Altered intrinsic functional organization of the brain in idiopathic generalized epilepsy

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***Abstract*: A robust and reproducible anticorrelation ship between the two synchronized low-frequency fluctuation networks of blood oxygen level dependent (i.e. the task positive network and the task negative network), was showed in subjects at the resting state and when performing cognitively demanding tasks. Using the resting-state fMRI, this study explored the antagonism of the two networks between the control group and the patients with idiopathic generalized epilepsy (IGE). Compared with the control group, the patient group revealed a significant decrease in functional connectivity in both networks and an attenuated pattern of antagonism between networks. These findings showed deficits related to epileptic neuropathology or cognitive alteration in the networks. Furthermore, they revealed unevenness and imbalance in the functional interaction between the networks.**

Keywords: resting-state fMRI, functional connectivity, idiopathic generalized epilepsy, antagonism

I. ITROCUDTION

Idiopathic generalized epilepsy (IGE) is characterized by tonic-clonic seizures, myoclonic jerks, absence seizures and paroxysmal 2- to 3-Hz spike-and-wave discharges, which occurs simultaneously over wide cortical regions in the Electroencephalography (EEG). The long-term cognitive and neuropsychological alterations have been observed in IGE, including memory deficits, learning disabilities, behavioral performance problems. and attentional lapses [1, 2]. Neuronal disorganization or disconnection might play an important role in these defictes. In our previous resting-state fMRI studies, we have found the abnormal functional connectivity in default mode network[3] and basal ganglia network in IGE [4]. The abnormal functional connectivity might be associated with the epileptic event and the cognitive and neuropsychological alterations in IGE.

Spontaneous low-frequency BOLD signal has revealed spatiotemporal synchrony between distinct anatomical brain regions in the absence of external input or task. Studies have confirmed that these fluctuations are highly coherent within anatomically or functionally linked areas of the brain. The brain is organized into multiple distinct, intrinsic networks, two of which have been extensively studied. The first was the task negative network (TNN), also named default mode network (DMN) [5], which included the posterior cingulate cortex(PCC), ventral or Dorsal medial prefrontal cortex (vmPFC or dmPFC), bilateral superior frontal cortex(SFG), parahippocampal gyrus(PHG), inferior temporal gyrus(ITG), lateral parietal cortex(LP). Negative activations were found in these regions during attention and goal-directed tasks, however, these regions were preferentially activated when individuals were not focused on the external environment. The second network was the task positive network (TPN) that was associated with externally directed cognition including covert and overt shifts of spatial attention, eye movements, and hand-eye coordination [6]. This brain system included regions in the bilateral frontal eye fields(FEF), dorsal lateral prefrontal cortex(dlPFC), inferior parietal lobule(IPL), intraparietal sulcus(IPS), ventral intraparietal sulcus(vIPS), motion-sensitive middle temporal area (MT), inferior precentral sulcus(IpreCS), supplementary motor area(SMA) and insula. In resting-state fMRI investigations, significant negative correlations were found between the two functional networks, which were referred to as anticorrelation [6]. Greicius et al. (2003) first found the negative correlations of resting state spontaneous fluctuation[7]. Then, Fox et al. (2005) and Fransson (2005) expanded the notion by showing significant negative correlations of spontaneous fluctuations between the TPN and the TNN[8, 9]. The correlations within and between networks might play an important role in coordination of competition between ongoing information processing, therefore, reflecting the dynamic, intrinsic brain functional organization [8]. Recently, altered intrinsic functional organization, featuring the presence of anticorrelated networks in resting-state, has been revealed in autism [10], schizophrenia and attention deficit hyperactivity disorder [11]. Based on these studies, the altered patterns of antagonism might be associated with the abnormal attention function and performance variability.

Since the patients with IGE had the deficits in cognition and neuropsychological test, the goal of the current study was to test the differences within and between the two networks, and to evaluate the patterns of antagonism in patients with IGE. First, we reconstructed the intrinsic functional brain organization in controls and patients respectively, bases on the functional connection analysis among the ROIs [8]. Then, we compared the correlation coefficient of each pairs of ROIs between the patients group and control group.

II. SUBJECTS AND METHODS

A. Participants

Eighteen patients with IGE were recruited for an EEG-fMRI study from the West China Hospital. All patients underwent clinical brain structural MRI and 24-hour-Video EEG. Diagnosis was established according to the diagnostic scheme published by the International League Against Epilepsy in 2001[12]. The clinical epilepsy syndromes were established with generalized tonic-clonic seizures only in 9 patients, childhood absence epilepsy in 8 patients, and juvenile myoclonic epilepsy in one patient. Twenty-three right-handed health participants matched for age and gender were selected as the control. Informed consent for the study was obtained from each participant.

B. Data acquisition

BOLD-sensitive MRI data was acquired using gradient-echo echo-planar imaging (EPI) sequences in 3T MRI scanner (EXCITE, GE, Milwaukee, USA). Thickness = 5mm(no gap), TR=2000 ms， TE=30 ms， FOV=24cm×24cm， flip angle=90°, matrix=64×64. Two hundred volumes (30 slices per volume) were acquired. During data acquisition, participants were asked to relax with eyes closed, and stay awake. Anatomical T1-weighted images were acquired using a three-dimensional (3D) spoiled gradient recalled (SPGR) sequence, resulting/generating 156 axial slices (thickness: 1mm(no gap), TR=8.5 ms, TE=3.4 ms, FOV=24cm×24cm, flip angle=12°, matrix=512×512).

The fMRI, EEG data was recorded continuously using the amplifier (Mizar 40, EBNeuro, Florence, Italy) with 32 channels applying for MR. The MR artifact was filtered out online [13], and the software was BE-MRI Toolbox (Galileo New Technology, Florence, Italy). If IED or seizure was found in a particular run, this run of fMRI data was excluded from the following analysis. Simultaneous EEG was not recorded in health participants.

C. Data preprocess analysis

The fMRI data were processed by SPM2 software package[Statistical parametric mapping http://www.fil.ion.ucl.ac.uk/spm].The slice time correction, 3D motion detecting and correction, spatially normalization to the MNI template supplied by SPM and spatially smoothing using an isotropic Gaussian kernel (8mm full width at half maximum) were included. The head motion was less than 1mm and 1 degrees during EEG-fMRI acquisition, otherwise the data was excluded.

D. Regionwise Functional Connectivity

To evaluate the functional connectivity within TNN and TPN, the correlation between each pair of these regions was analyzed. According to the reference[8], 29 nodes were selected in total. Averaged time series were extracted by averaging the time series of each peak voxel and its nearest 26 neighbors. Three procedures were used to remove the possible spurious variances from the averaging time series of seed. (i)Temporal band-pass filtering (pass band 0.01~0.08Hz) was conducted using a phase-insensitive filter, which was performed to reduce the effects of low-frequency drift and high-frequency noise. (ii)The time series was further corrected for the effect of six head motion parameters obtained in the realigning step, and for the signal from a region in cerebrospinal fluid (CSF) and that from a region centered in the white matter through linear regression. (iii)The residuals of these regressions was processed by the linear detrend. The resulting time series were correlated between nodes for each subject, and then a $N \times N$ (N = 29 in the current study) correlation matrix for each subject was obtained. A Fisher's r-to-z transformation was applied to normalize the correlation coefficients (r). For each group, z-score matrix was averaged across all subjects in each group.

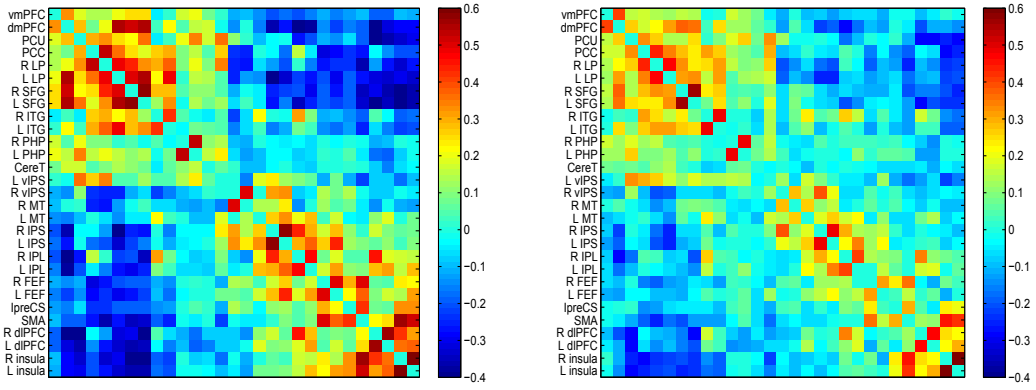

Figure I. the mean inter-region correlation matrix in controls (left) and in patients with IGE (right). The matrix is obtained by averaging the correlation coefficients across all the subjects.

To examine the difference between the patient group and control group, we performed two-sample two-tailed t-tests on all 406(C_{29}^2) possible connections represented in the 29×29 correlation matrices. Statistical significance level was set $p < 0.01$ (uncorrected).

Table I: Decreased functional connectivity within TNN in IGE patients

Region 1	Region 2	*p* value	T value	Mean(SD) CC in patients	Mean(SD) CC in controls
dmPFC	L SFG	0.0044	-2.98	0.359(0.237)	0.541(0.260)
dMPFC	L LP	0.0003	-3.87	0.313(0.244)	0.547(0.172)
R SFG	L LP	0.0009	-3.53	0.305(0.237)	0.503(0.178)
L SFG	L LP	0.0009	-3.52	0.321(0.24)	0.541(0.181)

CC: correlation coefficient

III. RESULTS

Twenty-nine putative ROIs were derived from the previous analyses described above[8]. 406(C_{29}^2)pairs of possible correlation were analyzed. For the control group, functional integration was found within TPN and TNN respectively. Furthermore, a significant negative correlation between the TPN and TNN emerged as well (Figure I), showing a pattern of results similar to Fox et al.'s (2005) and Fransson's (2005)[8, 9]. For the patient group, the tendency of the functional integration within each network and anticorrelation between networks was similar to the control. However, the value of correlation coefficient in patients decreased compared with that in controls (Figure I). To quantify the alteration of region-wise correlation in patients, two-tailed independent t-tests on 406 (C_{29}^2) possible connections were performed.

A. Altered positive correlations within network

Compared with the controls, a decrease in functional connectivity ($p<0.01$) was found inside the TNN (4 pairs) and TPN (14 pairs) respectively in the patients. An increased in FC was not found within the network (Table I and II). The result showed decreased correlations in fronto-parietal regions within TNN, which is consistent with the previous study [3]. In TPN, decreased correlations were related to the FEF and IPS (i.e., components of dorsal attention network) [14] and the insula (i.e., "core" of a system for task set implementation) [15].

B. Altered negative correlations between networks

There are 26 pairs of negative correlations that were significantly different in 208 (13×16) pairs of potential connections between the TNN and the TPN ($p<0.01$). Compared to the controls, 26 pairs of connections increased and no connection decrease was found in patients (Table III). Because the value of these connections is negative, the increased connection means that the value approached zero in patients. In other words, the patients had an attenuated pattern of antagonism between the task-positive network and DMN, compared with the normal subjects. In the control group, the anticorrelated relationship between two networks emerged, while in the patients, the reduced anticorrelation was shown.

Table II: Decreased functional connectivity in TPN in IGE patients

Region 1	Region 2	p value	T value	Mean(SD) CC in patients	Mean(SD) CC in controls
R dlMPFC	R IPS	0.0073	-2.80	0.004(0.200)	0.173(0.233)
L insula	R IPS	0.0095	-2.70	-0.094(0.185)	0.074(0.261)
L FEF	L IPS	0.0020	-3.26	0.212(0.270)	0.432(0.223)
IpreCS	L IPS	0.0048	-2.95	-0.047(0.204)	0.127(0.223)
R insula	R FEF	0.0091	-2.71	0.078(0.219)	0.239(0.212)
L insula	R FEF	0.0018	-3.30	0.025(0.171)	0.221(0.253)
R insula	L FEF	0.0002	-4.03	-0.105(0.169)	0.146(0.262)
L insula	L FEF	0.0000	-5.54	-0.004(0.147)	0.303(0.231)
IpreCS	L FEF	0.0015	-3.36	0.025(0.188)	0.222(0.231)
SMA	L FEF	0.0011	-3.45	0.154(0.242)	0.376(0.213)
R insula	L IPL	0.0067	-2.83	-0.024(0.210)	0.151(0.234)
L insula	L IPL	0.0012	-3.44	0.066(0.224)	0.281(0.228)
R MT	R vIPS	0.0010	-3.51	0.281(0.228)	0.502(0.241)
R insula	R dlMPFC	0.0045	-2.98	0.244(0.221)	0.426(0.209)

CC: correlation coefficient

Table III: Decreased anticorrelation functional between the TPN and TNN in IGE patients

Region in TPN	Region in TNN	p value	T value	Mean(SD) CC in patients	Mean(SD) CC in controls
R IPS	vmPFC	0.0066	2.83	-0.082(0.176)	-0.211(0.150)
R IPS	dmPFC	0.0081	2.76	-0.219(0.179)	-0.356(0.186)
R IPS	R SFG	0.0037	3.05	-0.071(0.174)	-0.252(0.255)
R IPS	L SFG	0.0015	3.35	-0.067(0.189)	-0.270(0.253)
R FEF	PCC	0.0012	3.43	-0.155(0.130)	-0.314(0.199)
R FEF	L SFG	0.0029	3.14	-0.044(0.153)	-0.193(0.186)
L FEF	PCC	0.0001	4.31	-0.036(0.209)	-0.277(0.194)
L FEF	L LP	0.0006	3.64	-0.096(0.200)	-0.296(0.200)
L FEF	R SFG	0.0066	2.83	-0.103(0.179)	-0.269(0.247)
L FEF	L SFG	0.0015	3.36	-0.040(0.147)	-0.213(0.219)
L FEF	L ITG	0.0078	2.77	-0.005(0.235)	-0.179(0.217)
R IPL	L LP	0.0099	2.68	-0.076(0.205)	-0.228(0.207)
L IPL	dmPFC	0.0001	4.43	-0.168(0.190)	-0.373(0.135)
L IPL	L LP	0.0003	3.84	-0.068(0.191)	-0.263(0.173)
L IPL	R SFG	0.0003	3.85	-0.096(0.178)	-0.303(0.205)
L IPL	L PHG	0.0002	3.97	0.106(0.146)	-0.058(0.151)
R vIPS	PCC	0.009	2.72	-0.096(0.219)	-0.244(0.158)
SMA	L SFG	0.0005	3.75	-0.124(0.229)	-0.336(0.170)
R dlMPFC	L LP	0.0024	3.19	-0.106(0.187)	-0.309(0.263)
R dlMPFC	L SFG	0.0058	2.88	-0.276(0.194)	-0.439(0.232)
L dlMPFC	dmPFC	0.0082	2.75	-0.118(0.223)	-0.313(0.290)
L dlMPFC	L LP	0.0041	3.01	-0.101(0.267)	-0.332(0.286)
L dlMPFC	R SFG	0.0029	3.13	-0.164(0.207)	-0.355(0.223)
R MT	PCC	0.0005	3.71	-0.072(0.175)	-0.258(0.189)
R insula	R SFG	0.0037	3.05	-0.208(0.239)	-0.389(0.184)
R insula	L SFG	0.0035	3.07	-0.238(0.225)	-0.401(0.155)

CC: correlation coefficient

IV. DISCUSSION

The present study assessed the intrinsic functional organization in patients with IGE during the interictal period without epileptic event. First, we reconstructed the intrinsic functional brain organization in the controls and patients respectively. Then, a comparison was performed between the controls and patients. In the patient group, the disconnection was found within TNN and TPN, and the disrupted intrinsic functional organization between networks was observed. These findings might reflect not only the deficits related to epileptic neuropathology or cognitive and neuropsychological alteration within networks, but also the unevenness and imbalance in the functional interaction in the two networks.

Consistent with our previous study on the absence epilepsy[3]., the correlations in fronto-parietal regions within TNN decreased We suggested that the disconnections between the fronto-parietal association cortex might reflect an underlying neuronal functional impairment, which could result in the impaired consciousness during general seizures. In TPN, we found 13 pairs of functional connections decreased in patients. Ten of them were related to the FEF or IPS. In previous studies, the FEF and IPS was considered mainly responded to the dorsal attention function, and the dorsal attention network (DAN) has been identified used the correlation analysis of the spontaneous BOLD activity seeded on the FEF and IPS [14]. Our findings that the decreased functional connections were related to the main regions of DAN might implicate the neuronal pathophysiological mechanism, which might cause attention impairment in IGE. The speculation was supported in temporal lobe epilepsy [16]. Additionally, eight of the 13 connections were related to the insula. The insular connected to the frontal, parietal and temporal lobes in anatomy, and was considered to take part in the task sets implementation [15] or emotional salience [17]. The disconnection between the insula and the frontal and parietal lobe might reflect the aberrant function about insula, such as the implementation or emotion. Besides, in the

refractory partial epilepsy, the insula might be involved in the epileptogenic zone[18]. In conclusion, the attention and behavior deficit in IGE mentioned in previous studies, might contribute to the reduced TPN disconnection in this study.

The brain activity was organized through both correlated spontaneous fluctuations within a network and anticorrelations between networks in resting state [5, 8, 19]. The apparent antagonism might reflect a dynamic, ongoing, underlying intrinsic functional organization of the brain[8]. Fransson has also proposed that the antagonism of the two networks might reflect a binding mechanism between an introspective and extrospective attentional orientation[9]. Here, the significant anticorrelation between the TPN and TNN in controls was concordant with the previous studies. However, these connections were significantly reduced in IGE compared with that in controls. The finding uncovers the disturbed antagonism, and means the unevenness and imbalance in the functional interaction in the two networks. In truth, the decreased antagonism was also found in the autism[10] and attention deficit/hyperactivity disorder[11], and the finding was interpreted by an imbalance in the switching between two networks, driven by a deficit of mental function, such as paucity of introspective thought in autism and attention lapses in attention deficit/hyperactivity. The attention impairment was found in IGE in behavior or fMRI studies. It might lead to the disturbed antagonism in the two networks. On the other hand, the disrupted antagonism might mean the decreased desynchronicity between the two networks, and probably related to the epileptic discharge synchronicity in the entire brain in IGE.

V. CONCLUSION

In this study, the intrinsic functional organization of the brain was investigated by functional connectivity analysis of the synchronized low-frequency fluctuations BOLD signal in the TPN and TNN in IGE. The disconnection within the network and decreased antagonism between two works were observed. These findings might reflect not only the deficits related to epileptic neuropathology or cognitive and neuropsychological alteration within network, but also the unevenness and imbalance in the functional interaction in the two networks.

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REFERENCE

[1] R. Caplan, P. Siddarth, L. Stahl, E. Lanphier, P. Vona, S. Gurbani, S. Koh, R. Sankar, and W.D. Shields, "Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities," Epilepsia, Vol. 49, pp. 1838-1846, 2008.

[2] C. Hommet, H.C. Sauerwein, B. De Toffol, and M. Lassonde, "Idiopathic epileptic syndromes and cognition," Neuroscience and biobehavioral reviews, Vol. 30, pp. 85-96, 2006.

[3] C. Luo, Q. Li, Y. Lai, Y. Xia, Y. Qin, W. Liao, S. Li, D. Zhou, D. Yao, and Q. Gong, "Altered functional connectivity in default mode network in absence epilepsy: A resting-state fMRI study," Human Brain Mapping, Vol. 32, pp. 438-49, 2011.

[4] C. Luo, Q. Li, Y. Xia, X. Lei, K. Xue, Z. Yao, Y. Lai, E. Martı´nez-Montes, W. Liao, D. Zhou, P.A. Valdes-Sosa, Q. Gong, and D. Yao, "Resting state Basal Ganglia Network in idiopathic generalized epilepsy," Human brain mapping, Vol. DOI:10.1002/hbm.21286, pp. In press.

[5] M.E. Raichle, A.M. MacLeod, A.Z. Snyder, W.J. Powers, D.A. Gusnard, and G.L. Shulman, "A default mode of brain function," Proc Natl Acad Sci U S A, Vol. 98, pp. 676-82, 2001.

[6] M. Corbetta, J.M. Kincade, and G.L. Shulman, "Neural systems for visual orienting and their relationships to spatial working memory," J Cogn Neurosci, Vol. 14, pp. 508-23, 2002.

[7] M.D. Greicius, B. Krasnow, A.L. Reiss, and V. Menon, "Functional connectivity in the resting brain: a network analysis of the default mode hypothesis," Proc Natl Acad Sci U S A, Vol. 100, pp. 253-8, 2003.

[8] M.D. Fox, A.Z. Snyder, J.L. Vincent, M. Corbetta, D.C. Van Essen, and M.E. Raichle, "The human brain is intrinsically organized into dynamic, anticorrelated functional networks," Proc Natl Acad Sci U S A, Vol. 102, pp. 9673-8, 2005.

[9] P. Fransson, "Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis," Hum Brain Mapp, Vol. 26, pp. 15-29, 2005.

[10] D.P. Kennedy and E. Courchesne, "The intrinsic functional organization of the brain is altered in autism," Neuroimage, Vol. 39, pp. 1877-85, 2008.

[11] F.X. Castellanos, D.S. Margulies, C. Kelly, L.Q. Uddin, M. Ghaffari, A. Kirsch, D. Shaw, Z. Shehzad, A. Di Martino, B. Biswal, E.J. Sonuga-Barke, J. Rotrosen, L.A. Adler, and M.P. Milham, "Cingulate-precuneus interactions: a new locus of dysfunction in adult attention-deficit/hyperactivity disorder," Biol Psychiatry, Vol. 63, pp. 332-7, 2008.

[12] J. Engel, Jr., "A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology," Epilepsia, Vol. 42, pp. 796-803, 2001.

[13] G. Garreffa, M. Carni, G. Gualniera, G.B. Ricci, L. Bozzao, D. De Carli, P. Morasso, P. Pantano, C. Colonnese, V. Roma, and B. Maraviglia, "Real-time MR artifacts filtering during continuous EEG/fMRI acquisition," Magn Reson Imaging, Vol. 21, pp. 1175-89, 2003.

[14] M.D. Fox, M. Corbetta, A.Z. Snyder, J.L. Vincent, and M.E. Raichle, "Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems," Proc Natl Acad Sci U S A, Vol. 103, pp. 10046-51, 2006.

[15] N.U. Dosenbach, K.M. Visscher, E.D. Palmer, F.M. Miezin, K.K. Wenger, H.C. Kang, E.D. Burgund, A.L. Grimes, B.L. Schlaggar, and S.E. Petersen, "A core system for the implementation of task sets," Neuron, Vol. 50, pp. 799-812, 2006.

[16] Z. Zhang, G. Lu, Y. Zhong, Q. Tan, Z. Yang, W. Liao, Z. Chen, J. Shi, and Y. Liu, "Impaired attention network in temporal lobe epilepsy: a resting FMRI study," Neurosci Lett, Vol. 458, pp. 97-101, 2009.

[17] A.D. Craig, "How do you feel? Interoception: the sense of the physiological condition of the body," Nat Rev Neurosci, Vol. 3, pp. 655-66, 2002.

[18] D.K. Nguyen, D.B. Nguyen, R. Malak, J.M. Leroux, L. Carmant, J.M. Saint-Hilaire, N. Giard, P. Cossette, and A. Bouthillier, "Revisiting the role of the insula in refractory partial epilepsy," Epilepsia, Vol. 50, pp. 510-20, 2009.

[19] S.J. Broyd, C. Demanuele, S. Debener, S.K. Helps, C.J. James, and E.J. Sonuga-Barke, "Default-mode brain dysfunction in mental disorders: a systematic review," Neurosci Biobehav Rev, Vol. 33, pp. 279-96, 2009.