



## Research paper

## Memory impairment in patients with spleen deficiency syndrome: Evidence from a resting-state fMRI study

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## ABSTRACT

**Introduction:** According to the basic theory of traditional Chinese medicine (TCM), the gastrointestinal function is considered the main function of spleen. The function of spleen is considered to be associated with memory. However, less evidence supports the notion from neuropsychological level. Our aim was to investigate the change of memory function and spontaneous brain activity in patients with spleen deficiency syndrome.

**Methods:** Twenty patients and 16 healthy subjects took part in the memory function test. Eighteen patients and 14 healthy controls underwent functional magnetic resonance imaging examination.

**Results:** Compared with healthy subjects, patients with spleen deficiency syndrome revealed significantly lower scores of memory quotient ( $P = 0.001$ ), directed memory ( $P \leq 0.001$ ), associative memory ( $P \leq 0.001$ ) and free recall of images ( $P = 0.025$ ), higher aptitude of low-frequency fluctuation (ALFF) values in bilateral temporal occipital fusiform cortices (TOC) and lateral occipital cortices (LOC), and lower ALFF values in left frontal pole cortex (FPC). Moreover, scores of clinical memory scale were significantly correlated with ALFF values in bilateral TOCs and LOCs, and left FPC.

**Conclusions:** Our results indicated that the abnormal brain regions were mainly involved in memory function, providing evidence for the memory functional impairment in patients with spleen deficiency syndrome.

## 1. Introduction

The enteric nervous system is regarded as a second brain and consists of a mesh-like system of neurons that governs the function of the gastrointestinal system. There exists intricate links between the gastrointestinal tract and the central nervous system via biochemical signals, which is referred as the “brain-gut axis” [1]. The two systems remain constantly exchanging streams of chemical and electrical messages, and affect each other. Recently, the gastric network has been found by recording brain activity with fMRI and stomach activity with electrogastragram, suggesting a link between the gastrointestinal system and spontaneous brain activity [2]. It is essential to indicate the relationship between brain function and enteric nervous system from different levels.

According to the basic theory of traditional Chinese medicine (TCM), the gastrointestinal function is considered the main function of

spleen, which means that once the spleen is dysfunctional, it will result in gastrointestinal disorders. Spleen deficiency syndrome, called by “Pi-deficiency Zheng” in Chinese, is one of the most common syndromes after spleen dysfunction. It could not only result in the gastrointestinal dysfunctions, such as diarrhea and edema, but also result in impairments of cognitive function, such as hypomnesia [3]. Spleen stores Yi and domains thoughts according to the Yellow Emperor’s Inner Classic (Huangdi Nei Jing). Yi is thought to mainly include the memory and thought, which could not only form short-term memory, process information and develop the long-term memory, but also extract information from the long-term memory [4,5]. In hence, the function of spleen is considered to be associated with memory. However, to our knowledge, there is little evidence supporting this notion.

During the latest thirty decades, resting-state functional magnetic resonance imaging (fMRI) has been widely used to investigate the neural mechanisms of TCM. The fMRI has helped to indicate the

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mechanisms of acupuncture on major depressive disorder, hemiplegia, migraine, and identifying different TCM patterns (Zheng) [6–9]. It is possible to apply fMRI to study the relationship between spleen deficiency syndrome and memory decline from the aspect of neuroimaging studies. Our previous study had shown enhanced functional connectivity of the default mode network in patients with spleen deficiency syndrome [10]. However, to our best of knowledge, there is no study focusing on intrinsic brain activity alterations in patients with spleen deficiency syndrome so far.

Recently, data-driven methods like aptitude of low-frequency fluctuation (ALFF) have gained increasing attention. The ALFF can reflect intrinsic brain activity and the neural processes of key brain regions, rather than correlations among different brain regions. Moreover, it has the best balance between test-retest replicability and reliability. ALFF has been widely applied to studies including Alzheimer's disease, migraine, chronic primary insomnia and so on [11–13]. Therefore, in the current study, we conducted a combination of fMRI and memory function test to characterize the changes in abnormality in patients with spleen deficiency syndrome from the aspect of neuropsychology. Twenty patients with spleen deficiency syndrome from sub-healthy populations and 16 age, gender-matched healthy subjects as controls were recruited. We applied ALFF to identify brain regions showing abnormal functional changes in patients with spleen deficiency syndrome, and performed correlation analysis among abnormal brain regions and scores of memory function test.

## 2. Materials and methods

This study was approved by the Beijing An Ding Hospital Ethics Committee. All enrolled subjects had signed informed consents before participating our study.

### 2.1. Participants

Twenty right-handed subjects (14 females, aged  $25.80 \pm 3.40$  years) were diagnosed as spleen deficiency syndrome according to the 1986 deficiency syndrome of criteria of TCM by Integrative Medicine Deficiency Syndrome and Senile Diseases Research Association [14]. Primary symptoms included: poor appetite, abdominal distension, loose stools, fat or toothed tongue. Meeting at least two primary symptoms could be diagnosed as spleen deficiency syndrome. while the patients with spleen deficiency syndrome met the criteria below: subhealthy subjects with no organic pathological disease; aged between 18 and 45 years old, right-handed; duration for at least six months; self-rating anxiety scale (SAS) < 50, depression self-rating scale (SDS) < 50 and brief psychiatric rating scale (BPRS) < 35. The exclusion criteria were as follows: subjects with history of psychiatric or neurological disorders; with history of drug or alcohol abuse; any MRI contraindication. Another sixteen healthy subjects (10 females, aged  $27.44 \pm 2.42$  years) were recruited free from any symptoms of spleen deficiency syndrome and with no history of organic pathological disease.

### 2.2. MRI acquisition

A 3.0 Tesla MRI scanner (Siemens, Erlangen, Germany) was employed to obtain resting-state and structural images in the Imaging Center for Brain Research at Beijing An Ding Hospital. Eighteen patients and 14 healthy subjects took part in the MRI scanning. All participants were asked to take a rest for 30 min before scanning, and were ordered to keep eyes closed and awake, stay still during scanning. Foam head holders were immobilized to minimize head movements during scanning. All MRI scanning would be conducted between 3 pm and 5 pm.

Before the functional scanning, high-resolution structural information for anatomical localization would be collected by using MRI sequences. A single-shot, gradient-recalled echo-planar imaging sequence was applied with the following parameters: repetition time = 2000 ms,

matrix =  $64 \times 64$ , echo time = 30 ms, flip angle =  $90^\circ$ , slice thickness = 3.5 mm, field of view =  $200 \text{ mm} \times 200 \text{ mm}$ , gap = 1 mm, 33 axial sections, and 240 volumes.

### 2.3. Experimental paradigm

During the study, we firstly conducted a 480-second resting scan, then a 250-second high-resolution structural scan.

### 2.4. Memory function test

During memory function test, the Clinical Memory Scale (CMS) was employed. We recruited 20 patients with spleen deficiency syndrome and 16 healthy subjects taking part in the memory function test.

CMS, a testing tool designed by the Chinese Academy Sciences Institute of Psychology, was applied to evaluate the short-term memory in the current study [15]. CMS test included verbal test and nonverbal test. The scale mainly consisted of five tests, which are directed memory (DM), associative memory (AM), free recall of images (FRI), meaningless image recognition (MIR) and associative memory of portraits (AMP). The DM and AM were used to test the ability to learn and memorize different pairs of words, which could reflect language abilities of left-hemispheric brain. Different stimuli of photos were displayed during AMP, MIR and FRI, which reflected nonverbal abilities of right-hemispheric brain. Firstly, we would conduct the auditory memory tests containing directed memory and associative memory. The instructions and stimuli would be released by a tape recorder. Six pairs of Chinese words would be released three times during the AM test, while only one time for the DM test. Then two sections were nonverbal tests. The operator would show fifteen grocery photos to participants during the FRI test, and five kinds of meaningless images during the MIR test according to the prescribed time. The last section was the combination of auditory and visual memory. Participants would be ordered to describe the characteristics of the photos (6 face portraits, rendering time 9 s per photo) during presenting the stimuli of pictures. The memory quotient (MQ), calculated by a computer according to the score of all sections, was applied to assess the memory level,

### 2.5. Data processing and analyzing

Data Processing Assistant for Resting-State fMRI (DPARSF, <http://rfmri.org/> DPARSF) and the statistical parametric mapping software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm>) were employed to conduct the data pre-processing. Firstly, we deleted 10 volumes for signal equilibrium. Then a total of 230 volumes for each participant would be corrected for slice timing. The following steps would be conducted in order: spatial realignment for head motions, normalization into the Montreal Neurological Institute (MNI) template, resampling to  $3 \times 3 \times 3 \text{ mm}^3$ , smoothing with a Gaussian kernel of  $4 \times 4 \times 4 \text{ mm}^3$  full width at half-maximum, spurious variances (ventricular and white matter signal, head motion, and derivatives of each of these signals) reduction and finally removing linear trends from the time courses. Two patients and two healthy controls were ruled out, for exhibiting head motion >  $1.5^\circ$  rotation maximum translation and 1.5 mm in the process of MRI scanning.

The REST software (<http://restfmri.net>) was applied to perform ALFF. Firstly, the time series were transformed into a frequency domain with a fast Fourier transform and the power spectrum was then obtained. The power spectrum, crossing 0.01–0.08 Hz at each voxel, was square-rooted and averaged, and the result was detected as the ALFF. The ALFF value was extracted from voxels in whole brain. P-values were set as 0.05 for group comparisons. The results were conducted within the whole brain mask corrected by Monte Carlo Simulations, iterated 5000 times, and cluster size > 60 voxels (DPABI, <http://rfmri.org/dpabi>) [16].

Statistical analysis was performed with Statistical Package for the

Social Science 24.0 program for windows (IBM Corp, Armonk, NY, USA). Clinical data including demographic and CMS variables would be shown as mean and standard deviation. The demographic and CMS data would be analyzed between the patient group and control group. All data of two groups would be compared at baseline by applying unpaired two-sample t-tests (continuous data) and Chi-square analysis (categorical data). Nonparametric methods would be performed if assumptions of normality were violated. The statistical significance threshold would be set at 0.05 (two-sided), with 95 % confidence intervals.

## 2.6. Correlation analysis

As we conducted a comparison between patients with spleen deficiency syndrome and healthy subjects, while we found the patients showed higher ALFF values in bilateral temporal occipital fusiform cortex (TOC) and lateral occipital cortex (LOC), and lower ALFF values in left right frontal pole cortex (FPC). We extracted bilateral TOCs and LOCs, and FPCs as the region of interest (ROI), by comparing patients and healthy controls. Then, we conducted a multiple regression analysis to examine the correlations between the ALFF values and the CMS scores.

## 3. Results

### 3.1. Demographic and clinical information

Demographic data of all subjects were displayed in Table 1. The two groups showed no significant difference in gender, age, education level ( $p > 0.05$ ). Clinical data were summarized in Table 2. The scores of CMS in patients with spleen deficiency syndrome showed patients with spleen deficiency syndrome were significantly lower than healthy subjects in the scores of MQ ( $P = 0.001$ ), DM ( $P \leq 0.001$ ), AM ( $P \leq 0.001$ ) and FRI ( $P = 0.025$ ).

### 3.2. ALFF analysis

During the resting state, compared with healthy subjects, the patients with spleen deficiency syndrome showed higher ALFF values in bilateral TOCs and LOCs, and lower ALFF values in left FPC (shown in Fig. 1,  $p < 0.05$ , corrected by Monte Carlo Simulations, iterated 1000 times, and cluster size  $> 60$  voxels). Specific cluster locations are displayed in Table 3.

### 3.3. Correlation analysis

We performed regression analysis to explore the correlations between the brain's regional spontaneous activity and scores of CMS. As shown in Fig. 2, scores of DM and AM were positively correlated with

**Table 1**  
The demographic information of patients and healthy subjects.

Items	Patients with spleen deficiency syndrome (N = 20)	Healthy subjects (N = 16)
Gender (male/female)	6/14*	6/10
Age (years)	25.80 $\pm$ 3.40 <sup>#</sup>	27.44 $\pm$ 2.42
Educational level (years)	18.40 $\pm$ 3.36 <sup>#</sup>	16.50 $\pm$ 2.48

Note: \* results from Chi-square test of the comparison between patients with spleen deficiency syndrome and healthy subjects,  $\chi^2 = 0.014$ ,  $p = 0.906$  (for gender); <sup>#</sup> results from two-sample T-test of the comparison between patients with spleen deficiency syndrome and healthy subjects,  $z = -1.67$ ,  $p = 0.167$  (for age),  $z = -1.75$ ,  $p = 0.081$  (for educational level).

**Table 2**

The results of clinical memory scale test between patients and healthy subjects.

Items	Patients with spleen deficiency syndrome (N = 20)	Healthy subjects (N = 16)	T/Z-value	P
MQ	100.00 $\pm$ 7.97	112.79 $\pm$ 9.98	-3.71	0.001
DM	21.07 $\pm$ 2.34	25.92 $\pm$ 2.84	-3.71 <sup>#</sup>	$\leq 0.001$
AM	21.60 $\pm$ 3.08	30.58 $\pm$ 3.62	-4.16 <sup>#</sup>	$\leq 0.001$
FRI	22.33 $\pm$ 3.37	25.83 $\pm$ 4.28	-2.38	0.025
MIR	22.80 $\pm$ 6.04	25.92 $\pm$ 5.05	-1.31 <sup>#</sup>	0.192
AMP	21.20 $\pm$ 3.71	21.25 $\pm$ 2.14	-0.04	0.967

Note: AM: associative memory; AMP: associative memory of portraits; DM: directed memory; FRI: free recall of images; MIR: meaningless image recognition; MQ: memory quotient; <sup>#</sup> results from two-sample non-parametric test of the comparison between patients with spleen deficiency syndrome and healthy subjects.

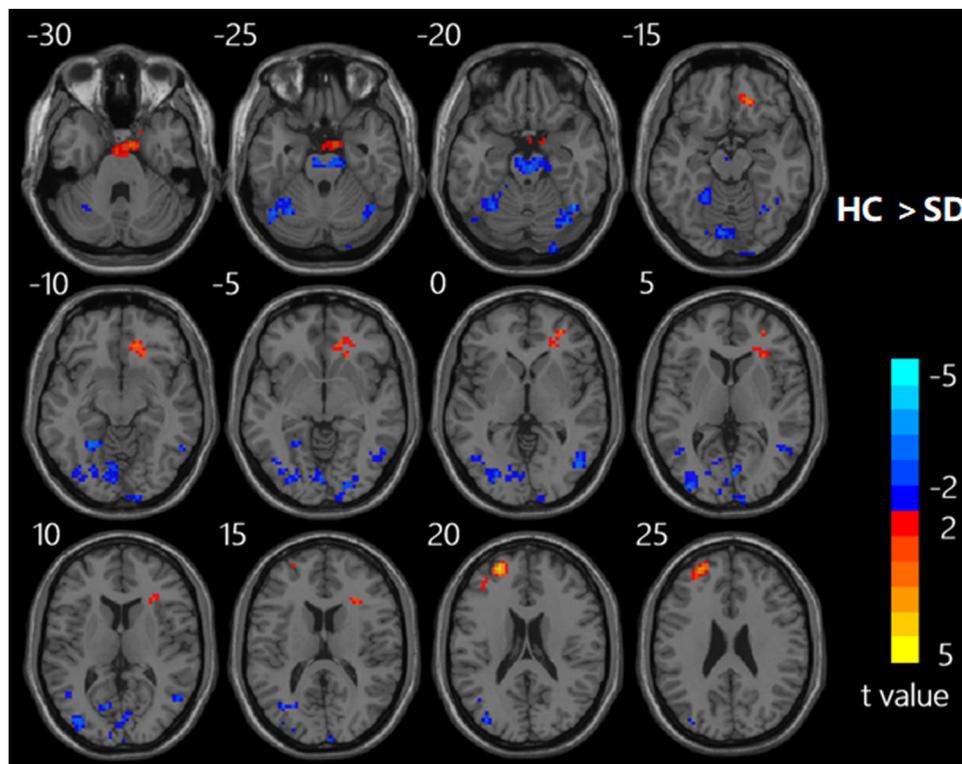
ALFFs in the left FPC (DM,  $r = 0.37$ ,  $p = 0.049$ ; AM,  $r = 0.79$ ,  $p < 0.0001$ ). Scores of FRI and MIR were negative correlated with ALFFs in the bilateral LOCs (FRI,  $r = -0.39$ ,  $p = 0.04$ ; MIR,  $r = -0.65$ ,  $p = 0.0002$ ). Scores of DM, AM and FRI were negative correlated with ALFFs in the bilateral TOCs (DM,  $r = -0.57$ ,  $p = 0.001$ ; AM,  $r = -0.65$ ,  $p = 0.0002$ ; FRI,  $r = -0.40$ ,  $p = 0.036$ ).

## 4. Discussion

To our best knowledge, it is the first study to investigate memory functional impairment in patients with spleen deficiency syndrome. We found lower scores of CMS, higher ALFF values in bilateral TOCs and LOCs, and lower ALFF values in left FPC in patients with spleen deficiency syndrome in comparison with healthy subjects. Moreover, scores of CMS were significantly correlated with ALFF values in bilateral TOCs and LOCs, and left FPC.

CMS was applied to measure the short-term memory of Chinese people, which included DM, AM, FRI, MIR and AMP. The AM and DM were used to test the ability to learn and memorize different pairs of words, which reflected language abilities of left-hemispheric brain. Different stimuli of pictures were displayed during FRI, MIR and AMP, reflecting nonverbal abilities of right-hemispheric brain. In our study, the scores of DM, AM, FRI and MQ in patients with spleen deficiency syndrome were significantly lower than healthy subjects, suggesting that patients with spleen deficiency syndrome had poorer short-term memory on aspects of auditory memory and visual memory than healthy subjects. Recently, numerous animal studies also demonstrated the relationship between memory and spleen deficiency syndrome. Decreased spatial memory was confirmed in rats with spleen deficiency syndrome [17]. Another study revealed learning and memory impairment in rats with spleen deficiency syndrome [18]. Our results supplied evidence from neuropsychological performance to support the notion that the function of spleen is associated with memory.

In our study, we also conducted resting-state fMRI in all subjects and detected ALFF values in bilateral TOCs and LOCs, and lower ALFF values in left FPC in patients with spleen deficiency syndrome. Then, we extracted bilateral TOCs and lateral LOCs, and FPC as the region of interest (ROI). FPC, as a part of the prefrontal cortex, locating in the telencephalon at the rostral end of the cerebral cortex, contributed to many aspects of cognition [19]. Neuroimaging studies revealed that the FPC contributed to different cognitive tasks, including prospective memory and episodic memory [20,21]. In this study, we found lower ALFF values in left FPC on patients with spleen deficiency syndrome. Furthermore, the ALFF values were positively correlated with scores of DM and AM. As we know, the prefrontal cortex involved encoding and retrieval of episodic memory, especially on linguistic representation [22]. In hence, we speculated that patients with spleen deficiency syndrome had poorer abilities encoding and retrieval of language, compared with healthy controls.



**Fig. 1.** Altered aptitude of low-frequency fluctuation of brain regions in patients with spleen deficiency syndrome and healthy controls. Note: HC: healthy controls; SD: patients with spleen deficiency syndrome.

**Table 3**  
Brain areas with ALFF differences between patients and healthy subjects.

Brain regions	BA	Vol, mm <sup>3</sup>	Stereotaxic coordinates, mm			Maximum <i>t</i>
			x	y	z	
TOC_L	19	159	-27	-54	-9	-3.86
TOC_R	37	64	42	-57	-21	-4.19
LOC_L	19	406	-36	-81	9	-3.76
LOC_R	37	73	48	-66	-3	-4.28
FPC_L	46	67	-24	54	21	5.45

BA, Brodmann's area; Vol, cluster volume; x, y, z, coordinates of primary peak locations in the space of MNI; TOC: Temporal occipital fusiform cortex; LOC: lateral occipital cortex; FPC: frontal pole cortex.

Moreover, We found higher ALFFs in the bilateral TOCs compared with healthy controls, and ALFFs were negative correlated with DM, AM and FRI. As we know, TOC is a part of fusiform gyrus, which plays important roles in high-level visual processing and face recognition processing [23]. Several studies demonstrated that lesions in the fusiform and occipito-temporal junction resulted in a series of recognition deficit [24–26]. Another study confirmed that fusiform gyrus was also a lexical semantic hub for heteromodal naming [27]. As it was mentioned above, FRI involved in recognition, while DM and AM involved in semantic memory. In hence, the abnormal TOC was considered as a hub on short memory for patients with spleen deficiency syndrome.

Our results also revealed higher ALFFs in bilateral LOCs for patients with spleen deficiency syndrome. LOC is the visual processing center of the mammalian brain, and plays an important role in human object recognition, which is activated strongly when subjects view pictures of objects [28]. Previous studies also demonstrated that LOC played a crucial role in face perception, which connected with occipital face area and fusiform face area via significant bidirectional connections [29,30]. In addition, scores of FRI and MIR were negative correlated with ALFFs in the bilateral LOCs, which meant that higher ALFFs in the LOC for

patients with spleen deficiency syndrome had poorer short memory. In conclusion, we found abnormal ALFFs in TOC, FPC and LOC for patients with spleen deficiency syndrome, following with significant correlations with scores of CMS.

However, there existed also some limitations to this current study. First, as a preliminary resting-state fMRI research, the sample size was relatively small. Studies with larger sample size are still needed to demonstrate our results in the future. Second, it would be better to differentiate different types of spleen deficiency syndrome, including spleen-qi deficiency syndrome, spleen-yang deficiency syndrome and spleen-yin deficiency syndrome in future studies.

**5. Conclusion**

In conclusion, we applied ALFF to detect abnormal spontaneous brain activity and memory decline in patients with spleen deficiency syndrome. Our results showed that the abnormal brain regions were mainly involved in memory function, providing evidence for memory functional impairment in patients with spleen deficiency syndrome.

**Declaration of competing interest**

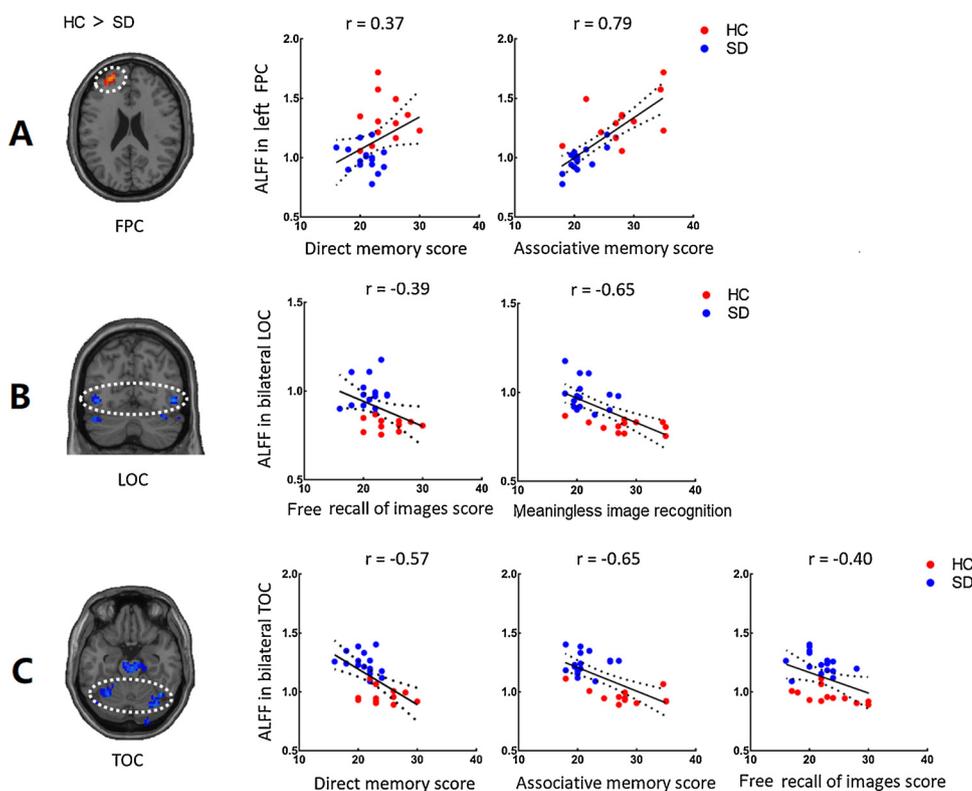
The authors declare that there is no conflict of interests regarding the publication of this paper.

**Authors' contribution**

Yanzhe Ning and Wenbin Jia contributed equally to this work.

**Data availability statement**

The clinical data used to support the findings of this study are available from the corresponding author upon request.



**Fig. 2.** Correlations between CMS score and the ALFF values in FPC, TOC, LOC for all participants. A, The ALFF values in FPC positively correlated with DM and AM in the left FPC (DM,  $r = 0.37$ ,  $p = 0.049$ ; AM,  $r = 0.79$ ,  $p < 0.0001$ ). B, Scores of FRI and MIR were negative correlated with ALFFs in the bilateral LOCs (FRI,  $r = -0.39$ ,  $p = 0.04$ ; MIR,  $r = -0.65$ ,  $p = 0.0002$ ). C, Scores of DM, AM and FRI were negative correlated with ALFFs in the bilateral TOCs (DM,  $r = -0.57$ ,  $p = 0.001$ ; AM,  $r = -0.65$ ,  $p = 0.0002$ ; FRI,  $r = -0.40$ ,  $p = 0.036$ ).  
**Note:** AM: associative memory; DM: directed memory; FPC: frontal pole cortex; FRI: free recall of images; HC: healthy controls; LOC: lateral occipital cortex; MIR: meaningless image recognition; SD: patients with spleen deficiency syndrome; TOC: Temporal occipital fusiform cortex.

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