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ORIGINAL RESEARCH

Aberrant topological organization of the functional brain network associated with prior overt hepatic encephalopathy in cirrhotic patients

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Abstract

A higher risk of cognitive impairments has been found after an overt hepatic encephalopathy (OHE) episode in cirrhotic patients. We investigated the effect of prior OHE episodes on the topological organization of the functional brain network and its association with the relevant cognitive impairments. Resting-state functional MRI data were acquired from 41 cirrhotic patients (19 with prior OHE (Prior-OHE) and 22 without (Non-Prior-OHE)) and 21 healthy controls (HC). A Psychometric Hepatic Encephalopathy Score (PHES) assessed cognition. The whole-brain functional network was constructed by thresholding functional correlation matrices of 90 brain regions (derived from the Automated Anatomic Labeling atlas). The topological properties of the brain network, including small-worldness, network efficiency, and nodal efficiency, were examined using graph theory-based analysis. Globally, the Prior-OHE group had a significantly decreased clustering coefficient and local efficiency, compared with the controls. Locally, the nodal efficiency in the bilateral medial superior frontal gyrus and the right postcentral gyrus decreased in the Prior-OHE group, while the nodal efficiency in the bilateral anterior cingulate/paracingulate gyri and right superior parietal gyrus increased in the Prior-OHE group. The alterations of global and regional network parameters progressed from Non-Prior-OHE to Prior-OHE and the clustering coefficient and local efficiency values were significantly correlated with PHES results. In conclusion, cirrhosis leads to the reduction of brain functional network efficiency, which could be aggravated by a prior OHE episode. Aberrant topological organization of the functional brain network may contribute to a higher risk of cognitive impairments in Prior-OHE patients.

Keywords Overt hepatic encephalopathy · Resting-state functional magnetic resonance imaging · Brain functional network · Graph theory analysis · Small-world Network

Abbreviations

HE	Hepatic encephalopathy
OHE	Overt hepatic encephalopathy
DMN	Default mode network
MMSE	Mini-mental state examination
PHES	Psychometric hepatic encephalopathy score
AUC	Area under the curve

Introduction

Hepatic cirrhosis commonly induces neurocognitive dysfunction, which ranges from mild cognitive impairments to mental status changes, such as hepatic encephalopathy (HE) (Bajaj et al. 2009; Weissenborn et al. 2001). Recent studies demonstrate the persistence of neurocognitive deficits even after adequate resolution of an episode of overt HE (OHE) (Bajaj et al. 2010; Umapathy et al. 2014). In addition, the neurocognitive deficits that occurred in a cirrhotic patient could predict a subsequent episode of OHE (Romero-Gomez et al. 2001). Thus, the spectrum of neurocognitive impairment in cirrhosis has been

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regarded as a continuum to better understand the evolution of neurocognitive dysfunction that is related to cirrhosis (Bajaj et al. 2009).

It is important to note, for this continuous spectrum, that the episode of OHE could be the critical factor that can predominately accelerate neurocognitive impairment in cirrhosis. Many studies have consistently shown poorer performance on neurocognitive tests by patients with treated OHE than those without OHE (Bajaj et al. 2010; Umapathy et al. 2014). An OHE episode is thought to result in the loss of learning ability and the deficit in executive function in cirrhotic patients, both of which are not reversible (Bajaj et al. 2010; Riggio et al. 2011; Umapathy et al. 2014). In addition, the OHE bouts play an independent role in producing a persistent effect on health-related quality-of-life of cirrhotic patients (Moscucci et al. 2011). A history of OHE is the factor strongly associated with cognitive deficits in cases of cirrhosis (Yoshimura et al. 2016). In fact, a higher risk of cognitive impairment has been found after an episode of OHE in cirrhotic patients (Bajaj et al. 2010, 2013).

The above phenomenon may be attributed to the brain dysfunction induced by an OHE episode. Zhang et al. (2012) revealed that an OHE episode is accompanied by the disruption of functional connectivity in the default mode network (DMN) based on the resting-state fMRI data and brain network analysis. Also, by using resting-state fMRI, Chen el al. (2013) found that this functional alteration of the brain network could remain after the resolution of OHE, which is helpful in accounting for the persistent and cumulative neurocognitive deficits related to prior OHE episodes. These previous studies suggest that *in vivo* resting-state brain network analysis could be useful in exploring the mechanisms underlying neurocognitive deficits related to prior OHE bouts. The existing studies only examined one single brain network (i.e., DMN) to investigate the effects of prior OHE on the neurocognitive function of cirrhotic patients (Chen et al. 2013). However, recent advances in the human brain connectome have shown that the whole brain operates as an interconnected network that is highly optimized in topological organization to promote cognitive demands (Bullmore and Sporns 2009; Rubinov and Sporns 2010; Sporns and Zwi 2004). For instance, the optimized topological organization of the whole brain network follows a "small-world" topology that is characterized by a high clustering coefficient and shortest characteristic path lengths linking individual network nodes, which enable high global and local efficiency of parallel information processing at a low wiring cost (Bullmore and Sporns 2009; Bullmore and Bassett 2011). A substantial body of evidence has suggested that whole brain network analysis based on various mathematical models (e.g., graph theory-based analysis (Bullmore and Bassett 2011)) can provide invaluable insights into how the brain topology dynamically reorganizes to respond to various diseases (Bullmore and Sporns 2009).To date, however, little is understood about the changes in the large-scale complex brain networks associated with prior OHE episodes in cirrhotic patients and their association with cognitive impairment after the events. Therefore, we questioned how the topological organization of the functional brain networks is altered in patients with prior OHE episodes.

Materials and Methods

Participants

There were 41 cirrhotic individuals (19 with prior OHE (Prior-OHE) and 22 without OHE (Non-Prior-OHE)) and 21 healthy controls (HC) who were included. Every one of the Prior-OHE patients had had an episode of OHE within the previous year (median time: 3 months, with the range of 2–12 months). Every patient's background involving prior OHE was noted using the West Haven criteria (Ferenci et al. 2002). The most severe disease conditions of the 19 Prior-OHE patients involved: 5 incidents that were Grade II OHE, 9 incidents that were Grade III OHE, and 5 incidents that were Grade IV OHE. There were 10 participants (52.6%) in the Prior-OHE group who experienced at least 2 OHE events. None of the participants had OHE symptoms upon examination and had a healthy mental status (Mini-Mental State Examination (MMSE) score ≥ 25) (Bajaj et al. 2010), when they were included. The degree of liver disease was established with a Child–Pugh score. The Psychometric Hepatic Encephalopathy Score (PHES) examination, involving the digit symbol test, number connection test A, number connection test B, serial dotting test, and line tracing test, was implemented for cognition evaluation (Chen et al. 2015). Twenty-one age-, gender-, and education level-matched healthy controls were also included in this study and underwent PHES examination. The subjects' demographic and clinical parameters are outlined in Table 1. This study was approved by the Ethics Committee of Fujian Medical University Union Hospital. All of the participants were given written informed consent prior to the start of the study.

Patients were eliminated if they presented with overt HE or other neuropsychiatric disorders, were taking psychotropic medications, experienced uncontrolled endocrine and metabolic diseases (e.g., thyroid dysfunction), or excessively drank alcohol in the 6 months leading up to the evaluation.

MRI data acquisition

All of the MRI data were obtained from a 3.0 T scanner (Siemens, Verio, Germany). Three-dimensional T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) sagittal images were gathered with the parameters: TR = 1.9 ms, TE = 2.48 ms, FOV = 256 mm × 256 mm, matrix = 256 × 256, flip angle = 9°, slice thickness = 1.0 mm, without interslice gap, voxel size = 1.0 × 1.0 × 1.0 mm^3, and 176 slices.

Table 1 Demographic and clinical characteristics of the subjects

	HC ($n = 21$)	Non-Prior-OHE ($n = 22$)	Prior-OHE ($n = 19$)	P value (ANOVA)
Age (years)	49.6 ± 9.8	51.5 ± 9.8	49.4 ± 9.9	0.531
Sex (male/female)	17/4	19/3	17/2	0.739 (χ^2-test)
Education level (years)	9.7 ± 3.5	8.5 ± 3.1	8.8 ± 1.9	0.331
Etiology of cirrhosis (HBV/alcoholism/ HBV + alcoholism/other)	–	16/3/2/1	11/4/2/2	–
Child–Pugh stage (A/B/C)	–	14/7/1	2/11/6	–
PHES test				
Final PHES score	0.5 ± 0.9	−1.1 ± 2.5†	−7.2 ± 3.6$^{*, \#}$	< 0.001
Number connection test A (seconds)	34.8 ± 7.9	39.4 ± 10.9	53.0 ± 18.9$^{*, \#}$	< 0.001
Number connection test B (seconds)	57.2 ± 16.1	75.3 ± 23.9	116.4 ± 59.1$^{*, \#}$	< 0.001
Serial dotting test (seconds)	41.4 ± 6.4	47.5 ± 9.6	60.4 ± 13.2$^{*, \#}$	< 0.001
Digit symbol test (raw score)	46.2 ± 12.2	40.2 ± 11.9	30.8 ± 10.1$^{*, \#}$	< 0.001
Line tracing test (raw score)	111.7 ± 19.6	150.0 ± 29.2†	188.2 ± 38.2$^{*, \#}$	< 0.001

OHE, overt hepatic encephalopathy; HC, healthy control; PHES, psychometric hepatic encephalopathy score; and ANOVA, analysis of variance. The markers *, †, and $^{\#}$ respectively indicate a significant difference in neurological performance between the Prior-OHE group and the HC group, the Non-Prior-OHE group and the HC group, and the Prior-OHE group and the Non-Prior-OHE group

Resting-state functional images were obtained with an echo planar imaging sequence using the parameters: 35 contiguous axial slices, TR = 2000 ms, TE = 25 ms, FOV = 240 mm × 240 mm, matrix = 64 × 64, flip angle = 90°, slice thickness = 4 mm, without interslice gap, voxel size = 3.75 × 3.75 × 4 mm^3, and 180 volumes. Participants were told to keep their eyes closed, not to think of anything specific, and to be sure their heads remained immobile.

Functional image preprocessing

Functional data were preprocessed using the SPM software and the Data Processing Assistant for Resting-State fMRI (DPARSF 3.0, http://www.restfmri.net/forum/DPARSF) tool. For each participant, the first 10 volumes were discarded to avoid the instability of the initial MR imaging signal. Slice-timing adjustment and realignment for head-motion correction were performed. A participant was included if the translational movement was less than 1.5 mm and the rotation was less than 1.5°. The individual structural image (T1-weighted MPRAGE images) was coregistered to the mean functional image. The transformed structural images were then segmented into gray matter, white matter, and cerebrospinal fluid using a unified segmentation algorithm. Then, the motion-corrected functional volumes were further normalized to the standard Montreal Neurological Institute (MNI) space using the normalization parameters estimated during unified segmentation and resampled to 3 × 3 × 3 mm^3. Subsequently, the images were spatially smoothed with a 4-mm full width at half maximum Gaussian kernel and were linearly detrended. The resulting fMRI data were band-pass filtered (0.01–0.08 Hz) to reduce the low-frequency drift and high frequency physiological respiratory and cardiac noise. In consideration of the possible effects of head motion and the global white matter and the cerebrospinal fluid signals on the results, we also removed several sources of spurious variance by linear regression, including six head motion parameters and the average signals from the cerebrospinal fluid, white matter, and the whole brain.

Network Construction

Nodes and edges are the two fundamental elements of a network. The individual functional network was constructed using the following procedures. After preprocessing, the functional images were parcellated into 90 anatomical regions using the Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al. 2002). Each region represented a node of the network. The representative time series of every region was computed by averaging the time series of all of the voxels within that region. Pearson's correlation coefficient was calculated between the representative time series of every pair of the brain regions, which resulted in a 90 × 90 correlation matrix for each subject. Finally, individual correlation matrices were converted into binarized matrices according to a predefined sparsity threshold (0.10–0.34, with an increment of 0.01). This threshold selection was based on the criteria proposed by previous studies (Lei et al. 2015; Zhang et al. 2011a), which could guarantee that the thresholded networks were estimable for small-worldness and had sparse properties with as few spurious edges as possible. The functional connection matrix and topology of the representative fully connected and sparse brain networks are shown in Fig. 1.

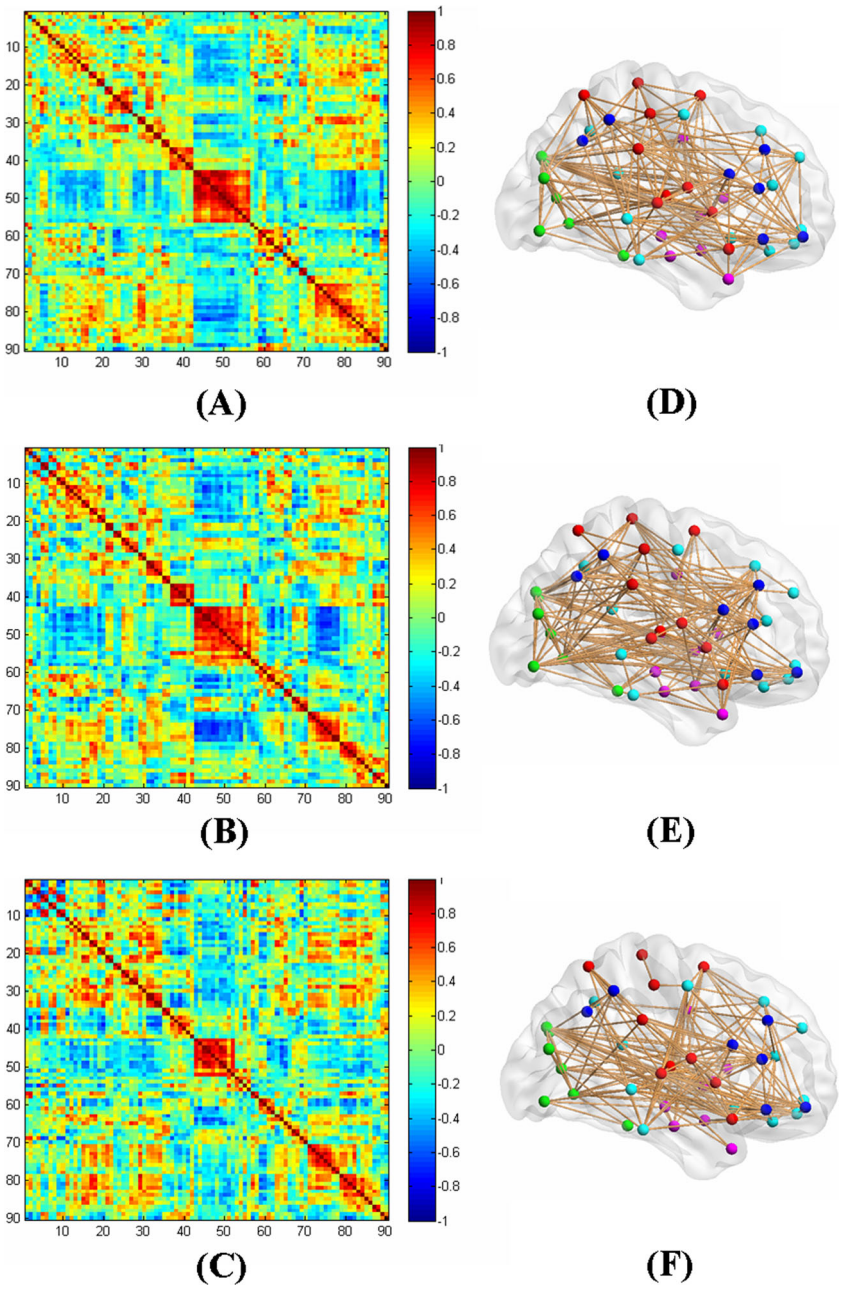

Fig. 1 Functional connectivity matrices and connectivity topology. (A-C) illustrate the connectivity matrices of the fully connected network of the representative healthy control, Non-Prior-OHE patient, and Prior-OHE patient, respectively. (D-F) show the corresponding connectivity topologies, with sparsity thresholds of 20%. The surface visualization of the brain networks was achieved with BrainNet Viewer software (http://nitrc.org/projects/bnv/)

Network Analysis

We performed the network analyses using graph-theoretical network analysis software (GRETNA 1.2.1, http://www.nitrc.org/projects/gretna/). To characterize the topological organization of the functional networks, several graph metrics were assessed: the small-world parameters (i.e., clustering coefficient (C_p), shortest path length (L_p), normalized clustering coefficient (γ), normalized shortest path length (λ), and small-worldness(σ)) and the network efficiency parameters (i.e., global efficiency (E_{glob}) and local efficiency (E_{loc})) (Rubinov and Sporns 2010; Watts and Strogatz 1998). For regional characteristics, we considered the nodal efficiency (Achard and Bullmore 2007). For the details about the network metric calculation, see reference (Wang et al. 2015) and the significance of each network metric see reference (Rubinov and Sporns 2010). Since each correlation matrix was thresholded repeatedly over a wide range of sparsity, the area under the curve (AUC) for each network metric was computed to be taken as a summarized scalar for the topological characterization of the brain networks. The AUC index has proven to be sensitive to reflect the topological alterations of the brain network in various neuropsychiatric disorders (Lei et al. 2015; Zhang et al. 2011a).

Statistical Analysis

The topological measures were compared across the three groups using analysis of variance (ANOVA). The Pearson's correlation analysis was applied to examine the relationship between the network parameters and cognitive performance in cirrhotic patients. $P < 0.05$ was considered to be of statistical significance.

Results

Compared with the controls, the two groups of cirrhotic patients showed impaired neurocognitive performances, which was reflected by the reduction of the PHES score. Specifically, the cirrhotic patients need a longer time to complete number connection test A, number connection test B, and the serial dotting test and had a lower score on the digit symbol test and the line tracing test. The Prior-OHE group showed significantly worse performances on all of the PHES tests compared with the Non-Prior-OHE group (Table 1).

For the global network metrics, the Prior-OHE group had significantly decreased C_p and E_{loc}, compared with the controls (Fig. 2 and Table 2). Other topological metrics, including L_p, γ, λ, σ, and E_{glob}, were not different among the three groups. From Non-Prior-OHE to Prior-OHE, the functional brain networks were progressively less clustered and less efficient. For the regional network characteristics, the two groups of cirrhotic patients showed reduced nodal efficiency in the bilateral medial superior frontal gyrus and the right postcentral gyrus and increased nodal efficiency in the bilateral anterior cingulate/paracingulate gyri and the right superior parietal gyrus. Moreover, alterations of nodal efficiency occurring in the above regions progressed from Non-Prior-OHE to Prior-OHE (Fig. 3 and Table 3).

The correlation analyses showed the clustering coefficient and local efficiency values were significantly correlated with the PHES results among the cirrhotic patients (Fig. 4). No significant correlation was found between nodal efficiency and the PHES results.

Discussion

Using graph-analytical methods, we found that the global network parameter abnormalities, such as the lower cluster coefficient and decreased local efficiency, occurred in the cirrhotic patients with prior OHE. Meanwhile, the regional efficiency in several network nodes, including bilateral medial superior frontal gyrus, right postcentral, bilateral anterior cingulate/paracingulate gyri, and right superior parietal gyrus, were altered even after clinical resolution of OHE. Thus, together with the existing evidence that OHE induced the abnormal brain network organization in the cirrhotic patients (Hsu et al. 2012; Jao et al. 2015; Zhang et al. 2012), our results suggest that the disrupted brain functional network resulting from a prior OHE episode would persist even after clinical resolution. In addition, we identified a progressive trend of global and regional network parameter alterations from Non-Prior-OHE to Prior-OHE. This alteration trend is very consistent with the clinical investigation, in which a higher proportion of cirrhotic patients develop cognitive impairments in the Prior-OHE group, relative to the Non-Prior-OHE group (Bajaj et al. 2010, 2013; Yoshimura et al. 2016). This consistency implies the association between the topological property of the brain functional network and the cognitive performance

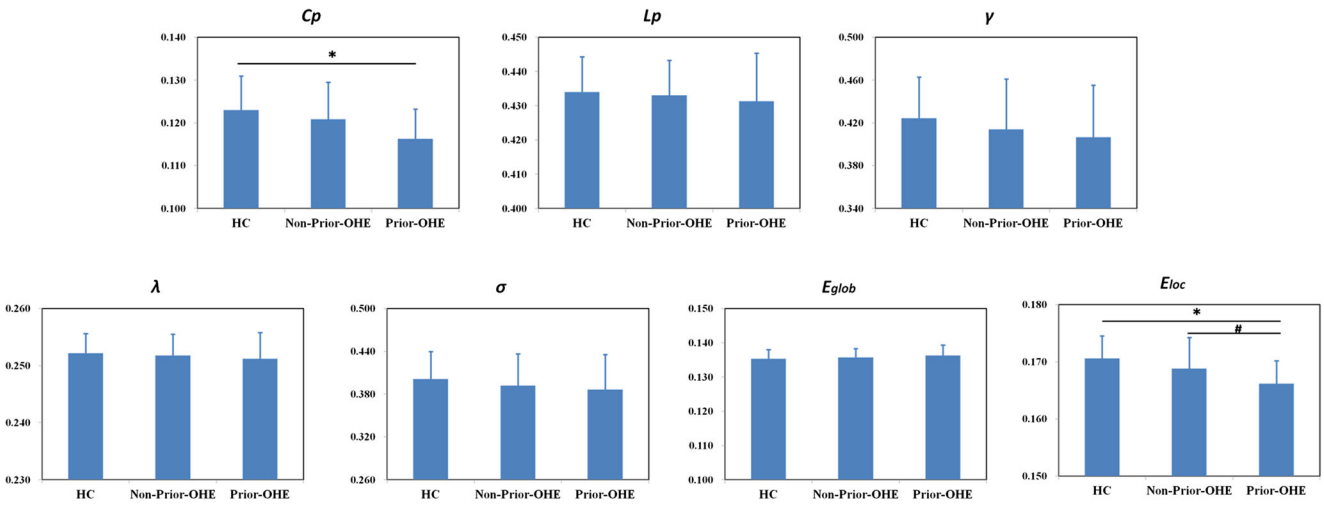

Fig. 2 The difference in the global topological properties of the brain functional network across three groups. The markers * and # indicate a significant difference between the HC and the Prior-OHE group and between the Non-Prior-OHE group and the Prior-OHE group, respectively. The significance level was set to $P < 0.05$ (with FDR correction)

Table 2 The area under the curve (AUC) of the network metric across the full range of sparsity thresholds

	HC	Non-Prior-OHE	Prior-OHE	*P* value (ANOVA)
C_p	0.123 ± 0.008	0.121 ± 0.008	0.116 ± 0.007*	0.031
L_p	0.434 ± 0.010	0.433 ± 0.010	0.431 ± 0.014	0.760
γ	0.424 ± 0.038	0.414 ± 0.047	0.407 ± 0.048	0.457
λ	0.252 ± 0.003	0.252 ± 0.004	0.251 ± 0.005	0.742
σ	0.401 ± 0.038	0.392 ± 0.044	0.386 ± 0.049	0.567
E_{glob}	0.135 ± 0.003	0.136 ± 0.003	0.136 ± 0.003	0.608
E_{loc}	0.171 ± 0.004	0.169 ± 0.005	0.166 ± 0.004*,#	0.012

OHE, overt hepatic encephalopathy; HC, healthy control; and ANOVA, analysis of variance. The markers * and # indicate a significant difference between the HC and the Prior-OHE group and between the Non-Prior-OHE group and the Prior-OHE group, respectively. C_p, clustering coefficient; L_p, shortest path length; γ, normalized clustering coefficient; λ, normalized shortest path length; σ, small-worldness; E_{glob}, global efficiency; and E_{loc}, local efficiency. The Prior-OHE group had significantly decreased C_p and E_{loc}, compared with the controls. The significance level was set to $P < 0.05$ (with FDR correction)

of the patients. Our finding of the correlation between the cluster coefficient/local efficiency and the PHES results supports this implication and suggests the important role of the changed topological organization of the brain function network in the mechanisms underlying persistent cognitive impairment related to prior OHEs. Moreover, given that the risk of recurring OHE dramatically increased if subjects have a history of previous bouts of OHE (Vilstrup et al. 2014), it is the clinicians' responsibility to develop an effective treatment strategy for secondary prophylaxis of HE in cirrhosis (Agrawal et al. 2012; Mullen et al. 2014). Cognitive impairment is the important predictor for OHE development; thereby, the brain network topological parameter that is correlated with cognitive impairment may become the biomarkers that serve to monitor disease evolution and the development of new treatment strategies.

A disruption of global functional organization was detected in the Prior-OHE patients, reflected by the reduction of clustering coefficient and local efficiency. The clustering coefficient is a measure of functional segregation, indicating the extent of the local cliquishness in a network (Rubinov and Sporns 2010; Watts and Strogatz 1998). The decreased clustering coefficient means a relatively lower local connectivity of the functional networks and may imply an inefficiency in the information transfer for cognitive processes between interconnected regions. The local efficiency is another measure of functional segregation of the brain network, which is predominantly associated with short-range connections between nearby regions that mediate modularized information processing and reveals how much the network is fault tolerant (Latora and Marchiori 2001; Rubinov and Sporns 2010). The reduction of local efficiency denotes less modularized information processing in the patients. Taken together, the loss of the small-world topological properties reported here represents a less optimal (increasing randomness) network organization in the Prior-OHE patients. These results are comparable to previous reports in which the authors found that during an OHE episode the functional brain networks were reconfigured toward a less clustered and less modular state (Hsu et al. 2012; Jao et al. 2015) (i.e., the global topology was closer to that of random networks (Watts and Strogatz 1998)). Our results provide the evidence that these alterations of the topological organization could remain after clinical resolution of OHE. Thus, we emphasize the vulnerability of the brain network after an OHE episode, which may be responsible for a higher risk of cognitive impairments and OHE recurrence.

Following the discovery of disrupted global functional network topology, we also identified the vulnerable nodes with altered nodal efficiencies in the patients with prior OHE. The Prior-OHE patients exhibited reduced nodal efficiency, which is believed to be linked with hindering cognitive function of the pertinent brain areas, in the bilateral medial superior frontal gyrus and the right postcentral gyrus, while increased nodal efficiency, which may be elucidated as compensatory processes or brain remolding because of its plasticity following destruction to the original neural networks, was noted in the bilateral anterior cingulate/paracingulate gyri and the right superior parietal gyrus. Our findings of decreased nodal efficiency are in accordance with those of previous studies. For example, Chen et al. (2013) investigated the residual reduction of functional connectivity of the medial prefrontal cortex within DMN, after an OHE episode. Also, Jao et al. (2015) found decreased connectivity strength in many brain regions, such as primary somatosensory and midline frontal areas, during an OHE episode, by using graph theory-based analysis. Together with these previous investigations, our study further confirmed

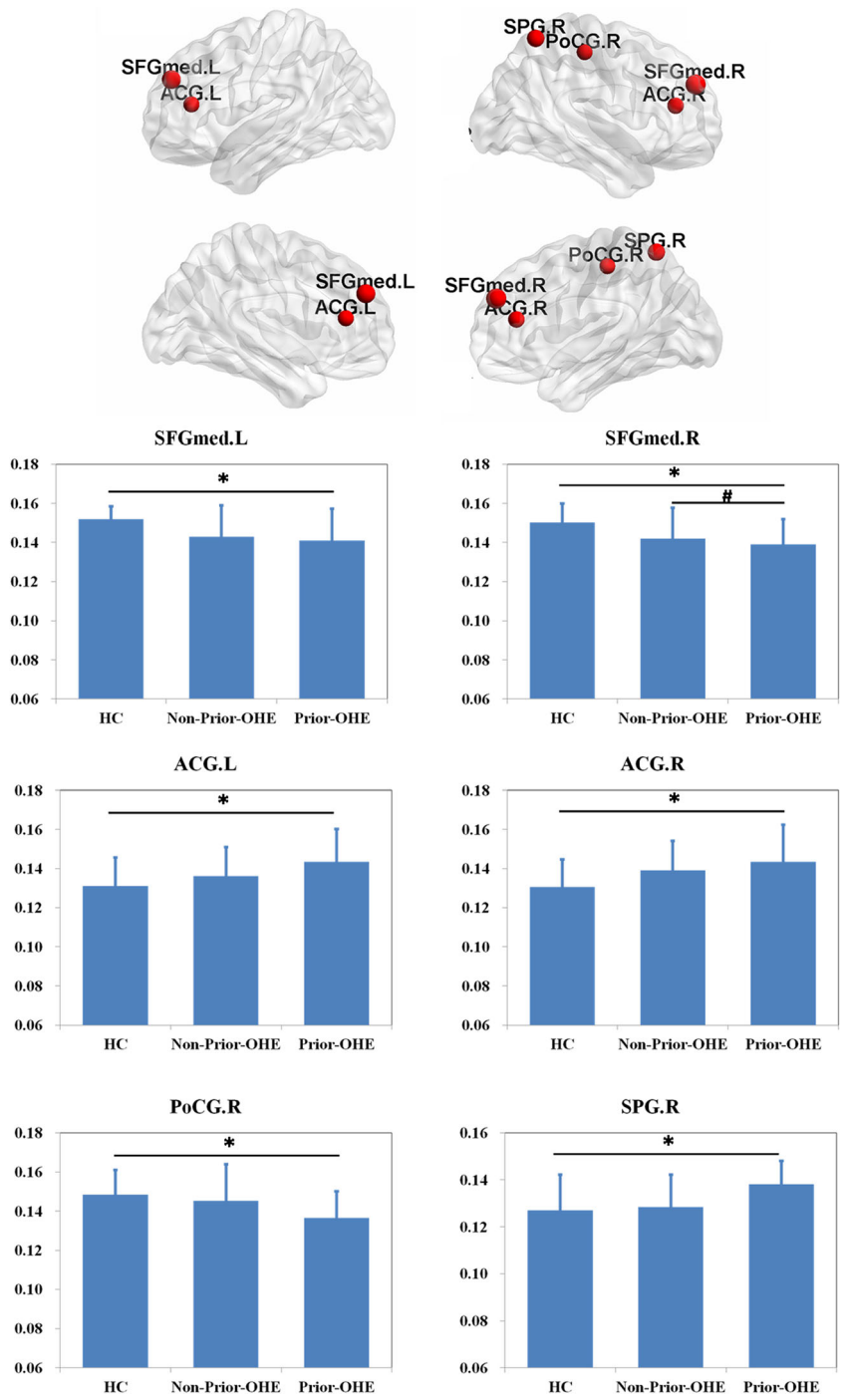

Fig. 3 Brain regions (indicated in red) with the significant group effects in nodal efficiency ($P < 0.05$, uncorrected). Node sizes point out the significance of between-group difference in regional efficiency. The nodal regions are situated based on the centroid stereotaxic coordinates. The markers * and # respectively indicate a significant difference between the Prior-OHE group and the HC group, and the Prior-OHE group and the Non-Prior-OHE group. SFGmed.L, left medial superior frontal gyrus; SFGmed.R, right medial superior frontal gyrus; ACG.L, left anterior cingulate and paracingulate gyri; ACG.R, right anterior cingulate and paracingulate gyri; PoCG.R, right postcentral gyrus; and SPG.R, right superior parietal gyrus

that several cognitive functions (i.e., executive function) involved in special regions (i.e., frontal cortex) could not be fully reversed after an OHE episode. In addition, the bilateral anterior cingulate/paracingulate gyri have been found to be other pathophysiological nodes affected by prior OHE (Chen et al. 2012; Hsu et al. 2012). The functional connectivity of the anterior cingulate cortex decreases even at the early stages of HE, which is associated with attention deficits and executive dysfunction (Chen et al. 2016, 2015; Zhang et al. 2013). An OHE episode also results in decreased nodal efficiency in the anterior cingulate and paracingulate cortex (Hsu et al. 2012; Jao et al. 2015). Converging these previous reports and our findings, the increased nodal efficiency of the bilateral anterior cingulate/paracingulate gyri may be considered as an index that reflects a resolution from OHE; it may be compensating for the loss of attention and execution function induced by OHE.

Table 3 Brain regions with significant group effects in nodal efficiency across three groups

Region		Category	HC	Non-Prior-OHE	Prior-OHE	*P* value (ANOVA)
SFGmed.L	Superior frontal gyrus, medial	Association	0.152 ± 0.007	0.143 ± 0.016	0.141 ± 0.016 *	0.027
SFGmed.R	Superior frontal gyrus, medial	Association	0.150 ± 0.009	0.142 ± 0.016	0.139 ± 0.013 *, #	0.022
ACG.L	Anterior cingulate and paracingulate gyri	Paralimbic	0.131 ± 0.014	0.136 ± 0.014	0.143 ± 0.016 *	0.046
ACG.R	Anterior cingulate and paracingulate gyri	Paralimbic	0.131 ± 0.014	0.139 ± 0.015	0.143 ± 0.019 *	0.043
PoCG.R	Postcentral gyrus	Primary	0.148 ± 0.013	0.145 ± 0.018	0.136 ± 0.014 *	0.048
SPG.R	Superior parietal gyrus	Association	0.127 ± 0.015	0.128 ± 0.013	0.138 ± 0.010 *	0.036

OHE, overt hepatic encephalopathy; HC, healthy control; and ANOVA, analysis of variance. The markers * and # respectively indicate a significant difference in nodal efficiency between the Prior-OHE group and the HC group/Non-Prior-OHE group. The significance level was set to $P < 0.05$ (without correction)

The present study had several limitations that merit further investigation. First, the functional brain networks were constructed at a coarse regional level by parcellating the whole brain into 90 brain regions. It has been demonstrated that the graph metrics are dependent on the resolution of the brain network (Hayasaka and Laurienti 2010; Zalesky et al. 2010). Future work with high-spatial-resolution network analysis should be performed to test the reproducibility of our results. Second, the network measures were calculated from a binary adjacency matrix. It is believed that a weighted network can assimilate supplementary data about functional connectivity strength on uninterrupted scales (Zhang et al. 2011b). Additional evaluations may decide to do a weighted network analysis to provide more precise knowledge of the network organization. Third, the local characteristic analyses were not corrected for multiple comparisons because of the small sample size. A large-cohort evaluation is required to strengthen statistical power. Fourth, the heterogeneous aetiologies for the cirrhosis (i.e. alcoholism) may be the confounding factor that affects our results, because previous studies have demonstrated that the distinct aetiologies could induce various degree of brain structural and functional alterations in cirrhotic patients (Guevara et al. 2011; Lee et al. 2016). Fifth, this is a cross-sectional evaluation that is not large enough to confirm the causal impact of previous OHE on the brain network organization; a longitudinal evaluation needs to be performed.

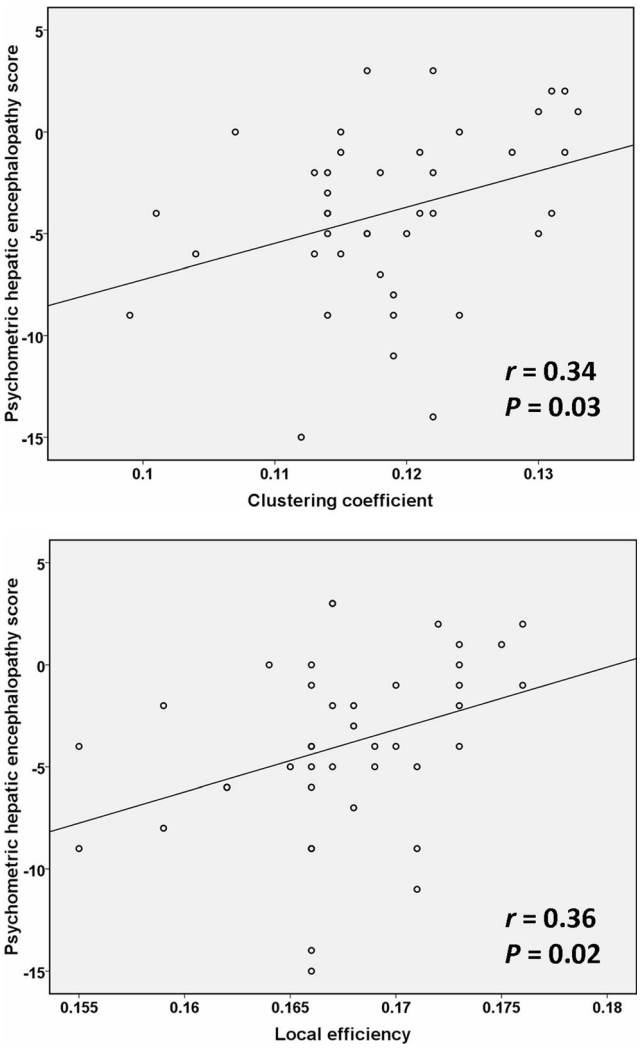

Fig. 4 The correlation between global network measures and cognitive performance in patients with cirrhosis

In summary, cirrhosis leads to a less optimal network organization, which could be aggravated by an episode of prior OHE. Aberrant topological organization of the functional brain network may contribute to the higher risk of cognitive impairments in Prior-OHE patients. Thereby, our findings support the concept that it is reasonable to treat the spectrum of neurocognitive impairment as a continuum in cirrhotic patients with and without prior OHE. The graph theoretical study has improved our understanding of the mechanism underlying neurocognitive dysfunctions related to prior OHE episodes and may be useful in providing biomarkers for monitoring disease evolution of HE. In consideration of the small sample size that limited the statistical power, the future study with a larger sample is encouraged to validate the reproducibility of our results.

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Compliance with Ethical Standards:

Conflicts of interest The authors declare that they do not have any conflicts of interest.

Ethical approval This study was approved by the Ethics Committee of Fujian Medical University Union Hospital.

Informed consent Informed consent was obtained from all individual participants included in the study.

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