RESEARCH ARTICLE

Regional gray matter abnormality in hepatic myelopathy patients after transjugular intrahepatic portosystemic shunt: a voxel-based morphometry study

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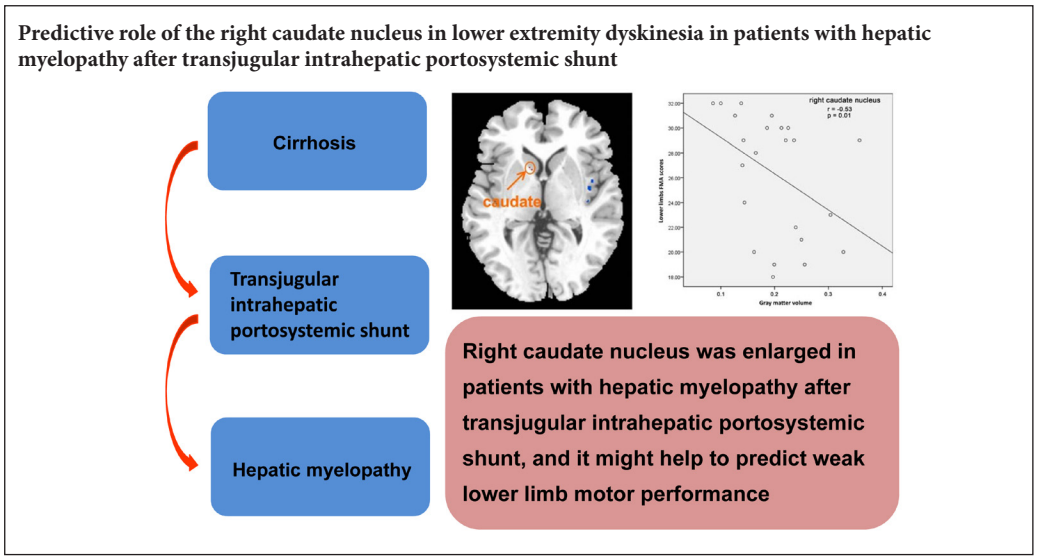
Graphical Abstract



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Abstract

Hepatic myelopathy is a complication seen in patients with chronic liver failure with physiologic or iatrogenic portosystemic shunting. The main symptom is progressive lower limb dyskinesia. The role of the brain motor control center in hepatic myelopathy is unknown. This study aimed to investigate the gray matter changes in patients with hepatic myelopathy secondary to transjugular intrahepatic portosystemic shunt and to examine their clinical relevance. This was a cross-sectional study. Twenty-three liver failure patients with hepatic myelopathy (hepatic myelopathy group), 23 liver failure patients without hepatic myelopathy (non-hepatic myelopathy group) after transjugular intrahepatic portosystemic shunt, and 23 demographically matched healthy volunteers were enrolled from March 2014 to November 2016 at Xijing Hospital, Air Force Military Medical University (Fourth Military Medical University), China. High-resolution magnetization-prepared rapid gradient-echo brain imaging was acquired. Group differences in regional gray matter were assessed using voxel-based morphometry analysis. The relationship between aberrant gray matter and motor characteristics was investigated. Results demonstrated that compared with the non-hepatic myelopathy group, gray matter volume abnormalities were asymmetric, with decreased volume in the left insula (P = 0.003), left thalamus (P = 0.029), left superior frontal gyrus (P = 0.006), and right middle cingulate cortex (P = 0.021), and increased volume in the right caudate nucleus (P = 0.017), corrected with open-source software. The volume of the right caudate nucleus in the hepatic myelopathy group negatively correlated with the lower limb clinical rating of the Fugl-Meyer Assessment (r = –0.53, P = 0.01). Compared with healthy controls, patients with and without hepatic myelopathy exhibited overall increased gray matter volume in both thalami, and decreased gray matter volume in both putamen, as well as in the globus pallidus, cerebellum, and vermis. The gray matter abnormalities we found predominantly involved motor-related regions, and may be associated with motor dysfunction. An enlarged right caudate nucleus might help to predict weak lower limb motor performance in patients with preclinical hepatic myelopathy after transjugular intrahepatic portosystemic shunt. This study was approved by the Ethics Committee of Xijing Hospital, Air Force Military Medical University (Fourth Military Medical University), China (approval No. 20140227-6) on February 27, 2014.

***Key Words:** portosystemic shunt; hepatic myelopathy; hepatic encephalopathy; magnetic resonance imaging; gray matter; lower limb; Fugl-Meyer Assessment; basal ganglia; caudate nucleus; voxel-based morphometry*

***Chinese Library Classification No.** R445; R575*

Introduction

Hepatic myelopathy is characterized by severe, mostly irreversible neurological symptoms. It may occur in patients with chronic liver disease with spontaneously portosystemic shunt, or after surgical shunting procedures, such as transjugular intrahepatic portosystemic shunt (Conn et al., 2006; Zhao et al., 2016). The condition is characterized by spastic paraparesis and walking difficulties, without sensory or sphincteric impairment increased muscle tone, tremor, brisk deep tendon reflexes, and extensor plantar responses (Leigh et al., 1949; Lefer et al., 1972). It has an insidious onset and slowly progresses to the point where the patient requires a wheelchair.

Early and accurate diagnosis of hepatic myelopathy, after excluding other possible spastic paraparesis causes (Caldwell et al., 2010), is clinically challenging mostly because of its unclear neuropathological mechanisms.

Extensive portosystemic shunting is strongly associated with hepatic myelopathy (Demirci et al., 1992). Most hepatic myelopathy patients previously had hepatic encephalopathy (Liversedge et al., 1966; Mendoza et al., 1994); paraparesis may accompany the hepatic encephalopathy, or may develop after recurrent overt hepatic encephalopathy. However, it is unknown why only some post-shunt patients are at risk of developing hepatic myelopathy.

Neuroimaging studies have revealed hyperintensity of the putamen and pallidum on T1-weighted magnetic resonance images (T1WI MRI) and increased fluid-attenuated inversion recovery signal in the subcortical white matter and spinal tracts (Kulisevsky et al., 1992). However, routine examinations do not reveal specific findings in hepatic myelopathy patients. Motor evoked potentials can detect the early asymptomatic stages of hepatic myelopathy (Nardone et al., 2002), but its specificity is poor.

Hepatic myelopathy responds poorly to conservative medical therapy. Treatment options currently include ligation, shunt reduction, or occlusion by surgical or interventional radiology procedures, but liver transplantation is considered to be the best long-term therapeutic approach (Troisi et al., 1999). Thus, early diagnosis is crucial, because timely liver transplantation could improve neurological outcomes.

Pathological studies, such as that of Campellone et al. (1996), report demyelination of the corticospinal tract, particularly the thoracic spinal cord, and proliferation of Alzheimer type II cells in the cerebral hemispheres, brainstem, and cerebellum, which may partly explain the clinical manifestations of the disease.

The role of the gray matter, and whether changes in specific gray matter areas are associated with decreased motor performance, and whether morphological changes in brain gray matter can provide specific neuroimaging markers for the early diagnosis of hepatic myelopathy, remain unknown. This study investigated gray matter changes in the brains of patients with and without hepatic myelopathy after transjugular intrahepatic portosystemic shunt to identify relationships between abnormal gray matter and poor motor performance.

Participants and Methods

Participants

This was a cross-sectional study. All procedures performed in this study were approved by the Ethics Committee of the Xijing Hospital, Air Force Military Medical University (Fourth Military Medical University), China (approval No. 20140227-6) on February 27, 2014, and was performed in accordance with the 1975 *Declaration of Helsinki* and its later amendments or comparable ethical standards. All participants gave written informed consent before the study. All data were analyzed anonymously.

The participants included: 23 (21 males and 2 females) patients with hepatic myelopathy after transjugular intrahepatic portosystemic shunt (hepatic myelopathy group; age range: 23–64 years, mean age: 50.4 years), twenty-three patients (21 males and 2 females) without hepatic myelopathy after transjugular intrahepatic portosystemic shunt (non-hepatic myelopathy group; age range: 34–55 years, mean age: 45.9 years), and twenty-three healthy control subjects (healthy control group; 20 males and 3 females, age range: 27–65 years, mean age: 51.8 years). To be included, patients (hepatic myelopathy and non-hepatic myelopathy) had to have a clear diagnosis of liver cirrhosis, based on clinical criteria (including results of physical, laboratory, and imaging examinations) or liver biopsy results. All patients had undergone placement of a transjugular intrahepatic portosystemic shunt. The diagnostic criteria for hepatic myelopathy were as follows (Caldwell et al., 2010): typical clinical features of myelopathy, including hyperreflexia, extensor plantar responses, and progressive spastic paraplegia of the lower limbs, without obvious atrophy, shallow sensory and sphincter dysfunction, and recurrent or transient hepatic encephalopathy. Hepatic myelopathy patients had no spinal cord space-occupying masses, multiple sclerosis, amyotrophic lateral sclerosis, human immunodeficiency virus infection, syphilis, or hepatolenticular degeneration. They had normal cerebrospinal fluid examinations.

Non-hepatic myelopathy patients had to have a diagnosis of liver cirrhosis, and had undergone placement of a transjugular intrahepatic portosystemic shunt. Non-hepatic myelopathy subjects had recurrent or transient hepatic encephalopathy, but no symptoms of myelopathy. Patients with previous overt hepatic encephalopathy had no current manifestation of encephalopathy.

Healthy control subjects were enrolled from the local community, and the age, sex, and education levels were matched with the patient groups. Healthy control subjects had no liver disease, and abdominal ultrasound scans revealed no abnormal findings.

Subjects (hepatic myelopathy, non-hepatic myelopathy and healthy controls) were excluded if they had psychiatric, neurological, inflammatory, traumatic, cerebrovascular, or severe organic diseases, such as renal failure; if they took psychotropic medications; or had abused alcohol in the previous 6 months before the study. All subjects were right-handed, had normal vision, and had no magnetic resonance imaging (MRI) contraindications.

Laboratory examinations

No more than 1 week before MRI examination, patients with hepatic myelopathy and non-hepatic myelopathy were evaluated with prothrombin time, protein metabolism, and bilirubin metabolism tests to assess liver function, and to

comply with the Child-Pugh grading standards and allow Child-Turcotte-Pugh scoring (Pugh et al., 1973). The scoring system classified the liver function into class A (scores 5–6), B (scores 7–9), or C (scores 10–15), higher scores meaning poorer liver function. West-Haven criteria were used for the assessment of the severity of hepatic encephalopathy (Ferenci et al., 2002), with a higher stage representing more severe hepatic encephalopathy. No laboratory tests were performed on the healthy control subjects.

The evaluation flow chart is shown in **Figure 1**.

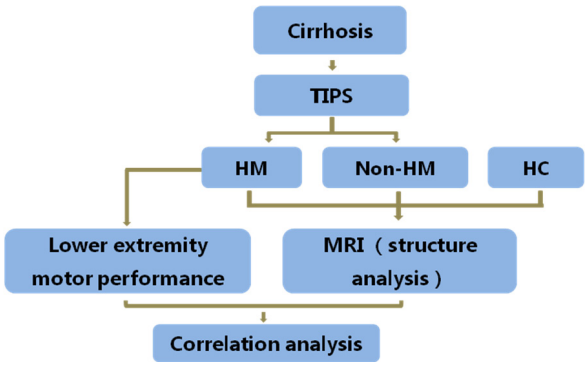

Figure 1 Flow chart of evaluation.
TIPS: Transjugular intrahepatic portosystemic shunt; HM: hepatic myelopathy; HC: healthy control; MRI: magnetic resonance imaging.

Clinical assessments

The Fugl-Meyer assessment (FMA) was performed to assess the motor function of the lower extremities (Berglund and Fugl-Meyer, 1986). Lower extremity FMA scores range from 0 to 34, with 34 indicating absence of motor deficits and lower scores indicating worsening of motor deficits. Lovette's Six Classification (Zhao et al., 2016) was used for the assessment of lower extremity muscle strength.

MRI scans

MRI scans were acquired with a 3.0 T system (Magnetom Trio Tim®, Siemens, Munich, Germany) using an eight-channel phased-array head coil. Conventional T1WI and T2-weighted images (T2WI) of the head and spinal cord were acquired, followed by three-dimensional magnetization-prepared rapid gradient-echo sequence (sagittal, repetition time = 1900 ms, echo time = 3.4 ms, flip angle = 7°, field of view = 240 × 240 mm^2, acquisition matrix = 256 × 256, section thickness = 1 mm with no gap, number of sections = 192, isotropic voxel = 1 × 1 × 1 mm^3).

Voxel-based morphometry (VBM) analysis

Data analysis was performed using open-access software (VBM8 toolbox, http://dbm.neuro.uni-jena.de/vbm) with default parameter settings in the statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) running on Matlab 2012a (Mathworks, Inc., Natick, MA, USA). The preprocessing included the following steps: (1) T1-weighted images of each individual were aligned to ensure that the anterior commissure was located at the origin of the three-dimensional Montreal Neurological Institute (MNI) coordinates. (2) Non-brain tissue was electronically removed, and brain was segmented into gray matter, white matter, and cerebrospinal fluid. (3) The diffeomorphic anatomical registration through exponentiated lie algebra algorithm (Ashburner, 2007; Goto et al., 2013) was applied for spatial normalization. (4) A gray matter image of each subject was spatially normalized to the MNI space to yield images with 2 × 2 × 2 mm^3 voxels. (5) Finally, the normalized images were smoothed using a 12-mm full-width-half-maximum isotropic Gaussian kernel. Considering the effects of age and sex on gray matter volume, these two factors were removed as covariates in SPM8. After spatial preprocessing, the normalized and modulated gray matter images were subjected to statistical analysis.

Statistical analysis

All data are expressed as the mean ± SD. Statistical analyses were performed using commercial software (SPSS 19.0®, IBM Inc., Armonk, NY, USA). Chi-square tests were used to assess sex differences. One-way analysis of variance was applied to compare the age, education, and FMA score. One-way analysis of variance followed by the Student-Newman-Keuls *post-hoc* test was used to compare the gray matter volumes. Independent-samples *t*-test was applied to compare the Child-Turcotte-Pugh scores. Nonparametric Kruskal-Wallis *H* tests were applied to compare the Child-Pugh stage, West-Haven hepatic encephalopathy grade, and lower extremity muscle strength. $P < 0.05$ was considered statistically significant.

One-way analysis of variance was performed to examine the intergroup differences of gray matter volume. The statistical threshold for significance was set at $P < 0.05$, corrected by using the AlphaSim program (http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf), with a cluster size exceeding 20 voxels.

A partial correlation analysis was used to assess the relationship between FMA scores and gray matter volume. For each hepatic myelopathy patient, we selected the peak voxel and the neighboring 20 voxels within each cluster showing different volumes between the hepatic myelopathy and non-hepatic myelopathy patient groups: right caudate nucleus, left insula, left superior frontal gyrus, left thalamus, and right middle cingulate cortex as the regions of interest for correlation analysis. Pearson correlation coefficients were calculated between FMA scores and the gray matter volume.

Results

Demographic and clinical data

The demographic data and clinical characteristics of all subjects are listed in **Table 1**. No significant differences were identified in age, sex, education level, Child-Pugh stage, Child-Turcotte-Pugh score, or hepatic encephalopathy grade between the two patient groups ($P > 0.05$). Compared with the non-hepatic myelopathy and healthy control groups, lower extremity motor performance was worse, FMA scores were lower, and muscle strength was weaker in the hepatic myelopathy group ($P < 0.05$).

VBM results in hepatic myelopathy patients

One-way analysis of variance across the hepatic myelopathy, non-hepatic myelopathy, and healthy control groups showed significant differences in gray matter volume in both thalami, putamina, globi pallidi, parahippocampi, and

in the cerebellum and vermis (**Table 2** and **Figure 2**). As compared with the healthy controls, both hepatic myelopathy and non-hepatic myelopathy patients showed increased gray matter volumes in both thalami and parahippocampi, with decreased gray matter volumes in the putamina, globi pallidi, cerebellum, and vermis (**Table 3** and **Figure 3A** & **B**). Additionally, compared with the non-hepatic myelopathy group, gray matter volume was increased in the right cau-

Table 1 Demographic and clinical characteristics of the subjects

Items	Hepatic myelopathy (n = 23)	Non-hepatic myelopathy (n = 23)	Healthy control (n = 23)	P value
Age (years)	50.4±10.3	45.9±6.3	51.8±9.9	0.08*
Sex (male/female)	21/2	21/2	20/3	1.00#
Education (years)	9.6±3.8	9.3±3.2	10.3±3.3	0.57*
Handedness (left/right)	0/23	0/23	0/23	—
Liver function				
Child-Pugh stage (A/B/C)	4/16/3	10/10/3	—	0.14†
Child-Turcotte-Pugh scores	8±2	7±2	—	0.08$
West-Haven HE grade (0/1/2/3/4)	5/6/8/2/2	0/9/12/2/0	—	0.06†
FMA score	26±5	34±0	34±0	< 0.01*
Lower extremity muscle strength grading	3±1	5±0	5±0	< 0.01†

Data are expressed as the mean ± SD with the exception of sex, handedness, Child-Pugh stage, and West-Haven HE grade (n). *: One-way analysis of variance; #: Chi-square test; †: nonparametric Kruskal-Wallis H test; $: independent-samples t test. HE: Hepatic encephalopathy; FMA: Fugl-Meyer assessment.

Table 2 Significant differences of gray matter volume among the three groups*

Brain regions	MNI coordinates (mm)			Cluster size (voxels)	F value
	X	Y	Z		
Left pallidum	–20	4	–2	121	95.94
Right pallidum	22	4	–4	125	164.63
Left putamen	–30	10	2	445	95.94
Right putamen	30	18	0	423	55.13
Left thalamus	–8	–10	8	651	77.52
Right thalamus	10	–14	14	628	63.45
Vermis	1	–59	–34	115	107.03
Left cerebellum	–26	–62	–34	275	35.96
Right cerebellum	28	–60	–34	425	61.53
Left parahippocampus	–24	–21	–11	68	9.42
Right parahippocampus	26	–26	–22	57	12.77
Left insular	–42	–14	8	68	19.55
Right caudate nucleus	18	–6	20	62	14.83
Left superior frontal gyrus	–20	50	44	28	15.13
Right middle cingulate cortex	6	–36	42	24	12.52

*: One-way analysis of variance; P < 0.05, AlphaSim corrected, cluster size > 20 voxels. MNI: Montreal Neurological Institute.

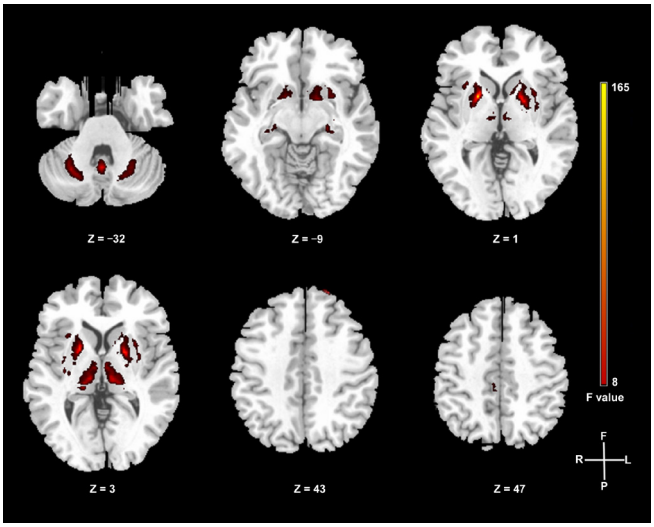

Figure 2 Gray matter volume differences among the hepatic myelopathy, non-hepatic myelopathy, and healthy control groups.
Gray matter volume differed among the three groups in the bilateral thalamus, putamen, pallidum, parahippocampus, cerebellum, vermis, left insula, left superior frontal gyrus, right caudate nucleus, and right middle cingulate cortex (one-way analysis of variance). Comparisons were performed at an AlphaSim corrected P < 0.05. R: Right; L: left; F: frontal; P: posterior.

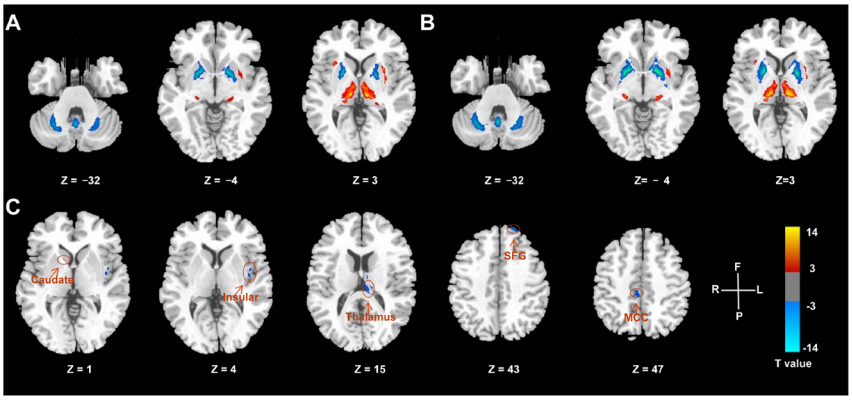

Figure 3 Gray matter volume differences among the hepatic myelopathy, non-hepatic myelopathy and healthy control groups.

(A) Compared with healthy controls, the hepatic myelopathy patients showed remarkably increased gray matter volume in both thalami and parahippocampi, and decreased gray matter volume in both putamina, globi pallidi, as well as in the cerebellum and vermis. (B) Compared with healthy controls, the non-hepatic myelopathy patients showed markedly increased gray matter volume in both thalami and parahippocampi, and decreased gray matter volume in the both putamina and globi pallidi, as well as in the cerebellum and vermis. (C) Compared with the non-hepatic myelopathy group, the hepatic myelopathy group showed dramatically increased gray matter volume in the right caudate nucleus, and decreased gray matter volume in the left insula, left thalamus, left superior frontal gyrus, and right middle cingulate cortex. Comparisons were performed using one-way analysis of variance (P < 0.05, AlphaSim corrected). R: Right; L: left; F: frontal; P: posterior.

date nucleus, and decreased in the left insula, left thalamus, left superior frontal gyrus, and middle cingulate cortex in the hepatic myelopathy group (**Table 4** and **Figure 3C**).

Correlations between gray matter volume and FMA scores in hepatic myelopathy patients

A significant negative correlation was detected between gray matter volume index and FMA scores in the right caudate nucleus (r = –0.53, P = 0.01) (**Figure 4**). Gray matter volume in other regions of interest did not seem to correlate with the FMA scores.

Discussion

High resolution magnetization-prepared rapid gradient-echo images and VBM analysis were used to investigate morphological changes in gray matter, and their relationship to motor performance in patients with hepatic myelopathy secondary to transjugular intrahepatic portosystemic shunt. As compared with non-hepatic myelopathy patients, hepatic myelopathy patients showed increased gray matter volume in the right caudate nucleus, and decreased gray matter volumes in the left thalamus, insular cortex, superior frontal gyrus, and right middle cingulate cortex. The gray matter volume in the right caudate nucleus correlated negatively with the lower limb FMA scores in patients with hepatic myelopathy. Previous studies on hepatic myelopathy were mainly case reports. However, a multi-sample study of changes in gray matter and its intrinsic association with poor motor performance in patients with hepatic myelopathy has not been reported. More importantly, in all the patients with hepatic myelopathy, the condition was directly associated with transjugular intrahepatic portosystemic shunt, and thus the patient group had a high level of homogeneity. Moreover, to avoid the effect of hepatic failure and hepatic encephalopathy on the brain (Guevara et al., 2011; Chen et al., 2012), we used a non-hepatic myelopathy control group matched for post-transjugular intrahepatic portosystemic shunt hepatic function score and hepatic encephalopathy grade.

Our findings indicated widespread reduction of gray matter volume in both the hepatic myelopathy and non-hepatic

Table 3 Significant differences of gray matter volume between patients and healthy participants*

Brain regions	MNI coordinates (mm)			Cluster size (voxels)	*t* values†
	X	*Y*	*Z*		
Hepatic myelopathy *vs.* healthy control					
Left pallidum	–16	6	4	111	–10.61
Right pallidum	22	4	–4	115	–14.14
Left putamen	–30	10	2	336	–10.61
Right putamen	30	18	0	364	–14.14
Left thalamus	–8	–10	8	582	11.27
Right thalamus	10	–14	14	554	10.16
Vermis	1	–56	–32	170	–11.89
Left cerebellum	–28	–56	–34	157	–6.91
Right cerebellum	28	–60	–34	226	–8.94
Right parahippocampus	28	–20	–28	34	4.04
Non-hepatic myelopathy *vs.* healthy control					
Left pallidum	–20	4	–2	65	–10.58
Right pallidum	22	4	–4	85	–13.49
Left putamen	34	6	–2	217	–10.58
Right putamen	–32	6	–4	197	–13.49
Left thalamus	–8	–10	8	422	9.01
Right thalamus	10	–14	14	358	8.13
Vermis	1	–58	–32	76	–10.98
Left cerebellum	–26	–62	–34	40	–6.19
Right cerebellum	28	–60	–34	121	–8.11
Left parahippocampus	–30	–40	–8	24	4.33
Right parahippocampus	26	–26	–22	21	4.91

*: One-way analysis of variance, P < 0.05, AlphaSim corrected, cluster size > 20 voxels. †: Positive sign represents increase, negative sign represents decrease. MNI: Montreal Neurological Institute.

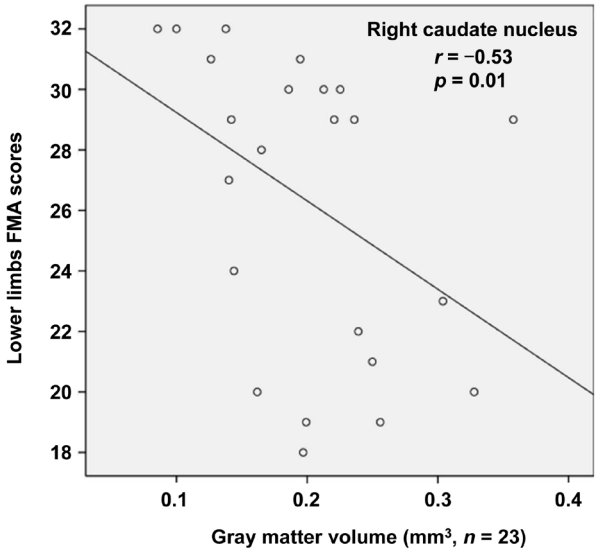

Figure 4 Correlation between abnormal gray matter volume and lower limb motor performance in patients with hepatic myelopathy (Pearson correlation analysis).

Gray matter volume of the right caudate nucleus showed significantly negative correlations with the lower limb FMA scores in hepatic myelopathy patients. FMA: Fugl-Meyer assessment.

Table 4 Significant differences of gray matter volume between hepatic myelopathy and non-hepatic myelopathy patients*

Brain regions	MNI coordinates (mm)			Cluster size (voxels)	*t* values†
	X	*Y*	*Z*		
Hepatic myelopathy *vs.* non-hepatic myelopathy					
Right caudate nucleus	10	2	4	61	4.98
Left insular	–42	–14	8	86	–6.21
Left thalamus	–8	–28	12	140	–4.78
Left superior frontal gyrus	–22	50	42	33	–5.27
Right middle cingulate cortex	6	–28	46	40	–4.79

*: One-way analysis of variance, P < 0.05, AlphaSim corrected, cluster size > 20 voxels. †: Positive sign represents increase, negative sign represents decrease. MNI: Montreal Neurological Institute.

myelopathy groups when compared with healthy control subjects, especially in the basal ganglia and cerebellum. Extensive gray matter loss in chronic liver failure and hepatic encephalopathy patients has been reported in many volumetric studies (Chen et al., 2012; Zhang et al., 2012). Hyperintensity of the globus pallidus and putamen on T1WI has been confirmed in patients with liver cirrhosis and hepatic encephalopathy (Kulisevsky et al., 1992). Autopsy and conventional MRI investigations have verified that this is due to the deposition of paramagnetic substances in the basal ganglia, especially manganese (Pomier-Layrargues et al., 1995; Rose et al., 1999; Ferreira et al., 2017). Maeda et al. (1997) explored the brain metal concentration and histopathological changes in patients with cirrhosis; they found that the mean manganese concentration was remarkably higher than normal values in brain regions that showed hyperintensity on T1WI, particularly in the globus pallidus and putamen. Further histopathological findings illustrated that hyperintense brain regions also demonstrated marked neuronal atrophy and even necrosis, accompanied by proliferation of glial cells and microglia. The presence of a portosystemic shunt may exacerbate this damage (Layrargues et al., 1998). Our findings are in line with those of early studies on nonhuman primates that were exposed to high doses of manganese; these animals demonstrated cell loss and gliosis in the basal ganglia structures, particularly in the globus pallidus (Eriksson et al., 1987). There are also measurable brain volume reductions in the globus pallidus and cerebellum of welders who are chronically exposed to manganese (Chang et al., 2013).

Regional differences in the cerebral ammonia metabolism in patients with cirrhosis and hepatic encephalopathy have also been explored using positron emission tomography (Ahl et al., 2004): the cerebellum, thalamus, and lenticular nucleus demonstrated the highest levels of regional variance. These brain regions are predominantly exposed to ammonia, which may influence the morphology and function of the astrocytes. Histopathological studies based on autopsies of patients with liver cirrhosis showed altered astrocytes—Alzheimer type II astrocytes—in the dentate nuclei (Adams et al., 1953). A new animal model demonstrated neuronal loss in the cerebellum, with ammonia as the precipitating factor (García-Lezana et al., 2017). Thus, we speculate that neuronal atrophy and necrosis induced by manganese and other neurotoxins, especially ammonia, may be the main cause of the volume reduction of the pallidum, putamen, and cerebellum in both hepatic myelopathy and non-hepatic myelopathy groups.

The left insular cortex was significantly atrophied in hepatic myelopathy patients relative to non-hepatic myelopathy patients. The insular cortex is a multimodal integration brain region. Resting state MRI-based functional connectivity analysis has recently revealed that the insula has numerous connections with the cingulate, frontal, motor, somatosensory, and temporal cortices (Cauda et al., 2011). It mediates a series of activities, including gustatory, visceral sensation, and visceral motor responses, and is involved in vestibular, attention, pain, emotion, verbal, and motor functions. A meta-analysis of functional neuroimaging data showed that motor tasks involving both the upper and lower extremities activated the posterior-superior part of the insular cortex, especially the region adjacent to the sulcus centralis insulae (Mutschler et al., 2009). Clinical evidence suggests that the insular cortex plays a role in motor function recovery of the limbs in post-stroke patients (Weiller et al., 1992). These findings indicate that the insular cortex is vital in the control of limb movements, and that gray matter volume reduction in the insula might contribute to the neuropathological basis for motor dysfunction in patients with hepatic myelopathy.

This study also observed that the right caudate nucleus was enlarged in the hepatic myelopathy group relative to the non-hepatic myelopathy group, and this was associated with poor lower limb motor performance. The motor and premotor areas mediate different aspects of motor behavior, which are in turn reflected both anatomically and physiologically in the caudate nucleus and putamen (Alexander et al., 1990; Haber et al., 2016). Volkow et al. (1998) explored the relationship between brain dopamine activity and motor function in healthy individuals, using dopamine transporter positron emission tomography, and found that a reduction in brain dopamine activity in the caudate nucleus was associated with worse performance in motor tasks. Dumurgier et al. (2012) discovered that a volume reduction in the caudate nucleus was strongly associated with a slower walking speed. The caudate nucleus is also important in the control of gait (Tian et al., 2017; Wennberg et al., 2017), and multiple infarcts of the caudate may lead to gait disorders (Finelli et al., 2007). Patients with Huntington's disease, who display an uncoordinated and lurching walk, as well as more subtle gait disturbances, predominantly show atrophy of the caudate nucleus (Rao et al., 2008). A recent genome-wide association study showed an association between the volume of the caudate nucleus and polymorphisms located in two genes that are involved in dopaminergic signaling and development related to motor control (Stein et al., 2011).

Correlation analysis demonstrated that an increased caudate nucleus volume was associated with poor lower extremity motor performance in patients with hepatic myelopathy. Since the caudate nucleus is key to the control of gait and walking speed, a larger caudate nucleus volume, representing more neurons and/or glial cells, probably implies dysfunction of its motor control (Moreno-Alcázar et al., 2016), and eventually causes the puppet gait and walking difficulties seen in patients with hepatic myelopathy. This could be used as a neuroimaging marker for predicting motor impairment in hepatic myelopathy secondary to transjugular intrahepatic portosystemic shunt.

The gray matter volume of bilateral thalamus was enlarged in both hepatic myelopathy and non-hepatic myelopathy patients compared with healthy controls. An increased thalamic volume in cirrhotic patients is considered to be a compensatory effect for basal ganglia dysfunction (Maeda et al., 1997; Zhang et al., 2012; Tao et al., 2013). The thalamus is a critical component of the frontal cortical-basal ganglia-thalamic circuits that mediate motivation, cognition, and motor control (McFarland et al., 2002; Obeso et al., 2014). Alterations of neurotransmission within the thalamus therefore may cause impaired cortical function. The gray matter volume of the left thalamus was decreased in hepatic myelopathy relative to non-hepatic myelopathy patients; it seems that the extent of enlargement of the left thalamus was less in patients with hepatic myelopathy, which may be useful for differentiating between hepatic myelopathy and non-hepatic myelopathy individuals.

The superior frontal gyrus is considered to be associated with error-monitoring in motor tasks (Rudebeck et al., 2008; Navarro-Cebrian et al., 2013; Amiez et al., 2016). A volume reduction in this region could be implicated in dysfunctional movement monitoring. Alternatively, this might cause disability in modulating performance in the case of motor errors, resulting in progressive motor dysfunction in hepatic myelopathy patients. The middle cingulate cortex plays a vital role in premotor functions (Procyk et al., 2016). Separate motor control studies have shown that the middle cingulate cortex is engaged during the planning and execution of motor function (Amiez et al., 2014). Activation of the cingulate cortex has been linked to motor recovery (Marshall et al., 2009). Volume reduction of the right middle cingulate cortex in hepatic myelopathy patients could be considered to be implicated in the impairment of motor programming and implementation.

The main limitation of our study was the cross-sectional design. Additionally, no postmortem examination could be performed to obtain pathological evidence or directly observe neuronal projections in the brain *in vivo*. Ideally, this study should be continued further in an appropriate animal model. A combination of preclinical and clinical findings may help to elucidate the neural underpinnings of hepatic myelopathy; future studies adopting a longitudinal design will be informative to elucidate the changes in neural deficits as the disease progresses.

In conclusion, abnormal variation was found in the gray matter in patients with and without hepatic myelopathy after transjugular intrahepatic portosystemic shunt; motor-related regions were predominantly involved, and these alterations may be associated with the motor dysfunction seen in patients with hepatic myelopathy. Moreover, enlargement of gray matter volume in the right caudate nucleus was accompanied by severe lower limb motor deficits in patients with hepatic myelopathy, which may be useful as a predictive marker for assessment of hepatic myelopathy. Traditionally, studies of hepatic myelopathy have focused more on the spinal cord and white matter, but our study revealed abnormalities in motor-related gray matter regions in hepatic myelopathy patients.

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