Gerontology & Geriatrics: Research

Open Access

Austin Publishing Group

Research Article

The Differences of Low-Frequency Amplitude between Kidney Deficiency and Marrow Reduction Syndrome and Heart - Liver Yin Deficiency Syndrome in Alzheimer's disease: A Functional Magnetic Resonance Study of Traditional Chinese Medicine Syndromes

Zhou Y[1#], Guo Z[1#], Xia H[1], Zhu H[1], Wu S[1], Li H[1], Zhu H[2], Wei F[1*] and Liu X[1*]

[1]Tongde Hospital of Zhejiang Province, Zhejiang Mental Health Center, China

[2]The Second Clinical Medical College, Zhejiang Chinese Medical University, China

[3]Department of Radiology of the Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, China

[#]These authors have contributed equally to this article

***Corresponding author:**

Fuquan Wei

Tongde Hospital of Zhejiang Province, No 234 Gucui Road, Hangzhou, Zhejiang, 310012, China

Xiaozheng Liu

Department of Radiology of the Second Affiliated Hospital and Yuying Children's Hospital, Wenzhou Medical University, Wenzhou 325027, China

Received: November 14, 2022; **Accepted:** December 19, 2022**; Published:** December 25, 2022

Abstract

Objective: A growing number of studies have shown that Traditional Chinese Medicine (TCM) treatments based on syndrome differentiation have therapeutic advantages for Alzheimer's Disease (AD). However, whether there are differences in brain material basis of AD with different TCM syndromes are still unclear. The purpose of this study is to explore the characteristics of Amplitude of Low-Frequency Fluctuation (ALFF) between AD patients with Kidney Deficiency and Marrow Reduction Syndrome (KDMRS) and Heart-Liver Yin Deficiency Syndrome (HLYDS).

Methods: 30 AD patients with KDMRS, 30 AD patients with HLYDS and 30 Healthy Controls (HCs) were enrolled from Tongde hospital of Zhejiang Province. All subjects underwent functional magnetic resonance imaging (fMRI) at resting state. ALFF was used to analyze fMRI datas. One-way ANOVA was used to compare the ALFF differences among the three groups and then Tukey post hoc compared between groups.

Results: Differential brain regions of ALFF among the three groups were: right cerebellum, right putamen, left insula, left Anterior Cingulate Gyrus (ACG), and right superior frontal gyrus. Compared with HCs, KDMRS group increased ALFF in the right cerebellum and the bilateral ACG, while HLYDS group increased ALFF in the right insula and the left inferior frontal gyrus. Compared with KDMRS group, HLYDS group decreased ALFF in the right cerebellum.

Conclusion: There were differences of brain function in AD patients between KDMRS and HLYDS, which provided neuro imaging evidence for the "the same disease with different treatments" of AD.

Keywords: fMRI; Amplitude of Low-Frequency Fluctuation; Alzheimer's Disease; Traditional Chinese Medicine; Syndrome Differentiation

Citation: Zhou Y, Guo Z, Xia H, Zhu H, Wu S, Li H, et al. The Differences of Low-Frequency Amplitude between Kidney Deficiency and Marrow Reduction Syndrome and Heart - Liver Yin Deficiency Syndrome in Alzheimer's disease: A Functional Magnetic Resonance Study of Traditional Chinese Medicine Syndromes. Gerontol Geriatr Res. 2022; 8(3): 1081.

Introduction

Alzheimer's Disease (AD) is a slowly progressive neurodegenerative disease, which is the most common form of dementia and affects more than 50 million people worldwide [1]. It is quickly becoming one of the most expensive, lethal, and burdening diseases of this century [2-3]. Currently, the approved drugs including cholinesterase inhibitors and excitatory amino acid receptor antagonists, cannot cure or prevent the progression of AD [4].

A growing number of studies have shown that TCM treatments based on syndrome differentiation have therapeutic advantages for AD. In the TCM theory, AD belongs to "chidai" (dementia). Based on the understanding of dementia in TCM, it is believed that AD is located in the brain, deficiency of kidney essence and brain dystrophy is the basic mechanism of its pathogenesis. Although the brain is the organ involved, AD also involves the kidneys, heart, liver, and spleen [5]. In general, the pathogenic process involves deficiency of qi, blood, kidney essence, and phlegm, stagnation. TCM has applied the concept of holistic view and syndrome differentiation in clinical practice to treat dementia and has achieved apparent therapeutic effects. Treatment based on syndrome differentiation is the characteristic advantage of TCM. The syndrome differentiation is the way to identify the etiology, nature, location of the disease, and the relationship between pathogenic factors and healthy factors by the analysis and synthesis of the data collected through looking, listening, questioning and feeling the pulse, then to summarize and judge the syndrome as a certain nature. So the syndrome type is a summary of pathological reflection at a certain stage in the development of disease, reflecting the essence of pathological changes in this stage. However, the traditional four diagnostic methods of TCM cannot visually and intuitively explain the material basis of syndrome, which hinders the process of modernization of TCM. TCM believes that the same disease can have different syndrome types which there should be different material bases. Therefore the principle of "the same disease with different treatments" can be adopted in the treatment of AD. Kidney Deficiency and Marrow Reduction Syndrome (KDMRS) and Heart-Liver Yin Deficiency Syndrome (HLYDS) are two common syndrome types of AD in clinical practice. At present, there is no research on the material basis of AD patients with the two TCM syndrome types. Studies about coronary heart disease have shown that kidney deficiency syndrome and yin deficiency syndrome have different material basis. There are different degrees of hormone disorders in the kidney deficiency syndrome, in which female E2 is significantly reduced [6], while tricarboxylic acid cycle is significantly decreased in patients with yin-deficiency syndrome [7]. Lin et al [8] reported that mild cognitive impairment subjects with KDMRS have more obvious delayed memory than patients with HLYDS, suggesting that TCM syndromes are closely related to clinical symptoms. So according to the above dementia theory of TCM and the clinical observation of the real world, we infer that there are differences in brain material basis between the KDMRS and HLYDS in AD patients.

Functional Magnetic Resonance Imaging (fMRI) can detect the human brain activity in vivo and fully reflect the information of whole brain, which conforms to the holistic view of TCM. fMRI has been applied to the study of the material basis of TCM syndromes of neurological diseases [19,10]. Zhang et al [11] have compared functional connectivity of the posterior cingulate cortex across major depression patients with the Deficiency Pattern (DP), major depression patients with the Excess Pattern (EP), and Normal Control (NC) subjects in a resting-state fMRI study. They have found that, the EP group has reduced functional connectivity of the posterior cingulate cortex with the bilateral cerebellum and left superior frontal gyrus relative to the DP group, suggesting that the TCM clinical syndromes of major depression are associated with correlates in cerebral functional activity. Wang et al [12] also have explored the spontaneous brain activities regarding DP and EP of Subcortical Vascular Mild Cognitive Impairment (svMCI) patients based on fMRI data. Their results have revealed that the DP group shows significant differences of Fractional Amplitude of Low-Frequency Fluctuation (fALFF) values in the right middle frontal gyrus and the right cerebellum, while the EP group shows significant differences in the left orbitofrontal gyrus and the left cerebellum when compared with the NC group, indicated that the DPs and EPs present the lateralization pattern in the bilateral frontal gyrus. However, there are no studies on the brain differences between KDMRS and HLYDS in AD.

In our study, we used fMRI and ALFF to analyze the differences in brain functional activity between AD patients with KDMRS and HLYDS, and to provide an objective basis for the quantification of microscopic syndrome differentiation.

Materials and Methods

Participants

All subjects were from outpatients and inpatients of Tongde Hospital of Zhejiang Province. Diagnostic criteria were in line with the "possible AD" diagnostic criteria recommended by the National Institute on Aging Alzheimer's Association (NIA-AA). The TCM Classification standard of KDMRS and HLYDS were based on the *Guiding Principles of Clinical Research on New Drugs of Traditional Chinese Medicine*. The main symptoms of KDMRS include mental decline, waist and knees soft, tired thinking, and the secondary symptoms include glazed expression, slow thinking, easy to panic, dizziness tinnitus, heavy walking, walking difficultly, or auditory hallucinations, cheeks flush, incontinence, fecal incontinence. The main symptoms of HLYDS include intelligence decline, mood swing, palpitation, and the secondary symptoms include restless, blurred vision, limbs difficult to stretch, less sleep, tinnitus deafness, red tongue, moss less, string, thin, and fast pulse. The differentiation of TCM syndrome types is carried out by professional TCM physicians. All AD patients were 60 to 75 years old, their education level ≥6 years, their Mini Mental State Exam (MMSE) scores ranged from 15 to 24. They are all right-handed. They were no psychosis, substance dependence or serious physical illness. The criteria for Healthy Controls (HCs) were: MMSE score 28–30, right-handed, 60 to 75 years old, no psychosis, substance dependence or serious physical illness.

The study has been conducted according to the recommendations of the Declaration of Helsinki and the principles of good clinical practice. The ethics committee of the Tongde Hospital of Zhejiang Province approved the study, and all participants (or their legal representatives) gave written informed consent to their inclusion in the study.

Data Processing

All resting-state fMRI (rs-fMRI) data preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and Data Processing Assistant for rs-fMRI software (http://www.restfmri.net). The preprocessing steps included slice-timing cor-

rection, head motion correction, linear trend removal, spatial smoothing with a 6-mm Gaussian kernel along all three directions, and spatial normalization to Montreal Neurological Institute (MNI) space with a resampling resolution of 3 × 3 × 3 mm^3. All smoothed images were then filtered using a typical temporal bandpass filter (0.01–0.08 Hz) to reduce low-frequency drift, physiological high-frequency respiratory and cardiac noise. Linear trends were also removed within each time series.

ALFF Calculation

ALFF was calculated using REST software (http://www.rest-fmri.net). The procedure for calculating ALFF was summarized below. The time series for a given voxel was first converted to the frequency domain using a fast Fourier transform. The square root of the power spectrum was calculated and averaged over a range of 0.01-0.08 Hz. The averaged square root was used to calculate the ALFF at the given voxel. The whole brain voxel average ALFF, which measures the absolute strength or intensity of spontaneous Low Frequency Oscillator (LFO), was then standardized.

Statistical Methods

For comparisons of demographic and psychometrics, we used one-way ANOVA when samples had a standard normal distribution and the Mann-Whitney U test when samples exhibited a skewed distribution, while a Chi-square test was applied to compare sex distributions.

A one-way ANOVA was used to compare the three groups' individual normalized resting-state functional connectivity ALFF maps voxel-by-voxel. Then, using the ANCOVA, we extracted brain masks that showed significant differences. Finally, using the ANCOVA brain masks, we performed post-hoc t-tests between each pair of groups. AlphaSim, a program based on Monte Carlo simulation and implemented in AFNI (http://afni.nimh.nih.gov), was used for multiple comparison corrections. The statistical threshold was set at $P < 0.005$ with a cluster size > 25 voxels, corresponding to a corrected $P < 0.05$.

Results

Demographic and Clinical Data

There were no significant differences in sex, age, years of education among AD patients with KDMRS, HLYDS and HCs, and there were no significant differences in duration years and MMSE scores between AD patients with KDMRS and HLYDS (Table 1).

ALFF Differential Brain Regions Among KDMRS Group, HLYDS Group and HCs Group

Through one-way ANOVA, the differential brain regions of ALFF among the KDMRS group, HLYDS group and HCs group were: right cerebellum, right putamen, left insula, left anterior cingulate, and right superior frontal gyrus. (Table 2, Figure1).

ALFF Differential Brain Regions between KDMRS Group and HCs Group

Compared with the HCs group, the ALFF increased in the right cerebellum 6 and the bilateral anterior cingulate gyrus in the KDMRS group (Table 3, Figure2).

Differential Brain Regions between HLYDS Group and HCs Group

Compared with HCs group, ALFF increased in the right insula and left inferior frontal gyrus of HLYDS group (Table 4, Figure 3).

Differential Brain Regions between HLYDS Group and KDMRS Group

Compared with KDMRS group, the ALFF of right cerebellum 6 in the HLYDS group was decreased (Table 5, Figure 4).

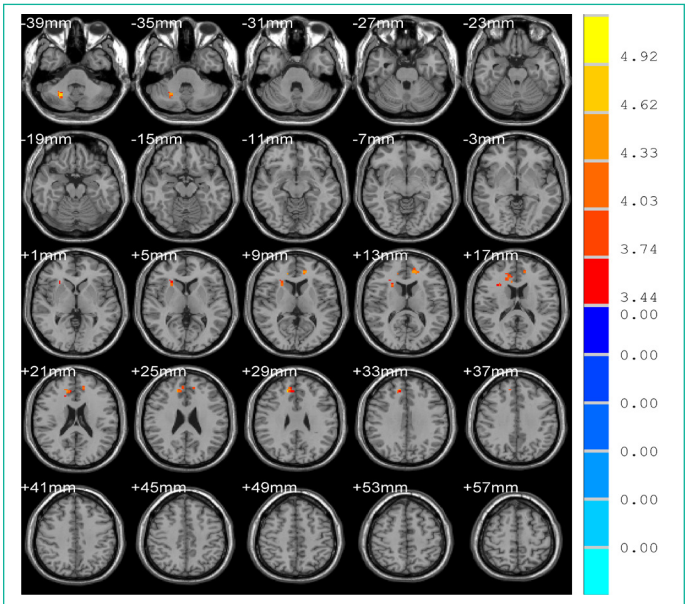

Figure 1: ALFF difference brain regions among KDMRS group, HLYDS group and HCs group.
The voxels with warm colors represent AD group with KDMRS and AD group with HLYDS related ALFF increases, and cool colors indicate decreases.
AD - Alzheimer's Disease; HCs - Healthy Controls; KDMRS - Kidney Deficiency and Marrow Reduction Syndrome; HLYDS - Heart-Liver Yin Deficiency Syndrome; ALFF- Amplitude Of Low-Frequency Fluctuation.

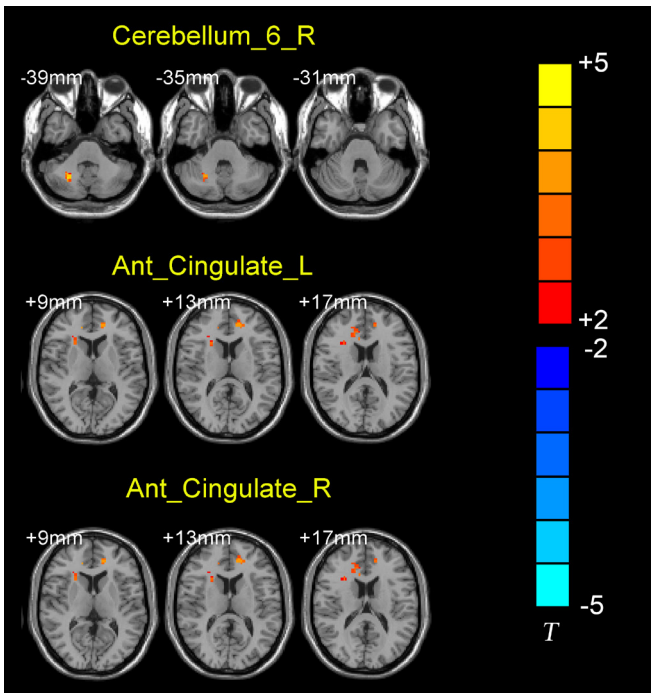

Figure 2: Differential brain regions between KDMRS group and HCs group.
The voxels with warm colors represent AD group with KDMRS related ALFF increases, and cool colors indicate decreases.
AD - Alzheimer's Disease; HCs - Healthy Controls; KDMRS - Kidney Deficiency and Marrow Reduction Syndrome; ALFF- Amplitude Of Low-Frequency Fluctuation.

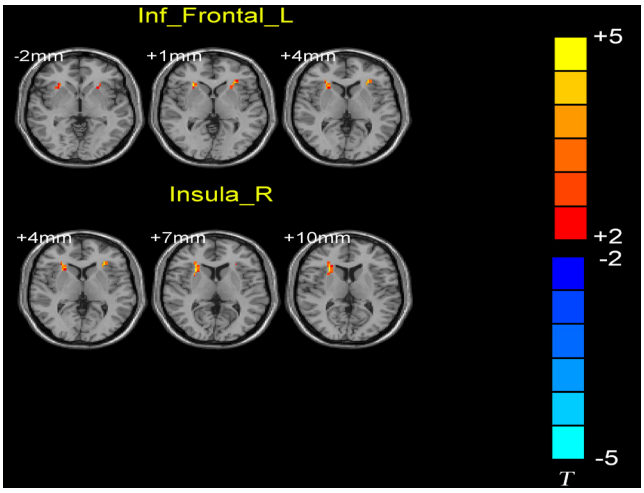

Figure 3: Differential brain regions between HLYDS group and HCs group.
The voxels with warm colors represent AD group with HLYDS related ALFF increases, and cool colors indicate decreases.
AD - Alzheimer's Disease; HCs - Healthy Controls; HLYDS - Heart-Liver Yin Deficiency Syndrome; ALFF- Amplitude Of Low-Frequency Fluctuation.

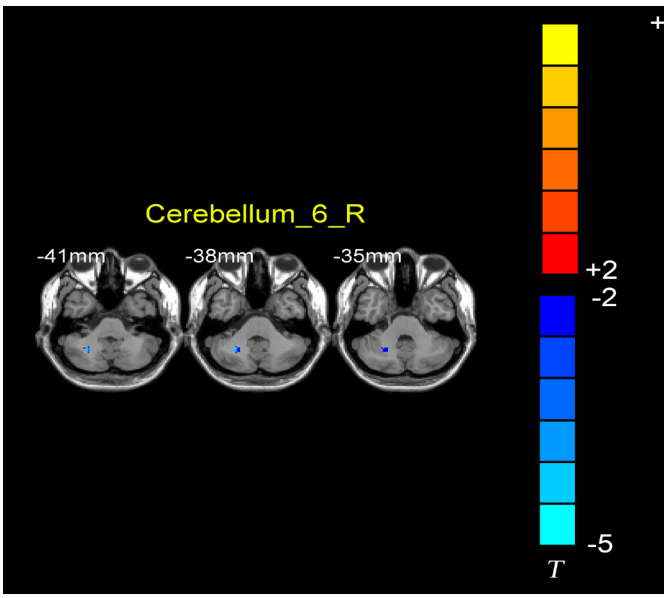

Figure 4: Differential brain regions between HLYDS group and KDMRS group.
The voxels with warm colors represent AD group with HLYDS related ALFF increases, and cool colors indicate decreases.
AD - Alzheimer's Disease; HCs - healthy controls; KDMRS - Kidney deficiency and marrow reduction syndrome; HLYDS - Heart-liver yin deficiency syndrome; ALFF- amplitude of low-frequency fluctuation.

Table 1: Comparison of general data among the three groups.

	HCs	AD		F/χ^2	*P*
		KDMRS	HLYDS		
Sex(M/F)	16/14	11/19	14/16	1.70	0.43
Age (years,x± s)	67.03±0.74	68.63±0.80	68.90±0.95	1.46	0.24
Education (years,x± s)	10.10±0.51	10.50±0.55	10.40±0.62	0.14	0.87
Duration (years,x± s)	—	2.33±1.47	2.07±1.23	0.70	0.41
MMSE (scores,x± s)	—	19.23±3.28	18.97±3.0	1.18	0.28

AD: Alzheimer's Disease; HCs: Healthy Controls; KDMRS: Kidney Deficiency and Marrow Reduction Syndrome; HLYDS: Heart-Liver Yin Deficiency Syndrome; M: Male; F; Female; MMSE: Mini-Mental State Examination.

Table 2: ALFF differential brain regions among KDMRS group, HLYDS group and HCs group.

Brain regions	Voxels	MNI coordinates			BA	*T* value
		x	y	z		
right cerebellum 8	5	27	-57	-39	-	15.6456
right putamen	7	27	21	12	48	12.0048
left insula	10	-30	30	3	47	11.3481
left anterior cingulate gyrus	6	-9	45	12	32	10.8155
right superior frontal gyrus	7	12	42	30	32	11.6198

Table 3: Differential brain regions between KDMRS group and HCs group.

Brain regions	Voxels	MNI coordinates			BA	*T* value
		x	y	z		
right cerebellum 6	3	27	-57	-34	-	5.062
left anterior cingulate gyrus	6	-12	48	12	32	4.61
right anterior cingulate gyrus	34	10	39	30	32	4.6746

Table 4: Differential brain regions between HLYDS group and HCs group.

Brain regions	Voxels	MNI coordinates			BA	*T* value
		x	y	z		
right insula	4	32	24	-4	47	4.6246
left inferior frontal gyrus	7	-30	30	0	-	4.6657

Table 5: Differential brain regions between HLYDS group and KDMRS group.

Brain regions	Voxels	MNI coordinates			BA	*T* value
		x	y	z		
right cerebellum 6	2	27	-57	-34	-	-4.8755

Discussion

In this study, it was found that the differential brain regions of ALFF among the AD KDMRS group, AD HLYDS group and HCs group were: right cerebellum, right putamen, left insula, left anterior cingulate gyrus, and right superior frontal gyrus. Compared with HCs group, the ALFF of AD KDMRS group increased in the bilateral cingulate gyrus and the right cerebellum, the ALFF of AD HLYDS group increased in the right insula and the left inferior frontal gyrus. It suggests that abnormal spontaneous nerve activity shows in the right cerebellum, the right putamen, bilateral insular lobes, anterior cingulate gyrus, superior frontal gyrus and inferior frontal gyrus of AD patients. Significant reduction of gray matter volume has been found in hippocampus, insula, frontal lobe and putamen in AD patients [13-14], cerebellar volume atrophy is associated with cognitive decline in AD patients [15]. Under optical microscope, senile plaques deposition and neurofibrillary tangles initially occur in the inner olfactory cortex, hippocampus, temporal lobe, frontal lobe and cerebellum [16], phosphorylated Tau is distributed in hippocampus, frontal lobe, putamen, thalamus and brainstem medulla [17]. In terms of neurophysiology, the imbalance of brain-derived neurotrophic factor in the prefrontal cortex [18] and the significant increase of mitochondrial oxidative stress in the putamen of AD patients all have proved that the pathophysiological changes of the frontal lobe and the putamen [19] play an important role in AD. Neuroimaging studies have found that the Default Mode Network (DMN) of AD is abnormal, and pathological studies have found that the brain regions of AD lesions are highly coincident with those of DMN [20], the pu-

tamen, bilateral insula, anterior cingulate gyrus, superior frontal gyrus, and inferior frontal gyrus brain regions found in this study are important nodes of the resting state network. These brain regions are closely related to important functions such as human emotion, memory, and consciousness. Wu et al [21] have found that Regional Homogeneity (ReHo) of the right cerebellar area 4, 5, bilateral temporal lobes and left frontal gyrus in AD group are abnormal. Zheng et al [22] have found that the local cerebral blood flow in the left cingulate gyrus, frontal lobe and temporal lobe of AD patients is significantly damaged compared with the normal control group, and found that the ALFF of bilateral frontal lobe is significantly increased. Yang et al [23] have found that ALFF/fALFF in right cingulate gyrus, hippocampus and frontal lobe increases with the development of cognitive impairment. Zhang et al [24] have found patients with Amnestic Mild Cognitive Impairment (aMCI) shows increased ALFF/fALFF in the bilateral parahippocampal gyrus/hippocampus, right amygdala, right cerebellum anterior lobe, left temporal lobe. King-Robson et al [25] have found that the connectivity between hippocampus and right frontal lobe, right cerebellar tonsil, insula, ingulate gyrus and a large number of cortical areas in AD patients is reduced. Ye et al [26] have found that with the progress of AD, the brain connections in the seed regions of these brain regions show extremely significant structural changes based on the superior frontal gyrus, middle frontal gyrus, bilateral insula, left hippocampus, left putamen and left thalamus. The results of our study are consistent with those of the above studies, showing abnormal spontaneous neural activity in the right cerebellum, right putamen, bilateral insula, anterior cingulate gyrus, superior frontal gyrus and inferior frontal gyrus.

According to the characteristics of TCM syndromes, AD patients with KDMRS often have glazed expressions, that is, indifference, some studies have shown that insufficient prefrontal perfusion in AD patients may be a neural factor leading to apathy [27]. In addition, hallucinations can also be found in AD patients with KDMRS. Blanc et al [28] have found that there is a correlation between hallucination intensity of cognitive neurodegenerative diseases and reduced brain metabolism in the left cingulate gyrus. Rootes-Murdy et al [29] found that delusion is associated with frontal gray matter reduction. It is found in our study that compared with HCs group, ALFF of bilateral cingulate gyrus in AD patients with KDMRS increases, that is, the activation of spontaneous nerve activity increases. Therefore, the appearance of stiff expression and hallucination in AD patients with KDMRS may be related to the abnormal activity of bilateral cingulate gyrus. AD patients with HLYDS often show moodiness, palpitation, restlessness and anxiety, some studies [30] have found that the left insular gray matter volume of AD patients with anxiety exist significant differences. The frontal lobe is also an important cortical region, which integrates information from a large number of cortical and subcortical regions, and is closely related to cognition and emotion [31]. However, it was found in our study that compared with the HCs group, the ALFF of the right insular lobe and the left inferior frontal gyrus in patients with AD HLYDS increased, that is, the activation of spontaneous neural activity in the corresponding brain regions increases, suggesting that the abnormal activity of these two brain regions may be related to anxiety in AD patients.

In this study, it was found that compared with the AD patients with KDMRS, the ALFF of patients with HLYDS in the cerebellum 6 was reduced, suggesting that the activation of spontaneous nerve activity in the superior cerebellum of patients with AD HLYDS is reduced. AD patients with KDMRS and HLYDS may have abnormal walking. The former shows “heavy walking and difficult walking”, and the latter shows “limbs difficultly to stretch”. The cerebellar hemisphere is involved in the coordination of random movement and the maintenance of tension stability, so the above differences between the two groups may also be related to the abnormal superior cerebellar nerve activity. In addition, the cerebellum is not only involved in the motor function, but also involved in a variety of sensory and cognitive processes, including the regulation of emotional response [32]. Gellersen et al [25] have suggested that the cerebellum has strong cortical and subcortical connections, and cerebellar atrophy is associated with decreased cognitive function. Previous studies have found similar changes in abnormal amyloid deposition in cerebellum of AD patients and AD disease mouse models. Some scholars [33] speculated that the cerebellum itself does not have a specific cognitive function, but participates in the specific processing of a series of cortical brain regions through jointly accepting cerebral cortex information, and then plays a regulatory role in cognition and emotion. Cheron et al [34] have found widespread electrophysiological changes in Purkinje cells and neurons in deep cerebellar nuclei of AD mice through animal experiments, suggesting that cerebellar output discharge regulation may indirectly affect the activities of subcortical and cortical targets. Toniolo et al [35] have found white matter microstructure changes in the Middle Cerebellar Peduncle (MCP), left and right superior cerebellar peduncle (SCPL, SCPR) of AD patients by Diffusion Tensor Imaging (DTI). Guo et al [36] have showed that the cerebellar atrophied regions share robust and selective intrinsic connectivity with the atrophied regions in the cerebral cortex in AD. Tang F et al [37] have found that defining the central lobule II and cerebellar lobule IX as the seed points, the connection between the seed points and the basal ganglia, frontal lobe, temporal lobe and cingulate gyrus is reduced in AD patients, Mild Cognitive Impairment (MCI) patients show increased connectivity with parietal lobe and frontal lobe, which is considered that increased frontal-parietal activity in MCI patients indicates that cerebellum may play a compensatory role in cognitive impairment. Baumann et al [32] have proved that different subregions of the cerebellum respond to the experiences of happiness, anger, disgust, fear and sadness, and they have detected partial overlaps in the activations related to fear and anger (parafoliolate VI and central lobe I), anger and disgust (parafoliolate IX) and happiness and sadness (parafoliolate VIIIA), and have found that they are connected to thalamus and cortex, participating in the detection, integration and filtering of emotional information. Some of the above brain regions belong to the right superior cerebellum, which is consistent with our study. It can be seen that there may be some differences in the degree of cognitive function or on different aspects of cognitive function between AD patients with KDMRS and with HLYDS, which will be explored further by combining with the neurocognitive scale. There are significant differences in emotion between the two groups. Patients with KDMRS have “glazed expression, slow thinking, easy to panic”, these patients have apathy, fear; patients with HLYDS have “mood swing, palpitation, restless, less sleep”, these patients can be accompanied by happiness, anger. The differences of emotion between the two syndrome types may be related to the regulation of cerebellar participation emotion.

Several limitations of the study should be noted when interpreting our results. First, in this study, we used the resting-state fMRI method to explore the characteristics of the brain function of AD patients with TCM syndromes. Our results reflected the

differences in the activity of neurons, but how the characteristics of white matter and nerve fibers in the brain were not reflected. Therefore, the future work should combine the resting state fMRI and diffusion tensor imaging technology to more comprehensively reflect the characteristics of brain function of TCM syndromes from the perspective of neurons and nerve fibers. Second, this study did not evaluate the severity of TCM syndrome, so it could not reflect the relationship between TCM syndrome changes and brain function. In the future, we should increase the integral evaluation of TCM syndromes and longitudinal observation, dynamically analyze the brain material basis of TCM syndromes.

Conclusions

In summary, through the resting-state fMRI, we have found that there were different spontaneous neural activities in brain regions between AD patients with KDMRS and HLYDS, ALFF can be used as an indicator of clinical differentiation, providing support for the objective identification of TCM syndromes.

Abbreviations: AD: Alzheimer's Disease; TCM: Traditional Chinese Medicine; ALFF: Amplitude of Low-Frequency Fluctuation; fALFF: Fractional Amplitude of Low-Frequency Fluctuation; KDMRS: Kidney Deficiency and Marrow Reduction Syndrome; HLYDS: Heart-Liver Yin Deficiency Syndrome; HCs: Healthy Controls; fMRI: functional Magnetic Resonance Imaging; rs-fMRI: Resting-State Functional Magnetic Resonance Imaging; ACG: anterior Cingulate Gyrus; DP: Deficiency Pattern; EP: Excess Pattern; NC: Normal Control; svMCI: Subcortical Vascular Mild Cognitive Impairment; aMCI: Amnestic Mild Cognitive Impairment; MCI: Amnestic Mild Cognitive Impairment; NIA-AA: Aging Alzheimer's Association; MMSE: Mini Mental State Exam; MNI: Montreal Neurological Institute; LFO: Low Frequency Oscillator; DMN: Default Mode Network; ReHo: Regional Homogeneity; MCP: Middle Cerebellar Peduncle; SCPL: Left Superior Cerebellar Peduncle; SCPR: Right Superior Cerebellar Peduncle; DTI: Diffusion Tensor Imaging

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

References

1. Hodson R. Alzheimer's disease. Nature. 2018; 559: S1.
2. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer's disease. Lancet. 2021; 397: 1577-1590.
3. Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine. 2019; 14: 5541-5554.
4. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020; 25: 5789.
5. Pei H, Ma L, Cao Y, Wang F, Li Z, Liu N, et al. Traditional Chinese Medicine for Alzheimer's Disease and Other Cognitive Impairment: A Review. Am J Chin Med. 2020; 48: 487-511.
6. Liu LC, Duan L, Liu C, Wang J. Correlation between estrogen levels and coronary heart disease with kidney deficiency and intervention effect of kidney-tonifying traditional Chinese medicine. Zhongguo Zhong Yao Za Zhi. 2021; 46: 1738-1742.
7. Zhou H,Li L,Zhao H,Wang Y,Du J,Zhang P, et al. A Large-Scale, Multi-Center Urine Biomarkers Identification of Coronary Heart Disease in TCM Syndrome Differentiation. J Proteome Res. 2019; 18: 1994-2003.
8. Lin Z, Huang T, Zheng G, Chen R, Yao M, Liu W, et al. Study on the Correlation between Chinese Medicine Syndrome and Cognitive Dysfunction in Mild Cognitive Impairment. Evid Based Complement Alternat Med. 2022; 2022: 7117704.
9. Xu Z, Zhang S, Huang L, Zhu X, Zhao Q, Zeng Y, et al. Altered Resting-State Brain Activities in Drug-Naïve Major Depressive Disorder Assessed by fMRI: Associations With Somatic Symptoms Defined by Yin-Yang Theory of the Traditional Chinese Medicine. Front Psychiatry. 2018; 9: 195.
10. Du Y, Zhao J, Wang Y, Han Y, Deng L, Jia H, et al. Brain Functional Differences in Drug-Naive Major Depression with Anxiety Patients of Different Traditional Chinese Medicine Syndrome Patterns: A Resting-State fMRI Study. Evid Based Complement Alternat Med. 2020; 2020: 7504917.
11. Zhang YF, Han Y, Wang YZ, Zhang YF, Jia HX, Jin EH, et al. Characterization of resting-state fMRI-derived functional connectivity in patients with deficiency versus excess patterns of major depression. Complement Ther Med. 2015; 23: 7-13.
12. Wang J, Kong F, Zheng H, Cai D, Liu L, Lian J, et al. Lateralized brain activities in subcortical vascular mild cognitive impairment with differential Chinese medicine patterns: A resting-state functional magnetic resonance imaging study. Front Neurosci. 2022; 16: 943929.
13. Wang ML, Wei XE, Fu JL, Li W, Yu MM, Li PY, et al. Subcortical nuclei in Alzheimer's disease: a volumetric and diffusion kurtosis imaging study. Acta Radiol. 2018; 59: 1365-1371.
14. Kutová M, Mrzílková J, Riedlová J, Zach P. Asymmetric Changes in Limbic Cortex and Planum Temporale in Patients with Alzheimer Disease. Curr Alzheimer Res. 2018; 15: 1361-1368.
15. Gellersen HM, Guo CC, O'Callaghan C, Tan RH, Sami S, Hornberger M. Cerebellar atrophy in neurodegeneration-a meta-analysis. J Neurol Neurosurg Psychiatry. 2017; 88: 780-788.
16. Mavroudis I. Cerebellar pathology in Alzheimer's disease. Hell J Nucl Med. 2019; 22: 174-179.
17. Zhu K, Wang X, Sun B, Wu J, Lu H, Zhang X, et al. Primary Age-Related Tauopathy in Human Subcortical Nuclei. Front Neurosci. 2019; 13: 529.
18. Aarons T, Bradburn S, Robinson A, Payton A, Pendleton N, Murgatroyd C. Dysregulation of BDNF in Prefrontal Cortex in Alzheimer's Disease. J Alzheimers Dis. 2019; 69: 1089-1097.
19. Michel TM, Gsell W, Käsbauer L, Tatschner T, Sheldrick AJ, Neuner I, et al. Increased activity of mitochondrial aldehyde dehydrogenase (ALDH) in the putamen of individuals with Alzheimer's disease: a human postmortem study. J Alzheimers Dis. 2010; 19: 1295-301.
20. Brier MR, JB Thomas, AZ Snyder, Benzinger TL, Zhang D, et al. Loss of Intranetwork and Internetwork Resting State Functional Connections with Alzheimer's Disease Progression. Journal of Neuroscience. 2012; 32: 8890-8899.
21. Wu YQ, Wang YN, Zhang LJ, Liu LQ, Pan YC, Su T, et al. Regional Homogeneity in Patients With Mild Cognitive Impairment: A Resting-State Functional Magnetic Resonance Imaging Study. Front Aging Neurosci. 2022 Apr 14; 14: 877281.
22. Zheng W, Cui B, Han Y, Song H, Li K, He Y, et al. Disrupted Regional Cerebral Blood Flow, Functional Activity and Connectivity in Alzheimer's Disease: A Combined ASL Perfusion and Resting State fMRI Study. Front Neurosci. 2019; 13: 738.
23. Yang L, Yan Y, Wang Y, Hu X, Lu J, Chan P, et al. Gradual Disturbances of the Amplitude of Low-Frequency Fluctuations (ALFF) and Fractional ALFF in Alzheimer Spectrum. Front Neurosci. 2018;

12: 975.

24. Zhang X, Xue C, Cao X, Yuan Q, Qi W, Xu W, Zhang S, et al. Altered Patterns of Amplitude of Low-Frequency Fluctuations and Fractional Amplitude of Low-Frequency Fluctuations Between Amnestic and Vascular Mild Cognitive Impairment: An ALE-Based Comparative Meta-Analysis. Front Aging Neurosci. 2021; 13: 711023.

25. King-Robson J, Wilson H, Politis M. Alzheimer's disease Neuroimaging Initiative. Associations Between Amyloid and Tau Pathology, and Connectome Alterations, in Alzheimer's Disease and Mild Cognitive Impairment. J Alzheimers Dis. 2021; 82: 541-560.

26. Ye C, Mori S, Chan P, Ma T. Connectome-wide network analysis of white matter connectivity in Alzheimer's disease. Neuroimage Clin. 2019; 22: 101690.

27. Jeong H, Kang I, Im JJ, Park JS, Na SH, Heo Y, et al. Brain Perfusion Correlates of Apathy in Alzheimer's Disease. Dement Neurocogn Disord. 2018; 17: 50-56.

28. Blanc F, Noblet V, Philippi N, Cretin B, Foucher J, Armspach JP, et al. Alzheimer's Disease Neuroimaging Initiative. Right anterior insula: core region of hallucinations in cognitive neurodegenerative diseases. PLOS One. 2014; 9: e114774.

29. Rootes-Murdy K, Goldsmith DR, Turner JA. Clinical and Structural Differences in Delusions Across Diagnoses: A Systematic Review. Front Integr Neurosci. 2022; 15: 726321.

30. Mohamed Nour AEA, Jiao Y, Teng GJ. Alzheimer's disease Neuroimaging Initiative. Neuroanatomical associations of depression,anxiety and apathy neuropsychiatric symptoms in patients with Alzheimer's disease. Acta Neurol Belg. 2021; 121: 1469-1480.

31. Xu P, Chen A, Li Y, Xing X, Lu H. Medial prefrontal cortex in neurological diseases. Physiol Genomics. 2019; 51: 432-442.

32. Baumann O, Mattingley JB. Functional topography of primary emotion processing in the human cerebellum. Neuroimage. 2012; 61: 805-11.

33. Sang L, Qin W, Liu Y, Han W, Zhang Y, Jiang T, et al. Resting-state functional connectivity of the vermal and hemispheric subregions of the cerebellum with both the cerebral cortical networks and subcortical structures. Neuroimage. 2012; 61: 1213-25.

34. Cheron G, Ristori D, Marquez-Ruiz J, Cebolla AM, Ris L. Electrophysiological alterations of the Purkinje cells and deep cerebellar neurons in a mouse model of Alzheimer disease (electrophysiology on cerebellum of AD mice). Eur J Neurosci. 2022.

35. Toniolo S, Serra L, Olivito G, Caltagirone C, Mercuri NB, Marra C, et al. Cerebellar White Matter Disruption in Alzheimer's Disease Patients: A Diffusion Tensor Imaging Study. J Alzheimers Dis. 2020; 74: 615-624.

36. Guo CC, Tan R, Hodges JR, Hu X, Sami S, Hornberger M. Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. Brain. 2016; 139: 1527-38.

37. Tang F, Zhu D, Ma W, Yao Q, Li Q, Shi J. Differences Changes in Cerebellar Functional Connectivity Between Mild Cognitive Impairment and Alzheimer's Disease: A Seed-Based Approach. Front Neurol. 2021; 12: 645171.