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Changes in the regional homogeneity of resting-state brain activity in minimal hepatic encephalopathy

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ABSTRACT

Resting-state functional magnetic resonance imaging (fMRI) has facilitated the study of spontaneous brain activity by measuring low-frequency oscillations in blood-oxygen-level-dependent signals. Analyses of regional homogeneity (ReHo), which reflects the local synchrony of neural activity, have been used to reveal the mechanisms underlying the brain dysfunction in various neuropsychiatric diseases. However, it is not known whether the ReHo is altered in cirrhotic patients with minimal hepatic encephalopathy (MHE). We recruited 18 healthy controls and 18 patients with MHE. The ReHo was calculated to assess the strength of the local signal synchrony. Compared with the healthy controls, the patients with MHE had significantly decreased ReHo in the cuneus and adjacent precuneus, and left inferior parietal lobe, whereas the regions showing increased ReHo in patients with MHE included the left parahippocampal gyrus, right cerebellar vermis, and bilateral anterior cerebellar lobes. We found a positive correlation between the mean ReHo in the cuneus and adjacent precuneus and the score on the digit-symbol test in the patient group. In conclusion, the analysis of the regional homogeneity of resting-state brain activity may provide additional information with respect to a clinical definition of MHE.

1. Introduction

Minimal hepatic encephalopathy (MHE) is a subclinical complication of liver cirrhosis in which the patients have no manifest mental deficiency or neurological disease, but have subtle cognitive and psychomotor deficits. The neurocognitive dysfunction in MHE is characterized by impaired attention, visuomotor coordination, psychomotor speed, and response inhibition [17]. Evidence that MHE has a negative effect on daily life has been increasing. For example, patients with MHE are unfit to drive [24] as they are at a higher risk of motor vehicle accidents [2]. Furthermore, MHE is thought to be associated with an increased tendency to progress to overt hepatic encephalopathy [9]. Therefore, the early detection of MHE is important for improving patients' prognosis because the appropriate treatment can be administrated in the initial phase. For example, treatment with lactulose improves both cognitive functions and the health-related quality of life in patients with MHE [19]. Unfortunately, the neuropsychological impairments in MHE are easily overlooked by clinicians because they have few apparent manifestations. The adequate evaluation of patients with MHE remains a clinical challenge.

Although many difficulties have impeded attempts to define MHE, neuroimaging methods, particularly magnetic resonance imaging (MRI), may prove useful for evaluating the consequences of pathology related to hepatic encephalopathy. Hyperintensity in the globus pallidus [18] and reduced brain tissue density [8] are seen on standard MRI. Apart from the structural changes, recent magnetic resonance spectroscopy studies demonstrated the cerebral metabolic disturbances in patients with MHE, including an increased glutamine/glutamate peak coupled with decreased myoinositol and choline signals [21], which were related to brain edema [12]. Additionally, task-dependent functional MRI (fMRI) revealed the MHE-related neuronal mechanisms underlying impaired visual judgment [27] and cognitive control [31]. More notably, Zhang et al. [30] recently demonstrated the disruption of default-mode connectivity in episodic hepatic encephalopathy using resting-state fMRI.

Resting-state fMRI has attracted increasing attention and several methods have been developed to assess the synchrony of brain activity at rest. For example, seed-based analysis which is hypothesis-driven has been used to define various brain resting state networks, including the systems for visual, sensorimotor, auditory, dorsal attention, executive control and default mode

Abbreviations: MHE, minimal hepatic encephalopathy; ReHo, regional homogeneity; TMT-A, trail-making test-A; TMT-B, trail-making test-B; DST, digit-symbol test; BDT, block-design test; KCC, Kendall's coefficient of concordance.

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networks [29]. Also, data-driven methods (e.g. independent component analysis), have been employed to clearly characterize these intrinsic brain networks [5,20]. Rather than the functional connectivity analysis between the remote brain regions, Zang et al. [28] proposed using regional homogeneity (ReHo), which targets the temporal synchronization of the inter-regional fMRI signals. This data-driven method provides the opportunity for the general search of abnormal local brain activity coherence across the whole brain, compare to the seed-based analyses. Many data-driven methods show some inherent drawbacks (e.g. independent component analysis needs statistically independent assumption; principal component analysis needs orthogonal patterns assumption [28]), which are not involved in ReHo method. The ReHo method is based on the assumption that the activity of each voxel within a specific brain area has temporal characteristics similar to those of the neighboring voxels (i.e., local synchrony). It should be noted that a higher ReHo was seen in the default mode network, which is involved in a wide spectrum of neurocognitive functions [4]. Moreover, disruption of the local synchrony in the default mode network may contribute to the amnestic type of mild cognitive impairment [1]. Indeed, an aberrant ReHo may be associated with the neurocognitive impairment seen in various neuropsychological disorders as a potential sign of disrupted local functionality. This method has been successfully used to investigate functional alterations in Alzheimer's disease [10], major depression [13], Parkinson's disease [26], and temporal lobe epilepsy [15]. Therefore, an analysis of regional coherence could help to improve our understanding of the neuropathological mechanisms underlying neuropsychological diseases.

Nevertheless, no study has examined the changes in regional brain activity in cirrhotic patients with MHE. Therefore, this study examined whether the synchrony of regional brain activity in patients with MHE patients differed from that in healthy controls and if so, whether the changes in the ReHo were associated with the neurocognitive impairment associated with MHE.

2. Patients and methods

We studied 18 cirrhotic patients with MHE and 18 age-, sex-, and education-matched healthy controls. Of the cirrhotic patients, 16 were post-hepatitis-B-virus (HBV) infection (of these, two also had alcohol-induced damage), and the other two had schistosomiasis. According to the Child–Pugh classification of liver function, six patients were grades A, B, and C, respectively. Of the 18 cirrhotic patients, five had a history of overt hepatic encephalopathy. The diagnosis of MHE was based on neuropsychological tests, including the trail-making test A (TMT-A), the trail-making test B (TMT-B), the digit-symbol test (DST), and the block-design test (BDT). TMT-A tests for psychomotor speed; TMT-B tests for psychomotor speed, set shifting, and divided attention; DST tests for psychomotor speed, attention, and visual memory; BDT tests for visuomotor coordination, visuospatial reasoning, praxis, and psychomotor speed. MHE was defined as present when scores on at least two tests showed impairments that were two standard deviations beyond the normative performance. The control values for the four tests were determined from the measurement in 160 age- and education-matched healthy volunteers.

Magnetic resonance images were acquired on a 1.5-T scanner (Vantage Atlas, TOSHIBA). Resting-state fMRI was performed using an echo planar imaging sequence with the following parameters: repetition time = 2500 ms, echo time = 40 ms, field of view = 240 mm × 240 mm, matrix = 64 × 64, flip angle = 90°. Twenty-two axial slices were collected with 5-mm thicknesses and a 1-mm gap. Each functional run lasted 5 min. The subjects were instructed to relax, keep their eyes closed, and "not to think of anything in particular" during the functional scanning. Three-dimensional high-resolution T1- and T2-weighted images were acquired to detect clinically silent lesions.

The first 10 volumes of each set of fMRI data were not analyzed to allow for signal equilibration. The remaining images were preprocessed using REST software (http://resting-fmri.sourceforge.net/). They were slice-time-corrected and realigned for head motion. The participants with head movement exceeding 2.0 mm of maximum translation in any of the x, y, and z directions or 2.0° of maximum rotation about the three axes were excluded from this study. The resulting images were normalized spatially to the normal EPI template and resampled to 3 mm × 3 mm × 3 mm voxels. Then, linear drift was removed. Finally, a temporal filter (0.01–0.08 Hz) was used to reduce the low-frequency drift and physiological high-frequency noise.

Kendall's coefficient of concordance (KCC) was calculated to measure the regional homogeneity of the time-series of a given voxel with its nearest 26 neighbor-voxels in a voxel-wise way. The formula used to calculate the KCC has been reported elsewhere [28]:

$$W = \frac{\sum (R_i)^2 - n(\bar{R})^2}{(1/12)K^2(n^3 - n)}$$

where W is the KCC among given voxels, ranging from 0 to 1; R_i is the sum rank of ith time point; $\bar{R} = ((n+1)K)/2$ is the mean of the R_i's; K is the number of time series within a measured cluster ($K = 27$, one given voexl plus the number of its neighbors); and n is the number of ranks ($n = 110$). The procedures used to obtain individual ReHo maps were implemented using REST software. Then, the data were smoothed with a Gaussian kernel of 4-mm full-width at half-maximum (FWHM).

A random-effect one-sample t-test ($P < 0.01$, corrected) was used to generate the ReHo maps for both groups. Threshold value was determined by Monte Carlo simulation (the AlphaSim program in AFNI, http://afni.nih.gov/afni/docpdf/AlphaSim.pdf. Parameters were single voxel $P = 0.01$, FWHM = 4 mm, minimum cluster size = 23 voxels, 10,000 simulations). Then, a mask file was created as the union of these two maps. Further analysis using a random-effect two-sample t-test ($P < 0.01$, corrected) was performed to compare the ReHo results of the controls and the patients within the mask. Threshold value was determined using Monte Carlo simulation (AlphaSim; single voxel $P = 0.01$, FWHM = 4 mm, minimum cluster size = 15 voxels, 10,000 simulations). Age and gray matter volume were included as nuisance covariates, to control for the possible influences of these two factors on the results. To obtain the gray matter volume map, voxel-based morphometry was performed using VBM5 toolbox (http://dbm.neuro.uni-jena.de/vbm).

Further correlation analysis was performed with SPSS ver.15.0 (SPSS, Chicago, IL, USA). First, the mean ReHo values of the clusters with significantly different homogeneity were extracted. Then, Pearson's correlation analysis was performed to measure the relationship between the ReHo and neurological performance.

3. Results

We found no significant differences between the groups in terms of demographic data. Compared with the healthy controls, the MHE patients performed poorly on all of the neuropsychological tests (Table 1). Table 2 shows the differences in the ReHo between the patients with MHE and the healthy controls. Compared with the controls, the patients with MHE had significantly lower ReHo in the cuneus and adjacent precuneus, and left inferior parietal lobe, whereas the regions with increased ReHo in the MHE patients included the left parahippocampal gyrus, right cerebellar vermis, and bilateral anterior cerebellar lobes (Fig. 1). We observed