Disrupted Structural and Functional Rich Club Organization of the Brain Connectome in Patients With Generalized Tonic-Clonic Seizure

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Abstract: Network studies have demonstrated that a small set of highly connected regions may play a central role in global information integration, together forming a rich club organization. Given that generalized tonic-clonic seizure (GTCS) has been conceptualized as a network disorder, we hypothesized that the rich club disturbances may be related to the network abnormalities of GTCS. Here, we used graph theoretical analysis to investigate the rich club organization of both structural and functional connectome in patients with GTCS ($n = 50$) and healthy controls ($n = 60$). We further measured the level of global efficiency and clustering in rich club and non-rich club organization. We, respectively, identified a small number of highly connected hubs as rich club organization from structural and functional networks. Patients were found to exhibit significantly reduced rich club connectivity among the central hubs. Meanwhile, both structural and functional network showed changed levels of global efficiency and clustering of rich club organization in GTCS. Furthermore, in patients, lower levels of rich club connectivity were found to be correlated with longer duration of illness and seizure frequency. Together, these findings suggest that GTCS is characterized by a selective disruption of rich club organization due to the long-term injurious effects of epileptic actions on the central hub regions, which potentially contribute to a reduced level of brain integration capacity among different functional domains and an added effect of illness on a preexisting vulnerability. Our findings emphasize a central role for abnormal rich club organization in the pathophysiological mechanism underlying GTCS. *Hum Brain Mapp* 37:4487–4499, 2016. © 2016 Wiley Periodicals, Inc.

Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

Human brain networks have been shown to display several properties of an efficient communication within a complex system of structurally and functionally interconnected regions [Sporns et al., 2005]. Studies of the brain networks are motivated by the view that brain function is not solely attributable to the properties of individual regions but rather emerges from the network organization of the brain as a whole, the human connectome [Sporns, 2011; van den Heuvel and Sporns, 2011]. Impairment or the disrupt architecture of this central system is proposed to lead to altered global information integration and behavior adaptation between different parts of the network [van den Heuvel et al., 2013].

Idiopathic generalized epilepsy (IGE) encompasses a group of epileptic types that is typically characterized by widespread generalized spike and slow-wave discharges [Engel, 2001]. The generalized tonic-clonic seizure (GTCS) is considered the cardinal manifestation of IGE [Andermann and Berkovic, 2001] and is marked by muscle contractions, lapses in consciousness and cognitive impairment, has been hypothesized as a disorder of brain connectivity [Kim et al., 2014; McGill et al., 2012]. Lately, neuroimaging studies have provided converging evidence for both white matter connectivity and intrinsic functional connectivity (FC) abnormalities in GTCS [Ji et al., 2014; Kim et al., 2014; Lee et al., 2014; Liao et al., 2010a]. Additionally, our previous works have revealed disrupted topological organization of the large-scale brain connectome with several cortical and subcortical regions in GTCS using graph theoretical analysis [Liao et al., 2013; Zhang et al., 2011].

Conceptualizing the brain as a network has potentially pivotal implications for understanding the pathophysiology of GTCS in the light of these prior studies. The existence of a relatively small but crucial set of highly connected regions, the so-called “hub nodes” are of particular interest as they have been noted to play a central role in the overall architecture of brain networks [Sporns et al., 2007; van den Heuvel and Sporns, 2011]. From the perspective of information integration, rich club mediates many of the long-distance connections between brain modules [Zamora-Lopez et al., 2010], and is functionally valuable for global neural signaling and interregional brain communication [van den Heuvel et al., 2012]. Recent network studies have reported disruptions in the rich club organization in schizophrenia, attention-deficit/hyperactivity disorder and autism spectrum disorder, together with a reduced density of centralized position in the frontal, parietal and subcortical hub regions [Collin

et al., 2014a; Ray et al., 2014; van den Heuvel et al., 2013].

Although the conventional viewpoint for GTCS is that the entire brain may be homogeneously involved, emerging evidence suggests that generalized seizures are not truly generalized, but rather affect specific networks, while others are relatively spared [Blumenfeld et al., 2009]. Thus, identification of the specific hub regions will be crucial to further understand the pathophysiologic mechanism underlying GTCS. The previous studies [Ji et al., 2014; Lee et al., 2014; Zhang et al., 2011] have reported GTCS display disruptions in the overall organization of structural connectivity (SC) and FC in prefrontal cortex, putamen, thalamus, and corpus callosum. However, it remains unknown whether these altered connections involve in selective disruption of brain connectivity among central hub regions. In this study, rich club organization of the both structural and functional connectome were investigated in a large-cohort patients with GTCS and healthy controls (HC), to test the hypothesis that the disturbed connections of this central rich club may contribute to pathophysiology of epilepsy.

MATERIALS AND METHODS

Participants

A group of 50 patients with GTCS (31 males and 19 females) and 60 sex- and age-matched HC (32 males and 28 females) were included in this study. Experiments were approved by the Ethics Committee of Jinling Hospital, Nanjing University School of Medicine. All subjects provided written informed consent prior to participation. Diagnosis was made according to International League against Epilepsy criteria [1989]. The inclusion criteria for patient recruitment were: (1) presence of typical clinical symptoms of GTCS, including tic of limbs followed by a clonic phase of rhythmic jerking of the extremities, loss of consciousness during seizures and no partial seizures; (2) presence of generalized spike-and-wave or polyspike-wave discharges in their interictal scalp EEG; (3) no evidence of a cause of secondary GTCS such as trauma, tumor, or intracranial infection; (4) no focal abnormality in the structural MRI; (5) no obvious history of aetiology; and (6) right handedness. Among the 50 patients, among the 32 patients treated with medication, there were 15 with monotherapy, 17 with polytherapy, 25 with valproic acid, 13 with carbamazepine, 5 with phenytoin, 5 with phenobarbitone, 4 with topiramate, 3 with traditional Chinese herbal medicine, 2 with lamotrigine, and 1 with clonazepam. General

TABLE I. Demographic characteristics of participants

Characteristics	GTCS (<i>n</i> = 50)	HC (<i>n</i> = 60)	<i>P</i> value
Age (year)	26.36 ± 7.73	25.52 ± 6.50	0.58 ^a
Gender (male/female)	31/19	32/28	0.37 ^b
Handedness (right/left)	50/0	60/0	—
Mean frame-wise displacement (FD)	0.17 ± 0.07	0.14 ± 0.06	0.12 ^a
Duration (year)	8.20 ± 8.90	—	—
Frequency (times/year)	26.02 ± 85.54	—	—

Note: Date is presented as mean ± standard deviation.

^aTwo-sample *t*-test was used.

^b χ^2 test was used.

patient information is summarized in Supporting Information Table S1.

HC had no current or lifetime neurologic disorders or psychiatric illnesses and no gross abnormalities on brain MR images. No significant difference in age or sex was found between the groups. Demographic and clinical characteristics of the participants are described in Table I.

Data Acquisition

Imaging was acquired on a 3T MR scanner (TIM Trio; Siemens Medical Solutions, Erlangen, Germany) with a standard birdcage head transmit and receive coil at Jinling Hospital, Nanjing, China. Data of patients were acquired during the interictal periods. Foam padding was used to minimize head motion for all participants. Data acquisition included a high-spatial-resolution three-dimensional T1-weighted images, diffusion tensor images and functional magnetic resonance imaging (fMRI) scan. The anatomical T1 images were acquired in the sagittal orientation using a magnetization-prepared rapid (repetition time [TR] = 2,300 ms, echo time [TE] = 2.98 ms, flip angle [FA] = 9°, field of view [FOV] = 256 × 256 mm², matrix size = 256 × 256 and zero filled and interpolated to 512 × 512, slice thickness = 1 mm, without interslice gap, voxel size = 0.5 × 0.5 × 1 mm³ and 176 slices). Diffusion-tensor imaging (DTI) data from the whole brain were obtained using spin-echo echo-planar imaging sequence, including 30 volumes with diffusion gradients applied along 30 non-collinear directions ($b = 1,000$ sec/mm²) and one volume without diffusion weighting ($b = 0$ sec/mm²). Each volume consisted of 45 contiguous axial slices (TR = 6,100 ms, TE = 93 ms, FA = 90°, FOV = 240 × 240 mm², matrix size = 256 × 256, voxel size = 0.94 × 0.94 × 3 mm³). The entire sequence was repeated four times to improve the signal to noise. Functional images were acquired using a single-shot, gradient-recalled echo planar imaging sequence (TR = 2,000 ms, TE = 30 ms and FA = 90°). Thirty transverse sections (FOV = 240 × 240 mm², in-plane matrix = 64 × 64, slice thickness = 4 mm, interslice gap = 0.4 mm, voxel size = 3.75 × 3.75 × 4 mm³), aligned along the anterior commissure–posterior commissure line were acquired. For each subject, a total of 250 volumes were acquired,

resulting in a total scan time of 500 sec. Subjects were told to relax, hold still, keep their eyes closed without falling asleep, and think of nothing in particular.

Preprocessing

Data processing steps are illustrated in Supporting Information Figure S1. First, the whole brain was divided into 90 distinct and non-overlapping regions by masking the Automated Anatomical Labeling (AAL) template [Tzourio-Mazoyer et al., 2002] to obtain the nodes of structural and functional connectome. The cerebellar templates were not included due to the limited directions of our DTI data to for fiber tracking. To construct the SC network in each subject, brain regions from MNI space were warped to the native diffusion space [Zhang et al., 2011]. Second, DTI images were realigned and corrected for motion and eddy current distortions. Whole-brain fiber tracking was performed in native diffusion space of each subject via Fiber Assignment by Continuous Tracking algorithm as implemented in the Diffusion Toolkit [Wang et al., 2007]. Third, functional images were slice-time corrected, realigned, normalized, spatial smoothing (6 mm full-width at half-maximum), regressed for nuisance signals (i.e., 24 head motion parameters, averaged signals from CSF, white matter and global brain) and temporal band-pass filtered (0.01–0.08 Hz) [Liu et al., 2015]. The mean frame-wise displacement (FD) was calculated to further determine the comparability of head movement across groups. The largest mean FD of all subjects was less than 0.3 mm and two-sample *t*-test showed that there was no significant difference in the mean FD between the two groups (0.17 ± 0.07 for GTCS and 0.14 ± 0.06 for HC, $P = 0.12$). The detailed preprocessing steps are given in the Supporting Information.

Structural Connectome Construction

For each data set, a SC network was constructed by combining the collection of reconstructed fiber tracts with the warped AAL regions. A network consists of nodes and connections that can be mathematically expressed as a graph $G = (V, E)$, with V the collection of nodes and E the collection of edges between the nodes [van den Heuvel

and Sporns, 2011]. Within this study, AAL regions in the native diffusion space were taken to represent the nodes V in the structural analysis. For each edge, we calculated the number of reconstructed streamlines (NOS) between the end-nodes as its weight E , and no threshold was applied to construct the brain network. To this end, the NOS weighted connectivity matrix M of each individual was constructed. The average density of the reconstructed matrices were as followed (HC: 0.2280 ± 0.0258 , GTCs: 0.2260 ± 0.0243). In addition, taking into account the influence of region size on NOS, the streamline density weighted matrix M (NOS divided by the mean volume of the connected regions) was also computed. The details of structural connectome construction are described in the Supporting Information.

Functional Connectome Construction

Using the preprocessed resting-state fMRI time-series, we then obtained a temporal correlation matrix ($N \times N$, where $N = 90$ is the number of regions of interest) for each subject by computing Pearson correlation coefficients between every pair of regions of interest. To implement graph analyses relevant to functional network, negative correlations were omitted, and group networks were thresholded to include only the strongest correlations. To enable comparison between functional and structural organization, the functional networks were thresholded at a connection density equal to the average density of the structural matrices (0.22) in this study. Moreover, we also validated the results within the range of 0.15–0.40 connection densities [Grayson et al., 2014].

Overall Organization of the Structural and Functional Connectome

Graph theoretical analyses were carried out both on structural and functional connectome using the Brain Connectivity Toolbox (<http://www.brain-connectivity-toolbox.net>). The connectome were examined in terms of a number of graph metrics, providing information on the global organization of the networks. Global metrics included (1) overall connectivity strength (S), as the sum of all connections in the brain networks; (2) global efficiency (GE), computed as the average inverse shortest path length between two nodes; and (3) overall clustering (C), computed as the average likelihood that the neighbors of a node are interconnected.

Rich Club Organization

The focus of our study was to investigate the possible differences in rich club organization of the brain's connectome between two groups. Rich club in networks describes the phenomenon that the highly connected (high-degree) hubs of a network are more densely

connected among themselves than predicted on the basis of their high degree alone [Colizza et al., 2006]. The weighted normalized rich club coefficient $\Phi_{\text{norm}}^w(k)$ across a range of degree k of the individual brain network was computed in the study and a formal description of the weighted normalized rich club coefficient is given in the Supporting Information. For convenience, in the main text $\Phi_{\text{norm}}^w(k)$ was referred to as $\Phi^w(k)$. By definition, $\Phi_{\text{norm}}^w(k) > 1$ for a range of k is indicative of a rich club organization within a network [Colizza et al., 2006], we first assessed the significance of rich club organization over the group of subjects, one-sample t -test (right tailed) was performed at each level of k to test whether $\Phi_{\text{norm}}^w(k) > 1$, with $P < 0.05$ taken to indicate statistical significance. Bonferroni correction was applied to correct for multiple testing across all examined levels of k (a total of 35 for structural networks and 27 for functional networks) [van den Heuvel et al., 2013].

Rich Club, Feeder and Local Connections, and Subnetworks

To define the rich club regions, a group-averaged network within each group was computed as followed: first, from the set of individual group matrices, only connections that were present in at least 60% of population of a given group were selected for averaging, while all other connections were set to 0. Then, the group-averaged matrix was computed by averaging only across the non-zero cell values of the individual subject matrices. Rich club regions were selected based on the structural and functional group-averaged network as the previous work did [Collin et al., 2014b], and the rich club level of the structural and functional network were set at $k > 24$ and $k > 15$, respectively [van den Heuvel et al., 2013]. The rich club regions were also selected at a range of k levels to test the robustness of rich club effects.

Classification of rich club nodes allowed for the categorization of the edges of the connectome into rich club connections, linking members of the rich club nodes; feeder connections, linking rich club nodes to non-rich club nodes; and local connections linking non-rich club nodes to non-rich club nodes [van den Heuvel et al., 2013]. For each structural and functional connectome, the level of rich club, feeder, and local connectivity strength were computed, which is defined as the sum of all the weights of rich club, feeder and local connections, respectively. In addition, to examine whether abnormal connectivity might be concentrated to rich club connections in the structural and functional networks, the connectivity ratios of rich club, feeder, and local connections were tested [van den Heuvel et al., 2013]. The connectivity strength for each connection class and the ratios "rich club/feeder" and "rich club/local" were between the two groups.

In addition to a group-averaged rich club definition, the rich club was defined at an individual level to allow for possible individual and between-group variation in rich club formation [Collin et al., 2014a; van den Heuvel et al., 2013]. For each subject, an individual rich club was selected as the subset of 12 top ranking nodes with the highest degree in the individual structural network. Next, using this individual rich club, edges of the network were classified into rich club, feeder and local connections. Connectivity strength of each class of connections was computed and compared between groups to examine whether potential group-differences in rich club connectivity could result from group-differences in rich club formation. This approach was discussed more detail in the Supporting Information. The rich club effects as reported in this study were based on the results of group-averaged analysis.

We further extended the concept of rich club phenomena and separated the brain connectome into two subnetworks as the previous work did [Ray et al., 2014]. The subnetworks were: (1) rich club organization and (2) non-rich club organization. The rich club organization was the network with rich club regions and the connections within them; the non-rich club organization was the network with non-rich club regions and the connections within them. For both groups, the level of GE and clustering C of the two subnetworks were computed.

Coupling Between Structural and Functional Connectome

For each subject, we quantified coupling between the union of structural and functional rich club regions. The correlation between structural and functional connectome was constrained by the edges inside the subnetworks. All nonzero entries of the structural subnetwork were selected, rescaled to a Gaussian distribution, and correlated with their functional counterparts selected from the FC matrix. This resulted in a single coupling metric for each of the brain networks [Zhang et al., 2011]. Rescaling of the structural weights to a Gaussian distribution was used to normalize the distribution of SC values [Hagmann et al., 2008]. To investigate clinical relevance of altered brain network topologies in patients with GTCS, we correlated the illness duration and seizure frequency with the structural and functional rich club connectivity. Pearson's correlation analysis was used, controlling for age and gender as confounding variables. Four patients with significant higher seizure frequency (3 patients with 360 times per year and 1 patient with 48 times per year) were not been included in the correlation analysis to account for the potential influence of outliers [Schwarzkopf et al., 2012]. The threshold of $P < 0.05$ was considered to be significant for these analyses.

Statistical Analysis

Permutation testing (two-tailed) was used to evaluate the statistical significance of observed effects (i.e., rich club

coefficient, graph metrics, rich club, feeder, and local connectivity strength and ratios, subnetwork properties). Accordingly, we computed actual between-group differences of the graph parameters. This difference was placed into a null permutation distribution of differences, calculated by randomly assigning each participant to one of the two groups with the same size as the original groups of patients and HC [Bassett et al., 2008]. This procedure was repeated for 10,000 permutations. We assigned a P value to the between-group difference by computing the proportion of differences exceeding the null distribution values. And values of $P < 0.05$ were considered to indicate statistical significance.

Reproducibility Analysis

To test the reproducibility of our findings, we carried out a post hoc permutation analysis as suggested by a previous study [van den Heuvel et al., 2013]. For the structural networks, the rich club regions were selected at a range of rich club levels ($k > 20$ to $k > 27$), and the number of rich club members were varying from 20 to 6.

Accordingly, the functional rich club regions were selected at a range of rich club levels ($k > 13$ to $k > 20$), and the number of rich club members were varying from 20 to 4. Connections were reclassified into rich club, feeder, and local based on this new definition of the rich club regions, and differences between patients and controls in rich club connections were recomputed.

In addition, we performed a subgroup analysis to examine the potential influence of the antiepileptic drugs on the rich club network, by dividing the patients into two subgroups, one group is those were treated with medication, another is those under no medication. Analysis details are described in Supporting Information.

RESULTS

Rich Club Organization of Structural and Functional Connectome

In line with the previous findings, rich club organization was found in the structural and functional connectome of both GTCS patients and HC. The results showed that for the SC networks, $\Phi_{\text{norm}}^w(k) > 1$ was found to be significantly higher than 1 for $k > 15$ and $k > 16$ in GTCS patients and HC, respectively ($P < 0.05$, Bonferroni corrected). Figure 1A illustrates the group averaged structural normalized $\Phi^w(k)$ rich club curves of both the GTCS patients and HC. Patients had a significantly reduced rich club organization, at the range of $k = 26$ to $k = 28$ ($P < 0.01$; 10,000 permutations). The structural rich club regions, selected on the basis of the group-averaged network, set at a rich club level of $k > 24$, included the bilateral hippocampus, insula, putamen, thalamus, precuneus and inferior orbitofrontal gyrus (Fig. 1B). Like the

Figure 1.

Rich club organization of structural and functional connectome. **(A)** Group-averaged structural rich club curve for HC (red) and patients (blue). Patients had a significantly reduced structural rich club organization for the range $k=26$ to $k=28$ ($P < 0.01$; 10,000 permutations). **(B)** The structural rich club members included bilateral hippocampus, insula, putamen, thalamus, precuneus, and inferior orbitofrontal gyrus in both group. This figure is based on the structural group-averaged network in controls (at a rich club level of $k > 24$). **(C)** Group-averaged functional rich club curve for both group. Patients had a significantly reduced functional rich club

organization for the range $k=16$ to $k=20$ ($P < 0.01$; 10,000 permutations). **(D)** The functional rich club regions included the bilateral insula, medial superior frontal gyrus, medial orbitofrontal gyrus, posterior cingulate gyrus, rolandic operculum, and postcentral gyrus in both group. This figure is based on the functional group-averaged network in controls (at a rich club level of $k > 15$). **(E)** Edges across individual brain networks were divided into rich club (red), feeder (orange), and local connections (yellow). [Color figure can be viewed at wileyonlinelibrary.com]

structural data, both GTCS patients and HC showed the existence of significant rich club organization in the functional connectome (Fig. 1C), $\Phi_{\text{norm}}^w(k) > 1$ was found to be significantly higher than 1 for $k > 14$ and $k > 13$ in GTCS patients and HC, respectively ($P < 0.05$, Bonferroni corrected). Patients had a significantly reduced rich club organization at the range of $k=16$ to $k=20$ ($P < 0.01$; 10,000 permutations). The functional rich club regions, also selected on the basis of the group-averaged network, set at a rich club level of $k > 15$, comprising the bilateral insula, medial superior frontal gyrus, medial orbitofrontal gyrus, posterior cingulate gyrus, rolandic operculum, and postcentral gyrus (Fig. 1D). In addition, the group differences in functional rich club organization persist across distinct connection densities (Supporting Information Figure S3). Selection of the rich club regions allowed for the classification of the connections into rich club, feeder, and local connections. Figure 1E shows the schematic

representation of the two classes of nodes and the three classes of connections.

Global Network Metrics

Consistent with previous reports [Zhang et al., 2011] on global network organization in GTCS patients, no significant differences in overall connectivity S , GE and overall C was found when the SC connectome was examined (S : $P = 0.19$, GE : $P = 0.08$, C : $P = 0.13$), as while as the FC connectome (S : $P = 0.36$, GE : $P = 0.42$, C : $P = 0.28$; Supporting Information Figure S4).

Connection Metrics

Permutation analysis revealed a significant reduced level of the SC strength of rich club connections in patients (rich club: $P < 0.01$, FDR corrected). However, no significant

Figure 2.

Connection metrics. Permutation analysis revealed a significant reduction in structural connectivity strength, structural connectivity density, and functional connectivity strength of rich club connections in patients but no significant effect in feeder and local connections. (A) SCN. (B) SCN dividing off the mean volume of the connected regions. (C) FCN. The vertical bar

indicates the standard deviation across subjects. The asterisks indicate the statistically significant difference between the two groups (all $P < 0.01$, 10,000 permutations, FDR corrected). SCN, structural connectivity network; FCN, functional connectivity network; ROI, region of interest. [Color figure can be viewed at wileyonlinelibrary.com]

change was found for feeder and local connections (feeder: $P = 0.13$ and local: $P = 0.38$, Fig. 2A). Weighting of connections according to streamline density (NOS divided by the mean volume of the connected regions), confirmed this finding (rich club: $P = 0.01$, feeder: $P = 0.29$ and local: $P = 0.49$, FDR corrected Fig. 2B), suggesting that the observed effect is independent of possible group-differences in region size. In addition, we also found a significant reduction of the FC strength of rich club connections in patients (rich club: $P < 0.001$, FDR corrected), and no difference was found for feeder and local connections (feeder: $P = 0.10$ and local: $P = 0.08$, Fig. 2C). Confirming our findings of the main analysis, both rich club/feeder as well as rich club/local ratios were significantly decreased in patients (SC: $P = 0.04$ and $P = 0.03$, respectively, 10,000 permutations; FC: $P < 0.001$ and $P < 0.001$, respectively, FDR corrected). These findings tend to suggest that, although connections are affected throughout the brain

network, connectivity effects might be concentrated to rich club connections.

Subnetworks

As described above, the level of GE and C of networks inside the rich club organization and non-rich club organization were used to analyze the specificity of over/under-connectivity in the brain networks. For both the structural and regional volume corrected structural connectome, statistical testing revealed a reduced level of GE of networks inside the rich club organization in patients (all $P < 0.01$, Fig. 3A,B, FDR corrected). For the functional networks, statistical testing also revealed a reduced level of GE and C of networks inside the rich club organization in patients (all $P < 0.01$, FDR corrected, Fig. 3C). In contrast, this effect was nonexistent for the non-rich club organization.

Figure 3.

Subnetworks metrics. Statistical testing revealed a reduced level of GE and C of the structural and functional rich club organization in patients. In contrast, this effect was nonexistent for the network in the non-rich club organization. **(A)** SCN. **(B)** SCN dividing off the mean volume of the connected regions. **(C)** FCN. The vertical bar indicates the standard deviation across subjects. The vertical bar indicates the standard deviation across

subjects. The asterisks indicate the statistically significant difference between the two group (all $P < 0.01$, 10,000 permutations, FDR corrected). GE, global efficiency; C, clustering; SCN, structural connectivity network; FCN, functional connectivity network; ROI, region of interest. [Color figure can be viewed at wileyonlinelibrary.com]

Clinical Correlates and Coupling

In patients, a negative linear relationship between duration of illness and rich club connectivity of structural connectome ($r = -0.55$, Fig. 4A), as well as functional connectome were observed ($r = -0.61$, Fig. 4C). The SC strength corrected for regional volume did not change the nature of our finding ($r = -0.55$, Fig. 4B), all $P < 0.001$ with Bonferroni corrected. In addition, functional rich club connectivity negatively correlated with the epilepsy frequency per year ($r = -0.35$, $P = 0.02$, uncorrected, Fig. 4F). No significant correlation was observed between the epilepsy and structural rich club connectivity. Coupling between SC and FC connectome of the union of structural and functional rich club regions were observed in both two groups (HC: $r = 0.19 \pm 0.11$, GTCS: $r = 0.20 \pm 0.12$), but no significant difference was found between them ($P = 0.35$, Fig. 4G).

Reproducibility of Findings

A post hoc analysis was performed to test the robustness of results pertaining to rich club connections against the different group-averaged rich club levels. For both the structural and regional volume corrected structural connectome, significant decreased rich club connectivity in patients was found at a range of levels, from $k > 21$ to $k > 27$ (all $P < 0.01$, FDR corrected, illustrated in Fig. 5A,B), indicating that rich club differences are also present at other rich club levels. In addition, significant decreased rich club connectivity was also found at a range of levels in the functional connectome, from $k > 13$ to $k > 20$ (all $P < 0.05$, FDR corrected, illustrated in Fig. 5C). Taken together, the result of reproducibility analysis was consistent with the main analysis, suggesting that the selection procedure of the rich club did not have a strong influence on the observed affected rich club organization in patients.

Figure 4.

Clinical correlates. (A) Correlation between SC strength and duration. (B) Correlation between SC density and duration. (C) Correlation between FC strength and duration. Significant negative linear relationship between duration of illness and rich club connectivity were observed in patients (SC: $r = -0.55$; SC density: $r = -0.55$; FC: $r = -0.61$, all $P < 0.001$, Bonferroni corrected). (D) Correlation between SC strength and seizure frequency. (E) Correlation between SC density and seizure frequency. (F) Correlation between FC strength and seizure

frequency. A significant negative linear relationship between seizure frequency and functional rich club connectivity was observed in patients ($r = -0.35$, $P = 0.02$, uncorrected). (G) The SC and FC coupling of the rich club connectivity were observed in both two groups (HC: $r = 0.19 \pm 0.11$, GTCS: $r = 0.20 \pm 0.12$) while no significant difference was found between them. SC, structural connectivity; FC, functional connectivity; ROI, region of interest. [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

In line with previous reports [Grayson et al., 2014; van den Heuvel and Sporns, 2011], we were able to show that brain network architecture as measured by fiber tractography and functional connections indeed has a rich club organization. Then, we demonstrated a reduced level of rich club connectivity in patients with GTCS, reflecting a lower level of connectivity among central hubs of the brain. In addition, results from both structural and functional connectome showed differentially changed levels of GE and clustering in the rich club organization and non-rich club organization. Furthermore, we found that the impaired rich club organization was associated with ill effects, in that lower structural and functional rich club connectivity strength were correlated with longer duration of illness and epilepsy frequency. Our findings suggest that GTCS is characterized by selectively disrupted brain connectivity within central hubs of brain due to seizure induced structural and functional damage, potentially leading to a reduced brain communication capacity among different functional domains and an added effect of illness on a preexisting vulnerability.

The findings of reduced structural rich club connectivity consist with emerging evidence of structural network

abnormalities in epilepsy patients [Bernhardt et al., 2011; Horstmann et al., 2010], reflecting the long-term injurious effects of epileptic actions on the structural damage. It has been suggested that seizure induced neuronal loss and axonal damage may lead to the development of aberrant connections between limbic structures [Spencer, 2002]. The gray matter volume reductions in thalamus and frontal areas were also consistently reported in the previous epilepsy studies [Bernhardt et al., 2009; Huang et al., 2011], which support a central pathophysiological role of the thalamocortical network in GTCS. Meanwhile, widespread fractional anisotropy reductions and less structurally tracts were found in several large white matter structures including the corpus callosum, longitudinal fasciculus, and thalamic radiation in generalized epilepsy patients [Focke et al., 2014; Lee et al., 2014]. Recent studies examining brain connectivity have demonstrated that GTCS is related to aberrant core hub role of cortical and subcortical regions and an altered topological organization in large-scale brain network [Kim et al., 2014; Zhang et al., 2011]. Going beyond these findings, the current study shows that the neocortical regions including precuneus and orbito-frontal cortex, as well as important subcortical regions including hippocampus, insula, putamen, and thalamus were found to be not only individual central but also

Figure 5.

Rich club connectivity effects at different rich club levels. The figure shows the average rich club connectivity strength for the group of controls (red), patients (blue), and the statistical P -values of the group differences (green) at a range of group-averaged rich club levels. **A**, **B**, and **C** depicted the effects of SCN, SCN

dividing off the mean volume of the connected regions and FCN, respectively. SCN, structural connectivity network; FCN, functional connectivity network; ROI, region of interest. [Color figure can be viewed at wileyonlinelibrary.com]

densely interconnected to form a structural rich club organization. Moreover, significant reductions in SC strength were found for rich club connections while other class of feeder and local connections seem to be relatively spared in patients with GTCS. As rich club regions normally combine both high topological value and high biological cost [Crossley et al., 2014], the disease induced pathological brain lesions are more likely to be concentrated in this concentrated organization. In this context, it is tempting to speculate that the disrupted structural network in patients may be concentrated to connections among rich club brain hubs rather than equally affecting all white matter connections of brain regions.

A central role of the rich club in GTCS may be further illustrated by an analysis of the graph metrics of GE and overall clustering. In this study, we examined the brain networks in three domains: rich club network, non-rich club network, and overall network. Here, relative to controls, the GTCS group was found to exhibit significant lower region-specific GE and clustering in structural networks but only in the rich club organization. Our findings suggested that although these rich club regions are highly connected regions in the network, the brain communication efficiency and global clustering for GTCS patient among these regions are reduced. Recent studies have showed that the high degree and highly efficient hub

nodes have higher blood flow, glucose metabolic rate, and longer connection distance than non-hub nodes, and their topological centrality and high biological cost could make hubs particularly vulnerable to pathogenic factors [Crossley et al., 2014; Tomasi et al., 2013]. Indeed, various previous interictal and ictal neuroimaging studies have demonstrated hypometabolism and hypoperfusion in hippocampus, frontal lobe, and dorsomedial thalamus of epilepsy patients [Akman et al., 2015; Blumenfeld et al., 2009]. It is likely that the epileptic process that restricts neuronal metabolism has disproportionate impact on the most metabolically regions. Our findings support the proposal that the high-degree regions are generally more susceptible, both biologically and statistically to the chronic seizure discharge effects. It has been suggested that various measures of brain network organization are interrelated [de Reus and van den Heuvel, 2013]. The existence of a strongly interlinked rich club has been proposed to underlie important organizational attributes, including GE and high clustering [Xu et al., 2010]. The topologically central role of the rich club could mean that pathological attack on a hub will have a disproportionate impact on the network's GE of information processing [Albert et al., 2000]. Indeed, the attenuated reductions in global effects and clustering for rich club network seem to suggest that the observed abnormalities may be partly due to impaired

rich club organization. Future studies are needed to examine the relationship between various brain network measures.

Importantly, similar to our SC network results, the FC analysis was consistent in identifying that functional rich club connectivity along with the GE and clustering within the rich club network were reduced in GTCS group. The rich club nodes for functional connectome were comprised of bilateral medial superior frontal and orbitofrontal cortex, together with posterior cingulate gyrus, rolandic operculum, postcentral gyrus, and the insula, comprising a number of previously identified brain segregated systems [Power et al., 2011], including default mode network, fronto-parietal and cingulo-opercular network. Rich club regions have been hypothesized correspond to one or more resting state networks and the connections between them are likely to form a backbone to link different functional modules in the brain [van den Heuvel and Sporns, 2011; Zamora-Lopez et al., 2011]. From the perspective of cognitive function, GTCS patients have consistently demonstrated impairments in different neurocognitive domains, such as attention, consciousness, and language dysfunctions [Hommet et al., 2006; Wang et al., 2011], while these high order cognitive functions depend on a more highly interconnected network topology [Dehaene and Changeux, 2011]. Our findings are in good agreement with previous reports [Kim et al., 2014; Wang et al., 2012], that showed IGE was associated with decreased FC mainly in the medial prefrontal cortex and precuneus/posterior cingulate gyrus. It is possible that the accumulated effects of seizure burden can disrupt the rich club connections that linked different functional systems, which may play a role in the cognitive decline observed in epilepsy patients. In addition, patients showed reduced levels of GE and clustering within functional rich club organization. It has been noted that synchronization and information transfer between hub regions may aid in the centralized processing and in the efficient integration between different functional domains [Collin et al., 2014b]. Thus, it is unsurprising that loss of connectivity to these rich club regions is associated with a reduced capacity to brain communication (lower GE and clustering), resulting in more functionally isolated subsystems. Taken together, our findings tend to imply that GTCS is characterized by reduced brain connectivity within topologically central brain regions due to the long-term injurious effects of epileptic actions on the structural and functional damage, which may eventually contribute to disruption of the global brain communication and cognitive decline observed in patients.

It was worth noting that the reduced structural and functional rich club connectivity was found to be correlated with longer illness duration of GTCS patients, which further supported the proposal that the chronic damaging effect of epilepsy might disrupt the interactions between rich club regions. In addition, functional rich club connectivity was found to be negatively correlated with the

epilepsy frequency in GTCS group while no significant correlation was observed between the epilepsy frequency and structural rich club connectivity. This result might suggest that the functional rich club connectivity of patients is more vulnerable to the accumulated and repeated seizures while the structural rich club connectivity is relatively stable. Although we revealed a clear coupling between structural and functional rich club organization in GTCS and HC, no significant difference was found between them. It has been suggested that structural connections are highly predictive of functional connections. And conversely, functional connections exert effects on structural connections through mechanisms of plasticity [Hagmann et al., 2010]. Further studies examining of a possible disrupted coupling between structural and functional rich club network in patients with GTCS are of potential importance.

Several limitations of our study should be noted. First, because of MRI data of our study were acquired without simultaneous EEG recording, possible effects of interictal epileptic discharges on the brain network organization cannot be totally excluded. Second, we did not assess whether rich club network changes occur as a consequence of seizures or whether these changes are the cause of seizures due to the cross-sectional design and relatively small number of subjects. A large longitudinal study is needed to further clarify the causal relationship between the epileptic activity and brain network changes. Third, region selection is an important issue when using graph theory approaches to study brain connectivity as results may change depending on number of regions, regions size and their location [Cohen et al., 2008]. Replicating the current findings in alternative parcellation schemes will be important in future work. Lastly, we used the deterministic tractography to construct the network according to previous studies [Liao et al., 2010b; Yan et al., 2011]. This may reduce the sensitivity, as the tracking procedure stops when it reaches regions with fiber crossings [Mori and van Zijl, 2002]. In future study, probabilistic tractography techniques [Gong et al., 2009] should be considered to address this issue.

CONCLUSION

In summary, this study identified a disrupted rich club organization of both structural and functional connectome in GTCS patients, which reflecting the long-term injurious effects of epileptic activity on the central hub regions. Additionally, our analyses further indicated that the disrupted interconnectivity of rich club network in patients with GTCS may contribute to the reduced brain communication capacity among different functional domains and an added effect of illness on a preexisting vulnerability. Our findings emphasize a central role for abnormal rich club organization in the pathophysiological mechanism underlying GTCS.

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