilepsy in the resting state. Previous dynamic studies mainly focused on the temporal variability, the present study investigatedboth temporal and spatial variability of functional connectivity, aiming to provide an integrated temporospatial view of the dynamics of the brain. Specifically, the functional connectivity density (FCD), a well-recognized approach, was employed as a measurement to depict the functional architecture of a given region. Then, the calculation of temporal, spatial, and temporospatialvariation of FCD was proposed. The epilepsy is a network disorder characterized by significantly disrupted dynamics of brain function. Thus, it is worthy to investigate the dynamic features of large-scale networks in epilepsy, which might make substantially contribution to revealing the pathomechanism. We forecast that the temporal and spatial dynamic characters revealed by the present approaches would provide novel evidence to replenish the understanding of dynamics in epilepsy.

2. Materials and Methods

2.1Participants

Eighty-three patients (mean age: 22.59±11.18 years; mean years of duration: 7.75±8.36; mean age of seizure onset: 14.84±10.86; all right-handed, 39 males) with IGE were recruited in the present study.All patients were diagnosed as IGE according to the epilepsy classification of the International League Against Epilepsy[37]. Specifically, the IGE group was made up of 58 patients with generalized tonic-clonic seizures and 25 patients with juvenile myoclonic epilepsy. Detailed demographic

and clinical information are shown in Table 1. No patients had brain lesions, developmental disabilities, or other accompanying neurological disorders.

Table 1. Clinical characteristics in IGE and HC

Characteristic	IGE	HC	P-value
Number	83	87	-
Age (year)	22.6±11.2	24.5±9.0	0.01[a]
Gender (M:F)	39:44	48:39	0.29[b]
AED (with:without)	66:15	-	-
Therapy (single: multiple)	26:40	-	-
Age at onset (year)	14.8±10.9	-	-
Duration (year)	7.7±8.4	-	-
mFD (mm)	0.12±0.06	0.09±0.05	0.002[a]

Abbreviation: AED: antiepileptic drug; mFD: mean frame-wise displacement; a. The P value was obtained by a two-sample two-tail t-test. b. The P-value was obtained by a $\chi 2$ test.

Eighty-seven healthy controls (HC) (mean age: 24.5±9.0 years, all right-handed, 48 males) without neurological and psychiatric disorders were recruited as controls. The present study was approved by the ethical committee of the University of Electronic Science and Technology of China. Written informed consents were obtained from all of the subjects.

2.2 Data Acquisition

MRI images were acquiredon a 3TIGE scanner equipped with an eight-channel-phased array head coil (EXCITE, IGE, Milwaukee, WI). An echo-planar imaging sequence was used for resting-state functional data (echo time (TE) = 30 ms, repetition time (TR) = 2000 ms, data matrix=64 × 64, field of view=24 cm × 24 cm, flip angle (FA) =90°, slice thickness=4 ms (no gap), and 32 axial slices in each volume).All of the subjects were asked to close eyes without falling asleep during the scan. Each scan lasts 400 seconds, generating 200 volumes.A three-dimensional fast spoiled gradient-echo sequence was used to acquire axial anatomical T1-weighted images. The parameters were as follows: TE= 3.2 ms,TR= 8.2 ms, field of view= 25.6 cm×25.6 cm, data matrix= 256 × 256, flip angle= 12°, andthickness= 1 mm (no gap). The diffusion tensor image (DTI) imageswere collected using a diffusion weighted spin-echoEPI sequence (128 × 128 base resolution,voxel size 2 × 2 × 2 mm^3, 75 slices, 64 directions, and b-value 1000 s/mm^2).

2.3 Preprocessing

A self-developed softwarepackage NIT [38]was used for preprocessing the fMRI datasets. The first five volumes of each run were discarded to eliminate magnetic field instability.Slice-timing correction, realignment, spatial normalization to the Montreal Neurological Institute (MNI) template were conducted successively. Then, these images were resampled to an isometric 3x3x3mm^3grid. We excluded the subjects with head motion exceeding 2 mm or/and 2 degrees.Besides, head-motion parameters, white matter signals, and cerebrospinal fluid signals were regressed out from normalized data and temporal filter in the 0.01–0.08 Hz band was performed in the functional images.Moreover, basedon frame-wise displacement (FD) defined by Power [39], the mean frame-wise displacement (mFD) of each subject was computed using the following formula:

$$\mathrm{mFD} = \left(\frac{1}{M-1}\right)\sum_{i=2}^{M}\left(\left|\Delta d_{x_i^1}\right| + \left|\Delta d_{y_i^1}\right| + \left|\Delta d_{z_i^1}\right| + \left|\Delta d_{x_i^2}\right| + \left|\Delta d_{y_i^2}\right| + \left|\Delta d_{z_i^2}\right|\right);$$

where M is the length of the time course; x_i^1/x_i^2, y_i^1/y_i^2, and z_i^1/z_i^2 are translations/rotations at the *i*th time point in the *x*, *y*, and z directions, respectively; and $\Delta d_{x_i^1} = x_i^1 - x_{i-1}^1$, and a similar pattern held for the others. Notably, by calculating displacement on the surface of a sphere with a radius of 50 mm, the rotations were converted from degrees to millimeters.

2.4Temporalvariability of functional connectivity density

To be brief, FCD is a measure of how closely one region functionally connects with the rest of the brain[40]. With different connect criteria (direct, indirect, and unrestricted connection), the global, local and,longRange FCD was defined[41], detailed calculation procedures could be referred to our previously published studies[6, 42]. To characterize the temporal variability of FCD,a sliding-window approach was adopted in the current study to investigate tvFCD as shown in Figure1A.

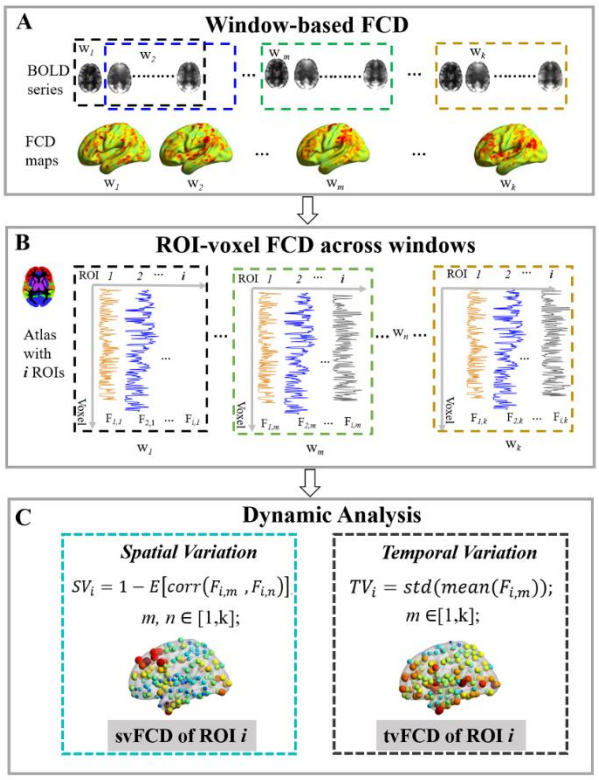

Figure 1. An overview of the analysis scheme of dynamic FCD. The (A) shows the sliding-window based approach and window-based FCD calculation; the (B) shows the atlas-based voxel-level FCD values in every ROI across windows; the (C) illustrates the calculation of temporal variation of FCD and the spatial variation of FCD for a given region.

Accumulated studies of the sliding-window approach used a window length ranging from 20 to 75 TR[29]. Since there was no consensus on the window length, we selected a window length = 50 TR according to a former study considering the frequency characteristic of spontaneous neural oscillation[43].In line with most previous studies, a step of 1 TR was used in the current study. For each window, the calculated voxel-wise FCD map is transformed to 246 values of sub-regions in the whole brain based on theatlas proposed by Jiang et al.[41]. For every subregion, the average FCD value of all voxels was calculated.The temporal variability of FCD of a given region was then calculated using the standard variation of averaged FCD value across windows (Figure1B and C).

2.5Spatial variabilityof functional connectivity density

The spatial variability of FCD was calculated using an approach recently proposed by Zhang et al[12]. As shown in Figure1B and C. For a given time window *m*, the FCD distribution of the*i*th region$F_{i,m}$ is a vector of FCD values of all voxels in this region. Then, the spatial variability of FCD (svFCD) for a given region*i* is defined as the following:

$$SV_i = 1 - E\left[corr\left(F_{i,m}, F_{i,n}\right)\right];$$

$$i = [1,246];\ \ m,n = [1,k]$$

For the *i*th region, the stability of the spatial distribution of FCD is the averaged correlation coefficient of distribution vector across different time windows. Finally, the deduction from 1 indicates the variability of the spatial distribution of a region over time, which is the named svFCD in the current study.

2.6 Temporospatialvariability of functional connectivity density

To integrate the temporospatial variability of functional connectivity density (tsvFCD), an index was proposed as the product of the unnormalizedtvFCD and svFCD.

2.7 Relevant subnetwork

To further study the interaction between sub-regionswith disrupted variations of FCD, a relevant subnetwork was identified. We consideredeachsubregion showed abnormaltvFCD/svFCD/tvFCD as a node and calculated Pearson's correlation coefficients across all pairs of nodes to construct a functional connectivity network. A series of binary networks weregenerated with a sparsityranging from 0.15 to 0.5 with a step of 0.05. We investigated nodal features in a graph theory method, including cluster coefficient, betweenness centrality, nodal efficiency, nodal local efficiency,and degree centrality.

2.8 Validation

AnAALatlas comprised of 90 sub-regions was adopted to further validation of the pattern of FCD variation in the HC group. Same processing procedure was performed to investigate the tvFCD, svFCD, and tsvFCD of 90 regions.

2.9 Statistical analysis

The tvFCD/svFCD/tsvFCD values were first z-scored across brain regions for normalization, aiming to eliminate individual differences. In HC group, high or low variation of brain nodes was identified by being above or below the mean. For each network, we calculated the ratio of high and lowtvFCD/svFCD/tsvFCD at the individual level.

Specifically, for a given network, the ratio of high and low variationwas calculated:$Ratio_{high}$= node number of high variation/ (node number of high variation + node number of low variation); $Ratio_{low}$= node number of low variation/ (node number of high variation + node number of low variation). Then, the subtraction of $Ratio_{high}$-$Ration_{low}$was calculated and z-scored. Furthermore, one-sample t-tests were used to determine whether the subtraction was significantly greater/lower than zero, suggesting the statistical differences between the ratios with high and low variation. Besides, to assess the weighted variation of high and low variation within each network, the absolute values of variation of nodes with high/low tvFCD/svFCD/tsvFCDwere summarized for each network. The between-group differences of tvFCD/svFCD/tsvFCD were investigated using two-sample t-tests, with the age, gender, and mFD as nuisance covariates.Furthermore, correlation analyses betweenthe altered tvFCD/svFCD/tsvFCD in IGE and clinical features (disease duration and onset age) were performed using a multiple linear regression modal with the age and gender as nuisance covariates.

3. Results

3.1 tvFCD, svFCD and tsvFCD patterns in HC

Accordingto the network parcellationofYeo et al. and assignment of Jiang et al., 246 nodes were labeled by eight brain networks: the visual network (VN), sensorimotor network (SMN), dorsal attention network (DAN), ventral attention network(VAN), limbic network (Limbic),frontoparietal network (FPN), DMN and an unnamed network[44, 45]. Since the eighth network mainly consists of subcortical structures, the present study named itthe subcortical network (SCN).

Figure 2 demonstrates the tvFCD pattern at the global level. As shown by the ratio of high and low tvFCD, a greater ratio of low variation was found in VN, Limbic, and SCN, and a greater ratio of high variation was observed in SMN and VAN. The DAN, FPN, and DMN showed the almost same ratio of high and low variation. Further analysis of the summary of high and low tvFCD within networks showed the lowest variation in SCN and Limbic and relative high variation in DMN and SMN.

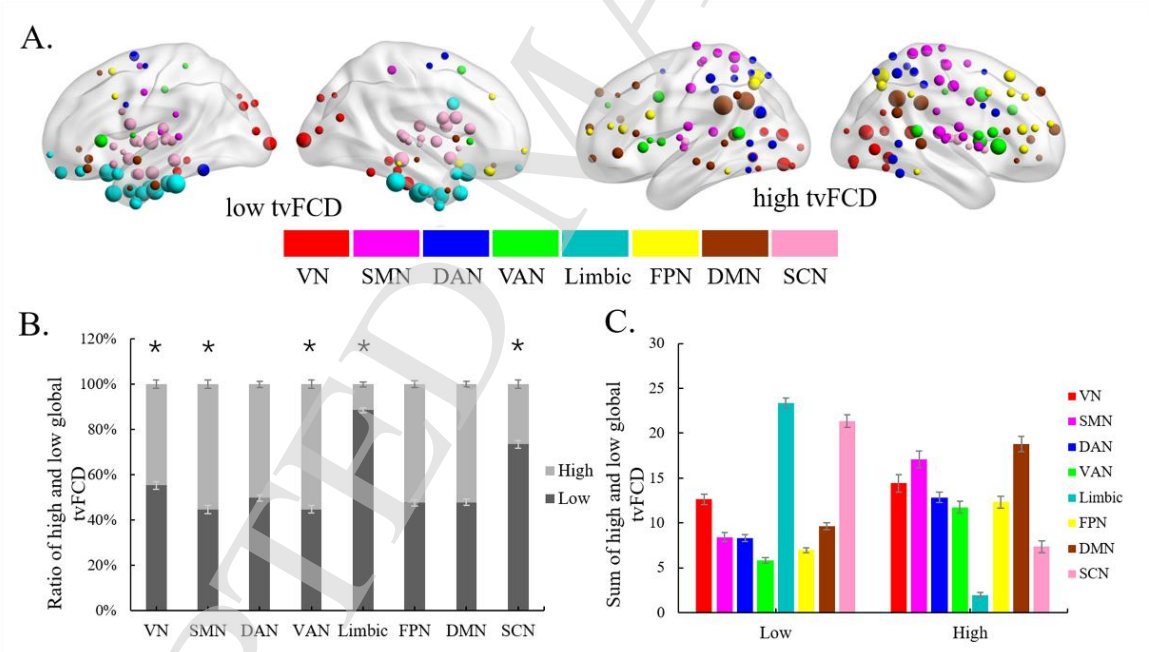

Figure 2. ThetvFCD pattern in HC. High and low tvFCD are shown at node-level in (A). The ratio of high and low tvFCD of each network is shown in (B), the gray star indicates a significant difference ($p<0.005$ without correction) between the ratio of high and low tvFCDand the error bars indicate standard errors. The respective tvFCDsummation of nodes with high and low values in each network isshown in (C).

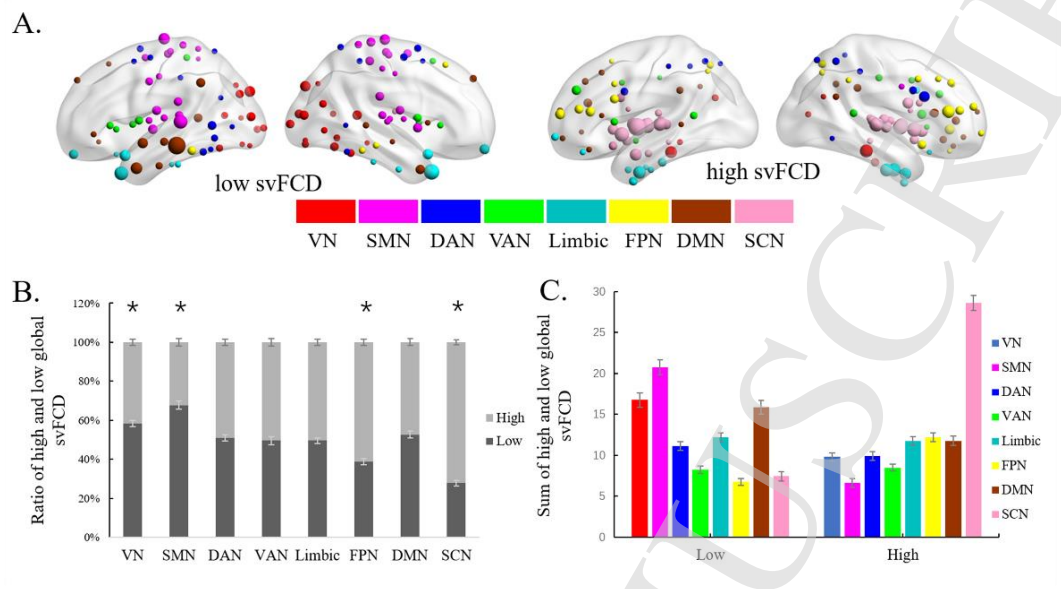

Figure 3. ThesvFCD pattern in HC. High and low svFCD are shown at node-level in (A). The ratio of high and low svFCD of each network is shown in (B), the gray star indicates a significant difference ($p<0.005$ without correction.) between the ratio of high and low svFCDand the error bars indicate standard errors. The respective svFCDsummation of nodes with high and low values in each network isshown in (C).

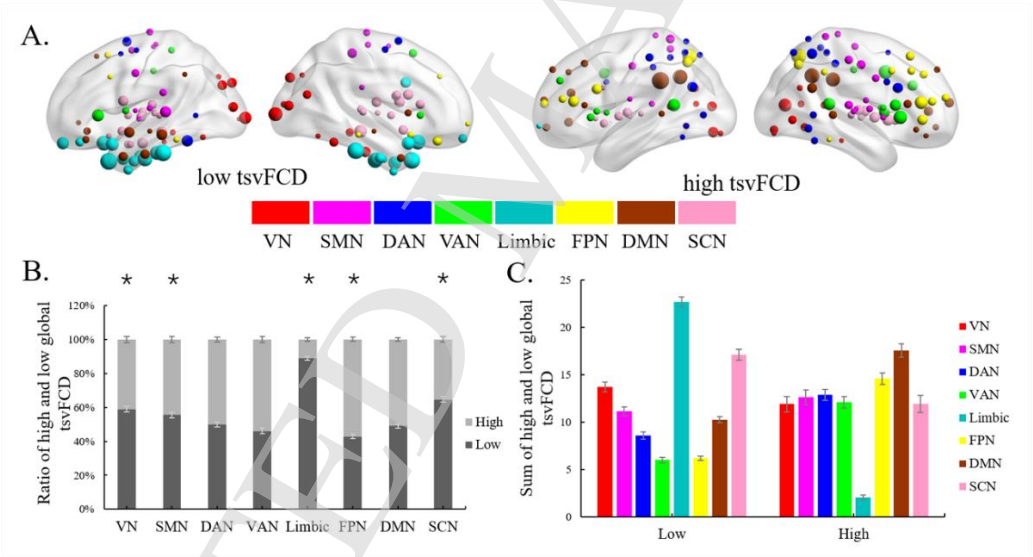

Figure 4. ThetsvFCD pattern in HC. High and low tsvFCD are shown at node-level in (A). The ratio of high and low tsvFCD of each network is shown in (B), the gray star indicates a significant difference ($p<0.005$ without correction.) between the ratio of high and low tsvFCDand the error bars indicate standard errors. The respective tsvFCDsummation of nodes with high and low values in each network isshown in (C).

For the svFCDat the global level (Figure 3), a greater ratio of low variation was found in VN and SMN, and a greater ratio of high variation was shown in FPN and SCN. The DAN, VAN, DMN, and Limbic showed almost equal ration of high and low variation. Moreover, the VN, SMN, and DMN showed lower variation and the SCN showed the highest variation among all of the networks.

For the tsvFCDat the global level (Figure 4), a greater ratio of low variation was found in Limbic, SCN, VN, and SMN, and a greater ratio of high variation was only shown in FPN. An almost equal ration of high and low variation was shown in the DAN, VAN, and DMN. Moreover, the Limbic showed the lowest variation and the SCN showed the highest variation among all of the networks.

The tvFCD, svFCD, and tsvFCD patterns at local and longRange levels were also investigated and presented integrated results supporting the present findings. The results of validation analysis using the AAL template with 90 nodes highly keeps in line with 246-nodes findings to a great extent.

3.2 Disruption of tvFCD, svFCD and tsvFCD in patients with IGE

For a straightforward presentation of the results, we described the alterations of each network in turn in the context.Forthe SCN, decreased tvFCD, svFCD, and tsvFCD were observed in patients with IGE at global, local and longRange levels. In IGE, the decrease of tvFCD and tsvFCD, and increase of svFCD at three levels were shown in DMN. For the SMN, the patients with IGE showed increased tvFCD and tsvFCD at global and longRange levels. Besides, increased svFCD at local and longRange levels were also found in SMN. The VAN showed increased svFCD at three levels and increased tsvFCD at global and longRange levels. For the DAN, the patients with IGE showed increased tvFCD and svFCD at the local level. For the FPN, increased tvFCD at longRange level and increased svFCD and tsvFCD at the local level were observed in patients. ForVN, the patients showed increased tvFCD, svFCD, and tsvFCD at the local level, increased svFCD at the longRange level, and decreased svFCD and tsvFCD at global and longRange levels.

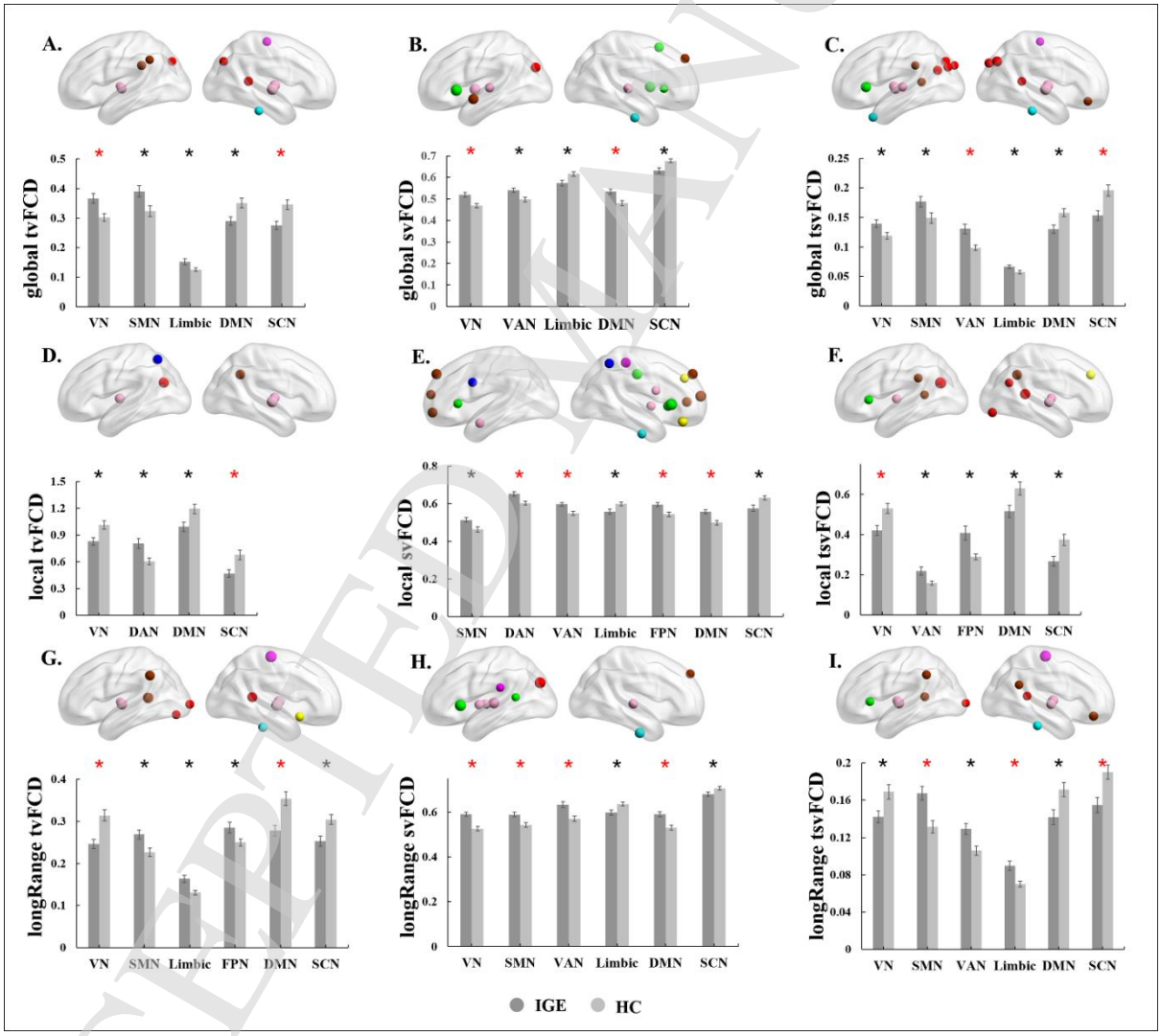

Figure 5. The significantly altered tvFCD, svFCD and tsvFCD at global(A,B,C), local (D,E,F)and longRangelevels(G,H,I) in patients with IGE. Nodal alterations are shown in brain panels and the network-level average results are shown with histograms. The black asterisk indicates a significance of $p<0.005$ without correction, the red

asterisks represent a significance of p<0.001, andthe error bars indicate standard errors.

For the Limbic, the patients showed decreased svFCD and increased tsvFCD at global, local, and longRange levels. Besides, increased svFCD at global and longRange levels were also found in our results.In Figure 5, we exhibited the nodes with significant between-group differences in brain panels and plottedthe variation of one representative node for each network in histograms(Figure 5). The global tvFCD of sub-regions of anterior cingulum positively related to the disease duration.Besides, the tsvFCD of thalamic sub-regions and prefrontal cortex showed significant correlations with disease duration and onset age. Detailed results of correlation were shown inFigure 6.

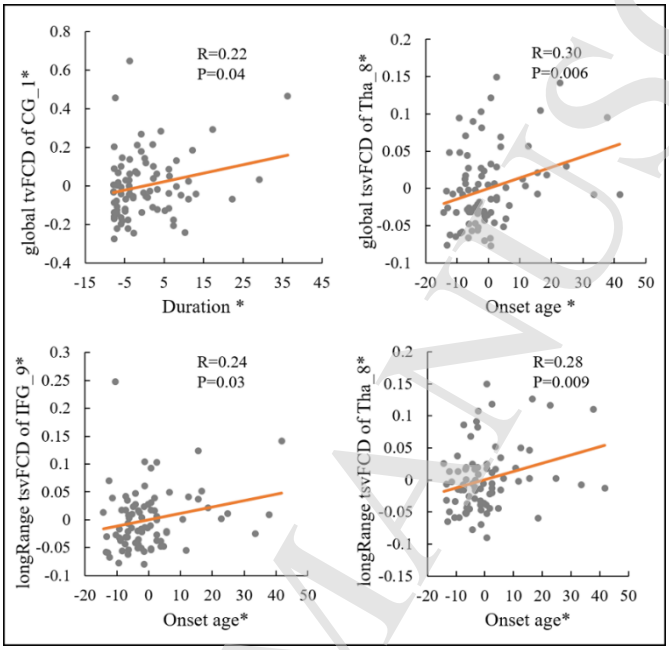

Figure 6. Significant correlation between disease duration/onset age and tvFCD/tsvFCD. The asterisk represents residuals after controlling for the influence of gender and age (linear regression with gender and ageas covariates).

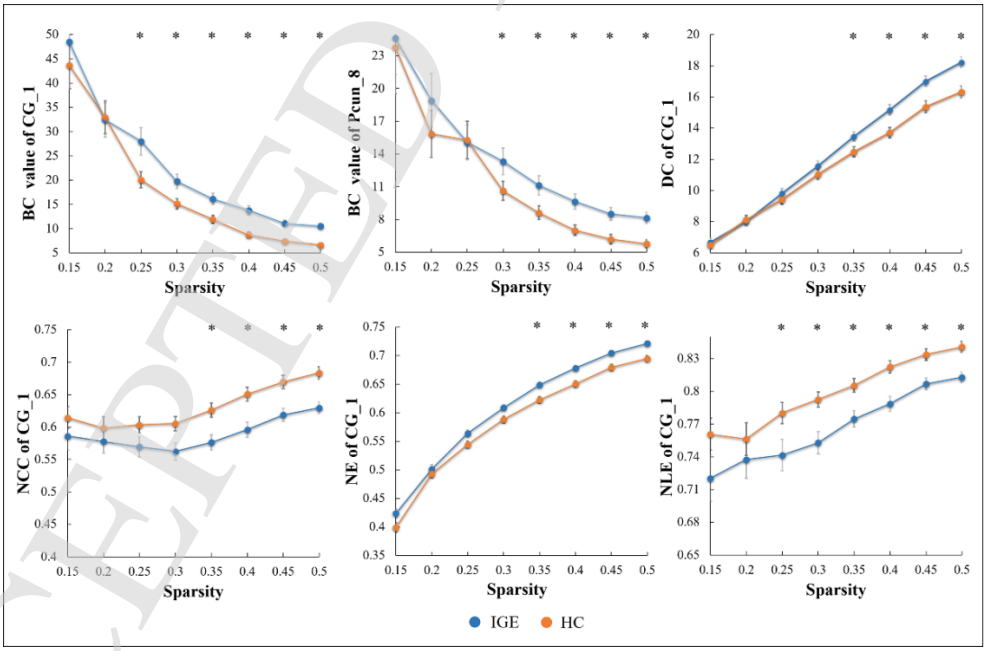

Figure 7. Analysis of nodal architectures in the relevant subnetwork. The gray asterisk indicates a significant between-group difference (p<0.05, FDR corrected). Notably, the error bar is invisible when the standard error of mean lies below 5%. BC, betweenness centrality; DC, degree centrality; NCC, nodal cluster coefficient; NE, nodal efficiency;

NLE, nodal local efficiency.

3.3 Abnormal functional architectures in the relevant subnetwork

In the present study, forty-two nodes were recognized to demonstrated abnormal variation of FCD in patients with IGE. Then, a 42*42 functional connectivity matrix was constructed for each subject and a further graph theory analysis was performed.

Under a significant threshold of $p<0.05$ with FDR correction, between-group differences of functional architectures in the relevant subnetwork were revealed using two-sample t-tests. Compared with HC, the patients with IGE showed increased betweennesscentrality, degree centrality, and nodal efficiency, and decreased nodal cluster coefficient and nodal local efficiencyin the nodesof DMN, located in anterior cingulate cortex. Besides, another DMN node, locating in the precuneus, also showed increased betweenness centrality relative to HC(Figure 7).

4. Discussion

In this study, we investigated the dynamic variation of functionalityin the whole brain from a comprehensive and novel view, integrating the temporal and spatial characteristics.Previously well-identified FCD was calculated as an index of functionality, thus the spatial and temporal variation of FCD were investigated in the present study.

Furthermore, according to the distinct functional role, cortical subnetworks are attributed to a more general classification: primary networks, high-level networks, the limbic system, and subcortical network[46].In HC, primary networks consistently demonstrated low spatial, high temporal variation, and low temporospatialvariation. High-level networks showedoverall high temporal, spatial, and integrated temporospatialvariation. The FCD of SCN wascharacterized by low temporal variation, high spatial variation, and low temporospatial variation. And the Limbic showed significantly low temporal and temporospatialvariation(Figure 8).

In the present study, the patients with IGE showed disrupted variations of FCD in distinct brain networks. First, decreased temporospatial variation of SCN (thalamic nodes), and decreased temporal variation and increased spatial variation of DMN were revealed. These findings contributed to the notion that hyper-synchronization in the epileptic networks responsible for the intrinsic propensity forthe generation and propagation of epileptic activities[47, 48]. Besides, the patients with IGE showed excessive temporal and spatial variations of FCD in SMN and high-level networks, which implied rapid spatial reconfiguration and over-flexibly temporal interaction, potentially associating with driven motor and cognitive phenotypes. Meanwhile,a complex disturbance was shown in VN and Limbic in patients.Our findings suggested disease-specific alterations of the variability of brain functionality, providing novel clues to the dynamics underlying neuropathological profiles of epilepsy (Figure9).

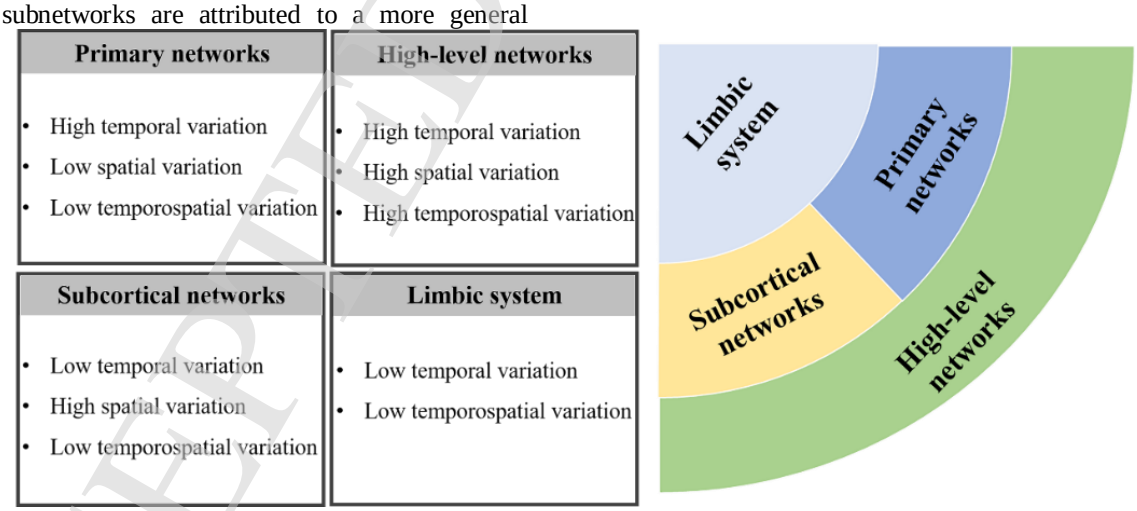

Figure 8. Demonstration of the patterns in the HC group. The left boxes summarize the patterns of variation in distinct networks. The right quarter-sphere illustrates the gradient of the variability of brain networks based on the temporal and spatial profiles revealed in the present study as summarized in the left boxes. The variation decreases from the center to the outermost edge of the circle.

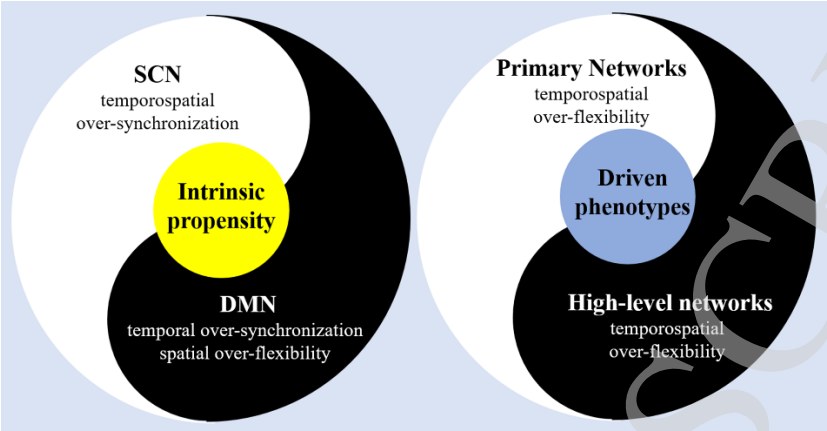

Figure 9. The overall conclusion of disrupted variations of brain networks in IGE. The dysfunction of SCN and DMN was inferred to be related to the intrinsic propensity of epilepsy, and the alterations of primary and high-level networks were viewed to contribute to the driven phenotypes of IGE.

4.1 tvFCD, svFCD and tsvFCD patterns in distinct brain networks

High tvFCD in high-level networks (DMN and FPN) was found in this study. It has been reported that high-level cognitive regions demonstrated low temporal variability in measurements ofregional activity and high temporal variability in FC-related indices[3]. Cortical hub regionsin high-level networks densely connect with other brain regions to process integrated activities, thus the connection characteristic is inferred to be flexible[49].The high tvFCDof DMN and FPN revealed in the current study also supported this view.Hightemporalvariability of functional interaction was viewed to be highly flexible, which is associated with brain adaptability and plasticity underpinning learning[12].The current research showed not only high temporal variability but also frequent spatial dynamic reorganization in high-level networks, which provided novel and further evidence to demonstrate an integrated flexible state.

A previous fMRI study has indicated that primary networkstend to be less active but more flexible during resting state[3]. In line with the previous findings, our results also revealed hightemporal variations of FC-related attributesinprimary networks. Meanwhile, low svFCDin primary networksindicated steady spatial organization when connecting with other regions, which contributed to maintainingtheirunimodal architectures in processing primary information[50].In all, the current findings in primary and high-level networks in HC supported and replenished previous notions.

In the present study, low tvFCD, high svFCD, and low tsvFCDwere revealed in the SCN.The thalamus and basal ganglia are known as relay complexesin SCN, which play crucial roles in the communication of information between multiple areas of the cerebral cortex[51, 52]. A large number of previous fMRI studiesrevealed that while the whole thalamus works together, different spatial regions within the thalamus have their specific functional characteristics, suggesting that the thalamus is a structure with flexible spatial organization[51, 53]. The basal ganglia is naturally composed of multiple nuclei, with flexible spatial integration and separation functions[54].The low variation of functional interaction in SCN was demonstrated by a prior study[3]. In the present study,the SCN demonstrated low tvFCD, high svFCD, and low tsvFCD, implying that the SCN tends to have stable functional interactions with the outside regions as a whole, but the organization of SCN has a flexible division of labor pattern adjusted dynamically over time. Our results revealed flexible internal spatial reorganization and stable external temporal interaction in SCN.

Limbic is an active network to interact with distinct functional networks, participating in various cognition performance, especially involving emotion and affection[55]. However, the Limbic is sparsely and weakly connected with other regions during resting state[3, 56], which might be a potential reason for the low tvFCD of Limbic.In line with the temporal stability,the low svFCDof Limbic reflected stereotyped spatial organization within networks,endowing a high stable state when connecting with outside.

The integrated indicator tsvFCD mainly reflects the synergic relationship between temporal and spatial variation. For high-level networks, the high tsvFCD indicated a codirectional pattern of spatial and temporal variation that coordinates each other. The low tsvFCD of primary networks and subcortical network reflected complementary effects between temporal and spatial variation. In a word,the tsvFCD measurement provided a novel view to understand the dynamics of different brain

networks.

4.2 Abnormal variation of FCD in patients with IGE

Abnormal simultaneous firing of a large number of neurons causes seizures and synchronized neural oscillation inwidespread brain regions facilitates generalized propagation[57].From a macroscopic perspective of behavioral expression, the brain state of patients seems to be saltatorial, while the underlying functional pattern of the brain networks tends to be gradually changed[58].More important, the pathologically dynamic changes related to seizures might be supported by underlying interictal intrinsic disruption of the brain state. The present study stands by the view that investigating the dynamic features would serve well for understanding the pathologicaldynamics of brain state in epilepsy.

4.2.1 Disruptedvariability of FCDinthalamusandDMN in IGE

It is acknowledged that the suspension of DMNand activation of thalamusgreatly contribute to the generation and propagation of GSWD[59].Theprecuneus and prefrontal nodes of DMN are proposed to be crucial for triggering GSWDevents[60]. And the thalamus is a notable relay site to amplify and synchronize abnormal neural activity and projects it to wide cerebral cortex[61, 62].Prior simultaneous EEG-fMRI studies also suggested that the interaction between DMN and thalamus was dynamically changed in preictal, ictal, and postictal periods[63, 64].Accumulated evidence has suggested that the abnormality of thalamus and DMN is tightly linked with the intrinsic propensity of epilepsy[47, 65].

It has been suggested that the GSWD induced a brain state characterized byincreased large-scale synchronization of brain activity during ictal than the period before and after seizures[66].Strong connectivity and low variability in the core epileptic networks were observed as seizures initiate and progress[67], which revealed thecore characteristics of an epileptic brain state.Aprevious study revealed increased temporal variations of FC within DMN and inferred it to be associated with epileptic activities[30]. From the respective of functional interaction with the whole brain,decreased tvFCD found in the current study supported the disease-oriented stable brain state in DMN and thalamus, which was consistent with their persistent hyper-synchronization during seizures. Besides, decreased svFCD in thalamussuggested firm spatial organization when connecting with outer regions, which might be an assimilation effect of long-term seizures.The increased svFCD in DMN might be interpreted as a spatial compensatory effect for temporal steady. Affected by recurrent hypersynchronous epileptic activities, the thalamus, and DMN trend to demonstrate a more stable disease-related pattern of functional interaction with other regions. This strengthened connectivity and temporospatial stable brain state predominantly contributed to the epileptic actions[67].

Therelevantsubnetwork analysis revealedsignificantly abnormal network propertiesintwo core nodes of DMN. Increased BC, DC,and NE of precuneus and cingulum further highlighted the overly centralized role of DMN in patients with IGE.The decreased NLE of cingulum might be related tothe decreased functional integration within DMN in IGE[68].In a word, the present findings provided evidence from temporal and spatial aspects to reveal the pathologically-related state in DMN and thalamus.

4.2.2Excessive variability of FCD in SMN andhigh-levelnetworks in IGE

It has been revealed that strong and weak functionalconnectivityhas been suggested to play different roles in supporting brain function[69].Excessive or insufficientvariabilityof brain activitycould occurinthe different phenomenon and might be the potential cause of cognitive impairment and specific pathologicalstates[70].The abnormality of SMN has been revealed by many studiesandisassociated with motor abnormalities in variousdisorders[71-73].Simultaneous EEG-fMRI studieshave shown that hyper-synchronization of SMN often occurred in the later ictal and postictal periods[74], suggesting its passive involvementinthe GSWD.In the current study, abnormally increased tvFCD in SMN suggested a hyper-variabilitystate when interacting with other regions, which might be related to the susceptibility of SMN to be over-excited and inspired by abnormal neural oscillation[74]. We also found increased svFCD in patients, indicating a spatial redistribution of the internal structure of the SMN when it interacts with outside regions. The present study revealed both temporal and spatial hyper-variability state of SMN in patients with IGE.

Actually,impaired cognitive function in patients with epilepsy is not a rare phenomenon and various cognitive phenotypes have been widely reported in prior studies, including attention, memory, and executive functions[75, 76]. Besides, abnormal spontaneous activity and functional interaction of cognitive networks in epilepsy have been

widely demonstrated[28, 77-79].Current results suggested temporalhyper-variability of FCD in high-level networks, which was in line with findings reported in a priorfMRI study[30].In patients with IGE, Jia et al. suggested an abnormal functional state of brain depicted by increased variabilities of FC within and between high-levelnetworks and inferred it to be associated with the potential cognitive impairment.Increased spatial reconfiguration when interacting with the whole brain in high-level networks suggested a coordinated spatial synergic effect for supporting the abnormally temporal variation in patients with IGE.The current study revealed overall temporospatial hyper-variability of high-level networks and shed new insights into the pathologic dynamics of functionality associated with thecognitive state in epilepsy.

4.2.3Complexalterationof variation ofFCDinVNand Limbic

Although some of the researches linked dysfunction of VN with photosensitivity of patients ordisrupted visual perception, the identified clinical evidence was absent[80, 81].In the present study, the patients showed different variations of FCD at global, local, and longRange levels, which further blurred the interpretation in patients with IGE. Cause the uncertainty of photosensitivity in all of the patients in the current study, we could not make more solid references.

In the presentstudy, the patients with IGE demonstrated increased temporal and temporospatial variation and decreased spatial variation, suggesting hyper-flexibility of functional interaction and over-rigescent spatial organization in the Limbic. Although the Limbic is relatively sparse connecting with others, the Limbic is highly correlated with emotion and has been widely studied in mental disorders[82]. Dysfunctions inthe limbic system are generally viewed to contribute the cognitive impairment in patientswith epilepsy[83].Complex alterations of temporal and spatial variation of FCD indicatedmultiphase disruption the functionality ofLimbic, which might share contribution to the potential memory, emotion, and behavior changes in patients with epilepsy[84]. Because of the lack of efficient cognitive and emotional scales of patients, we just made aconservative inference for our results according to previously reported studies. Avoidingover-stating, we reserved further interpretation for the alterations of variation in Limbic in patients with IGE.

4.3Limitation

There are several limitations in the present study. First, not well-matched age between IGE and HC groups might influence the present findings. Even though the ages have been regressed out as a nuisance covariate in the statistical procedure, we still could not completely eliminate its potential effects. The AED is a considerable factor when investigating the brain function. The AED has been demonstrated to be partially responsible for the cognitive impairment in patients with IGE[85, 86], thus the dysfunction of cognitive networks might be related with AED[87].Although accumulated evidence from previous studies indicated the cognitive dysfunction in IGE, the lack of cognition assessment diminished our discussion of cognitive impairment in the present study to some extent. The effects of AED on the dynamics of the brain would be taken into consideration in the future study.The electroencephalogram is an important approach to investigate the intrinsic neural activity behind the changes in metabolism, which can provide supplementary and distinctive information to the BOLD study. The further deep study should combine the two approaches in the study of epilepsy.

5. Conclusion

In summary, the present study investigated the dynamic profiles of functional connectivity of patients with IGE from temporal and spatial aspects. Congregated evidence suggested the temporospatial over-synchronization in SCN, and temporal over-synchronization and spatial over-flexibility in DMN, which were inferred to contribute to the intrinsic propensity of epilepsy. Besides, excessive temporospatialflexibility of the primary and high-level networks was predominantly observed in patients with IGE, which might be associated with driven phenotypes in patients. Our work provided novel evidence to shed light on the dynamics underlying neuropathological profiles of epilepsy.

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CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

References

1. Hutchison R. M., Womelsdorf T., Allen E. A., Bandettini P. A., Calhoun V. D., Corbetta M., Della Penna S., Duyn J. H., Glover G. H., Gonzalez-Castillo J., Handwerker D. A., Keilholz S., Kiviniemi V., Leopold D. A., de Pasquale F., Sporns O., Walter M. and Chang C. 2013, "Dynamic functional connectivity: promise, issues, and interpretations," *Neuroimage* **80**, 360-78.

2. Schmidt C., Piper D., Pester B., Mierau A. and Witte H. 2018, "Tracking the Reorganization of Module Structure in Time-Varying Weighted Brain Functional Connectivity Networks," *International Journal of Neural Systems* **28**.

3. Yan C. G., Yang Z., Colcombe S. J., Zuo X. N. and Milham M. P. 2017, "Concordance among indices of intrinsic brain function: Insights from inter-individual variation and temporal dynamics," *Science Bulletin* **62**, 1572-1584.

4. delEtoile J. and Adeli H. 2017, "Graph Theory and Brain Connectivity in Alzheimer's Disease," *Neuroscientist* **23**, 616-626.

5. Yuvaraj R., Murugappan M., Acharya U. R., Adeli H., Ibrahim N. M. and Mesquita E. 2016, "Brain functional connectivity patterns for emotional state classification in Parkinson's disease patients without dementia," *Behavioural Brain Research* **298**, 248-260.

6. Jia X. Y., Ma S., Jiang S. S., Sun O. B., Dong D. B., Chang X. B., Zhu Q., Yao D. Z., Yu L. and Luo C. 2018, "Disrupted Coupling Between the Spontaneous Fluctuation and Functional Connectivity in Idiopathic Generalized Epilepsy," *Frontiers in Neurology* **9**.

7. Dong D., Luo C., Guell X., Wang Y., He H., Duan M., Eickhoff S. B. and Yao D. 2020, "Compression of Cerebellar Functional Gradients in Schizophrenia," *Schizophr Bull*.

8. Allen E. A., Damaraju E., Plis S. M., Erhardt E. B., Eichele T. and Calhoun V. D. 2014, "Tracking whole-brain connectivity dynamics in the resting state," *Cereb Cortex* **24**, 663-76.

9. Handwerker D. A., Roopchansingh V., Gonzalez-Castillo J. and Bandettini P. A. 2012, "Periodic changes in fMRI connectivity," *Neuroimage* **63**, 1712-1719.

10. He H., Luo C., Luo Y. L., Duan M. J., Yi Q. Z., Biswal B. B. and Yao D. Z. 2019, "Reduction in gray matter of cerebellum in schizophrenia and its influence on static and dynamic connectivity," *Human Brain Mapping* **40**, 517-528.

11. Luo Y. L., He H., Duan M. J., Huang H., Hu Z. F., Wang H. M., Yao G., Yao D. Z., Li J. F. and Luo C. 2020, "Dynamic Functional Connectivity Strength Within Different Frequency-Band in Schizophrenia," *Frontiers in Psychiatry* **10**.

12. Zhang J., Cheng W., Liu Z., Zhang K., Lei X., Yao Y., Becker B., Liu Y., Kendrick K. M., Lu G. and Feng J. 2016, "Neural, electrophysiological and anatomical basis of brain-network variability and its characteristic changes in mental disorders," *Brain* **139**, 2307-21.

13. Jia X., Xie Y., Dong D., Pei H., Jiang S., Ma S., Huang Y., Zhang X., Wang Y., Zhu Q., Zhang Y., Yao D., Yu L. and Luo C. 2020, "Reconfiguration of dynamic large-scale brain network functional connectivity in generalized tonic-clonic seizures," *Hum Brain Mapp* **41**, 67-79.

14. Laufs H. 2012, "Functional imaging of seizures and epilepsy: evolution from zones to networks," *Curr Opin Neurol* **25**, 194-200.

15. Moeller F., Maneshi M., Pittau F., Gholipour T., Bellec P., Dubeau F., Grova C. and Gotman J. 2011, "Functional connectivity in patients with idiopathic generalized epilepsy," *Epilepsia* **52**, 515-22.

16. Acharya U. R., Oh S. L., Hagiwara Y., Tan J. H. and Adeli H. 2018, "Deep convolutional neural network for the automated detection and diagnosis of seizure using EEG signals," *Computers in Biology and Medicine* **100**,

270-278.

17. Preti M. G., Leonardi N., Karahanoglu F. I., Grouiller F., Genetti M., Seeck M., Vulliemoz S. and Van de Ville D. 2014, "Epileptic Network Activity Revealed by Dynamic Functional Connectivity in Simultaneous Eeg-Fmri," *2014 IEEE 11th International Symposium on Biomedical Imaging (ISBI)*, 9-12.

18. Sharma P., Khan Y. U., Farooq O., Tripathi M. and Adeli H. 2014, "A Wavelet-Statistical Features Approach for Nonconvulsive Seizure Detection," *Clinical Eeg and Neuroscience* **45**, 274-284.

19. Shanir P. P. M., Khan K. A., Khan Y. U., Farooq O. and Adeli H. 2018, "Automatic Seizure Detection Based on Morphological Features Using One-Dimensional Local Binary Pattern on Long-Term EEG," *Clinical Eeg and Neuroscience* **49**, 351-362.

20. Tangwiriyasakul C., Perani S., Centeno M., Yaakub S. N., Abela E., Carmichael D. W. and Richardson M. P. 2018, "Dynamic brain network states in human generalized spike-wave discharges," *Brain* **141**, 2981-2994.

21. Mammone N., Duun-Henriksen J., Kjaer T. W. and Morabito F. C. 2015, "Differentiating Interictal and Ictal States in Childhood Absence Epilepsy through Permutation Renyi Entropy," *Entropy* **17**, 4627-4643.

22. Wagner F. B., Truccolo W., Wang J. and Nurmikko A. V. 2015, "Spatiotemporal dynamics of optogenetically induced and spontaneous seizure transitions in primary generalized epilepsy," *Journal of Neurophysiology* **113**, 2321-2341.

23. Mammone N., Labate D., Lay-Ekuakille A. and Morabito F. C. 2012, "Analysis of Absence Seizure Generation Using Eeg Spatial-Temporal Regularity Measures," *International Journal of Neural Systems* **22**.

24. Gotman J., Grova C., Bagshaw A., Kobayashi E., Aghakhani Y. and Dubeau F. 2005, "Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain," *Proceedings of the National Academy of Sciences of the United States of America* **102**, 15236-15240.

25. Kramer M. A., Eden U. T., Kolaczyk E. D., Zepeda R., Eskandar E. N. and Cash S. S. 2010, "Coalescence and Fragmentation of Cortical Networks during Focal Seizures," *Journal of Neuroscience* **30**, 10076-10085.

26. Khambhati A. N., Davis K. A., Oommen B. S., Chen S. H., Lucas T. H., Litt B. and Bassett D. S. 2015, "Dynamic Network Drivers of Seizure Generation, Propagation and Termination in Human Neocortical Epilepsy," *Plos Computational Biology* **11**.

27. Yang C. Z., Luan G. M., Wang Q., Liu Z., Zhai F. and Wang Q. Y. 2018, "Localization of Epileptogenic Zone With the Correction of Pathological Networks," *Frontiers in Neurology* **9**.

28. Liu H. L., Li W. L., Zhao M. J., Wu J., Wu J., Yang J. K. and Jiao B. H. 2019, "Altered temporal dynamics of brain activity in patients with generalized tonic-clonic seizures," *Plos One* **14**.

29. Liu F., Wang Y. F., Li M. L., Wang W. Q., Li R., Zhang Z. Q., Lu G. M. and Chen H. F. 2017, "Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure," *Human Brain Mapping* **38**, 957-973.

30. Jia X. Y., Xie Y., Dong D. B., Pei H. N., Jiang S. S., Ma S., Huang Y., Zhang X. X., Wang Y. H., Zhu Q., Zhang Y. N., Yao D. Z., Yu L. and Luo C. 2019, "Reconfiguration of dynamic large-scale brain network functional connectivity in generalized tonic-clonic seizures," *Human Brain Mapping*.

31. Dong L., Luo C., Cao W. F., Zhang R., Gong J. N., Gong D. K. and Yao D. Z. 2015, "Spatiotemporal consistency of local neural activities: A new imaging measure for functional MRI data," *Journal of Magnetic Resonance Imaging* **42**, 729-736.

32. Chen X., Jiang Y. C., Chen L., He H., Dong L., Hou C. Y., Duan M. J., Yang M., Yao D. Z. and Luo C. 2017, "Altered Hippocampo-Cerebello-Cortical Circuit in Schizophrenia by a Spatiotemporal Consistency and Causal Connectivity Analysis," *Frontiers in Neuroscience* **11**.

33. Ma S., Jiang S. S., Peng R., Zhu Q., Sun H. B., Li J. F., Jia X. Y., Goldberg I., Yu L. and Luo C. 2017,

"Altered Local Spatiotemporal Consistency of Resting-State BOLD Signals in Patients with Generalized Tonic-Clonic Seizures," *Frontiers in Computational Neuroscience* **11**.

34. Adeli H., Ghosh-Dastidar S. and Dadmehr N. 2008, "A spatio-temporal wavelet-chaos methodology for EEG-based diagnosis of Alzheimer's disease," *Neuroscience Letters* **444**, 190-194.

35. Ahmadlou M., Adeli H. and Adeli A. 2013, "Spatiotemporal Analysis of Relative Convergence of EEGs Reveals Differences Between Brain Dynamics of Depressive Women and Men," *Clinical Eeg and Neuroscience* **44**, 175-181.

36. Baier G., Goodfellow M., Taylor P. N., Wang Y. J. and Garry D. J. 2012, "The importance of modeling epileptic seizure dynamics as spatio-temporal patterns," *Frontiers in Physiology* **3**.

37. Engel J., Jr. and International League Against E. 2001, "A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology," *Epilepsia* **42**, 796-803.

38. Dong L., Luo C., Liu X., Jiang S., Li F., Feng H., Li J., Gong D. and Yao D. 2018, "Neuroscience Information Toolbox: An Open Source Toolbox for EEG-fMRI Multimodal Fusion Analysis," *Front Neuroinform* **12**, 56.

39. Power J. D., Barnes K. A., Snyder A. Z., Schlaggar B. L. and Petersen S. E. 2012, "Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion (vol 59, pg 2142, 2012)," *Neuroimage* **63**, 999-999.

40. Tomasi D. and Volkow N. D. 2010, "Functional connectivity density mapping," *Proceedings of the National Academy of Sciences of the United States of America* **107**, 9885-9890.

41. Ding J. R., An D. M., Liao W., Wu G. R., Xu Q., Zhou D. and Chen H. F. 2014, "Abnormal functional connectivity density in psychogenic non-epileptic seizures," *Epilepsy Research* **108**, 1184-1194.

42. Luo C., Tu S. P., Peng Y. H., Gao S., Li J. F., Dong L., Li G. J., Lai Y. X., Li H. and Yao D. Z. 2014, "Long-Term Effects of Musical Training and Functional Plasticity in Salience System," *Neural Plasticity* **2014**.

43. Leonardi N. and Van De Ville D. 2015, "On spurious and real fluctuations of dynamic functional connectivity during rest," *Neuroimage* **104**, 430-6.

44. Fan L. Z., Li H., Zhuo J. J., Zhang Y., Wang J. J., Chen L. F., Yang Z. Y., Chu C. Y., Xie S. M., Laird A. R., Fox P. T., Eickhoff S. B., Yu C. S. and Jiang T. Z. 2016, "The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture," *Cerebral Cortex* **26**, 3508-3526.

45. Yeo B. T. T., Krienen F. M., Sepulcre J., Sabuncu M. R., Lashkari D., Hollinshead M., Roffman J. L., Smoller J. W., Zoller L., Polimeni J. R., Fischl B., Liu H. S. and Buckner R. L. 2011, "The organization of the human cerebral cortex estimated by intrinsic functional connectivity," *Journal of Neurophysiology* **106**, 1125-1165.

46. Margulies D. S., Ghosh S. S., Goulas A., Falkiewicz M., Huntenburg J. M., Langs G., Bezgin G., Eickhoff S. B., Castellanos F. X., Petrides M., Jefferies E. and Smallwood J. 2016, "Situating the default-mode network along a principal gradient of macroscale cortical organization," *Proceedings of the National Academy of Sciences of the United States of America* **113**, 12574-12579.

47. Liao W., Zhang Z. Q., Mantini D., Xu Q., Ji G. J., Zhang H., Wang J., Wang Z. G., Chen G. H., Tian L., Jiao Q., Zang Y. F. and Lu G. M. 2014, "Dynamical intrinsic functional architecture of the brain during absence seizures," *Brain Structure & Function* **219**, 2001-2015.

48. Amor F., Baillet S., Navarro V., Adam C., Martinerie J. and Van Quyen M. L. 2009, "Cortical local and long-range synchronization interplay in human absence seizure initiation," *Neuroimage* **45**, 950-962.

49. Buckner R. L., Sepulcre J., Talukdar T., Krienen F. M., Liu H., Hedden T., Andrews-Hanna J. R., Sperling R. A. and Johnson K. A. 2009, "Cortical hubs revealed by intrinsic functional connectivity: mapping,

assessment of stability, and relation to Alzheimer's disease," *J Neurosci* **29**, 1860-73.

50. Sepulcre J., Sabuncu M. R., Yeo B. T. T., Liu H. S. and Johnson K. A. 2012, "Stepwise Connectivity of the Modal Cortex Reveals the Multimodal Organization of the Human Brain," *Journal of Neuroscience* **32**, 10649-10661.

51. Kim D. J., Park B. and Park H. J. 2013, "Functional connectivity-based identification of subdivisions of the basal ganglia and thalamus using multilevel independent component analysis of resting state fMRI," *Human Brain Mapping* **34**, 1371-1385.

52. Yuan R., Di X., Taylor P. A., Gohel S., Tsai Y. H. and Biswal B. B. 2016, "Functional topography of the thalamocortical system in human," *Brain Structure & Function* **221**, 1971-1984.

53. O'Muircheartaigh J., Keller S. S., Barker G. J. and Richardson M. P. 2015, "White Matter Connectivity of the Thalamus Delineates the Functional Architecture of Competing Thalamocortical Systems," *Cerebral Cortex* **25**, 4477-4489.

54. Wichmann T. and DeLong M. R. 1996, "Functional and pathophysiological models of the basal ganglia," *Current Opinion in Neurobiology* **6**, 751-758.

55. Mansour A. R., Farmer M. A., Baliki M. N. and Apkarian A. V. 2014, "Chronic pain: The role of learning and brain plasticity," *Restorative Neurology and Neuroscience* **32**, 129-139.

56. Baliki M. N., Chang P. C., Baria A. T., Centeno M. V. and Apkarian A. V. 2015, "Resting-state functional reorganization of the rat limbic system following neuropathic injury (vol 4, pg 6186, 2014)," *Scientific Reports* **5**.

57. Kramer M. A. and Cash S. S. 2012, "Epilepsy as a Disorder of Cortical Network Organization," *Neuroscientist* **18**, 360-372.

58. Burns S. P., Santaniello S., Yaffe R. B., Jouny C. C., Crone N. E., Bergey G. K., Anderson W. S. and Sarma S. V. 2014, "Network dynamics of the brain and influence of the epileptic seizure onset zone," *Proceedings of the National Academy of Sciences of the United States of America* **111**, E5321-E5330.

59. Gotman J., Grova C., Bagshaw A., Kobayashi E., Aghakhani Y. and Dubeau F. 2005, "Generalized epileptic discharges show thalamocortical activation and suspension of the default state of the brain," *Proc Natl Acad Sci U S A* **102**, 15236-40.

60. Tenney J. R., Fujiwara H., Horn P. S., Jacobson S. E., Glauser T. A. and Rose D. F. 2013, "Focal corticothalamic sources during generalized absence seizures: a MEG study," *Epilepsy Res* **106**, 113-22.

61. Blumenfeld H. 2012, "Impaired consciousness in epilepsy," *Lancet Neurol* **11**, 814-26.

62. Jiang S., Luo C., Gong J., Peng R., Ma S., Tan S., Ye G., Dong L. and Yao D. 2018, "Aberrant Thalamocortical Connectivity in Juvenile Myoclonic Epilepsy," *International Journal of Neural Systems* **28**.

63. Danielson N. B., Guo J. N. and Blumenfeld H. 2011, "The default mode network and altered consciousness in epilepsy," *Behav Neurol* **24**, 55-65.

64. Moeller F., Siebner H. R., Wolff S., Muhle H., Boor R., Granert O., Jansen O., Stephani U. and Siniatchkin M. 2008, "Changes in activity of striato-thalamo-cortical network precede generalized spike wave discharges," *Neuroimage* **39**, 1839-49.

65. Lopes R., Moeller F., Besson P., Ogez F., Szurhaj W., Leclerc X., Siniatchkin M., Chipaux M., Derambure P. and Tyvaert L. 2014, "Study on the relationships between intrinsic functional connectivity of the default mode network and transient epileptic activity," *Frontiers in Neurology* **5**.

66. Kramer M. A., Eden U. T., Kolaczyk E. D., Zepeda R., Eskandar E. N. and Cash S. S. 2010, "Coalescence and fragmentation of cortical networks during focal seizures," *J Neurosci* **30**, 10076-85.

67. Khambhati A. N., Davis K. A., Oommen B. S., Chen S. H., Lucas T. H., Litt B. and Bassett D. S. 2015, "Dynamic Network Drivers of Seizure Generation, Propagation and Termination in Human Neocortical Epilepsy," *PLoS Comput Biol* **11**, e1004608.

68. Luo C., Li Q. F., Lai Y. X., Xia Y., Qin Y., Liao W., Li S. S., Zhou D., Yao D. Z. and Gong Q. Y. 2011,

"Altered Functional Connectivity in Default Mode Network in Absence Epilepsy: A Resting-State fMRI Study," *Human Brain Mapping* **32**, 438-449.

69. Santarnecchi E., Galli G., Polizzotto N. R., Rossi A. and Rossi S. 2014, "Efficiency of weak brain connections support general cognitive functioning," *Hum Brain Mapp* **35**, 4566-82.

70. Christoff K., Irving Z. C., Fox K. C., Spreng R. N. and Andrews-Hanna J. R. 2016, "Mind-wandering as spontaneous thought: a dynamic framework," *Nat Rev Neurosci* **17**, 718-731.

71. Vulliemoz S., Vollmar C., Koepp M. J., Yogarajah M., O'Muircheartaigh J., Carmichael D. W., Stretton J., Richardson M. P., Symms M. R. and Duncan J. S. 2011, "Connectivity of the supplementary motor area in juvenile myoclonic epilepsy and frontal lobe epilepsy," *Epilepsia* **52**, 507-14.

72. Darbin O., Hatanaka N., Takara S., Kaneko N., Chiken S., Naritoku D., Martino A. and Nambu A. 2020, "Parkinsonism Differently Affects the Single Neuronal Activity in the Primary and Supplementary Motor Areas in Monkeys: An Investigation in Linear and Nonlinear Domains," *International Journal of Neural Systems* **30**.

73. Darbin O., Hatanaka N., Takara S., Kaneko M., Chiken S., Naritoku D., Martino A. and Nambu A. 2020, "Local field potential dynamics in the primate cortex in relation to parkinsonism reveled by machine learning: A comparison between the primary motor cortex and the supplementary area," *Neurosci Res*.

74. Tangwiriyasakul C., Perani S., Centeno M., Yaakub S. N., Abela E., Carmichael D. W. and Richardson M. P. 2018, "Dynamic brain network states in human generalized spike-wave discharges," *Brain* **141**, 2981-2994.

75. Kleen J. K., Scott R. C., Lenck-Santini P. P. and Holmes G. L. 2012, "Cognitive and Behavioral Co-Morbidities of Epilepsy," in Jasper's Basic Mechanisms of the Epilepsies, ed.^eds. Editior Bethesda (MD)).

76. Lenck-Santini P. P. and Scott R. C. 2015, "Mechanisms Responsible for Cognitive Impairment in Epilepsy," *Cold Spring Harb Perspect Med* 5.

77. Moeller F., Muhle H., Wiegand G., Wolff S., Stephani U. and Siniatchkin M. 2010, "EEG-fMRI study of generalized spike and wave discharges without transitory cognitive impairment," *Epilepsy Behav* **18**, 313-6.

78. Liao W., Zhang Z., Mantini D., Xu Q., Ji G. J., Zhang H., Wang J., Wang Z., Chen G., Tian L., Jiao Q., Zang Y. F. and Lu G. 2014, "Dynamical intrinsic functional architecture of the brain during absence seizures," *Brain Struct Funct* **219**, 2001-15.

79. Vlooswijk M. C., Jansen J. F., de Krom M. C., Majoie H. M., Hofman P. A., Backes W. H. and Aldenkamp A. P. 2010, "Functional MRI in chronic epilepsy: associations with cognitive impairment," *Lancet Neurol* **9**, 1018-27.

80. Anderson J. and Hamandi K. 2011, "Understanding juvenile myoclonic epilepsy: Contributions from neuroimaging," *Epilepsy Research* **94**, 127-137.

81. Bartolini E., Pesaresi I., Fabbri S., Cecchi P., Giorgi F. S., Sartucci F., Bonuccelli U. and Cosottini M. 2014, "Abnormal response to photic stimulation in Juvenile Myoclonic Epilepsy: An EEG-fMRI study," *Epilepsia* **55**, 1038-1047.

82. Chen S. H., Wu X. T., Lui S., Wu Q. Z., Yao Z. P., Li Q. F., Liang D. M., An D. M., Zhang X. Y., Fang J. J., Huang X. Q., Zhou D. and Gong Q. Y. 2012, "Resting-state fMRI study of treatment-naive temporal lobe epilepsy patients with depressive symptoms," *Neuroimage* **60**, 299-304.

83. Cornaggia C. M., Beghi M., Provenzi M. and Beghi E. 2006, "Correlation between cognition and behavior in epilepsy," *Epilepsia* **47**, 34-39.

84. Swinkels W. A., Kuyk J., van Dyck R. and Spinhoven P. 2005, "Psychiatric comorbidity in epilepsy," *Epilepsy Behav* **7**, 37-50.

85. Park S. P. and Kwon S. H. 2008, "Cognitive Effects of Antiepileptic Drugs," *Journal of Clinical Neurology* **4**, 99-106.

86. Loring D. W. and Meador K. J. 2004,

"Cognitive side effects of antiepileptic drugs in children," *Neurology* **62**, 872-877.

87. Barr W. B. 2019, "Understanding the Cognitive Side Effects of Antiepileptic Drugs: Can Functional Imaging Be Helpful?," *Epilepsy Currents* **19**, 22-23.