Resting-State fMRI Degree Centrality for Evaluating Cognitive Impairment in Minimal Hepatic Encephalopathy: A Postprint

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Abstract

In the MHE group, brain regions with decreased DC values included the right precentral gyrus, right middle occipital gyrus, and left angular gyrus, with all inter-group comparisons showing statistical significance (P<0.05); brain regions with increased DC values included the right middle frontal gyrus, right inferior parietal lobule, and left middle temporal gyrus, with all inter-group comparisons showing statistical significance (P<0.05). Correlation analysis revealed that Digital Symbol Test (DST) scale scores in the MHE group were positively correlated with DC values in the left superior temporal gyrus, Number Connection Test-A (NCT-A) scale scores were negatively correlated with DC values in the right inferior temporal gyrus (both P<0.05), Montreal Cognitive Assessment (MoCA) scores were positively correlated with DC values in the bilateral inferior frontal gyrus (P<0.05), and negatively correlated with DC values in the left inferior temporal gyrus (P<0.05). Conclusion: Resting-state MHE patients exhibit abnormal brain functional network connectivity properties, and DC values may serve as a useful indicator for quantifying MHE-related pathophysiological changes and a potential neuroimaging marker for cognitive impairment in MHE.

Full Text

Evaluation of Cognitive Impairment in Patients with Minimal Hepatic Encephalopathy Based on Degree Centrality of Resting-State fMRI

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Abstract

Background: Minimal hepatic encephalopathy (MHE), as a special type of hepatic encephalopathy (HE), presents with atypical clinical symptoms but mild neurological and psychiatric deficits that are easily overlooked by patients and their families. However, the neurobiological mechanisms underlying these deficits remain incompletely understood.

Objective: To investigate abnormal patterns of brain functional network connectivity properties and characterize changes in functional brain regions in MHE patients from a network node perspective using degree centrality (DC) analysis of resting-state functional magnetic resonance imaging.

Methods: We prospectively enrolled 28 hepatitis B cirrhosis patients with MHE (MHE group), 30 hepatitis B cirrhosis patients without MHE (cirrhosis group), and 34 healthy volunteers (healthy control group). All subjects underwent conventional magnetic resonance imaging (MRI) and resting-state blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI). Whole-brain DC values were compared among the three groups, and Pearson correlation analysis was used to evaluate the relationship between brain region DC values and cognitive scale scores in MHE patients. DC values from brain regions showing significant differences were extracted for correlation analysis with cognitive scores.

Results: Compared with both the healthy control and cirrhosis groups, the MHE group showed significantly decreased cognitive scores (all $P < 0.05$). Relative to healthy controls, the MHE group exhibited decreased DC values in the right precentral gyrus, right middle occipital gyrus, and left angular gyrus, along with increased DC values in the right middle frontal gyrus, right inferior parietal lobule, and left middle temporal gyrus (all $P < 0.05$). Correlation analysis revealed that in the MHE group, the Digital Symbol Test (DST) score was positively correlated with DC values in the left superior temporal gyrus, while the Number Connection Test-A (NCT-A) score was negatively correlated with DC values in the right inferior temporal gyrus (both $P < 0.05$). Montreal Cognitive Assessment (MoCA) scores were positively correlated with DC values in the bilateral inferior frontal gyrus ($P < 0.05$) and negatively correlated with DC values in the left inferior temporal gyrus ($P < 0.05$).

Conclusions: Resting-state brain functional network connectivity properties

are abnormal in MHE patients, and DC values may serve as a useful indicator for quantifying MHE-related pathophysiological changes and a potential neuroimaging marker for MHE cognitive impairment.

Keywords: Minimal hepatic encephalopathy; Cognitive impairment; Degree centrality; Resting-state

Introduction

Hepatic encephalopathy (HE) is a neurocognitive dysfunction disorder based on metabolic disturbances caused by severe liver disease and represents a common neuropsychiatric complication in cirrhotic patients, with clinical manifestations ranging from mild cognitive impairment to coma and death [1, 2]. Minimal hepatic encephalopathy (MHE), as a special type of HE, presents with atypical clinical symptoms, manifesting only as various cognitive deficits including memory and attention impairments [3]. The occurrence of MHE significantly impacts the health-related quality of life for both patients and their caregivers [4, 5] and is associated with high mortality [6]. Therefore, early diagnosis and treatment of MHE is crucial for improving patient outcomes. Currently, the neuropathophysiological mechanisms of MHE remain unclear.

Degree centrality (DC) analysis based on resting-state functional magnetic resonance imaging can characterize the centrality of different nodes in brain networks and detect topological functional network changes in the connectivity relationships between different nodes and whole-brain functional network nodes [7], thereby quantifying the importance of each node in the brain network. This method has been widely used to reveal mechanisms of other neuropsychiatric diseases such as Alzheimer' s disease, type 2 diabetes, and depression [8-10]. However, its application in MHE research is limited, with only Chen et al. [11] using this method to identify abnormalities in intrinsic functional connectivity across multiple brain regions in MHE. Notably, that study lacked a simple cirrhosis control group; adding such a group could better observe cognitive changes at various stages in MHE patients and enable preventive treatment.

Therefore, this study employed DC analysis to explore changes in brain network nodes in MHE patients, aiming to provide neuroimaging evidence from a brain network node perspective for the possible pathogenic mechanisms underlying cognitive impairment in MHE.

Methods

This prospective study was approved by the Research Ethics Committee of the General Hospital of Ningxia Medical University (KYLL-2021-841). Initially, 40 healthy volunteers were recruited. Exclusion criteria included: (1) left-handedness; (2) education level < 6 years; (3) brain parenchymal lesions such as tumors, infectious diseases, or trauma based on medical history and

conventional imaging; (4) head motion > 2.0 mm translation or > 2.0° rotation during MRI; (5) contraindications to MRI examination; (6) severe cardiac, renal, or pulmonary disease; (7) liver cancer, hepatitis C infection, or other hepatitis virus infections; (8) hepatic encephalopathy due to acute liver failure or psychiatric and behavioral abnormalities caused by other diseases (toxic encephalopathy, metabolic encephalopathy, intracranial hemorrhage, tumors, infections, etc.). All participants were informed about the study and provided written informed consent prior to the experiment.

Two experienced radiologists diagnosed MHE according to guidelines from the 11th World Congress of Gastroenterology Working Party report in Vienna (1998) [12]. Each patient underwent two neuropsychological tests [Number Connection Test-A (NCT-A) and Digital Symbol Test (DST)] and one cognitive assessment test [Montreal Cognitive Assessment (MoCA)]. Patients with positive results on both neuropsychological tests were assigned to the MHE group, while those with one positive result were assigned to the simple cirrhosis group. Reference ranges for NCT-A and DST positivity followed Li et al. [13].

MRI data were acquired using a 3.0T MRI scanner (Architect, GE, USA). All subjects were instructed to lie quietly with eyes closed and remain awake during scanning, with foam pads used to stabilize the head and minimize motion. Conventional MRI sequences (T2-FLAIR) were first performed to exclude organic lesions (parameters: TR = 4000 ms, TE = 107 ms, slice thickness = 6 mm, slice gap = 1 mm, field of view = 250 mm × 250 mm), followed by acquisition of 3D-T1WI structural images and fMRI functional images with parameters detailed in Table 1 .

Image data post-processing was performed using the resting-state fMRI data processing package DPABI V4.3.5.0 Advanced Edition (http://rfmri.org/DPABI) based on Matlab2012a, following the processing pipeline described by Yan et al. [14]. The preprocessing steps included: (1) format conversion; (2) removal of the first 10 time points for each subject; (3) slice timing correction; (4) head motion correction; (5) spatial normalization; (6) smoothing with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel; (7) linear detrending and band-pass filtering (0.01–0.08 Hz); and (8) nuisance regression to remove signals from cerebrospinal fluid, white matter, and head motion parameters. Weighted DC was calculated for each voxel as the sum of weights of effective connections ($r > 0.25$) [15], representing the number of nodes with significant functional connections to each node. Finally, voxel-wise DC values were transformed into Z-score weighted DC distribution maps for each subject using Fisher-Z transformation. In brain networks, a node' s DC value represents its connection strength with all other nodes and reflects its importance in functional integration.

Statistical analyses were performed using SPSS 23.0 (International Business Machines Corporation, USA) for cognitive scale scores, education level, age, and gender. ANOVA was used to compare differences among the control, cirrhosis, and MHE groups, with post-hoc comparisons using LSD tests. Categorical data (gender) were compared using ^{2} tests, with $P < 0.05$ considered statisti-

cally significant. GraphPad Prism 9.3 (GraphPad, USA) was used for graphical presentation.

For imaging data, two-sample t-tests were performed on normalized DC brain maps among the three groups using DPARSF and SPM8 software [14]. AlphaSim correction was applied to P-values, with voxel clusters > 18 and $P < 0.05$ considered statistically significant. Pearson correlation analysis was used to evaluate relationships between brain region DC values and cognitive scale scores in MHE patients, with DC values extracted from significantly different brain regions for correlation analysis with cognitive scores. Correlation results were also AlphaSim-corrected, with $P < 0.05$ considered statistically significant.

Results

Table 2 presents the clinical and demographic characteristics of the cirrhosis, MHE, and control groups. Data from 3 cirrhosis patients, 4 MHE patients, and 6 control subjects were excluded due to excessive motion or poor image resolution. The final analysis included 34 healthy controls, 30 cirrhosis patients, and 28 MHE patients. The three groups showed no significant differences in gender ($P = 0.656$), age ($P = 0.452$), or education level ($P = 0.392$). The MHE group demonstrated significantly different NCT-A, DST, and MoCA scores compared with both the cirrhosis and healthy control groups (all $P < 0.001$), while no significant differences were observed between the healthy control and cirrhosis groups (all $P > 0.05$).

Compared with healthy controls, the MHE group showed increased DC values in the right middle frontal gyrus, left middle temporal gyrus, and right inferior parietal lobule, and decreased DC values in the left angular gyrus, right middle occipital gyrus, and right precentral gyrus (all $P < 0.05$). Compared with the cirrhosis group, the MHE group exhibited decreased DC values in the right middle temporal gyrus and left precuneus (both $P < 0.05$). Compared with healthy controls, the cirrhosis group showed increased DC values in bilateral middle temporal gyri and decreased DC values in the left angular gyrus (both $P < 0.05$). These findings are detailed in Table 3 and Figure 1 [Figure 1: see original paper].

Correlation analysis revealed that in the MHE group, DST scores were positively correlated with DC values in the left superior temporal gyrus, while NCT-A scores were negatively correlated with DC values in the right inferior temporal gyrus (both $P < 0.05$) (Figure 2 [Figure 2: see original paper]). Additionally, MoCA scores were positively correlated with DC values in the bilateral inferior frontal gyrus ($P < 0.05$) and negatively correlated with DC values in the left inferior temporal gyrus ($P < 0.05$) (Figure 3 [Figure 3: see original paper]).

Discussion

This study used voxel-based DC analysis to investigate brain functional network connectivity properties in cirrhosis and MHE patients, assessing changes in relevant brain regions within the whole-brain functional connectivity network. We found abnormal DC values in multiple brain regions in both cirrhosis and MHE patients, involving the frontal lobe, temporal lobe, motor cortex, and subcortical areas. Furthermore, we identified significant correlations between DC values in certain brain regions and cognitive scale scores in MHE patients. Based on these observations, we speculate that cognitive impairment in MHE patients is associated with altered DC values in brain regions, providing objective neuroimaging evidence for further elucidating the neuropathological mechanisms of MHE.

Our results demonstrated significantly decreased DC values in the right precentral gyrus, right middle occipital gyrus, and left angular gyrus in MHE patients compared with controls, indicating reduced connection strength and node centrality of these regions within the whole-brain network. The precentral gyrus is closely associated with motor control and response selection and is considered a core region of the mirror neuron system, playing an important role in action understanding and imitation [16, 17]. The decreased DC value in the right precentral gyrus in MHE patients suggests significantly reduced centrality of this region within the whole-brain network, implying functional deficits. Reduced DC values in motor-related cortical areas may be a key factor underlying motor function impairment in MHE patients. Zhan et al. [18] also found decreased functional connectivity between the precentral gyrus and the second major brain subnetwork, primarily comprising default mode network regions (such as bilateral posterior cingulate cortex and medial prefrontal cortex), consistent with our findings.

The middle occipital gyrus is involved in visual information collection, formation, and processing [19] as well as visual attention activities [20, 21]. The decreased DC value in the right middle occipital gyrus in MHE patients may indicate dysfunction in visual information processing and top-down modulation of visuospatial selective attention. Consistently, we found significantly lower visuospatial scores in MHE patients based on MoCA assessments. Zhang et al. [22] also confirmed abnormal dynamic graphical properties of brain networks in MHE patients, manifesting as visual memory deficits. Visual association areas (middle occipital gyrus, temporal lobe) may represent vulnerable brain regions in MHE patients, and structural damage to these areas may be the primary cause of visual function decline.

The angular gyrus plays a critical role in memory retrieval and integrates visual and auditory imagery to facilitate comprehension. Bottom-up attention drives attention to relevant memory cues through the ventral attention network in parietal cortex (including the angular gyrus) [23]. Our finding of decreased DC values in the left angular gyrus in MHE patients suggests that reduced node

number and centrality in this region may interfere with information processing, potentially representing the main cause of attention and memory impairment in MHE.

We used NCT-A, DST, and MoCA scores to assess the primary domains of cognitive impairment in MHE patients, which involve multiple cognitive areas including visuospatial and executive function, attention and reaction speed, memory, motor speed, motor accuracy, delayed recall, and calculation and abstract thinking [24, 25]. Our experiments revealed abnormal performance in MHE patients across these scales, specifically including reduced visuospatial function, short-term memory decline, and decreased reaction speed and fine motor abilities. Notably, correlation analysis between cognitive scale scores and brain region DC values in MHE patients revealed that DST scores were positively correlated with DC values in the left superior temporal gyrus, NCT-A scores were negatively correlated with DC values in the right inferior temporal gyrus, and MoCA scores were negatively correlated with DC values in the left inferior temporal gyrus while positively correlated with bilateral inferior frontal gyrus DC values. The superior temporal gyrus, inferior temporal gyrus, and inferior frontal gyrus play key roles in advanced cognitive functions and response inhibition processing, including memory and attention [27]. These abnormal correlation results may provide neuroimaging evidence for cognitive impairment in MHE patients. Moreover, these findings align with the abnormal cognitive scale scores observed in MHE patients, suggesting that more significant alterations in DC values of the superior temporal gyrus, inferior temporal gyrus, and inferior frontal gyrus correspond to more severe cognitive impairment. Therefore, we speculate that cognitive dysfunction in MHE patients may be related to abnormal resting-state brain functional connectivity, and DC values may serve as a neuroimaging marker for quantifying the severity of cognitive impairment in MHE.

Additionally, we found increased DC values in the right middle frontal gyrus, left middle temporal gyrus, and right inferior parietal lobule in MHE patients, as well as increased DC values in bilateral middle temporal gyri in cirrhosis patients. The frontal lobe is the most functionally advanced brain region, associated with executive control, somatomotor function, attention control, and emotional activity [28]. The inferior parietal lobule is an important component of the default mode network, playing a critical role in memory and attention [29]. The middle temporal gyrus serves as a core region for visual-auditory information processing and is closely related to visual information integration and processing [30]. While decreased DC values are associated with functional impairment, increased DC values may reflect functional compensation [31]. The elevated DC values in these regions may provide evidence for early impairment and compensatory neural mechanisms during visual, motor, and memory judgment processes in MHE and cirrhosis patients. This interpretation aligns with previous task-based fMRI studies that demonstrated impaired and compensatory neural mechanisms during visual judgment in early hepatic encephalopathy [32]. Therefore, we hypothesize that increased DC values may represent a compensatory manifestation of

cognitive deficits induced by MHE, particularly in visual, memory, and selective attention domains.

This study has several limitations. First, the small sample size may introduce bias. Second, patients with overt hepatic encephalopathy were not included due to poor compliance with MRI scanning. Finally, neurocognitive impairment represents a reversible manifestation of early hepatic encephalopathy; therefore, longitudinal studies should be conducted in the future to better elucidate the neural basis of MHE development.

Conclusion

In summary, this study used DC analysis to investigate topological changes in brain functional networks in MHE from a network node perspective. We found abnormal functional connectivity in multiple brain regions in MHE patients, with DC values in some brain regions correlating with cognitive scale scores. These findings suggest that DC values may serve as a potential neuroimaging marker for quantifying the severity of cognitive impairment in MHE patients. This study provides imaging evidence for cognitive dysfunction in MHE and may offer a potential imaging indicator for disease progression.

Conflict of Interest: All authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.