Impaired Small World Efficiency in Functional Networks in Liver Cirrhosis Patients

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Introduction

Hepatic encephalopathy (HE) is one of the major complications of liver cirrhosis and a complex neurophysiological syndrome. It will be acts of confusion, personality changes, conscious changes and ups and downs of the neurological manifestations. Network efficiency was defined using a 'small-world' network model that quantifies the effectiveness of information transfer within brain networks. Our purpose of this study is to investigate abnormalities of neuronal connectivity among widely distributed brain regions in patients with liver cirrhosis by using resting-state fMRI.

Methods

The subject group comprised 37 patients with liver cirrhosis (53±8 years) and 34 normal healthy subjects (53±9years). The patients were divided into no HE (n=19), Minimal HE (MHE) (n=9) and over HE (OHE) (n=9) according to the *West Haven criteria* [1] and *Neuropsychological tests* test [2]. Those with two or more abnormal *Neuropsychological tests* test results were classified as MHE [2]. The functional images were obtained using an EPI sequence with the following parameters: 33 axial slices, image resolution = 3.75*3.75*4, and TR= 2000 ms on a GE 3T scanner in Kaohsiung Chang Gung Memorial Hospital. Each subject was scanned in a resting state for 10 min. All resting data underwent the following preprocess procedure: slice timing, head motion correction, spatial normalization with re-sampling to 2x2x2 mm and smooth with 6mm (FWHM) Gaussian kernel using Statistical Parametric Mapping (SPM5, http://www.fil.ion.ucl.ac.uk/spm). Resting-state fMRI Data Analysis Toolkit (REST, http://restingfmri.sourceforge.net), was used for removing the linear trend of time courses and for temporally band-pass filtering (0.01–0.08 Hz) [3]. Prior to the correlation analysis, a linear regression was performed to remove the effects of nine nuisance covariates: the white matter signal; the cerebrospinal fluid signal; and six head motion parameters. Regional mean time series were estimated for each individual by averaging the fMRI time series over all voxels in each of 90 regions utilizing AAL model. We then obtained the inter-regional correlation matrix Rij (i, j=1, 2...N, here N=90) by calculating Pearson's correlation coefficients across subjects between every pair of regions. We applied a cost threshold value (0<C<1) and correlation threshold value (0<R<1) to construct the functional brain networks. This allows us to examine the relative and absolute network efficiency [4] in each group. The absolute and relative network efficiency measurements quantify distinct aspects of topological network organization. To determine whether the network topology in liver cirrhosis were correlated with the degree of severity, we performed a linear regression analysis of each network parameter, [$\int_0^1 E_{global}(r)dr$, $\int_0^1 E_{global}(c)dc$, $\int_0^1 E_{local}(r)dr$, $\int_0^1 E_{local}(c)dc$, $S_{node}(i)$, $\int_0^1 E_{node}(i,r)dr$, $\int_0^1 E_{node}(i,c)dc$] against the severity of liver cirrhosis.

Results

Graph theoretical analysis revealed that the local efficiency curves of functional connectivity networks were intermediate compared with those of the matched regular and random networks over a wide range of network costs and correlation threshold (Fig. 1A, 1B). The patients with liver cirrhosis exhibited significantly decreased integrated absolute local efficiency [$t(2) = -2.01, P=.048$] and integrated relative local efficiency [$t(2) = -2.747$ $P=.008$] in the functional connectivity networks and was negatively correlated with the grades of HE, from healthy controls, no HE to MHE and OHE.

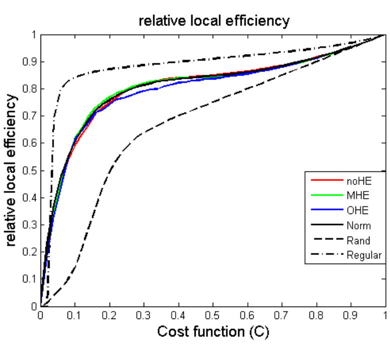

Fig.1A

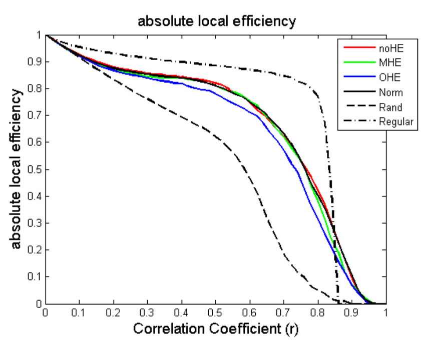

Fig.1B

Anatomal regions	t-score (P-value)		
	Correlation Strength	Absolut Efficiency	Relative Efficiency
Frontal_Sup_Orb_L	−2.611 (0.011)	NS	NS
Frontal_Sup_Orb_R	−2.112 (0.038)	NS	NS
Frontal_Mid_Orb_R	−2.613 (0.034)	−2.748 (0.008)	−2.692 (0.009)
Rolandic_Oper_L	−3.534 (0.001)	−3.120 (0.003)	−2.988 (0.004)
Frontal_Sup_Med_Orb_L	NS	−2.356 (0.021)	−4.044 (0.000)
Frontal_Sup_Med_Orb_R	−2.356 (0.021)	−3.448 (0.001)	−2.818 (0.006)
Calcarine_L	−3.192 (0.002)	−3.009 (0.004)	−2.942 (0.004)
Lingual_R	−2.294 (0.025)	−2.353 (0.021)	−2.466 (0.016)
Occipital_Inf_L	NS	−2.352 (0.022)	−2.160 (0.035)
Occipital_Inf_R	NS	−2.305 (0.046)	NS
Fusiform_L	NS	−2.222 (0.030)	NS
Fusiform_R	NS	−2.323 (0.023)	NS
Temporal_Sup_R	NS	−2.038 (0.046)	−2.986 (0.004)
Temporal_Mid_L	NS	NS	−2.105 (0.039)
Temporal_Mid_R	NS	NS	−2.607(0.011)
Temporal_Inf_R	NS	−2.514 (0.014)	NS

Table.1 NS = non-significant

We also examined the correlations between the **regional** functional connectivity and the severity of HE. Table 1 showed the t-values decreases significantly in nodal characteristics according to the severity of HE.

Discussions and Conclusions

In this study, we used resting-state functional MRI measurements to demonstrate that human brain functional networks exhibited economical small-world properties as characterized by high local efficiency at a relatively low wiring cost. Furthermore, we showed that the network efficiency decreased significantly in proportional to severity of HE, especially in the medial prefrontal cortex and temporal association areas. Our results suggest that resting-state fMRI can supplement relevant information and bedside assessments on HE patients.

References

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