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Abnormal spontaneous brain activity in minimal hepatic encephalopathy: resting-state fMRI study

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PURPOSE
We aimed to assess the abnormality of baseline spontaneous brain activity in minimal hepatic encephalopathy (MHE) by amplitude of low frequency fluctuation (ALFF) and fraction ALFF (fALFF).

METHODS
A total of 14 MHE patients and 14 healthy controls were included in our study. Both ALFF and fALFF of functional magnetic resonance imaging were calculated for statistical analysis.

RESULTS
Compared with healthy controls, patients with MHE had significantly decreased ALFF in the bilateral medial prefrontal cortex (MPFC), left superior frontal gyrus, right precentral gyrus, left opercular part of inferior frontal gyrus, left gyrus rectus, bilateral precuneus, and the posterior lobe of right cerebellum; and they had significantly decreased fALFF in the bilateral MPFC, right middle frontal gyrus, right superior temporal gyrus, and the posterior lobe of left cerebellum.

CONCLUSION
ALFF and fALFF changes in many brain regions demonstrate abnormality of the spontaneous neuronal activity in MHE. Especially the impairment of right precuneus and left MPFC may play a critical role in manifestation of MHE. Changes of ALFF and fALFF in the precuneus and the MPFC can be used as a potential marker for MHE.

Minimal hepatic encephalopathy (MHE), as an early stage of hepatic encephalopathy (HE), shows only mild attention deficit, visual motor dysfunction, cognitive control impairment and working memory network disorder, without any obvious neurologic manifestations (e.g., confusion, hepatic coma). As a transitional stage, 20%–80% of MHE cases develop from liver cirrhosis (1). Patients usually have weaker capabilities of handling an emergency situation and higher risk of accident (2). MHE is potentially reversible, because of the minor damage to the neurons (3).

Previously, diffusion tensor imaging and magnetic resonance spectrum were used to get an insight into HE. These modalities found neuron swelling or interstitial edema and abnormal metabolism in related brain regions (4–8).

Currently, blood oxygenation level dependent-functional magnetic resonance imaging (BOLD-fMRI), which has the ability to detect brain dysfunction, is a focus in the field of HE research. Some task-related fMRI studies found impairments in multiple cognitive and spatial memory functional regions of the brain (9, 10). Different from task-related fMRI, resting-state fMRI demonstrates spontaneous neuronal activity. Using resting-state fMRI, studies found decreased regional homogeneity in brain regions that are related to cognition and memory function, and the changes of regional homogeneity in the precuneus were closely related to the development of MHE (11, 12). Functional connectivity was also used in HE studies, which revealed disturbed brain networks (13–18).

A different approach from regional homogeneity and functional connectivity, amplitude of low frequency fluctuation (ALFF) analysis, which detects the alternation of spontaneous brain activity by measuring the energy of low frequency oscillation, was first used by Zang et al. (19) in a study of patients with attention deficit hyperactivity disorder, becoming a new method to study the brain function. Recently, Chen et al. (20) and Qi et al. (21) used it in MHE and revealed aberrant brain activity and continuous impairment. Based on the ALFF, the fraction ALFF (fALFF) proposed by Zou et al. (22) not only gets rid of physiological noise

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effectively, but also has a higher sensitivity and specificity compared with the ALFF. But until now, few studies employed the ALFF to investigate MHE and even fewer employed the fALFF. Moreover, study of MHE by means of ALFF and fALFF continues to be regarded as controversial. In this study, we used the ALFF and fALFF to investigate alternations of spontaneous brain activity in MHE.

Table 1. Summary of demographic information and neuropsychologic tests

Variables	Patients with MHE (n=14)	Healthy controls (n=14)	*P*
M/F ratio	7/7	7/7	0.334
Age (years)	54.57±10.57	50.86±9.38	
Education (years)	10.4±3.50	11.00±2.39	0.618
NCT-A (seconds)	57.63±30.96	21.33±3.80	0.001
DST (raw score)	23.29±10.99	48.86±10.29	0.001

MHE, minimal hepatic encephalopathy; M/F, male/female; NCT-A, number connection test A; DST, digit-symbol test.

Methods

Subjects

This study was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants. In total, 25 patients with nonalcoholic liver cirrhosis and 19 healthy control subjects were recruited in our study. All participants were right-handed and had no alcohol or drug abuse history, related neurologic or/and psychiatric illness, or MRI contraindications. Healthy control subjects had no history of liver disease. Nonalcoholic liver cirrhosis was diagnosed through clinical manifestations, signs, and examinations (biochemical laboratory examinations and radiologic examinations such as computed tomography, MRI, and ultrasonography). The neuropsychologic tests including the number connection test A and digit-symbol test and fMRI were performed in all participants. MHE was diagnosed by two senior gastroenterologists based on the final report of the working party of 11th World Congress of Gastroenterology in Vienna in 1998 (23); nonalcoholic liver cirrhosis patients with abnormal neuropsychological test scores (more than one standard deviation beyond for number connection test A or under the mean value for digit-symbol test) were regarded as MHE. The normal values of neuropsychiatric tests were determined in a sample of 120 healthy volunteers in a prior study (24). We excluded four cases of MHE and two healthy control subjects with intolerable motion (translation of more than 1.0 mm or rotation of more than 1.0°), one case of MHE with bad registration, two cases of MHE with dentures artifact and four cases of MHE and three healthy control subjects with intracranial complications in the data preprocessing. Finally 14 MHE and 14 healthy control subjects were included in our study.

Main points

- Minimal hepatic encephalopathy (MHE) is difficult to diagnose because of its mild brain dysfunction.
- It is important to be aware of MHE, given its higher risk of accidents and morbidity and potentially reversible nature.
- Amplitude of low frequency fluctuation (ALFF) and fraction ALFF (fALFF) changes in many brain regions demonstrate abnormality of the spontaneous neuronal activity in MHE, especially in the right precuneus and the left medial prefrontal cortex (MPFC).
- Changes of ALFF and fALFF in the precuneus and MPFC play a critical role in the manifestation of MHE.

MRI data acquisition and preprocessing

MRI data was acquired on a 3.0 T scanner (Achieva Intera, Phillips Medical System) using an eight-channel head coil. The functional image was acquired by using an echo-planar imaging sequence (repetition time, 2000 ms; echo time, 30 ms; flip angle, 90°; matrix, 64×64; field of view, 240 mm×240 mm; section thickness, 4.0 mm; number of sections, 34; dynamics, 180). All participants were instructed to keep their head still and eyes closed. We provided the participants with earplugs and fixed their head with sponges of different thickness before MRI scanning.

Preprocessing was performed by the data processing assistant for resting-state fMRI (DPARSF) (http://www.restfmri.net). The procedures included removing the first 10 time points (for adaption to the scanning noise and the steady state of machine), slice-timing correction, realign correction, spatial normalization, smoothing (full width at half maximum, 4 mm), linear detrend and band-pass filtering (0.01–0.08 Hz).

Then the time courses were converted to the frequency domain by using a fast Fourier transform and the averaged square root of the spectrum across 0.01–0.08 Hz at each voxel was taken as the ALFF. The fALFF was calculated as ALFF divided by the value of the entire detectable frequency band. For standardizing variability across the participants, mean ALFF was obtained as ALFF divided by the global mean ALFF; mean fALFF was also calculated in a similar manner. Finally, mean ALFF and mean fALFF maps of the whole brain of MHE and healthy control subjects, which reflected the degree of the raw value relative to the global mean value, were used for statistical analysis.

ALFF and fALFF analysis

The two-sample t-test was performed by Resting-State fMRI Data Analysis Toolkit v1.8 (REST1.8) (http://www.restfmri.net) to determine the mean ALFF and mean fALFF differences within the whole-brain between the two groups.

We used the significant regions of ALFF or fALFF respectively to make a new union mask. Pearson's correlation analysis was performed by REST1.8 software to find the correlation between the ALFF or fALFF and poor neurocognitive performances within the union mask. The gray matter volume and age were added as covariants for excluding the related effects. The threshold was set at $P < 0.05$ (corrected by using the AlphaSim program) and the minimum cluster size was 54 voxels.

Results

There were no significant differences in terms of age ($P = 0.334$) and education ($P = 0.618$) between MHE patients and healthy controls. The number connection test A and digit-symbol test showed significant difference between the two groups ($P < 0.001$) (Table 1).

Compared with healthy controls, MHE showed regions of increased ALFF in the right inferior temporal gyrus, right temporal pole/middle temporal gyrus, left insular, and the posterior lobe of right cerebellum. On the other hand, clusters of decreased

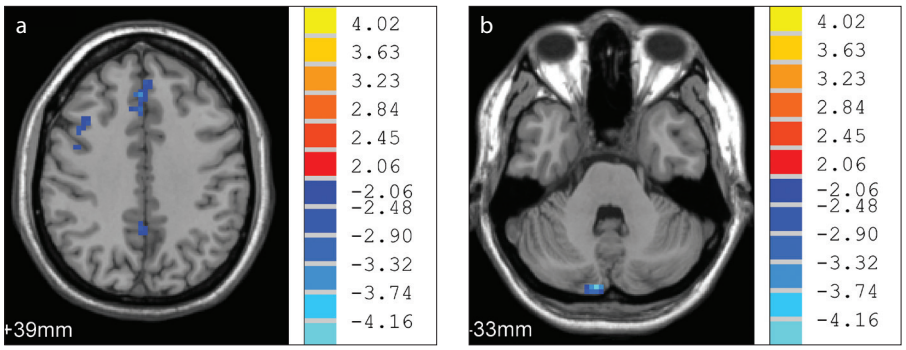

Figure 1. a, b. Axial T1-weighted images **(a, b)** show minimal hepatic encephalopathy (MHE) group with decreased amplitude of low frequency fluctuation (ALFF) in bilateral precuneus, medial prefrontal cortex (MPFC) **(a)** and the posterior lobe of right cerebellum (R-PLC) **(b)** compared with the healthy controls. (REST1.8, http://www.restfmri.net)

Table 2. Regions showing significant differences in ALFF between MHE patients and healthy controls

Regions	BA	Voxels	MNI coordinates (x, y, z)	Peak t value
ALFF increased in MHE				
L-Insula	34	54	(-27, 3, -15)	4.4098
R-ITG	20	76	(54, -48, -27)	4.3602
R-Temporal pole/MTG	21	60	(39, 9, -39)	3.8904
R-PLC		58	(45, -45, -42)	3.6982
ALFF decreased in MHE				
L-Oper/IFG	48	77	(-42, 9, 21)	-4.6821
L-SFG	10	54	(-33, 63, 3)	-4.0135
L-Gyrus rectus	47	80	(-15, 15, -15)	-3.4602
R-PLC		54	(9, -90, -33)	-4.5152
R-PrCG	4	59	(36, -21, 51)	-3.4411
B-MPFC	6	121	(3, 33, 39)	-3.5014
B-Precuneus	7	71	(3, -42, 45)	-3.5021

ALFF, amplitude of low frequency fluctuation; MHE, minimal hepatic encephalopathy; BA, Brodmann's area; MNI (x, y, z), Montreal Neurologic Institute (x, y, z); L, left; R, right; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; PLC, posterior lobe of cerebellum; Oper/IFG, opercular part of inferior frontal gyrus; SFG, superior frontal gyrus; PrCG, precentral gyrus; B, bilateral; MPFC, medial prefrontal cortex.

ALFF were located in the bilateral frontal lobes including the bilateral medial prefrontal cortex (MPFC), left superior frontal gyrus, right precentral gyrus, left opercular part of inferior frontal gyrus, left gyrus rectus, bilateral precuneus, and the posterior lobe of right cerebellum (Fig. 1, Table 2).

Compared with healthy controls, MHE showed regions of increased fALFF in the right middle cingulum gyrus/middle and inferior frontal gyrus, left triangular part of inferior frontal gyrus, left middle frontal gyrus, left gyrus rectus, left precentral gyrus, right precuneus/post cingulum cortex, right insula, right lentiform nucleus, left pallidum and pons/the anterior lobe of left cerebellum. On the other hand, clusters of decreased fALFF were found in the bilateral MPFC, right middle frontal gyrus, right superior temporal gyrus, and the posterior lobe of left cerebellum (Fig. 2, Table 3).

There were no correlations between ALFF or fALFF changes and poor neurocognitive performances in the MHE group.

Discussion

In this study, ALFF and fALFF were used to detect the abnormal brain activity in MHE. We found that patients with MHE had decreased ALFF in the frontal lobes including the bilateral MPFC, left superior frontal gyrus, right precentral gyrus, left opercular part of inferior frontal gyrus, left gyrus rectus, bilateral precuneus, and the posterior lobe of right cerebellum; while they had decreased fALFF in the bilateral MPFC, right middle frontal gyrus, right superior temporal gyrus, and the posterior lobe of left cerebellum. These findings suggest the presence of abnormal brain spontaneous activity in MHE at the baseline.

Our study revealed that the ALFF and fALFF changes of the MHE group happened mainly in the frontal lobes. As we know, the frontal lobe is the most advanced part of the brain and it is closely related to working memory and cognition (25, 26). The prefrontal cortex is responsible for spatial memory (10, 25, 26). As the integration and processing center of spatial working memory, it has functions of noticing, inhibiting, coding, integrating, storing, extracting and processing the information from the outside (25). Decreased ALFF and increased fALFF in the frontal lobe reflect decreased brain spontaneous activity, which may lead to brain dysfunction and result in cognition deficits such as distracted attention, decreased memory, and slow reaction of MHE patients. A MHE study by Liao et al. (10) also suggested the impairment of prefrontal lobes as the mechanism of dysfunction of spatial working memory.

As we know, default mode network includes the precuneus and cuneus, post cingulum cortex, MPFC, bilateral inferior parietal lobule, and the lateral temporal lobes. It attends the basic functional activities in the resting state, such as processing the episodic memory, monitoring the cognitive control, and switching the state of external stimuli and internal brain activity (27–29). The precuneus mainly participates in the process of visual spatial information integration (30). Our study showed that patients with MHE had lower ALFF in the bilateral precuneus and MPFC, while they had lower fALFF in the bilateral MPFC and higher fALFF in the precuneus. This finding indicates decreased neuronal activity in those regions led by reduced cerebral oxygen consumption and cerebral blood flow (31). Previous MHE studies showed decreased regional homogeneity in the cuneus and precuneus (11, 12) and weakened functional connectivity among the default mode network (14, 15) suggesting an abnormal connection among these regions. As members of the default mode network, the precuneus and MPFC are responsible for cognition. Decreased neuronal activity and consequent abnormal functional

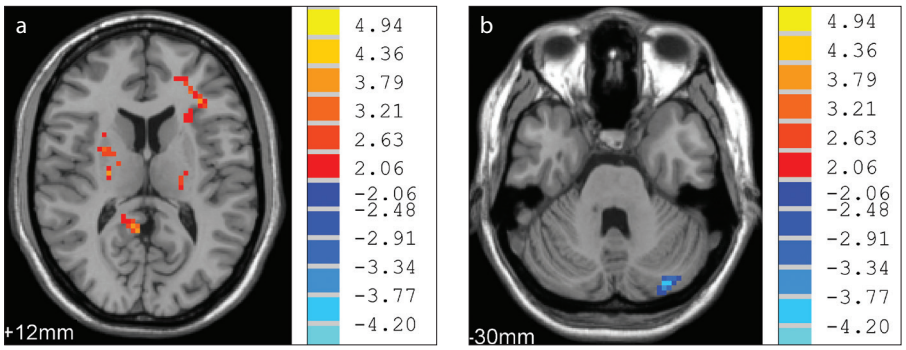

Figure 2. a, b. Axial T1-weighted images **(a, b)** show MHE group with increased fraction amplitude of low frequency fluctuation (fALFF) in right precuneus **(a)** and decreased fALFF in the posterior lobe of left cerebellum (L-PLC) **(b)** compared with the healthy controls. (REST1.8, http://www.restfmri.net)

Table 3. Regions showing significant differences in fALFF between MHE patients and healthy controls

Regions	BA	Voxels	MNI coordinates (x, y, z)	Peak t value
fALFF increased in MHE				
L-Tri/IFG	48	93	(-27, 33, 6)	4.4042
Pons/L-ALC		81	(-21, -48, -33)	4.6300
L-MFG	11	76	(-21, 42, -6)	3.5792
L-Pallidum		60	(-18, -3, 3)	3.9015
L-PrCG	24	58	(-15, -18, 42)	4.7522
L-Gyrus rectus	11	54	(-15, 33, -27)	5.5160
R-MCC-M/IFG	31/6	315	(18, 0, 48)	4.6569
R-Precuneus/PCC	29/23	64	(9, -48, 12)	4.2656
R-Insula		72	(24, -15, 15)	4.9575
R-Lentiform nucleus		73	(21, -3, 21)	4.0159
fALFF decreased in MHE				
B-MPFC	8	121	(-1, 30, 48)	-4.1249
R-MFG	9	62	(42, 9, 48)	-3.5478
L-PLC		61	(-30, -84, -30)	-3.9211
R-STG	48	54	(51, -6, 0)	-4.3696

fALFF, fraction amplitude of low frequency fluctuation; MHE, minimal hepatic encephalopathy; BA, Brodmann's area; MNI (x, y, z), Montreal Neurologic Institute (x, y, z); L, left; Tri/IFG, triangular part of inferior frontal gyrus; ALC, anterior lobe of cerebellum; MFG, middle frontal gyrus; PrCG, precentral gyrus; R, right; MCC, middle cingulum cortex; M/IFG, middle and inferior frontal gyrus; PCC, post cingulum cortex; B, bilateral; MPFC, medial prefrontal cortex; PLC, posterior lobe of cerebellum; STG, superior temporal gyrus.

connection cause cognitive dysfunction in MHE. We speculate that the dysfunction of precuneus and MPFC are manifestations of MHE, and changes in those two regions could provide a potential marker to detect MHE.

Previous studies suggested opposite patterns of changes in the cerebellum: decreased ALFF in the posterior lobe of left cerebellum in low-grade HE (20) and increased ALFF in the posterior lobe of left cerebellum in HE (21). Our results showed more complicated changes in the cerebellum in MHE (increased or decreased ALFF in different regions of the posterior lobe of right cerebellum, while increased and decreased fALFF in the anterior lobe and the posterior lobe of left cerebellum, respectively). As a regulator of the whole brain, the cerebellum influences several regions of prefrontal cortex via the thalamus (32). The anterior lobe of cerebellum is responsible for communication between cerebral and spinal motor systems, while the posterior lobe attends the cognitive control and emotion regulation (33, 34). Our complicated findings in the cerebellum may be interpreted as impairments and compensations happening in different regions of the cerebellum at the same time. Further study is needed to clarify these findings.

Interestingly, we detected increased ALFF in the right inferior temporal gyrus, right temporal pole/middle temporal gyrus, and left insula and increased fALFF in the right insula, right lentiform nucleus, and left pallidum in MHE, suggesting an increased spontaneous neuronal activity in those regions. We speculate that this may reflect the compensation of brain dysfunction in MHE.

This study has some limitations. First, although we instructed all participants to keep their head still and eyes closed during the scan, we cannot completely exclude uncontrolled factors such as the noise during the scanning affecting our results. Second, our sample size was small. Although we found significant differences in ALFF and fALFF in our study, further research with larger sample size is needed to confirm our findings.

In conclusion, we found ALFF and fALFF changes in many brain regions in MHE, demonstrating abnormality of the spontaneous neuronal activity. Especially, impairment of the right precuneus and left MPFC may represent the underlying manifestations in MHE. ALFF and fALFF can be used as potential markers for MHE.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Cordoba J. New assessment of hepatic encephalopathy. J Hepatol 2011; 54:1030–1040. [CrossRef]
2. Roman E, Cordoba J, Torrens M, et al. Minimal hepatic encephalopathy is associated with falls. Am J Gastroenterol 2011; 106:476–482. [CrossRef]
3. Shavakhi A, Hashemi H, Tabesh E, Derakhshan Z, Farzamnia S. Multistrain probiotic and lactulose in the treatment of minimal hepatic encephalopathy. J Res Med Sci 2014; 19:703–708.
4. Goel A, Yadav S, Saraswat V, et al. Cerebral oedema in minimal hepatic encephalopathy due to extrahepatic portal venous obstruction. Liver Int 2010; 30:1143–1151. [CrossRef]

5. Kale RA, Gupta RK, Saraswat VA, et al. Demonstration of interstitial cerebral edema with diffusion tensor MR imaging in type C hepatic encephalopathy. Hepatology 2006; 43:698–706. [CrossRef]
6. Kumar R, Gupta RK, Elderkin-Thompson V, et al. Voxel-based diffusion tensor magnetic resonance imaging evaluation of low-grade hepatic encephalopathy. J Magn Reson Imaging 2008; 27:1061–1068. [CrossRef]
7. Singhal A, Nagarajan R, Hinkin CH, et al. Two-dimensional MR spectroscopy of minimal hepatic encephalopathy and neuropsychological correlates in vivo. J Magn Reson Imaging 2010; 32:35–43. [CrossRef]
8. Mechtcheriakov S, Schocke M, Kugener A, et al. Chemical shift magnetic resonance spectroscopy of cingulate grey matter in patients with minimal hepatic encephalopathy. Neuroradiology 2005; 47:27–34. [CrossRef]
9. Zafiris O, Kircheis G, Rood HA, Boers F, Haussinger D, Zilles K. Neural mechanism underlying impaired visual judgement in the dysmetabolic brain: an fMRI study. Neuroimage 2004; 22:541–552. [CrossRef]
10. Liao LM, Zhou LX, Le HB, Yin JJ, Ma SH. Spatial working memory dysfunction in minimal hepatic encephalopathy: an ethology and BOLD-fMRI study. Brain Res 2012; 1445:62–72. [CrossRef]
11. Ni L, Qi R, Zhang LJ, et al. Altered regional homogeneity in the development of minimal hepatic encephalopathy: a resting-state functional MRI study. PLoS One 2012; 7:e42016. [CrossRef]
12. Chen HJ, Zhu XQ, Yang M, et al. Changes in the regional homogeneity of resting-state brain activity in minimal hepatic encephalopathy. Neurosci Lett 2012; 507:5–9. [CrossRef]
13. Zhang LJ, Zheng G, Zhang L, et al. Altered brain functional connectivity in patients with cirrhosis and minimal hepatic encephalopathy: a functional MR imaging study. Radiology 2012; 265:528–536. [CrossRef]
14. Qi R, Zhang LJ, Xu Q, et al. Selective impairments of resting-state networks in minimal hepatic encephalopathy. PLoS One 2012; 7:e37400. [CrossRef]
15. Chen HJ, Jiao Y, Zhu XQ, et al. Brain dysfunction primarily related to previous overt hepatic encephalopathy compared with minimal hepatic encephalopathy: resting-state functional MR imaging demonstration. Radiology 2013; 266:261–270. [CrossRef]
16. Qi R, Zhang LJ, Zhong J, et al. Altered effective connectivity network of the basal ganglia in low-grade hepatic encephalopathy: a resting-state fMRI study with Granger causality analysis. PLoS One 2013; 8:e53677. [CrossRef]
17. Zhang LJ, Qi R, Zhong J, et al. Disrupted functional connectivity of the anterior cingulate cortex in cirrhotic patients without overt hepatic encephalopathy: a resting state fMRI study. PLoS One 2013; 8:e53206. [CrossRef]
18. Qi R, Zhang LJ, Zhong J, et al. Disrupted thalamic resting-state functional connectivity in patients with minimal hepatic encephalopathy. Eur J Radiol 2013; 82:850–856. [CrossRef]
19. Zang YF, He Y, Zhu CZ, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev 2007; 29:83–91. [CrossRef]
20. Chen HJ, Zhu XQ, Jiao Y, Li PC, Wang Y, Teng GJ. Abnormal baseline brain activity in low-grade hepatic encephalopathy: a resting-state fMRI study. J Neurol Sci 2012; 318:140–145. [CrossRef]
21. Qi R, Zhang L, Wu S, et al. Altered resting-state brain activity at functional MR imaging during the progression of hepatic encephalopathy. Radiology 2012; 264:187–195. [CrossRef]
22. Zou QH, Zhu CZ, Yang Y, et al. An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. J Neurosci Methods 2008; 172:137–141. [CrossRef]
23. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy: definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35:716–721. [CrossRef]
24. Bao ZJ, Qiu DK, Ma X, et al. The application of psychometric measures in diagnosis of minimal hepatic encephalopathy. Chin J Dig 2006; 26:606–609.
25. Funahashi S. Prefrontal cortex and working memory processes. Neuroscience 2006; 139:251–261. [CrossRef]
26. Wagner AD, Maril A, Bjork RA, Schacter DL. Prefrontal contributions to executive control: fMRI evidence for functional distinctions within lateral prefrontal cortex. Neuroimage 2001; 14:1337–1347. [CrossRef]
27. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci USA 2001; 98:676–682. [CrossRef]
28. Mantini D, Perrucci MG, Del Gratta C, Romani GL, Corbetta M. Electrophysiological signatures of resting state networks in the human brain. Proc Natl Acad Sci USA 2007; 104:13170–13175. [CrossRef]
29. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 2005; 102:9673–9678. [CrossRef]
30. Wenderoth N, Debaere F, Sunaert S, Swinnen SP. The role of anterior cingulate cortex and precuneus in the coordination of motor behaviour. Eur J Neurosci 2005; 22:235–246. [CrossRef]
31. Iversen P, Sorensen M, Bak LK. Low cerebral oxygen consumption and blood flow in patients with cirrhosis and an acute episode of hepatic encephalopathy. Gastroenterology 2009; 136:863–871. [CrossRef]
32. Middleton FA, Strick PL. Cerebellar projections to the prefrontal cortex of the primate. J Neurosci 2001; 21:700–712.
33. Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 2010; 46:831–844. [CrossRef]
34. Schmahmann JD, Caplan D. Cognition, emotion and the cerebellum. Brain 2006; 129:290–292. [CrossRef]