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Renormalization of Thalamic Sub-Regional Functional Connectivity Contributes to Improvement of Cognitive Function after Liver Transplantation in Cirrhotic Patients with Overt Hepatic Encephalopathy

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Objective: The role of preoperative overt hepatic encephalopathy (OHE) in the neurophysiological mechanism of cognitive improvement after liver transplantation (LT) remains elusive. This study aimed to explore changes in sub-regional thalamic functional connectivity (FC) after LT and their relationship with neuropsychological improvement using resting-state functional MRI (rs-fMRI) data in cirrhotic patients with and without a history of OHE.

Materials and Methods: A total of 51 cirrhotic patients, divided into the OHE group (n = 21) and no-OHE group (n = 30), and 30 healthy controls were enrolled in this prospective study. Each patient underwent rs-fMRI before and 1 month after LT. Using 16 bilateral thalamic subregions as seeds, we conducted a seed-to-voxel FC analysis to compare the thalamic FC alterations before and after LT between the OHE and no-OHE groups, as well as differences in FC between the two groups of cirrhotic patients and the control group. Correction for multiple comparisons was conducted using the false discovery rate ($p < 0.05$).

Results: We found abnormally increased FC between the thalamic sub-region and prefrontal cortex, as well as an abnormally decreased FC between the bilateral thalamus in both OHE and no-OHE cirrhotic patients before LT, which returned to normal levels after LT. Compared with the no-OHE group, the OHE group exhibited more extensive abnormalities prior to LT, and the increased FC between the right thalamic subregions and right inferior parietal lobe was markedly reduced to normal levels after LT.

Conclusion: The renormalization of FC in the cortico-thalamic loop might be a neuro-substrate for the recovery of cognitive function after LT in cirrhotic patients. In addition, hyperconnectivity between thalamic subregions and the inferior parietal lobe might be an important feature of OHE. Changes in FC in the thalamus might be used as potential biomarkers for recovery of cognitive function after LT in cirrhotic patients.

Keywords: *Hepatic encephalopathy; Liver transplantation; Thalamus; Sub-region; Functional connectivity*

INTRODUCTION

Hepatic encephalopathy (HE) is an altered level of consciousness resulting from liver failure, encompassing a broad range of neuropsychiatric abnormalities of varying severity [1]. Up to 30%–45% of end-stage cirrhotic patients experience episodes of overt hepatic encephalopathy (OHE), the most severe clinical type of HE, while they are waiting for liver transplantation (LT) [2]. HE, especially OHE, has adverse effects on the quality of life, cognitive function,

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and working ability [3,4]. Although LT is the most effective strategy to restore cognitive function, it is still debated whether cognition can be fully reversed after LT [5,6]. Moreover, increasing evidence indicates that OHE may be an important factor for residual cognitive deficits after LT [2,7]. Campagna et al. [8] found that although OHE patients showed greater improvements after LT than patients with a negative history, their global cognitive function remained slightly worse. As the impact of OHE on recovery of cognitive function after LT is still elusive, the underlying pathophysiological mechanism remains to be clarified.

To date, changes in brain structure and function in HE have been well studied, and extensive involvement of the thalamus has been consistently demonstrated. Volumetric studies have described thalamic hypertrophy in contrast to diffuse cortical atrophy [9,10], with thalamic volume increasing in a stepwise manner from minimal HE to OHE [11]. PET studies have reported redistribution of the cerebral blood flow and metabolic rate of glucose and ammonia from various cortical regions to the basal ganglia and thalamus [12]. Resting-state functional MRI (rs-fMRI) studies have reported increased brain activity and thalamic functional connectivity (FC) in cirrhosis [13-16]. Notably, our previous research showed an abnormal increase in thalamus FC in OHE patients, rather than in those without such a history [17,18]. However, it is still unclear to what extent the abnormal thalamic FC could recover after LT, and what is the role of preoperative bouts of OHE. Thus, it is of great significance to assess how thalamic FCs change over the course of transplantation, which may shed new light on how HE influences high-level cognitive function.

Importantly, the thalamus is a heterogeneous structure with several nuclei, each with dense and specific cortical or subcortical connections [19]. Different thalamic subregions may act differently in cirrhosis, while the majority of previous studies regarded the thalamus as a whole in mapping thalamo-cortical FC [20,21]. Thus, more precise locations of abnormal FCs between thalamic sub-regions and cortical regions might lend further insight into specific OHE-related abnormalities. The presence, extent, and dynamic evolution of these sub-regional thalamic FC abnormalities might contribute to cognitive impairment in HE/OHE, as well as recovery of cognitive function post-LT, which has not been fully elucidated.

Thus, we hypothesized that there is a re-establishment or reorganization of thalamic FC in HE/OHE before and after LT. In the present study, we investigated alterations in thalamic FC after LT using rs-fMRI in cirrhotic patients with and without a history of OHE. In addition, we used thalamic sub-regions, parcellated according to their functional and constructional connectivity [22,23], to perform FC analysis. Specifically, we investigated the following objectives: 1) specific sub-regional thalamic FC abnormalities in OHE, 2) dynamic evolution of sub-regional thalamic FC in patients with and without a history of OHE before and after LT, and 3) the relationship between changes in the sub-regional thalamic FC and neuropsychological improvement.

MATERIALS AND METHODS

Subjects

This prospective study was approved by the Ethics Committee of Tianjin First Central Hospital, and written informed consent was obtained from each subject prior to the start of the study (IRB No. 2018N086KY). From July 2012 to March 2018, 51 inpatients with end-stage cirrhosis who were scheduled to undergo LT and 30 age-, sex -, and education-matched healthy controls (referred to as the control group) from the local community were recruited. Figure 1 shows the flowchart of patient selection. The diagnosis of cirrhosis was based on a consistent clinical history, radiologic studies, and liver biopsy when available. OHE was diagnosed as West Haven criteria of stage II disease or higher [1]. Subsequently, patients were divided into the OHE group (n = 21) and no-OHE group (n = 30) according to OHE history. All patients completed a series of laboratory examinations, neuropsychological tests, and MRI before LT and 1 month after it. The following additional exclusion criteria were applied: 1) history of drug or alcohol abuse, 2) history of any neuropsychological disorder or neurosurgery, 3) brain lesions such as tumors or strokes, 4) severe post-LT complications, and 5) excessive head motion (> 2.0 mm or 2.0°) during MRI.

Neuropsychological and Laboratory Tests

All participants underwent neuropsychological tests, including the number connection test type A (NCT-A) and the digit symbol test (DST), within 1 hour before each MRI. NCT-A evaluates the domain of psychomotor speed, while DST is associated with psychomotor speed, attention, and visual memory.

All patients completed laboratory tests to evaluate liver function within 1 week before MRI at baseline and

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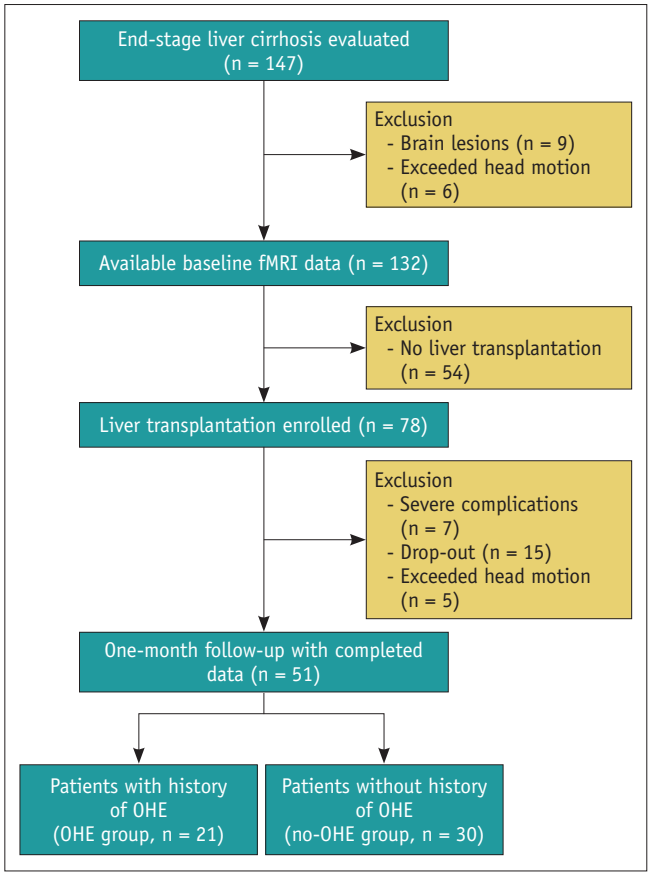

Fig. 1. Participant inclusion and exclusion flowchart. fMRI = functional MRI, no-OHE = cirrhosis patients without overt hepatic encephalopathy, OHE = overt hepatic encephalopathy

at 1-month follow-up, which included blood ammonia, prothrombin time, total bilirubin, and albumin.

Data Acquisition

All subjects underwent MRI using a 3T MRI system (TIM-Trio, Siemens Medical Solutions) with a 32-channel phased-array head coil. In addition, rs-fMRI data were obtained using gradient echo-planar imaging (repetition time = 2500 ms, echo time = 30 ms, field of view = 220 x 220 mm, matrix size = 96 x 96, slice thickness = 3 mm, number of slices = 40). Each acquisition contained 200 measurements, which lasted 509 seconds.

During scanning, subjects were instructed to relax with their eyes closed without falling asleep. The patients underwent MRI examination before LT and one month after, while the controls were examined only once. In addition, conventional T1- and T2-weighted MRI were conducted, which were interpreted by two neuroradiologists (with 12 and 4 years of experience, respectively) to exclude prominent cerebral abnormalities (e.g., stroke and tumor).

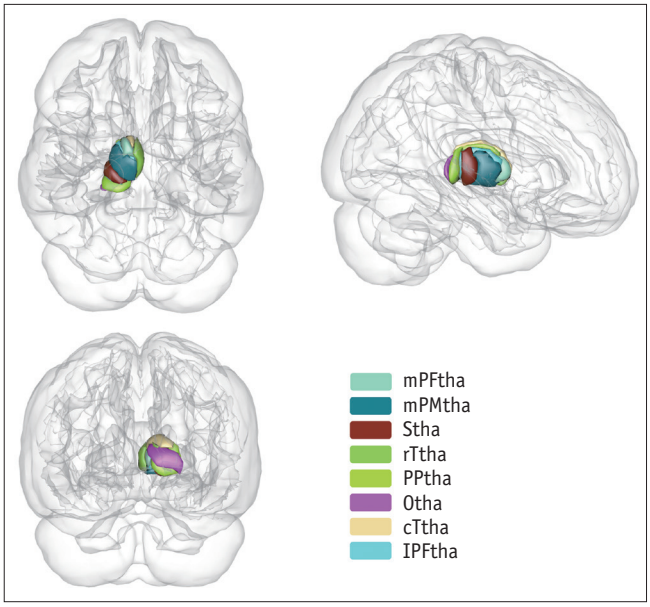

Fig. 2. Segmentation of thalamic sub-regions. cTtha = caudal temporal thalamus, lPFtha = lateral pre-frontal thalamus, mPFtha = medial pre-frontal thalamus, mPMtha = pre-motor thalamus, Otha = occipital thalamus, PPtha = posterior parietal thalamus, rTtha = rostral temporal thalamus, Stha = sensory thalamus

Data Preprocessing

Rs-fMRI data were preprocessed using the Graph-Theoretical Network Analysis (GRETNA) Toolbox (ver. 2.0.0, http://www.nitrc.org/projects/gretna/) executed in MATLAB (ver. 2013a; MathWorks). Briefly, the first 10 time points of functional data for each subject were discarded for signal equilibrium and participant adaptation. Then, the remaining 190 time points were preprocessed by slice timing correction, motion correction, spatial normalization, and resampling to 3 x 3 x 3 mm^3. Next, the nuisance covariates including 24 motion parameters, white matter, and cerebrospinal fluid signals were regressed out, and linear detrending was performed. Finally, temporal filtering (0.01–0.1 Hz) and smoothing (full width at half maximum [FWHM] = 6 mm) were performed. Subjects with head motion of more than 2 mm translations and rotation of the head higher than 2° were excluded.

FC Analysis

We employed the REST (ver. 1.8, http://www.restfmri.net) to perform a seed-to-voxel FC analysis between the subregions of the thalamus and the whole brain. The Human Brainnetome Atlas (http://atlas.brainnetome.org/index.html) was used to define 16 thalamic subregions (8 on each side) (Fig. 2). Specifically, they included the bilateral medial pre-frontal thalamus (mPFtha), pre-motor thalamus

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(mPMtha), sensory thalamus (Stha), rostral temporal thalamus (rTtha), posterior parietal thalamus (PPtha), occipital thalamus (Otha), caudal temporal thalamus (cTtha), and lateral pre-frontal thalamus (lPFtha). Each sub-region was selected as the seed region, and its average time sequence was acquired. Then, the Pearson's correlation coefficients between the time sequence of each seed and each voxel of the brain were calculated. Correlation coefficients were converted to Z-scores using Fisher's r-to-z transform to improve normality [24].

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp.) for demographic, neuropsychological, and clinical data, and SPM 12.0 software (http://www.fil.ion.ucl.ac.uk/spm) for fMRI data.

We used the two-way repeated measure analysis of covariance to examine the group-time interaction, main effects of group (OHE and no-OHE groups) and time (before and after LT) in thalamic FC between the OHE and no-OHE groups over time, with sex, age, and level of education as covariates. A cluster-level false discovery rate corrected threshold of $p < 0.05$ was applied to report statistically significant clusters [25]. When interaction or main effects were statistically significant in a brain region, the mean Z-scores were extracted for post-hoc comparisons using a two-sample *t* test or paired *t* test as appropriate.

Subsequently, the changes in Z-scores and clinical indices (e.g., ΔZ, ΔNCT-A, ΔDST, and Δammonia) were calculated. The correlation between Z-scores and clinical indices pre- and post-LT, as well as the correlation between ΔZ and ΔNCT-A, ΔDST, and Δammonia were calculated using Pearson's correlation analysis. Considering that these analyses were exploratory in nature, a statistical significance level of uncorrected $p < 0.05$ was used.

RESULTS

Demographic and Clinical Data

There were no significant differences in sex ($p = 0.813$), age ($p = 0.936$), and level of education ($p = 0.271$) among the OHE, no-OHE, and control groups (Table 1).

In both the OHE and no-OHE groups, the DST score was significantly increased, while the NCT-A score was markedly decreased (all $p < 0.001$) 1 month after LT compared with the baseline, indicating improved cognitive ability. However, the post-LT DST score in the OHE group was lower than that in the no-OHE group ($p < 0.05$) (Table 2). Compared with the HC group, the no-OHE group showed similar neuropsychological performance after LT, while the DST and NCT-A scores in the OHE group remained worse ($p < 0.001$ and $p < 0.002$, respectively).

One month after LT, in both patient groups, blood ammonia levels, prothrombin time, and total bilirubin levels decreased significantly compared with pre-LT (all $p < 0.01$), while albumin levels increased noticeably ($p < 0.001$) (Table 2).

FC Analysis

Main Effects

Significant main effects of time were found on FC of the right mPMtha with the left superior frontal gyrus (SFG) and left thalamus (R mPMtha-L SFG and R mPMtha-L thalamus). Post-hoc analyses revealed that for the R mPMtha-L SFG, in both the OHE and no-OHE groups, FC was elevated at baseline compared with the control group. After LT, the hyperconnectivity in the two groups similarly decreased, and there was no significant difference when compared with the control group. For the FC of the R mPMtha-L thalamus, before LT, the OHE group showed a decrease in comparison with the no-OHE and control groups, and the no-OHE group showed a declining trend compared to the control group. One month later, the hypoconnectivity in the two patient groups was elevated without any significant difference from the control group (Fig. 3A, Tables 3, 4).

Table 1. Demographic and Clinical Characteristics of the Subjects

Protocols	HC (n = 30)	no-OHE (n = 30)	OHE (n = 21)	*P*
Age, year	49.90 ± 7.62	49.57 ± 9.55	50.48 ± 9.27	0.936†
Sex, male:female	23:7	21:9	16:5	0.813*
Education level, year	12.77 ± 2.92	11.50 ± 3.31	12.9 ± 4.55	0.271†
Child-Pugh stage, A, B, C	NA	5, 9, 16	0, 3, 18	NA

Data are presented as the mean ± standard deviation or number of patients. *Pearson χ^2 test, †One-way analysis of variance test. HC = healthy control, no-OHE = cirrhosis patients without overt hepatic encephalopathy, OHE = overt hepatic encephalopathy

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Table 2. Cognitive Performance and Blood Biochemical Tests of the Subjects

Protocols	Pre-LT (Baseline)	1-Month Post-LT	*P*
Neuropsychological tests			
NCT-A, seconds			
OHE	69.05 ± 19.51	54.57 ± 14.03	< 0.001†
no-OHE	58.40 ± 18.41	46.63 ± 14.11	< 0.001†
p value	0.053*	0.053*	F = 0.610, *p* = 0.440‡
DST, score			
OHE	29.19 ± 11.01	36.67 ± 10.31	< 0.001†
no-OHE	35.50 ± 15.04	45.03 ± 12.82	< 0.001†
p value	0.108*	0.017*	F = 1.937, *p* = 0.170‡
Blood biochemical tests			
Blood ammonia, μmoL/L			
OHE	89.29 ± 24.90	50.62 ± 21.16	< 0.001†
no-OHE	58.33 ± 19.27	40.80 ± 12.14	< 0.001†
p value	< 0.001*	0.041*	F = 7.004, *p* = 0.015‡
Albumin, mg/dL			
OHE	29.48 ± 4.755	38.25 ± 6.585	< 0.001†
no-OHE	30.41 ± 7.147	40.11 ± 5.711	< 0.001†
p value	0.604*	0.287*	F = 1.260, *p* = 0.275‡
Total bilirubin, mg/dL			
OHE	68.17 ± 54.30	26.34 ± 29.31	0.003†
no-OHE	60.26 ± 83.26	20.50 ± 15.67	0.014†
p value	0.705*	0.3612*	F < 0.001, *p* = 0.996‡
Prothrombin time, seconds			
OHE	18.10 ± 3.881	13.51 ± 5.356	0.006†
no-OHE	17.13 ± 5.238	13.23 ± 2.381	< 0.001†
p value	0.475*	0.805*	F = 0.171, *p* = 0.681‡

Data are presented as mean ± standard deviation. *Two-sample *t* test, †Paired *t* test, ‡Two-way repeated measures analysis of variance. DST = digit symbol test, NCT-A = number connection test of type A, no-OHE = cirrhosis patients without overt hepatic encephalopathy, OHE = overt hepatic encephalopathy

No significant main effects of group in thalamic FC were observed in this study.

Group-Time Interaction

A group-time interaction effect was identified in the FC of the right PPtha and right Otha with the right inferior parietal lobe (R PPtha-R inferior parietal lobule [IPL] and R Otha-R IPL). Post-hoc analyses indicated that the OHE group had higher values in these two connections prior to LT, while there was no significant difference between the no-OHE group and the control group. One month after LT, the enhanced FC in the OHE group was markedly recovered compared to that in the control group (Fig. 3B, Tables 3, 4).

Pearson's Correlation Analysis

For all the patients (both OHE and no-OHE groups) as a whole, the FC values of the R PPtha-R IPL and R Otha-R IPL showed significant negative correlations with DST scores and positive correlations with blood ammonia level at baseline. ΔZ-scores of R Otha-R IPL and R mPMtha-L SFG were positively correlated with changes in blood ammonia levels (Fig. 4, Supplementary Tables 1, 2).

No correlation between Z-scores and NCT-A, DST scores, or ammonia was detected post-LT (Supplementary Table 3).

DISCUSSION

To our knowledge, this is the first study to investigate the effects of preoperative OHE on thalamic FC alterations after LT, using a region of interest approach with subregions of the thalamus. Specifically, we found that LT had a normalizing effect on abnormally higher FC between the thalamus and cortex, and abnormally lower FC between the bilateral thalamus, accompanied by a significant cognitive improvement. Furthermore, the improvement of FC in the OHE group was more prominent than that in the no-OHE

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group, which might be due to more severe brain damage occurring in OHE before LT.

We found increased FC between the thalamic subregion (R mPMtha, right premotor thalamus) and prefrontal cortex (L SFG, right SFG) in both OHE and no-OHE groups prior to LT, which decreased to normal levels after LT. The mPMtha, along with the prefrontal sub-region, included areas of the ventral anterior (VA) nucleus [26]. VA nuclei of the thalamus exhibit anatomical connections with the prefrontal cortex [27], and direct projections among them could support working memory [28]. Moreover, many studies have found that lesions of VA nuclei can impair the working memory [29]. Additionally, previously reported fMRI data revealed that areas of the VA nucleus could be activated during

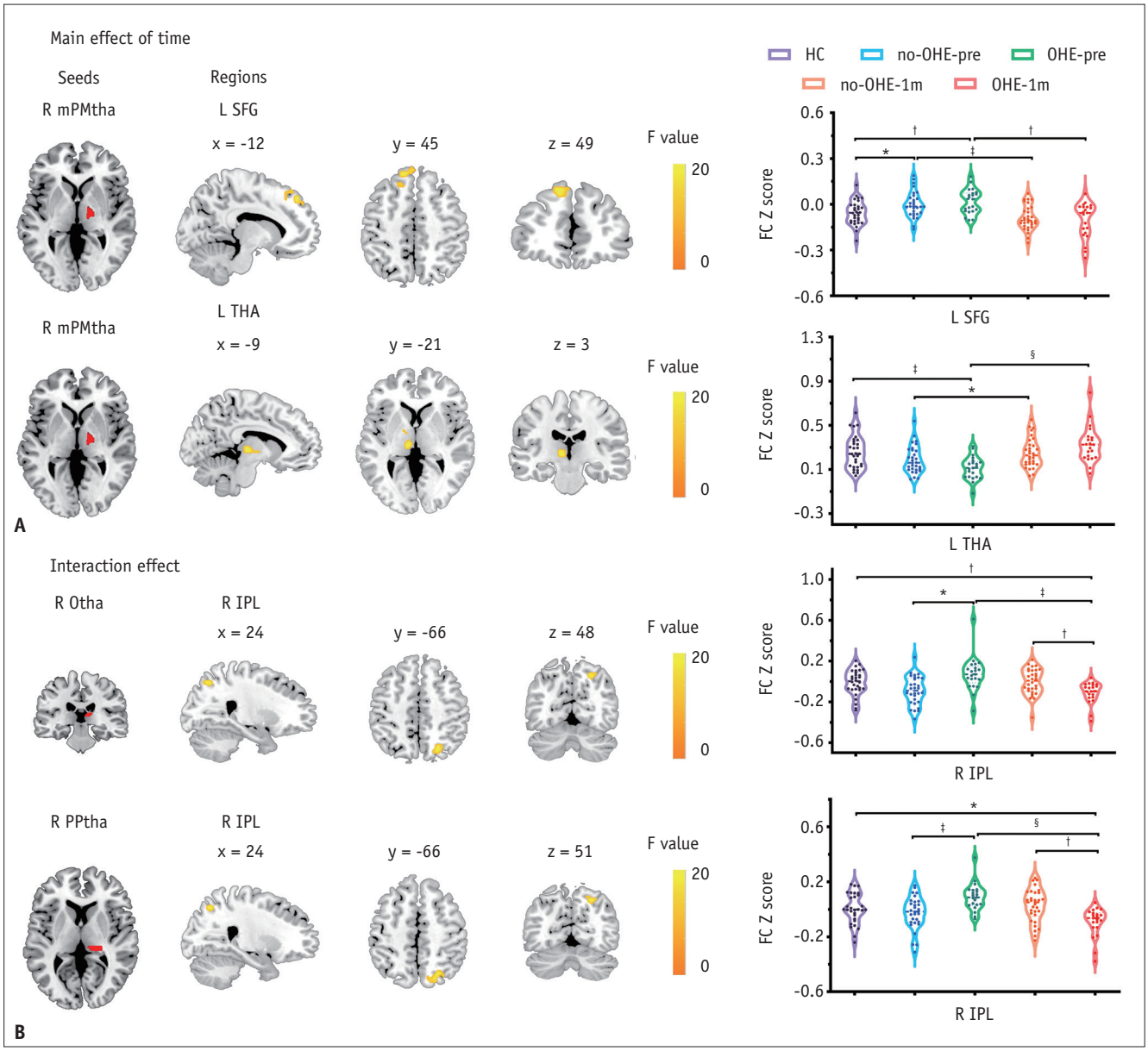

Fig. 3. Main effect of time and interaction effect in thalamic functional connectivity alterations in OHE and no-OHE patients.
$^{*}p < 0.05$, $^{\dagger}p < 0.01$, $^{\ddagger}p < 0.001$, $^{\S}p < 0.0001$.
A. Multiplanar MR images and violin plot show a significant main effect of time on thalamic functional connectivity alterations in OHE and no-OHE patients. **B.** Multiplanar MR images and violin plots show significant interaction effects in thalamic FC alterations in OHE and no-OHE patients. Functional connectivity values were extracted for post hoc analysis, and healthy controls were analyzed using a two-sample *t* test as a reference. FC = functional connectivity, IPL = inferior parietal lobule, L = left, mPMtha = pre-motor thalamus, no-OHE = cirrhosis patients without overt hepatic encephalopathy, no-OHE-pre = no-OHE patients before liver transplantation, OHE = overt hepatic encephalopathy, OHE-pre = OHE patients before liver transplantation, Otha = occipital thalamus, PPtha = posterior parietal thalamus, R = right, SFG = superior frontal gyrus, THA = thalamus

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working memory paradigms [30]. Notably, working memory impairments are regarded as a characteristic of HE [31]. Therefore, the higher connection between mPMtha and SFG in our results might reflect functional reorganization for cognitive impairment in all patients with cirrhosis. Importantly, one month after LT, the hyperconnectivity in

Table 3. Between-Group Differences in Functional Connectivity of the Thalamic Subregions (p < 0.05, FDR Corrected)

Thalamic Seed Region	Side	Connected Region	MNI Coordinates			BA	Voxels	F Value
			x	y	z			
Main effect of time								
mPMtha	R	L SFG	-12	45	48	8	93	24.896
mPMtha	R	L thalamus	-9	-21	3	-	41	26.474
Interaction effect								
Otha	R	R IPL	24	-66	48	7	31	21.629
PPtha	R	R IPL	24	-66	51	7	42	22.246

BA = Brodmann area, FDR = false discovery rate, IPL = inferior parietal lobule, L = left, MNI = Montreal Neurological Institute, mPMtha = pre-motor thalamus, Otha = occipital thalamus, PPtha = posterior parietal thalamus, R = right, SFG = superior frontal gyrus

Table 4. Z-Scores of Functional Connectivity between the Thalamic Seeds and Connected Region

Connectivity	Functional Connectivity Strength (Z-Scores)				
	HC	No-OHE		OHE	
		Pre-LT	Post-LT	Pre-LT	Post-LT
R mPMtha to L SFG	-0.06 ± 0.08	-0.0008 ± 0.08	-0.09 ± 0.08	0.02 ± 0.08	-0.10 ± 0.10
R mPMtha to L THA	0.26 ± 0.15	0.19 ± 0.12	0.25 ± 0.13	0.11 ± 0.10	0.33 ± 0.16
R Otha to R IPL	-0.0092 ± 0.12	-0.089 ± 0.14	-0.0031 ± 0.13	0.075 ± 0.17	-0.11 ± 0.10
R PPtha to R IPL	0.0043 ± 0.11	-0.028 ± 0.12	0.027 ± 0.12	0.090 ± 0.098	-0.092 ± 0.11

Data are presented as mean ± standard deviation. HC = heathy control, IPL = inferior parietal lobule, L = left, LT = liver transplantation, mPMtha = pre-motor thalamus, no-OHE = cirrhosis patients without overt hepatic encephalopathy, OHE = overt hepatic encephalopathy, Otha = occipital thalamus, PPtha = posterior parietal thalamus, R = right, SFG = superior frontal gyrus, THA = thalamus

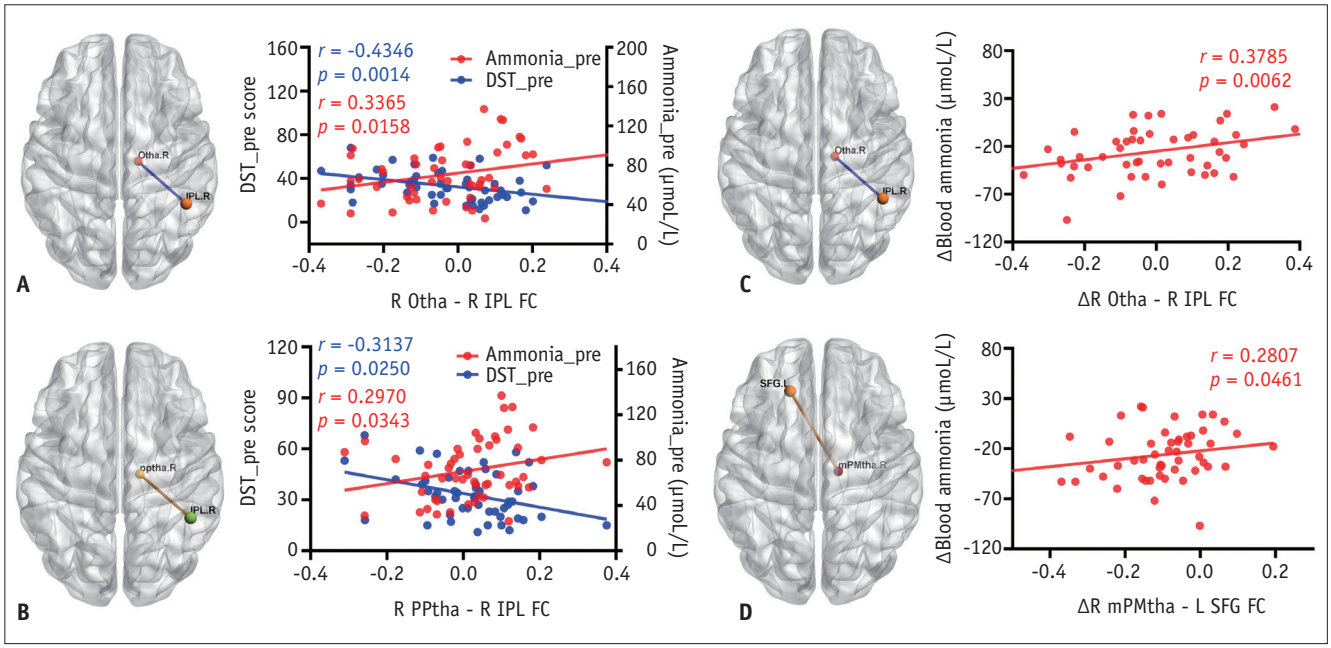

Fig. 4. Pearson correlation analysis between thalamic sub-regional FC and neuropsychological tests.
A, B. The brain graph illustration and scatterplot show the FC between R Otha and R IPL, between R PPtha and R IPL in all patients at baseline, which negatively correlated with DST scores and positively correlated with blood ammonia test. **C, D.** The alteration of the FC (ΔFC) between R Otha and R IPL, and between R mPMtha and R SFG in all patients before and after liver transplantation was positively correlated with the alteration of the blood ammonia (Δblood ammonia). DST = digit symbol test, FC = functional connectivity, IPL = inferior parietal lobule, L = left, mPMtha = pre-motor thalamus, Otha = occipital thalamus, PPtha = posterior parietal thalamus, R = right, SFG = superior frontal gyrus

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both groups returned to normal levels, which indicates the positive effects of LT on brain function. SFG is an important part of the executive control network, which is critical for the active maintenance and manipulation of information in working memory, and for decision-making in the context of goal-directed behavior. The recovery of FC between the thalamus and SFG may be related to the improvement of executive function after LT. Moreover, the current study displayed similar changes in thalamic FC to SFG after LT in both OHE and no-OHE groups, which may assist in delineating the shared characterization of cirrhotic patients with cognitive deficits and post-LT recovery.

Moreover, we noted a decreased FC between the bilateral thalamus (R mPMtha-L thalamus) prior to LT, which was restored after LT. Converging evidence suggests the importance of the cortico-thalamic loop for neuropsychiatric disorders including HE [32]. Functional imbalances within the loop appear to impair cognitive function. In the present study, we found a decreased inner FC within the subcortical nucleus (left and right thalamus) along with an increased cortical-subcortical connectivity (R mPMtha-L SFG) before LT. Taken together, these results indicate the overall connectivity strength in the loop, which might suggest a balance in the cortico-thalamic loop [33]. After 1 month, LT renormalized the balance by enhancing connections between the bilateral thalamus and attenuating connections between the thalamus and the cortex. As the thalamus regulates cognition via the cortico-thalamic loop, the dynamic alterations in FC within the loop may be essential for recovery of cognitive function after LT.

Functional normalization of the cortico-thalamic loop can be interpreted in the context of the ammonia hypothesis of HE [34,35]. LT effectively removes the underlying liver disease that, by definition, causes HE and hyperammonemia; hence, the regional function may be relatively normalized [36,37]. This viewpoint is also supported by the strong relationship between abnormal FC levels and blood ammonia levels in the current study: hyperammonemia was associated with more severe cortico-thalamic FC abnormalities before LT, and the change in blood ammonia level was positively correlated with FC alterations 1 month after LT. Furthermore, the instant change in cortico-thalamic connection shortly after LT in our study may suggest that the compensatory response of the thalamus is reversible.

Another interesting and important finding was that OHE patients specifically demonstrated increased FC between thalamic subregions (R Otha, right occipital thalamus and R PPtha, posterior parietal thalamus) and high-level cognitive cortex (e.g. IPL) at baseline, which may be related to severe brain injury caused by episodes of OHE [37,38]. As the hyperconnectivity of thalamic subregions with IPL only appeared in the OHE group, we speculated that this may be an important feature for OHE. IPL is related to the integration of perceptual and cognitive processing [39] and is a core component of the default mode network (DMN). The DMN is an important high-level cognitive network, and thus the enhanced thalamus-IPL FC may be due to more severe cognitive impairment in patients with OHE. This evidence was further verified by the observed negative correlations between FC of these two thalamic subregions and cognitive ability in the present study, where higher FC values of R PPtha-R IPL and R Otha-R IPL were significantly correlated with lower DST scores, indicating poor neuropsychological performance. After LT, all abnormally enhanced FCs were markedly reduced to normal levels. Because of more extensive and broader changes in thalamic FC, it was not surprising that OHE patients showed more improvement in cognitive performance after LT. Our findings are consistent with those of several neuropsychological studies, in which OHE patients showed greater cognitive improvements after LT [7,8].

In this study, the OHE group had residual cognitive deficits, while the FC in the cortico-thalamic loop was normalized after LT, which seemed to be a "clinical-image discrepancy." Apart from the potential influence of immunodepressants [40], there might be some other possible reasons for this discrepancy. For instance, we only focused our attention on FC in the cortico-thalamic loop, rather than a whole-brain FC perspective. The recovery of the FC in the cortico-thalamic loop after LT may only be one part of the whole brain network reorganization. Some other FC pathways might remain malfunctioning to some extent, which could not be reflected in this study.

There are several limitations to the current study. First, a relatively small sample size might limit the statistical findings. Second, the present study mainly concentrated on short-term FC alterations after LT; therefore, long-term follow-up at multiple time points after LT is warranted. Third, the use of immunosuppressants after LT might have some side effects, which could influence cognitive function [40]. This was inevitable since it was unethical to deprive post-LT patients of these drugs. Both patient groups were administered the drugs to minimize this limitation.

In conclusion, we found an interesting dynamic change in thalamic FC before and after LT. Our findings suggest that

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the renormalization of FC in the cortico-thalamic loop might be a neuro-substrate for recovery of cognitive function after LT in cirrhotic patients. In addition, hyperconnectivity between thalamic sub-regions with IPL might be an important feature for OHE. The improvement of FC in the OHE group was more prominent than that in the no-OHE group, which might be due to more severe brain damage occurring in OHE before LT. Changes in FC in the thalamus might be used as potential biomarkers for recovery of cognitive function after LT in cirrhotic patients.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2020.1432.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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REFERENCES

1. Weissenborn K. Hepatic encephalopathy: definition, clinical grading and diagnostic principles. *Drugs* 2019;79:5-9
2. Garcia-Martinez R, Rovira A, Alonso J, Jacas C, Simón-Talero M, Chavarria L, et al. Hepatic encephalopathy is associated with posttransplant cognitive function and brain volume. *Liver Transpl* 2011;17:38-46
3. Hadjihambi A, Arias N, Sheikh M, Jalan R. Hepatic encephalopathy: a critical current review. *Hepatol Int* 2018;12:135-147
4. Wong RJ, Aguilar M, Gish RG, Cheung R, Ahmed A. The impact of pretransplant hepatic encephalopathy on survival following liver transplantation. *Liver Transpl* 2015;21:873-880
5. Hopp AE, Dirks M, Petrusch C, Goldbecker A, Tryc AB, Barg-Hock H, et al. Hepatic encephalopathy is reversible in the long term after liver transplantation. *Liver Transpl* 2019;25:1661-1672
6. Kornerup LS, Pflugrad H, Weissenborn K, Vilstrup H, Dam G. Cognitive impairment after liver transplantation: residual hepatic encephalopathy or posttransplant encephalopathy? *Hepat Med* 2019;11:41-46
7. Sotil EU, Gottstein J, Ayala E, Randolph C, Blei AT. Impact of preoperative overt hepatic encephalopathy on neurocognitive function after liver transplantation. *Liver Transpl* 2009;15:184-192
8. Campagna F, Montagnese S, Schiff S, Biancardi A, Mapelli D, Angeli P, et al. Cognitive impairment and electroencephalographic alterations before and after liver transplantation: what is reversible? *Liver Transpl* 2014;20:977-986
9. Chen HJ, Zhu XQ, Shu H, Yang M, Zhang Y, Ding J, et al. Structural and functional cerebral impairments in cirrhotic patients with a history of overt hepatic encephalopathy. *Eur J Radiol* 2012;81:2463-2469
10. Qi R, Zhang L, Wu S, Zhong J, Zhang Z, Zhong Y, et al. Altered resting-state brain activity at functional MR imaging during the progression of hepatic encephalopathy. *Radiology* 2012;264:187-195
11. Tao R, Zhang J, You Z, Wei L, Fan Y, Cui J, et al. The thalamus in cirrhotic patients with and without hepatic encephalopathy: a volumetric MRI study. *Eur J Radiol* 2013;82:e715-e720
12. Ahl B, Weissenborn K, van den Hoff J, Fischer-Wasels D, Köstler H, Hecker H, et al. Regional differences in cerebral blood flow and cerebral ammonia metabolism in patients with cirrhosis. *Hepatology* 2004;40:73-79
13. Qi R, Xu Q, Zhang LJ, Zhong J, Zheng G, Wu S, et al. Structural and functional abnormalities of default mode network in minimal hepatic encephalopathy: a study combining DTI and fMRI. *PLoS One* 2012;7:e41376
14. Jao T, Schröter M, Chen CL, Cheng YF, Lo CY, Chou KH, et al. Functional brain network changes associated with clinical and biochemical measures of the severity of hepatic encephalopathy. *Neuroimage* 2015;122:332-344
15. Zhang G, Cheng Y, Shen W, Liu B, Huang L, Xie S. The short-term effect of liver transplantation on the low-frequency fluctuation of brain activity in cirrhotic patients with and

without overt hepatic encephalopathy. *Brain Imaging Behav* 2017;11:1849-1861
16. Zhang G, Cheng Y, Shen W, Liu B, Huang L, Xie S. Brain regional homogeneity changes in cirrhotic patients with or without hepatic encephalopathy revealed by multi-frequency bands analysis based on resting-state functional MRI. *Korean J Radiol* 2018;19:452-462
17. Zhang G, Cheng Y, Liu B. Abnormalities of voxel-based whole-brain functional connectivity patterns predict the progression of hepatic encephalopathy. *Brain Imaging Behav* 2017;11:784-796
18. Cheng Y, Zhang G, Shen W, Huang LX, Zhang L, Xie SS, et al. Impact of previous episodes of hepatic encephalopathy on short-term brain function recovery after liver transplantation: a functional connectivity strength study. *Metab Brain Dis* 2018;33:237-249
19. Herrero MT, Barcia C, Navarro JM. Functional anatomy of thalamus and basal ganglia. *Childs Nerv Syst* 2002;18:386-404
20. Lv H, Liu C, Wang Z, Zhao P, Cheng X, Yang Z, et al. Altered functional connectivity of the thalamus in tinnitus patients is correlated with symptom alleviation after sound therapy. *Brain Imaging Behav* 2020;14:2668-2678
21. Byun JI, Kim HW, Kang H, Cha KS, Sunwoo JS, Shin JW, et al. Altered resting-state thalamo-occipital functional connectivity is associated with cognition in isolated rapid eye movement sleep behavior disorder. *Sleep Med* 2020;69:198-203
22. Fan Y, Nickerson LD, Li H, Ma Y, Lyu B, Miao X, et al. Functional connectivity-based parcellation of the thalamus: an unsupervised clustering method and its validity investigation. *Brain Connect* 2015;5:620-630
23. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, et al. The human brainnetome atlas: a new brain atlas based on connectional architecture. *Cereb Cortex* 2016;26:3508-3526
24. Liu F, Wang Y, Li M, Wang W, Li R, Zhang Z, et al. Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. *Hum Brain Mapp* 2017;38:957-973
25. Chumbley J, Worsley K, Flandin G, Friston K. Topological FDR for neuroimaging. *Neuroimage* 2010;49:3057-3064
26. Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. *Nat Neurosci* 2003;6:750-757
27. Collins DP, Anastasiades PG, Marlin JJ, Carter AG. Reciprocal circuits linking the prefrontal cortex with dorsal and ventral thalamic nuclei. *Neuron* 2018;98:366-379.e4
28. Mitchell AS. The mediodorsal thalamus as a higher order thalamic relay nucleus important for learning and decision-making. *Neurosci Biobehav Rev* 2015;54:76-88
29. Tanaka M. Cognitive signals in the primate motor thalamus predict saccade timing. *J Neurosci* 2007;27:12109-12118
30. de Bourbon-Teles J, Bentley P, Koshino S, Shah K, Dutta A, Malhotra P, et al. Thalamic control of human attention driven by memory and learning. *Curr Biol* 2014;24:993-999
31. Zarantonello L, Turco M, Formentin C, Izquierdo-Altarejos P, Vuerich A, Barcenas Jimenez MJ, et al. The influence of HE history, HE status and neuropsychological test type on learning ability in patients with cirrhosis. *Liver Int* 2019;39:861-870
32. Peters SK, Dunlop K, Downar J. Cortico-striatal-thalamic loop circuits of the salience network: a central pathway in psychiatric disease and treatment. *Front Syst Neurosci* 2016;10:104
33. Wang J, Jiang Y, Tang Y, Xia M, Curtin A, Li J, et al. Altered functional connectivity of the thalamus induced by modified electroconvulsive therapy for schizophrenia. *Schizophr Res* 2020;218:209-218
34. McPhail MJ, Patel NR, Taylor-Robinson SD. Brain imaging and hepatic encephalopathy. *Clin Liver Dis* 2012;16:57-72
35. Ellul MA, Gholkar SA, Cross TJ. Hepatic encephalopathy due to liver cirrhosis. *BMJ* 2015;351:h4187
36. Atluri DK, Asgeri M, Mullen KD. Reversibility of hepatic encephalopathy after liver transplantation. *Metab Brain Dis* 2010;25:111-113
37. Chavarria L, Cordoba J. Encephalopathy and liver transplantation. *Metab Brain Dis* 2013;28:285-292
38. Chen HJ, Jiao Y, Zhu XQ, Zhang HY, Liu JC, Wen S, 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
39. Cheng Y, Huang L, Zhang X, Zhong J, Ji Q, Xie S, et al. Liver transplantation nearly normalizes brain spontaneous activity and cognitive function at 1 month: a resting-state functional MRI study. *Metab Brain Dis* 2015;30:979-988
40. Schmitz B, Pflugrad H, Tryc AB, Lanfermann H, Jäckel E, Schrem H, et al. Brain metabolic alterations in patients with long-term calcineurin inhibitor therapy after liver transplantation. *Aliment Pharmacol Ther* 2019;49:1431-1441

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