Brain Dysfunction Primarily Related to Previous Overt Hepatic Encephalopathy Compared with Minimal Hepatic Encephalopathy: Resting-State Functional MR Imaging Demonstration

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Purpose:
To investigate whether resting-state brain functional connectivity (FC) differed among cirrhotic patients without overt hepatic encephalopathy (HE) (OHE), those who currently had minimal HE (MHE), or those who had recovered from previous OHE and to investigate whether previous bouts of OHE rather than current MHE predominantly contributed to brain dysfunction in patients without current OHE.

Materials and Methods:
This study was approved by the institutional ethics committee, and informed consent was obtained. Resting-state functional magnetic resonance (MR) data were compared between healthy controls and the following groups of cirrhotic patients: (a) patients without MHE and without previous OHE, (b) patients with current MHE and without previous OHE, and (c) patients with previous OHE. Independent component analysis was applied to identify the best-fit component for the default-mode network (DMN). One-way analysis of variance was performed to detect different FC among groups. Pearson correlation analyses were conducted to determine the relationships between FC and neurocognitive performance.

Results:
Two important regions within the DMN, including the precuneus and posterior cingulate cortex and left medial frontal gyrus, showed significantly different FC among the four groups. A trend of gradually reduced FC in two regions was observed from controls, to patients without HE, and to patients with current MHE, while patients with previous OHE showed remarkably reduced FC in these two regions. Significant correlations were found between FC and neurocognitive performance in cirrhotic patients.

Conclusion:
The reduced resting-state FC within DMN was associated with neurocognitive impairments in MHE and after clinical resolution of OHE. Previous OHE rather than current MHE might be primarily related to brain dysfunction in patients with latent OHE.

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Hepatic encephalopathy (HE) is a common and serious complication in patients with liver dysfunction. As a subclinical condition, minimal HE (MHE) induces a spectrum of neuropsychiatric dysfunctions, including deficits in attention, working memory, and executive functions (1). There is increasing evidence that MHE decreases the quality of life of patients, causes occupational disability, and is associated with worsening clinical outcome (2–4). More important, MHE can be used to predict conversion to overt HE (OHE) (5). OHE includes a series of recognizable clinical symptoms, such as personality change, disorientation, and consciousness disorders, which are associated with the increased risk of death among cirrhotic patients (6). It has been previously reported that residual cognitive impairments could persist after clinical resolution of OHE (7). These cognitive impairments were similar to those seen in MHE. Moreover, there is a relatively higher prevalence of abnormal neuropsychiatric performance in patients with previous OHE (7,8). Indeed, a previous episode of OHE contributes to the incremental recurrence rate in patients with hepatic decompensation (9). Therefore, both MHE and previous bouts of OHE are important factors that can be used to predict a subsequent episode of OHE.

Resting-state functional magnetic resonance (MR) imaging has provided a new perspective to study intrinsic coherence of neural activity between distinct regions (functional connectivity [FC]), on the basis of measuring the low-frequency oscillations of blood oxygenation level–dependent signals (10). Notably, the default-mode network (DMN) is an intrinsic network that exhibits high metabolic activity in the resting state and consistent deactivation during goal-directed tasks. It has become a primary target in neuropsychiatric studies of functional imaging, because of its important role in brain function (11). The DMN engages in collecting and evaluating information, monitoring the external environment, envisioning the future, and self-referential mental activity (11–13). It is believed that deactivation of the DMN contributes to reallocation of cognitive resources for smoothly completing tasks. For example, the failure to reduce activity within the DMN during attention-related tasks can affect goal-oriented behaviors in humans (14). Furthermore, it has been demonstrated that abnormal FC within the DMN is sensitive to brain dysfunction related to neuropsychiatric disorders and may become an alternative biological marker for these diseases (11,15).

It was recently discovered that reduced FC within the DMN is associated with the level of blood ammonia, an important biomarker for OHE (16). In this study, we aimed to investigate whether resting-state FC differed among cirrhotic patients without OHE, including those who currently had MHE and those who had recovered from previous OHE. Moreover, we sought to test the hypothesis that abnormal FC within the DMN may be associated with neurocognitive impairments in MHE and after clinical resolution of OHE. Considering the independent role of previous OHE in structural and functional impairments in patients without OHE (17,18), we would further test whether previous bouts of OHE rather than current MHE predominantly contribute to brain dysfunction in patients without current OHE.

### Materials and Methods

This prospective study was approved by the Institutional Ethics Committee of Zhongda Hospital, Medical School of Southeast University (Nanjing, China), and all participants gave written informed consent.

### Subjects

The demographic and clinical data are shown in Table 1. In this study, we included the following: 21 cirrhotic patients without MHE and without previous OHE (no-HE group), with an age range of 37–62 years and a mean age of 48.4 years; 22 cirrhotic patients with current MHE and without previous OHE (MHE group), with an age range...
Table 1

Demographic and Clinical Variables of Healthy Control Subjects and Cirrhotic Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (n = 19)</th>
<th>No-HE Group (n = 21)</th>
<th>MHE Group (n = 22)</th>
<th>Post-OHE Group (n = 20)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (y)</td>
<td>51.3 ± 7.8</td>
<td>48.4 ± 7.6</td>
<td>54.2 ± 7.8</td>
<td>51.3 ± 9.6</td>
<td>.15</td>
</tr>
<tr>
<td>Age range (y)</td>
<td>34–68</td>
<td>37–62</td>
<td>35–65</td>
<td>26–68</td>
<td>...</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.94†</td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
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<td>19</td>
<td>17</td>
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<tr>
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<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>Mean years of education ± SD</td>
<td>8.5 ± 2.4</td>
<td>8.0 ± 2.5</td>
<td>6.9 ± 3.3</td>
<td>8.4 ± 2.2</td>
<td>.21</td>
</tr>
<tr>
<td>No. with cause of cirrhosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>HBV</td>
<td>...</td>
<td>19</td>
<td>18</td>
<td>14</td>
<td>...</td>
</tr>
<tr>
<td>Alcoholic type</td>
<td>...</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Both HBV and alcoholic type</td>
<td>...</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>Other</td>
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<td>0</td>
<td>2</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>No. with Child–Pugh stage</td>
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<td></td>
<td></td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>A</td>
<td>...</td>
<td>13</td>
<td>12</td>
<td>2</td>
<td>...</td>
</tr>
<tr>
<td>B</td>
<td>...</td>
<td>7</td>
<td>3</td>
<td>8</td>
<td>...</td>
</tr>
<tr>
<td>C</td>
<td>...</td>
<td>1</td>
<td>7</td>
<td>10</td>
<td>...</td>
</tr>
<tr>
<td>Mean NCT-A score ± SD (sec)</td>
<td>46.9 ± 14.7</td>
<td>43.8 ± 11.5</td>
<td>73.0 ± 19.4†</td>
<td>63.7 ± 21.2‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean DST score ± SD†</td>
<td>43.6 ± 9.3</td>
<td>41.9 ± 7.3</td>
<td>25.8 ± 6.0†</td>
<td>30.1 ± 11.0‡</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean BDT score ± SD§</td>
<td>31.7 ± 7.8</td>
<td>29.7 ± 8.3</td>
<td>18.4 ± 6.2‡</td>
<td>22.1 ± 7.6‡</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note.— BDT = block design test, DST = digit symbol test, HBV = hepatitis B virus, NCT-A = number connection test A, SD = standard deviation.

* Indicated the P value in one-way analysis of variance (ANOVA) among the four groups.
§ P value with χ² test.
† Indicated that the group showed significant differences in the results of neuropsychiatric tests, compared with healthy control subjects and with the no-HE group (P < .05). There was no difference in neurocognitive performance between other pairs of groups.
‡ Data are raw scores.

of 35–65 years and a mean age of 54.2 years; 20 cirrhotic patients with previous OHE (post-OHE group), with an age range of 28–68 years and a mean age of 51.3 years; and 19 healthy control subjects, with an age range of 34–68 years and a mean age of 51.3 years. This classification of patients referred to a previous study (18) in which the authors demonstrated much greater brain atrophy in patients with previous OHE than in those without it. Diagnosis of liver cirrhosis was based on liver biopsy results or clinical criteria (including results of physical, laboratory, and imaging examinations). MHE was diagnosed by using the neuropsychiatric tests described below. Patients with previous OHE had no current manifestation of encephalopathy, and their score in the Mini-Mental State Examination was normal (score > 25) (7). Of 20 patients in the post-OHE group, three (15%), three (15%), and 14 (70%) subjects had grade II, III, and IV OHE, respectively.

To be included, patients had to have received a diagnosis of cirrhosis of the liver, and the healthy control subjects were matched to patients in terms of age, sex, and education. The subjects were excluded if they had the following: current OHE (n = 3) or other neuropsychiatric diseases (n = 7); severe organic diseases, such as cardiac disease, advanced pulmonary disorders, and renal failure (n = 6); took psychotropic medications (n = 3); had uncontrolled endocrine or metabolic diseases, such as diabetes mellitus and thyroid dysfunction (n = 6); or had alcohol abuse 6 months prior to the study (n = 1). As a result, a total of 82 subjects were included in this study (Table 1).

Neuropsychiatric Tests and Diagnosis of MHE

The neuropsychiatric tests consisted of the Number Connection Test A, DST, and BDT. The DST and BDT are subtests of the Wechsler Adult Intelligence Scale-Revised for China. The program for defining MHE is described in Appendix E1 (online).

MR Imaging Data Acquisition

MR imaging data were acquired with a 1.5-T imaging unit (Vantage Atlas; Toshiba, Nasu, Japan). The functional images were acquired by using an echo-planar imaging sequence with the following parameters: repetition time msec/echo time msec, 2500/40; field of view, 240 × 240 mm; matrix, 64 × 64; section thickness, 5 mm; section gap, 1 mm; number of sections, 22; and plane of imaging, axial. Subjects were instructed to relax, to keep their eyes closed, and “not to think of anything in particular” during imaging. The functional imaging lasted for 5 minutes. High-spatial-resolution T1-weighted images were obtained by using a gradient-echo sequence with the following parameters: repetition time msec/echo time msec/inversion time msec,
Data Preprocessing

Image analyses were performed by three authors (H.J.C., Y.J., and J.C.L., with 3, 5, and 10 years of experience in image analyses, respectively). Data preprocessing was performed by using software (Data Processing Assistant for Resting-State MRI; http://www.restfmri.net/forum/DPARSF) with statistical parametric mapping software (SPM5; http://www.fil.ion.ucl.ac.uk/spm). This process is described in Appendix E1 (online).

Independent Component Analysis

Independent component analysis was used to obtain the map of each individual’s DMN by using software (GIFT toolbox; Medical Image Analysis Lab, http://icatb.sourceforge.net). The process of defining the DMN component has been described in Appendix E1 (online).

Statistical Analysis

For each group, the subjects’ DMN maps were entered into a random-effect analysis by using the one-sample t test. Threshold levels were set at \( P < .01 \), with correction by using the false discovery rate criterion (cluster size, 270 mm\(^3\)). We then created a DMN mask to confine further group analyses within the DMN. In brief, the mean DMN component for all subjects was obtained after independent component analysis processing, and this DMN map was distributed according to the Z value. We generated the DMN mask by setting the threshold level at a Z value greater than 1.0 in the former DMN map.

One-way ANOVA was performed by using a software tool kit (REST; http://restfmri.sourceforge.net), to determine the different FC within the DMN among the four groups in the study. The threshold level was set at \( P < .05 \), with correction by using false discovery rate criterion and one-tailed analysis (cluster size, 270 mm\(^3\)). An individual’s age and number of years of education were included as nuisance covariates. Recent studies of functional MR imaging have suggested functional results could be influenced by structural differences among groups (19,20). Researchers in a previous study (18) demonstrated the remarkable reduction of brain tissue density in cirrhotic patients without OHE; thus, we took the voxelwise gray matter volume as covariates in this study to eliminate possible confounding from structural differences among groups. Voxel-based morphometric analysis was conducted to generate the gray matter volume map of each subject, with parameters corresponding to functional analysis by using structural brain mapping software (VBM5 toolbox; http://dbm.neuro.uni-jena.de/vbm).

Subsequently, the mean Z value of each cluster with a significant FC difference in the ANOVA analysis was extracted by using the software tool kit (REST) and was compared across four groups by using an ANOVA model and software (SPSS 15.0; SPSS, Chicago, Ill.).

To examine the between-group FC differences, post hoc random-effect analyses by using the two-sample t test were further performed between every pair of four groups. The significance threshold levels were set at \( P < .05 \), with correction by using Monte Carlo simulations and the following parameters: \( P < .05 \) for a single voxel and a minimum cluster size of 810 mm\(^3\). This correction was performed by using a software program (AFNI AlphaSim). Age, number of years of education, and the voxelwise gray matter volume were included as nuisance covariates. Of note, the correlation analyses were performed only for those regions that showed a significant FC difference in the ANOVA analysis.

In addition, we performed Pearson correlative analyses by using software (SPSS 15.0; SPSS) to measure the relationships between the neuropsychiatric data and the mean Z values of clusters with a significant FC difference in the ANOVA analysis.

Results

The results of neuropsychiatric tests were summarized in Table 1. The MHE group and the post-OHE group showed significantly worse neurocognitive performance, compared with the performance of healthy control subjects.

In each group, the DMN could be reproducibly identified as a set of brain regions (Fig 1), including the precuneus and posterior cingulate cortex (PCC), medial prefrontal cortex, bilateral inferior parietal lobule and lateral temporal lobes, and the posterior lobe of the cerebellum. These DMN patterns were well consistent with those reported in previous studies (11,21,22).

Figure 2 and Table 2 show the results of one-way ANOVA among the four groups. There were two regions that showed significant FC differences within the DMN, namely the precuneus and PCC and left medial frontal gyrus. A trend of gradually reduced FC in two regions was observed from control subjects, to patients without HE, and to patients with current MHE. Of note, patients with previous OHE showed remarkably reduced FC in these two regions.

Figures 3 and 4 and Table 3 show the results of post hoc comparisons, by
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This trend of functional changes is in concordance with brain structural impairments that is more serious in patients with previous OHE than in those without it (18). Therefore, the combined findings of the functional and structural data indicate that previous bouts of OHE should be considered as an independent factor during the role of MHE and previous OHE in prediction of a subsequent episode of OHE (5,9).

The second important finding in this current work was the trend toward decreased FC within the DMN among the patients without OHE, namely a gradual reduction in MHE and remarkable reduction after previous OHE.

Discussion

In this study, two major findings were obtained. The first one was the reduction of FC within the DMN in cirrhotic patients without OHE, in those who had current MHE, and in those who had recovered from previous OHE. This evidence supports the current concept that HE represents a continuous dimension of neurocognitive impairments, from MHE to OHE, which may share the same pathologic mechanisms (1), because a previous study has demonstrated a trend of reduced FC within the DMN in the case of OHE (16). Thus, the aberrant FC within the DMN may become a useful biomarker for dynamically monitoring the development of HE in vivo. Among the patients without current OHE, identifying the abnormal FC within the DMN would be helpful in early therapy and prevention of serious OHE, in consideration of the two-sample t test, between every pair of four groups. Compared with healthy control subjects, the no-HE group and MHE group showed decreased FC in the precuneus, whereas the post-OHE group showed remarkably decreased FC in the precuneus and PCC and left medial frontal gyrus. Compared with the no-HE group or MHE group, the post-OHE group showed significantly reduced FC in the precuneus and PCC and left medial frontal gyrus. There was no difference in FC between the no-HE group and MHE group.

Figure 5 and Table 4 show results of the correlation analyses. Between the mean Z value, described in Appendix E1 (online), and the scores of the DST and BDT, for all cirrhotic patients, the significantly positive correlations were found in the precuneus. In addition, we investigated the relationships between the FC, in two clusters that survived after ANOVA, and neuropsychiatric performance. The significant correlations were found between the mean Z value in the precuneus and PCC and the score of the DST (r = 0.26, P = .04) and between the mean Z value in the precuneus and PCC and the score of the BDT (r = 0.12, P = .005).

Figure 1

Group-level analyses of the DMN in, A, healthy control subjects, B, the cirrhotic patients without MHE and without previous OHE, C, the cirrhotic patients with current MHE and without previous OHE, and, D, the cirrhotic patients with previous OHE. T = results from one-sample tests; X, Y, and Z = x, y, and z Montreal Neurological Institute (MNI) coordinates, respectively.

Discussion

In this study, two major findings were obtained. The first one was the reduction of FC within the DMN in cirrhotic patients without OHE, in those who had current MHE, and in those who had recovered from previous OHE. This evidence supports the current concept that HE represents a continuous dimension of neurocognitive impairments, from MHE to OHE, which may share the same pathologic mechanisms (1), because a previous study has demonstrated a trend of reduced FC within the DMN in the case of OHE (16). Thus, the aberrant FC within the DMN may become a useful biomarker for dynamically monitoring the development of HE in vivo. Among the patients without current OHE, identifying the abnormal FC within the DMN would be helpful in early therapy and prevention of serious OHE, in consideration of the role of MHE and previous OHE in prediction of a subsequent episode of OHE (5,9).

The second important finding in this current work was the trend toward decreased FC within the DMN among the patients without OHE, namely a gradual reduction in MHE and remarkable reduction after previous OHE. This trend of functional changes is in concordance with brain structural impairments that is more serious in patients with previous OHE than in those without it (18). Therefore, the combined findings of the functional and structural data indicate that previous bouts of OHE should be considered as an independent factor during...
evaluation of the patient’s condition and selection of therapeutic protocol, such as liver transplantation (23).

It is noted that two pivotal nodes of DMN, including the precuneus and PCC and medial frontal gyrus, showed consistently decreased FC in cirrhotic patients compared with healthy control subjects. The precuneus and PCC is an important node of integration on which the subsystems of DMN converge (11, 21, 22). In particular, the medial precuneus engages in elaboration of egocentric and allocentric information and regulation of a wide spectrum

Table 2

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Volume (mm³)</th>
<th>Brodmann Area</th>
<th>MNI x Coordinate</th>
<th>MNI y Coordinate</th>
<th>MNI z Coordinate</th>
<th>F-Value of Peak Voxel</th>
<th>Maximum Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral precuneus and PCC</td>
<td>3888</td>
<td>7 and 31</td>
<td>3</td>
<td>-69</td>
<td>30</td>
<td>11.1</td>
<td>4.61</td>
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<tr>
<td>Left medial frontal gyrus</td>
<td>378</td>
<td>10</td>
<td>-3</td>
<td>54</td>
<td>0</td>
<td>7.85</td>
<td>3.83</td>
</tr>
</tbody>
</table>

Figure 2: Images detail regions showing significantly different FC within the DMN among four groups: A, precuneus and PCC and, B, left medial frontal gyrus. The average Z value of each significant cluster was extracted and compared across four groups by using the ANOVA model. Box plots indicate the trend of gradually reduced FC from controls, to patients without HE, and to patients with current MHE and the remarkable reduction of FC in patients with previous OHE in these two regions. Box plots in A and B, respectively, show the FC change in region A (bilateral precuneus and PCC) and region B (left medial frontal gyrus). There was no difference in mean Z value between other pairs of groups. * = group that had significantly different Z values in a specific region (P < .05), compared with the other three groups. F = results from ANOVA.

Figure 3: Images detail regions showing decreased FC in, A, cirrhotic patients without MHE and without previous OHE, B, cirrhotic patients with current MHE and without previous OHE, and, C, cirrhotic patients with previous OHE, compared with healthy control subjects. T = results from two-sample t tests, Z = MNI coordinate.
of highly integrated functions, including visuospatial integration, voluntary attention shift, and working memory (24). In addition, the medial frontal gyrus participates in mediation of the interplay between emotional processes and cognitive functions (12). Abnormal activity in the anterior cingulate cortex and prefrontal cortex has been suggested to be associated with the impaired cognitive control in MHE (25). Therefore, considering the important functions of the regions just discussed, the reduction of FC within the DMN may underly the mechanisms of cognitive impairments that are frequently seen in cirrhotic patients, such as impaired attention, working memory, and executive ability (1). This implication is further supported by the significant correlations between decreased FC within the DMN and poor neuropsychiatric performance in cirrhotic patients without OHE.

The patients with current MHE only showed mild reduction of resting-state FC within the DMN, in line with the notion that MHE represents the mildest form of HE. Unexpectedly, the reduced FC in the precuneus was also observed in patients without HE, yet whose neuropsychiatric performance was normal. This inconsistency may have resulted from the patient selection and the demise of neuropsychiatric tests. All patients recruited in our study received a diagnosis of chronic liver cirrhosis, which could exert early, subtle, and chronic influences on the neurologic system (18,25–27). Thus, the disorder in brain intrinsic functional organization may accompany hepatic dysfunction, in consideration of those definite impairments (eg, brain atrophy [18]) at the early stage of cirrhosis of the liver. Nevertheless, neuropsychiatric tests can

### Table 3

<table>
<thead>
<tr>
<th>Group Comparison and Brain Region</th>
<th>Volume (mm³)</th>
<th>Brodmann Area</th>
<th>MNI x Coordinate</th>
<th>MNI y Coordinate</th>
<th>MNI z Coordinate</th>
<th>t Value of Peak Voxel</th>
<th>Maximum Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls vs no-HE</td>
<td>Bilateral precuneus</td>
<td>486</td>
<td>7</td>
<td>6</td>
<td>-57</td>
<td>45</td>
<td>-3.34</td>
</tr>
<tr>
<td>Controls vs MHE</td>
<td>Bilateral precuneus</td>
<td>513</td>
<td>7</td>
<td>3</td>
<td>-54</td>
<td>42</td>
<td>-4.40</td>
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<tr>
<td>Controls vs post-OHE</td>
<td>Bilateral precuneus and PCC</td>
<td>3753</td>
<td>7 and 31</td>
<td>3</td>
<td>-72</td>
<td>33</td>
<td>-5.97</td>
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<tr>
<td>Controls vs post-OHE</td>
<td>Left medial frontal gyrus</td>
<td>378</td>
<td>10</td>
<td>-3</td>
<td>54</td>
<td>0</td>
<td>-4.48</td>
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<tr>
<td>No-HE vs post-OHE</td>
<td>Bilateral precuneus</td>
<td>3294</td>
<td>7 and 31</td>
<td>0</td>
<td>-69</td>
<td>33</td>
<td>-4.55</td>
</tr>
<tr>
<td>No-HE vs post-OHE</td>
<td>Left medial frontal gyrus</td>
<td>297</td>
<td>10</td>
<td>-6</td>
<td>54</td>
<td>-3</td>
<td>-3.40</td>
</tr>
<tr>
<td>MHE vs post-OHE</td>
<td>Bilateral precuneus</td>
<td>3375</td>
<td>7 and 31</td>
<td>-3</td>
<td>-69</td>
<td>30</td>
<td>-5.07</td>
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<tr>
<td>MHE vs post-OHE</td>
<td>Left medial frontal gyrus</td>
<td>108</td>
<td>10</td>
<td>-3</td>
<td>63</td>
<td>-6</td>
<td>-3.99</td>
</tr>
</tbody>
</table>

### Figure 4

- **A**: Images detail regions showing decreased FC in the cirrhotic patients with previous OHE, compared with, A, cirrhotic patients without MHE and without previous OHE and, B, cirrhotic patients with current MHE and without previous OHE. T = results from two-sample t tests, Z = z MNI coordinate.
Table 4

<table>
<thead>
<tr>
<th>Correlation and Brain Region</th>
<th>Volume (mm³)</th>
<th>Brodmann Area</th>
<th>MNI x Coordinate</th>
<th>MNI y Coordinate</th>
<th>MNI z Coordinate</th>
<th>r Value of Peak Voxel</th>
<th>Maximum Z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z value and DST score</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Bilateral precuneus</td>
<td>1323</td>
<td>7</td>
<td>−6</td>
<td>−78</td>
<td>42</td>
<td>0.45</td>
<td>3.57</td>
</tr>
<tr>
<td>Right precuneus</td>
<td>189</td>
<td>31</td>
<td>6</td>
<td>−51</td>
<td>30</td>
<td>0.41</td>
<td>3.25</td>
</tr>
<tr>
<td>Left precuneus</td>
<td>27</td>
<td>31</td>
<td>−9</td>
<td>−63</td>
<td>27</td>
<td>0.34</td>
<td>2.68</td>
</tr>
<tr>
<td>Z value and BDT score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral precuneus</td>
<td>2403</td>
<td>7</td>
<td>−3</td>
<td>−69</td>
<td>42</td>
<td>0.51</td>
<td>4.14</td>
</tr>
</tbody>
</table>

Figure 5

Images detail regions in which the mean Z values showed significantly positive correlations with the scores of, A, DST and, B, BDT. C, Scatterplot shows the significant correlations between neuropsychiatric data and the mean Z values of precuneus and PCC. 

be used to only examine the temporary mental status of patients and can be affected by various subject factors (28). Thus, we proposed the possibility that resting-state FC might be a more reliable index for reflecting early brain dysfunction induced by liver decompensation than neuropsychiatric assessments, to some extent.

The dominant reduction of FC within the DMN was observed in cirrhotic patients with previous OHE, as compared with the no-HE and MHE patient groups. This finding is well consistent with data in previous reports that patients with previous OHE had higher prevalence of neurocognitive impairments than those without it (7,29) and that previous OHE rather than MHE predominantly impaired health-related quality of life in cirrhotic patients without OHE (17). Two potential reasons may account for the reduction of FC in these patients even after clinical resolution from OHE. The first potential reason is that the reduction of FC may be the representation of residual brain dysfunction owing to previous OHE, because it was recently proposed that OHE could induce irreversible impairments in neurocognitive functions (7). Furthermore, brain structural and resting-state functional impairments have also been found in patients with previous OHE (30). Thus, the disconnection within the DMN may be partly implicated in the mechanisms underlying incomplete improvement of cognitive functions after resolution of OHE. The second possible reason is that the reduction of FC may be the representation of residual brain dysfunction owing to previous OHE, because it was recently proposed that OHE could induce irreversible impairments in neurocognitive functions (7). Furthermore, brain structural and resting-state functional impairments have also been found in patients with previous OHE (30). Thus, the disconnection within the DMN may be partly implicated in the mechanisms underlying incomplete improvement of cognitive functions after resolution of OHE. The second possible reason is that the reduction of FC within the DMN may indicate the cerebral reorganization after OHE. The adaptive reorganization of the brain intrinsic network has been observed in various neurologic diseases, such as ischemic infarct (31) and traumatic brain injury (32). Likewise, Blauenfeldt et al (33) have proposed the possibility...
of cortical reorganization in HE patients, on the basis of an electrophysiological investigation. Therefore, the remarkably decreased FC within the DMN might be associated with brain functional remodeling, yet which could induce the reduction of brain working efficiency, as revealed in other neurologic diseases (31,32).

The correlation between resting-state FC and neuropsychiatric performance in cirrhotic patients may suggest that resting-state FC could be an alternative index to characterize the neuropathologic findings of HE. It is noted that the post-OHE group showed poor neuropsychiatric performance, indicating the persistence of neurocognitive impairments after resolution of OHE. However, it is not well understood that the post-OHE group with the lower FC showed the better neurocognitive performance, compared with the MHE group. This mismatching may be associated with therapeutic effect of correcting the systemic metabolic disorder for OHE patients. For example, six patients in the post-OHE group had received treatments by using an artificial liver support system, but the improvement of neurocognitive functions secondary to these treatments often is extent and time limited, while the brain intrinsic functional organization, reflected by FC within the DMN, may hardly recover, in consideration of the irreversible structural impairments occurring during OHE (18).

There were several limitations that should be acknowledged in this study. First, we used a relatively lower sample rate (repetition time, 2.5 seconds) to obtain functional images, because of the finite capability of the MR imaging unit. Second, we chose to analyze only the resting-state FC within the DMN, in consideration of its novel role in brain function. However, other brain resting-state networks may be also affected by HE, such as the attention network and the executive control network, because the cognitive impairments in corresponding domains have been confirmed in HE patients. Third, we did not include patients with OHE in this study, considering their serious medial conditions and poor compliance. We thought that the majority of patients with OHE (especially grades II–IV) could not well maintain the “resting state” during functional MR imaging. Therefore, a longitudinal study is needed in the future to better investigate the dynamic alterations of resting-state brain function in cirrhotic patients.

In conclusion, we determined the existence of reduced resting-state FC in cirrhotic patients without OHE, which was associated with neurocognitive impairments. The trend of decreased FC within the DMN, namely mild reduction in MHE and remarkable reduction after previous OHE, implied that previous bouts of OHE rather than current MHE might predominantly contribute to brain dysfunction in cirrhotic patients without OHE. These findings suggest that FC within the DMN may become a supplementary imaging marker to evaluate the mental status of cirrhotic patients with latent OHE.

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