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Disrupted thalamic resting-state functional connectivity in patients with minimal hepatic encephalopathy

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ABSTRACT

Background and purpose: Little is known about the role of thalamus in the pathophysiology of minimal hepatic encephalopathy (MHE). The purpose of this study was to investigate whether the thalamic functional connectivity was disrupted in cirrhotic patients with MHE by using resting-state functional magnetic resonance imaging (rs-fMRI).
Materials and Methods: Twenty seven MHE patients and twenty seven age- and gender- matched healthy controls participated in the rs-fMRI scans. The functional connectivity of 11 thalamic nuclei were characterized by using a standard seed-based whole-brain correlation method and compared between MHE patients and healthy controls. Pearson correlation analysis was performed between the thalamic functional connectivity and venous blood ammonia levels/neuropsychological tests scores of patients.
Results: The ventral anterior nucleus (VAN) and the ventral posterior medial nucleus (VPMN) in each side of thalamus showed abnormal functional connectivities in MHE. Compared with healthy controls, MHE patients demonstrated significant decreased functional connectivity between the right/left VAN and the bilateral putamen/pallidum, inferior frontal gyri, insula, supplementary motor area, right middle frontal gyrus, medial frontal gyrus. In addition, MHE patients showed significantly decreased functional connectivity with the right/left VPMN in the bilateral middle temporal gyri (MTG), temporal lobe, and right superior temporal gyrus. The venous blood ammonia levels of MHE patients negatively correlated with the functional connectivity between the VAN and the insula. Number connecting test scores showed negative correlation with the functional connectivity between the VAN and the insula, and between the VPMN and the MTG.
Conclusion: MHE patients had disrupted thalamic functional connectivity, which mainly located in the bilateral ventral anterior nuclei and ventral posterior medial nuclei. The decreased connectivity between thalamus and many cortices, and basal ganglia indicated reduced integrity of thalamic RSN in MHE.

1. Introduction

Hepatic encephalopathy (HE) is a common and important neuropsychiatric complication in patients with liver cirrhosis [1]. Minimal hepatic encephalopathy (MHE), the mildest form of spectrum of HE, usually has no recognizable clinical symptoms of HE but has mild cognitive, motor control, and concentration attention deficits [2,3]. The prevalence of MHE is high in cirrhotic patients and varies between 30% [4] and 84% [5]. MHE is associated with impaired health-related quality of life, and gets worse as time passes [6–8]. Therefore, it is important to diagnose and treat MHE before major neurological damage occurs. However, so far, the exact pathophysiological mechanisms of MHE remain not very clear.

Previous functional neuroimaging studies have greatly advanced our understandings of the pathogenesis of MHE, in which accumulating evidence suggest that an alteration of the cortico-striato-thalamic pathway may play an important role in this disease [9,10]. In particular, previous position emission tomography (PET) studies had uniformly demonstrated that MHE

Abbreviations: MHE, minimal hepatic encephalopathy; rs-fMRI, resting-state functional MRI; PLC, posterior lobe of cerebellum; PHG, parahippocampal gyrus; MTG, middle temporal gyrus; MFG, middle frontal gyrus; NCT-A, number connecting-A; DST, digit symbol test.

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patients exhibited a redistribution of cerebral blood flow and metabolic rate of glucose and ammonia from various cortical regions to basal ganglia and thalamus [10,11].

However, many brain regions are functionally related and interconnected. It is now generally accepted that the intrinsically connected functional architecture composes some resting-state networks (RSNs), and plays a role in maintaining baseline human cognition and metabolic equilibrium in the resting state [12,13]. Functional connectivity analysis algorithms, which focused on the temporal synchrony or correlation between two or more spatially separate regions, contribute to the understanding of neuro-pathophysiological mechanism of many neuropsychiatric diseases. It has been widely used in social anxiety disorder [14], mild cognitive impairment [15] etc.

A few previous studies have investigated the functional connectivity of HE. Zhang et al. first reported a decreased functional connectivity within the brain default mode network (DMN) in HE patients in a resting-state fMRI (rs-fMRI) study [16]. Chen et al. showed that the decreased functional connectivity between some regions within the DMN still persisted after clinical recovery from previous episodes of overt HE [17]. Qi et al. also found that MHE patients had selective impairments of RSNs, with aberrant dorsal attention network, DMN, visual and auditory network, and spared sensorimotor network and self-referential network [18]. However, to the best of our knowledge, the resting functional networks of deep gray matter structures, such as the thalamus, have little been investigated in HE.

Thalamus is a vital subcortical gray matter region which integrates neural activity from widespread neocortical inputs and outputs, and is believed to modulate and facilitate communication in all areas of the cerebral cortex [19,20]. Hence, the thalamic functional connectivity network is critical for integrating information across the functional circuits of the central nervous system. In cirrhotic patients with HE, the thalamus usually showed abnormal regional metabolism [10,21] and lower thalamo-cortical coupling [22], suggesting important role in the neuro-pathophysiology of HE. In the current study, we hypothesized that thalamic resting-state functional connectivity was disrupted in MHE, the mildest form of HE. To test our hypothesis, we used different thalamic nuclei as seed regions to investigate the features of specific thalamic functional connectivity in MHE patients.

2. Materials and methods

2.1. Subjects

This study was approved by the local Medical Research Ethics Committee. Twenty seven MHE patients (20 male, 7 women, mean age: 54.81 ± 6.59 years) hospitalized at our hospital were included in this study, after giving the written informed consents. The inclusion criteria for recruitment of the patients were as follows: the patients with clinical proven hepatic cirrhosis, without clinical manifestation of HE, had abnormal neuropsychological tests scores, who could finish the MR exam without any MRI contraindication, age 18 years or older. The exclusion criteria for all the subjects included any drug abuse history, brain lesions such as tumor, stroke, diffuse white matter abnormalities assessed on basis of medical history and conventional MRI, or translation more than 1.0 mm or rotation than 1.0° during MR scanning.

Twenty seven age-and gender-matched right-handed healthy controls from local community were recruited in this study (20 male, 7 women, and mean age: 52.07 ± 9.00 years). All healthy controls had no diseases of the liver and other systems, with no abnormal findings in abdominal ultrasound scans and conventional brain MR imaging. All controls underwent neuropsychological tests before the MR scanning. No laboratory tests were performed thus unavailable for them.

2.2. Neuropsychological tests

The diagnosis of MHE was made according to the recommendation by the working party of 11th World Congress of Gastroenterology in Vienna in 1998 [3]. The test battery includes number connecting-A (NCT-A) and digit symbol test (DST), which are recommended by the working party. NCT-A tests for psychomotor speed, with the test score being the time the subject performs the test, and the worse performance is indicated by a longer time for completion with the test; DST tests for psychomotor speed, attention, and visual memory, with the test score being the total number of correct sequential matching of symbols to numbers in a 90-s interval [6]. When the scores of at least one test were beyond 2SD (standard deviation) of mean value of age-matched healthy controls, the cirrhotic patients could be regarding having MHE [6,23].

2.3. Laboratory examinations

Laboratory parameters including prothrombin time, protein metabolism tests, venous blood ammonia were obtained from all patients to assess the severity of liver disease, within one week before MR scanning. The grade of hepatic function was determined according to the Child–Pugh score. The score system considered five variables, i.e., ascites, encephalopathy, prothrombin time, and serum levels of bilirubin and albumin, and assigned a score ranging from 1 to 3 to each variable. Of these 27 MHE patients, 12 patients had Child–Pugh grade A and 15 patients had Child–Pugh grade B. The etiology of cirrhosis was hepatitis B in 25 patients, hepatitis A and C in each one patient.

2.4. MRI data acquisition

MRI data were acquired on a 3 T MR scanner (TIM Trio, Siemens Medical Solutions, Erlangen, Germany). All the patients and healthy controls were instructed to close their eyes but be awake during the resting-state functional MR imaging examination. Foam pad was used to minimize the head motion of all subjects. Axial anatomical images were acquired using a T1-FLASH sequence (TR/TE = 350 ms/2.46 ms, matrix = 320×256, field of view (FOV) = $240 \times 240\,mm^2$, slice thickness/gap = 4.0 mm/0.4 mm, 30 slices covered the whole brain). Functional images were then obtained aligned along the anterior commissure–posterior commissure line with a single-shot, gradient-recalled echo planar imaging sequence (TR/TE = 2000 ms/30 ms, FOV = $240 \times 240\,mm^2$, flip angle = 90°, matrix = 64×64, voxel size = $3.75 \times 3.75 \times 4\,mm^3$). A total of 250 brain volumes were collected, resulting in a total scan time of 500 s. Then, images with coronal T2-FLASH sequence (TR/TE = 8500/93 ms, slices = 24, matrix = 256×204, flip angle = 130°, FOV = $22 \times 9.06\,cm^2$, thickness/gap = 5.0 mm/1.5 mm) were acquired to exclude other brain lesions.

2.5. Data preprocessing

Data were pre-processed using SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm). The first 10 images were excluded for magnetization to reach equilibrium. The remaining 240 consecutive volumes were used for data analysis. Slice-timing adjustment and realignment for head-motion correction were performed. No translation or rotation parameters in any given data set exceeded 1.0 mm or 1.0°. We also evaluated the group differences in translation and rotation of head motion