Abnormal Interhemispheric Functional Connectivity in Neurologically Asymptomatic Patients With End-Stage Renal Disease

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Research Article

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Abstract

Objective: This study aims to investigate the alterations in interhemispheric functional connectivity in neurologically asymptomatic patients with end-stage renal disease (ESRD) undergoing maintenance hemodialysis (HD) using resting-state functional magnetic resonance imaging (rs-fMRI) with voxel-mirrored homotopic connectivity (VMHC) algorithm.

Methods: The rs-fMRI data were acquired from 40 neurologically asymptomatic patients with ESRD and 34 matched healthy control (HC) subjects. All subjects underwent neuropsychological tests, and patients with ESRD underwent laboratory tests. Intergroup VMHC differences in the voxel manner were analyzed. Correlation analysis was performed to evaluate the relationships between VMHC values and clinical variables in patients with ESRD. We further performed a receptive operation characteristic (ROC) analysis to confirm the sensitivity and specificity of our results.

Results: Compared with HCs, patients with ESRD exhibited significantly decreased VMHC values in the inferior parietal lobule (IPL), superior temporal gyrus (STG), insula, precentral gyrus (PreCG), middle occipital gyrus (MOG), and calcarine/lingual/cuneus. Patients with ESRD did not exhibit increased VMHC values in any brain regions compared with HCs. Furthermore, the VMHC value of MOG was positively correlated with hemoglobin levels in patients with ESRD.

Conclusions: The results revealed that the impairment of interhemispheric coordination in patients with ESRD, which provided preliminary evidence of VMHC as a potential biomarker of patients with ESRD.

1. Introduction

End-stage renal disease (ESRD) is defined as chronic kidney disease (CKD) stage 5 when the kidneys are permanently functioning at less than 10% of their capacity (Foley and Collins 2007). To maintain their health, patients with ESRD usually suffer regular hemodialysis (HD) 3 times per week to remove toxic metabolites from the body. The irreversible damage of renal function and continuous accumulation of toxic metabolites in the brain will significantly increase the incidence of cerebrovascular disease and cognitive-related complications in patients with ESRD. Many patients with ESRD exhibit memory disturbance, impaired attention, slow motor performance, severe depression, and anxiety disorders (Murray et al 2006; Luo et al 2016), which may decrease the quality of life and increase health care expenses. Therefore, it is very valuable for the treatment of patients with ESRD and the improvement of their prognosis to early assess the brain abnormalities in neurologically asymptomatic patients with ESRD.

The development of neuroimaging techniques is useful for detecting ESRD -related neurologic abnormalities. For example, voxel-based morphometry (VBM), diffusion tensor imaging (DTI), and arterial spin labeling (ASL) perfusion imaging have been used to reveal the widespread abnormalities in brain structure and cerebral metabolism in patients with ESRD(Zhang et al 2013; Zhang et al 2015; Cheng et al 2018). Recently, the resting-state functional magnetic resonance imaging (rs-fMRI), which was designed

to analyze the intrinsic neural activity of gray matter regions, revealed that functional abnormalities were widespread in several regions of bilateral hemispheres in patients with ESRD. For example, regional homogeneity (ReHo) and amplitude of low-frequency fluctuations (ALFF) algorithm showed decreased neural activity in the multiple areas of the bilateral frontal, parietal, occipital, and temporal lobes in patients with ESRD compared with HCs (Liang X et al 2013 ; Chen et al 2015; Luo et al 2016), which reflect early signs for the development of uremic encephalopathy or dialysis encephalopathy. Functional connectivity (FC) showed widespread impairment in several resting-state functional networks in patients with ESRD, particularly in the default-mode network (DMN)(Ni et al 2014; Zheng et al 2014; Li et al 2016).

Interhemispheric connectivity reflects the information exchange and integration between the bilateral hemispheres, which plays an important role in the process of cognitive, behavioral, and emotional functions.(Kelly et al 2011) A robust homotopic functional connection is one of the most fundamental characteristics of the brain's intrinsic functional architecture.(Stark et al 2008) It demonstrates the high degree of synchrony in spontaneous activity between geometrically corresponding interhemispheric regions.(Salvador et al 2005; Stark et al 2008) However, to our knowledge, few studies investigated the changes in interhemispheric connectivity in patients with ESRD, which restricts the full understanding of these patients. Voxel-mirrored homotopic connectivity (VMHC), which is developed by Zuo, et al. (Zuo et al 2010), provides a direct method for quantifying hemispheric interaction by identifying the temporal correlation of the low-frequency blood oxygen level-dependent (BOLD) signals between the two mirrored voxels across the contralateral hemispheres. Abnormal interhemispheric connectivity has been widely observed in various kinds of psychiatric and neurological diseases, such as postpartum depression(Chen and Schlaug 2013), major depressive disorder (MDD) (Yang et al 2018), Parkinson disease (Hu et al 2015), generalized anxiety disorder (GAD)(Wang et al 2019), multiple sclerosis (Zhou et al 2013). It has been demonstrated that VMHC is a sensitive resting-state fMRI measurement for detecting the altered interhemispheric functional coordination.

The purpose of this study was to explore the early changes in interhemispheric synchronous in patients with ESRD using the VMHC technique. Based on previous studies, we hypothesized that the functional coordination between the cerebral hemispheres was compromised in patients with ESRD, which might be associated with emotional and cognitive deficits. We also looked for the relationship between the VMHC values and clinical variables.

2. Material And Methods

2.1 Subjects

This prospective study was approved by the Ethics Committee of the 960th Hospital of the People's Liberation Army (PLA) and written informed consent of each subject was obtained before the study. From February 2018 to November 2018, all adult patients with right-handedness receiving hospital HD for ESRD at the dialysis center of the 960th Hospital of the PLA were considered. The following exclusion criteria were applied in this study: (a) age 18 years or younger, (b) dialysis duration less than 3 months,

(c) history of drug or alcohol abuse, (d) history of psychiatric or neurologic disorders, (e) visible brain lesions such as a tumor, stroke and visible infarction on conventional MR imaging, and (f) head motion more than 1 mm or 1°during MR scanning. A total of 48 neurologically asymptomatic patients with ESRD participated in MR scanning and performed clinical tests on a nondialysis day. 8 patients were excluded because of visible infarction (n = 2) and head motion (n = 6). The remaining 40 patients with ESRD were included in the final data analysis.

All subjects performed a questionnaire including gender, age, education level, dialysis duration, cognitive tests, and affective tests before MR scanning. Cognitive assessments used in the present study were validated by the Chinese version of the Mini-mental state examination (MMSE) test and the Montreal cognitive assessment (MoCA) test. We strictly did according to the instructions, using the accepted cut-off of MMSE $\geq$ 28 and MoCA $\geq$ 26 to define the normal global cognition. Depression and anxiety were measured by using validated the Chinese version of the self-rated depression scale (SDS) and self-rated anxiety scale (SAS).

A total of 40 right-handedness, age- and gender-matched healthy subjects were recruited from the local community. The exclusion criteria were similar to those used for patients with ESRD. Hence, 6 subjects were excluded because of head motion. The remaining 34 subjects were included in the final data analysis.

2.2 Data acquisition

MR data were collected using a 3.0T MR system (MR750, General Electric, Milwaukee, Wisconsin, USA) with an eight-channel head coil. Each scan consisted of 200 EPI functional volumes with the following parameters: TR 2000 ms, TE 35 ms, slice thickness 4 mm, slices 35, flip angle (FA) 90°, matrix 64×64, a field of view (FOV) 24×24 cm^2. A high-resolution T1-weighted sequence was obtained: TR, 8.2 ms; TE 3.2 ms, slices 132, slice thickness 1.0 mm, FOV 24×24 cm^2, FA 12°. Additionally, the conventional imaging was performed by an axial T1- and T2 weighted spin-echo sequence and T2-fluid attenuated inversion recovery sequence to exclude subjects with visible brain lesions.

2.3 Data processing

The rs-fMRI data preprocessing was conducted in MATLAB scripts (MathWorks, Natick, Mass) using Data Processing Assistant for Resting-State fMRI Advanced Edition (DPARSFA) and Statistical Parametric Mapping toolkit 8 (SPM8). The images were corrected for slice timing and head motion. The functional images were normalized to the Montreal Neurological Institute (MNI) space and resampled to 3×3×3 mm^3. The images were spatially smoothed with a 4 mm full-width-half-maximum (FWHM), temporally band-pass filtered (0.01–0.08 Hz), and linearly detrended removal to reduce low-frequency drift and high-frequency noise. Finally, several sources of spurious covariates along with their temporal derivatives were then removed from the data by using linear regression, including six head motion parameters obtained by rigid body correction, the signal from a ventricular region of interest, and the signal from a region centered in the white matter.

2.4 Interhemispheric correlation

VMHC has performed with REST 1.8 software. For each subject, individual VMHC maps were generated by computing the Pearson correlation between each voxel in one hemisphere and its corresponding voxel in the opposite hemisphere. The correlation coefficients were then Fisher z-transformed to improve the normality. The resultant values generated VMHC maps and were applied for group comparisons.

2.5 Statistical Analysis

The demographic and clinical data were performed by SPSS version 22 (SPSS Inc, Chicago, USA). All the quantitative data were presented as mean ± standard deviation and statistical significance was accepted at $p<0.05$. Two-sample independent Student's t-tests were used to compare the difference in age, education, MMSE score, MoCA score, SDS score, and SAS score between the ESRD group and HC group. The Chi-squared test was performed to compare gender-based differences between groups.

SPM8 toolkit was used to analyze the rs-fMRI data. Individual-level VMHC maps were entered into a group-level voxel-wise two-tailed t-test to determine group differences in VMHC. Age and gender were used as a covariate in this statistical analysis. The resulting statistical result was set at $p<0.01$ for multiple comparisons (False Discovery Rate (FDR)corrected, cluster size>20 voxels).

Brain areas exhibiting significant VMHC differences between groups were identified as masks. Mean VMHC values were separately extracted from masks for further analysis. The receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity characteristics in the mean VMHC values. Pearson correlation analysis was performed to evaluate the relationships between VMHC values and clinical variables in patients with ESRD. All $p<0.05$ were regarded as statistically significant.

3. Result

3.1 Demographics and clinical characteristics

The demographic and clinical data of all subjects were summarized in Table 1. There were no significant differences in age ($p = 0.735$), gender ($p = 0.979$), and education level ($p = 0.886$) between the ESRD group and the HC group. For the global cognitive tests, patients with ESRD showed significantly lower MoCA score ($p=0.003$) compared with HCs. For the affective tests, patients with ESRD showed significantly higher SDS and SAS scores compared with HCs (all $p<0.001$).

Table 1
Demographic and clinical characteristics of ESRD group and HC group.

Variables	ESRD (n = 40)	HC (n = 34)	t/χ^2	*P*-value
Age (years)	48.15 ± 13.08	46.94 ± 16.86	0.340	0.735[a]
Gender (male/female)	26/14	22/12	0.001	0.979[b]
Education (years)	11.82 ± 2.52	11.73 ± 2.82	0.144	0.886[a]
Dialysis duration (months)	68.95 ± 63.10			
MMSE score	28.57 ± 1.46	29.14 ± 1.10	-1.911	0.060[a]
MoCA score	27.10 ± 1.23	28.03 ± 1.40	-3.029	0.003[a]
SDS score	45.05 ± 8.79	32.50 ± 6.37	6.915	0.001[a]
SAS score	42.87 ± 8.00	31.82 ± 7.27	6.173	0.001[a]
Hemoglobin (g/L)	106.55 ± 14.16			
Serum albumin (g/L)	39.34 ± 3.86			
Serum calcium (mmol/L)	2.32 ± 0.24			
Serum phosphorus (mmol/L)	1.74 ± 0.49			
Systolic pressure (mm Hg)	145.70 ± 19.65			
Diastolic pressure (mm Hg)	85.62 ± 9.56			
[a] the *p* values were obtained by Student's t test				
[b] the *p* value was obtained by Chi-square test				
Abbreviations: ESRD, end-stage renal disease; HC, healthy control; MMSE, mini-mental state examination; MoCA, montreal cognitive assessment; SDS, self-rated depression scale; SAS, self-rated anxiety scale.				

3.2 VMHC differences

The group comparison results of VMHC were shown in Fig. 1 and Table 2. Compared with HCs, patients with ESRD showed significantly decreased VMHC values mainly located in the inferior parietal lobule (IPL), superior temporal gyrus (STG), insula, precentral gyrus (PreCG),middle occipital gyrus (MOG), and calcarine/ lingual/ cuneus. Compared with HCs, there was no increased VMHC value in any region in patients with ESRD.

Table 2
Brain regions with significant VMHC differences between ESRD group and HC group.

Regions	BA	MNI coordinates			Voxels	Tmax
		x	y	Z		
Precentral gyrus	6	± 51	24	23	-6.242	
Superior temporal gyrus	48/22	± 60	-18	9	83	-5.958
Inferior parietal lobule	40	± 48	-51	42	20	-5.390
Middle occipital gyrus	19	± 42	-69	6	41	-5.146
Insula	-	± 36	9	-3	72	-5.759
Calcarine/ Lingual/ Cuneus	17/18/19	± 12	-69	9	82	-6.648

Abbreviations: BA, brodmann area; MNI, montreal neurological institute; VMHC, voxel-mirrored homotopic connectivity; ESRD, end-stage renal disease; HC, healthy control.

3.3 Correlation analysis

There were no significant correlations between VMHC values and MMSE score, MoCA score, SDS score, SAS score, dialysis duration, albumin, calcium, phosphorus, systolic pressure, and diastolic pressure in the patients with ESRD (all $p > 0.05$). A positive correlation was observed between VMHC values of the MOG and hemoglobin levels in patients with ESRD ($p = 0.003$).

3.4 ROC analysis

To confirm if the VMHC differences between the two groups are useful diagnostic markers, we performed a ROC analysis for brain regions exhibiting significant VMHC differences. The results showed that the areas under the ROC curve (AUCs) were 0.863 for IPL(p＜0.001，95%CI:0.779-0.948)); 0.887 for STG (p＜0.001，95%CI:0.805-0.968) ; 0.904 for insula (p＜0.001，95%CI:0.831-0.976); 0.829 for PreCG (p＜0.001，95%CI:0.736-0.923; 0.849 for MOG (p＜0.001, 95%CI: 0.763-0.936); 0.869 for calcarine/lingual/cuneus (p＜0.001，95%CI:0.788-0.950).

4. Discussion

The results of our study showed predominantly decreased interhemispheric connectivity in some DMN regions, insula, PreCG, MOG, and calcarine/lingual/cuneus compared in patients with ESRD. Also, the VMHC values of MOG were positively correlated with hemoglobin levels in patients with ESRD. The ROC analysis demonstrated the VMHC values in these regions have high sensitivity and specificity in distinguishing the two groups.

An important finding of this study was that decreased VMHC in the DMN regions mainly in the IPL and STG were observed in patients with ESRD, indicating impaired interhemispheric connectivity within the DMN. The DMN brain regions are involved in different high-level cognitive functions, including memory,

visual and auditory attention, motor activity, and language processing.(Ni et al 2014) Based on various rs-fMRI imagines, previous studies had demonstrated that brain spontaneous neuronal activity and functional connectivity in the DMN regions are abnormal in patients with ESRD. For example, Luo et al. (Luo et al 2016) reported decreased ALFF values in some DMN regions including the precuneus, IPL, and STG in patients with ESRD undergoing PD and HD. Liang et al. (Liang X et al 2013) reported significantly decreased ReHo values in bilateral IPL and STG in patients with ESRD. Chen et al. (Chen et al 2015) reported decreased ReHo values in right IPL and STG in patients with ESRD undergoing HD. These studies supported that decreased spontaneous neuronal activities in patients with ESRD are associated with the domains of attention, visual memory, and psychomotor speed impairments. Furthermore, Luo and Liang (Liang X et al 2013 ; Luo et al 2016) reported that a significant positive relationship between digit-symbol test (DST) scores and ALFF values and ReHo values in the IPL in patients with ESRD, which further suggested that cognitive impairment was related to spontaneous brain activity abnormalities in the DMN region. Further functional connectivity analysis showed decreased FC in the left IPL and left precuneus and increased connectivity in depression-related regions including bilateral inferior frontal gyrus and right STG in patients with ESRD, revealing an abnormal dysconnectivity pattern of the DMN functional networks in these patients. (Li et al 2016) Widespread weakening of cortical and subcortical network connectivity in patients with ESRD was more directly related with neuropsychological impairments.(Zheng et al 2014) To date, the changes of interhemispheric connectivity within the DMN in patients with ESRD has not been assessed. Our findings of decreased VMHC values in IPL and STG provide further evidence from the interhemispheric functional network integrity view that the impaired interhemispheric connectivity within the DMN is prevalent in patients with ESRD. The deficits in the DMN might suggest higher cognitive impairment. The impaired interhemispheric connectivity within the DMN may play a critical role in the pathophysiology of cognitive dysfunction in patients with ESRD.

We observed a decreased VMHC in the insula in patients with ESRD comparing with HCs. Similar to our results, Zheng et al. (Zheng et al 2014)reported the decreased positive FC in bilateral insula within the whole brain network in patients with ESRD undergoing HD. Insula receives and integrates the interoceptive signals, and is also engaged in the processing of negative emotions and anticipating pain (Uddin et al 2017). Affective disorders are common clinical manifestations in patients with ESRD, such as the prevalence of depression in patients with ESRD up to 20–25% (Jin et al 2020). The present study showed an increase in SDS score and SAS score in patients with ESRD compared with HCs, which was consistent with the previous study. The decreased VMHC between the bilateral insula represents insufficient interhemispheric communications, which might result in disturbed emotion regulation(Wang et al 2019). For example, Yang and Wang et al. (Yang et al 2018; Wang et al 2019) reported significantly decreased VMHC values in the insula in patients with GAD and MDD compared with HCs. In this study, decreased VMHC values in the insula may reflect a functional decline in the processing of emotion-related functions, which might partly contribute to the emotional symptoms seen in patients with ESRD. Furthermore, a recent study reported that patients with mild or moderate/severe depression symptoms had a higher prevalence of general cognitive impairment, executive dysfunction, and impaired immediate and delayed memory (Dong et al 2016). Emotional dysfunction may further aggravate cognitive

impairment. Li et al.(Li et al 2018) demonstrated the abnormal interaction between depressive mood and cognitive control deficits in patients with ESRD using the FC approach. The negative emotion may be one of the risk factors that promote dysregulation of the cognitive control network, which would thus be associated with worse performance in cognitive control in patients with ESRD. (Zheng et al 2014; Luo et al 2016; Li et al 2018) Considering that the decreased VMHC values in multiple depression-related regions were observed in patients with ESRD, the decline in cognitive score observed in this study may be due in part to the affective complication.

In this study, decreased VMHC was also observed in bilateral PreCG in patients with ESRD. The PreCG, known as the primary motor cortex, is responsible for motor control, especially in complex motor behavior (Kakei et al 1999). Chen et al. (Chen et al 2015)found decreased ReHo values in bilateral PreCG in patients with ESRD in both HD and non-HD groups. Liang et al. (Liang X et al 2013) showed that decreased ReHo values in bilateral PreCG negatively correlated the number connection test-A (NCT-A), a test of the psychomotor speed domain in patients with ESRD. This indicated that patients with ESRD with abnormal brain activity in bilateral PreCG have more impairment of cognitive function. Decreased interhemispheric connectivity represents insufficient interhemispheric communications and weak synergistic balance between the bilateral brain regions. Previous studies reported the closed relationship between decreased VMHC in PreCG and motor control deficit in chronic stroke patients and Parkinson's patients, which revealed the interference of insufficient inter-hemispheric communication in PreCG on the motor control function(Chen and Schlaug 2013; Hu et al 2015). In this study, the weak communications between bilateral PreCG might contribute to motor control dysregulation in patients with ESRD.

Another important finding was impaired VMHC in multiple visual cortexes of the occipital lobe including MOG, cuneus, lingual, and calcarine in patients with ESRD. Many previous investigators reported neuronal activity abnormalities and structural abnormalities in visual cortexes in patients with ESRD. For example, Zhang et al. (Zhang et al 2013) found decreased gray matter volume in bilateral cuneus, lingual, calcarine, and occipital lobes in patients with ESRD. Liang et al. (Liang X et al 2013) found decreased ReHo value in bilateral cuneus in patients with ESRD. MOG is involved in the perception of face processing, which is crucial for social interaction (Sato et al 2014). Calcarine/lingual/cuneus is involved in visual processing and visual pathway (Kapadia et al 2000). Recent, neuroimaging (Luo et al 2016) showed that the ALFF values in bilateral calcarine and cuneus negatively correlated with serial dotting test (SDT) scores and line-tracing test (LTT) scores in patients with ESRD, revealing that the abnormal brain activity in the visual brain regions plays an important role in the visual-motor movement dysfunction in patients with ESRD. It is well known that the visual information from each hemifield is transmitted to the contralateral side of the primary visual cortex simultaneously, and this information needs to be integrated into bilateral cortical hemispheres (Wang et al 2018).The activation of interhemispheric connections in the visual cortex is very important for the early stage of visual information processing(Goto et al 2004). Given that most of these occipital lobe and visual signal encoding functional areas are related to visual information processing and modulation of top-down visuospatial selective attention. The decreased VMHC in the visual cortex could disorder the visual

information exchange and processing between the bilateral hemispheres, which may manifest as a visual cognitive dysfunction.

Although the global cognitive function was normal on the MMSE and MoCA tests, the MoCA score of the ESRD group was significantly lower than that of HCs in this study. Patients with ESRD with clinically normal global cognitive function do not mean that these patients are totally free of cognitive decline. Post et al.(Post et al 2010)reported that HD patients have a high probability of mild cognitive impairment despite normal global cognitive function. The reason may be that cognitive assessments are self-rating scales that may be affected by some confounders, such as educational levels, intelligence, illness duration, and social environment. The sensitivity of the cognitive test is lower when patients in the early stages of cognitive dysfunction are examined (Schultz-Larsen et al 2007). In this study, our results showed impaired interhemispheric synchronous in several regions in patients with ESRD, revealing that the resting-state fMRI technique was a sensitive measurement for detecting brain dysfunction at the early stage. These findings were supported by the results of a previous neuroimaging study. For example, compared with HCs, neurologically asymptomatic patients with ESRD showed significantly abnormal ReHo in the bilateral STG and left medial frontal gyrus, right middle temporal gyrus and abnormal intrinsic disconnectivity pattern of whole-brain functional networks at the voxel level. (Li et al 2014; Li et al 2016) Compared with HCs, non-nephrotic encephalopathy patients with ESRD showed decreased ReHo in the bilateral frontal, parietal and temporal lobes and decreased intrinsic FC in the precuneus, posterior cingulate cortex and medial prefrontal cortex.(Liang X et al 2013 ; Ni et al 2014) Besides, the ROC analysis demonstrated the VMHC values in all regions have acceptable accuracy and high specificity in distinguishing the two groups. The ROC results revealed that AUCs of the IPL, STG, insula, PreCG, MOG and calcarine/lingual/cuneus were 0.863, 0.887, 0.904, 0.829, 0.849 and 0.869, respectively. An AUC in the range of 0.7–0.9 means a perfect diagnostic value. These results showed that the VMHC values in these regions might be early diagnostic markers for cognitive decline in patients with ESRD.

Furthermore, we found that hemoglobin levels positively correlated with VMHC values in the MOG in patients with ESRD. Our finding was supported by previous neuroimaging results. For example, Zheng et al.(Zheng et al 2014) found that hematocrit levels were associated with altered FC in patients with ESRD. Luo et al. (Luo et al 2016)found that hemoglobin levels positively correlated with ALFF values in patients with ESRD. Therefore, these results suggest that hemoglobin levels influence brain function in patients with ESRD. Besides, Kamata et al. (Kamata et al 2000) reported that hematocrit negatively correlated with brain atrophy index in patients with ESRD. Results of several previous studies have shown a significant negative correlation between hemoglobin levels and CBF in patients with ESRD (Jiang et al 2016; Cheng et al 2018; Liu et al 2018). Anemia-induced hypoxia caused low cerebral oxygen delivery, with a detrimental effect on brain metabolism. Anemia is associated with mild-to-moderate cognitive impairment in patients with ESRD and treatment of anemia improved neuropsychologic and neurophysiological performance. (Radic et al 2010; Shaker et al 2018) It is possible that decreased hemoglobin levels cause low oxygen delivery and weakened interhemispheric connectivity, contributing to cognitive decline.

Our study is also subject to several potential limitations. First, the small sample size may limit the statistical power of presenting differences between groups. Second, we do not investigate specifically whether the patients with and without cognitive dysfunction have different interhemispheric connectivity patterns. Third, we do not address the effect of other dialysis modality on interhemispheric connectivity in patients with ESRD. Finally, a battery of neuropsychological tests (e.g., NCT-A, DST, SDT, LTT, and trial marking test-A&B) should be used in a follow-up study to evaluate cognitive dysfunction in patients with ESRD.

5. Conclusion

Our results indicated predominantly decreased VMHC values mainly in bilateral frontal, occipital, parietal, and temporal lobes in patients with ESRD undergoing HD, which may be correlated with hemoglobin levels. Our findings complement previous studies with interhemispheric connectivity disruption in these regions, which implies a functional deficit. VMHC may serve as a sensitive and stable neuroimaging biomarker to some extent for characterizing patients with ESRD.

Declarations

Disclosure statement

None of the authors have potential conflicts of interest to be disclosed

Author contributions

Fengyu Jia, Gang Sun, and Kai Liu conceived the experiment; Yan Xue and Fengyu Jia recruited participants; Yan Xue and Bo Li collected and analyzed the data; Yan Xue wrote the paper; Zhuanzhuan Wu, Shuyan Li, and Kai Liu revised and reviewed the manuscript.

Data Availability Statements

The datasets generated during and/or analysed during the current study are not publicly available due to [REASON(S) WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

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Figures

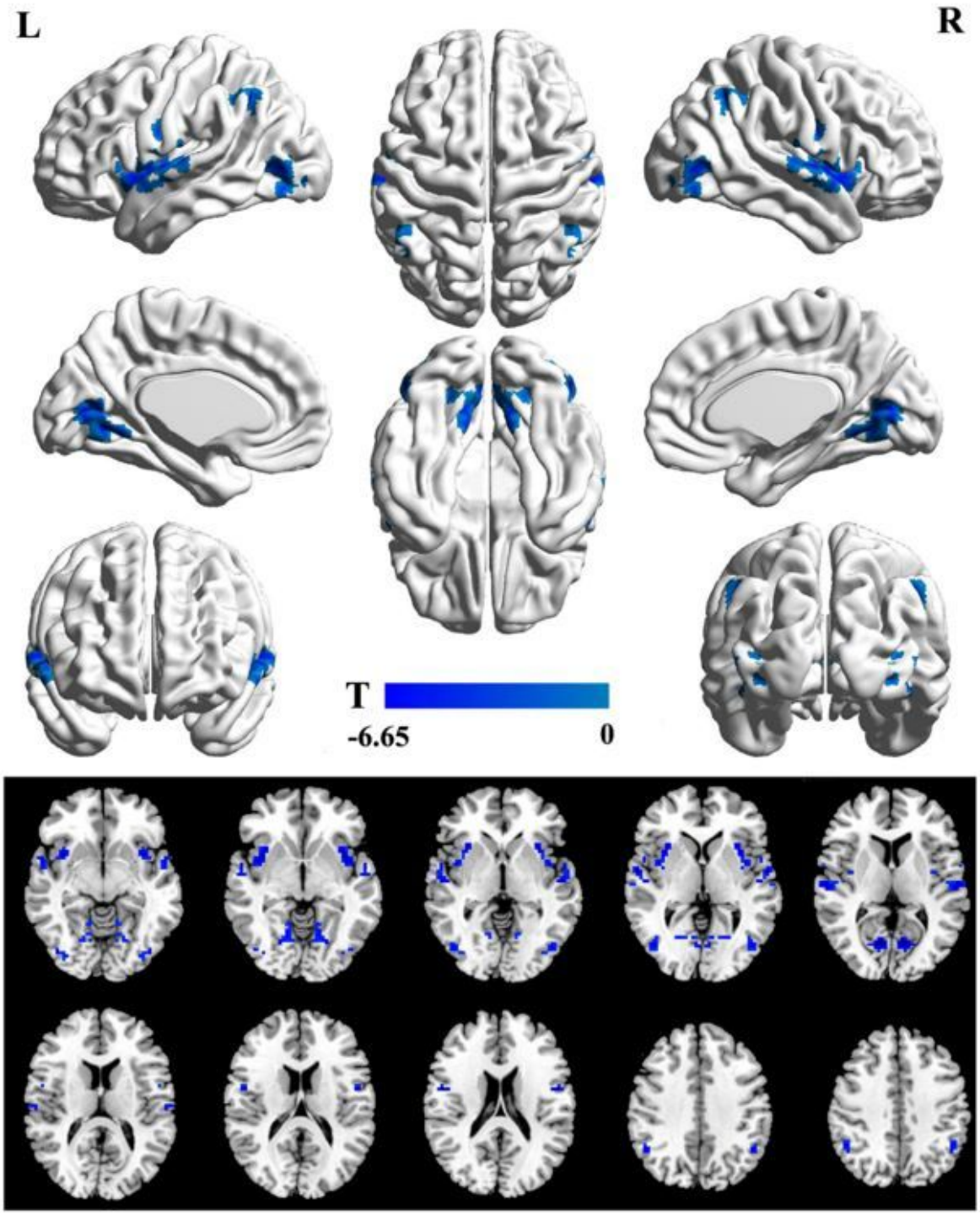

Figure 1

Regions showing group differences in interhemispheric functional connectivity in the ESRD group and HC group. Compare with the HC group, the ESRD group showed significantly decreased VMHC values in the inferior parietal lobule, superior temporal gyrus, insula, precentral gyrus, middle occipital gyrus, and calcarine/ lingual/ cuneus. Color bars indicate the t values from the global voxel-based two-sample t-test.

(p<0.05, FDR corrected). Abbreviations: VMHC, voxel-mirrored homotopic connectivity; ESRD, end-stage renal disease; HC, healthy control.

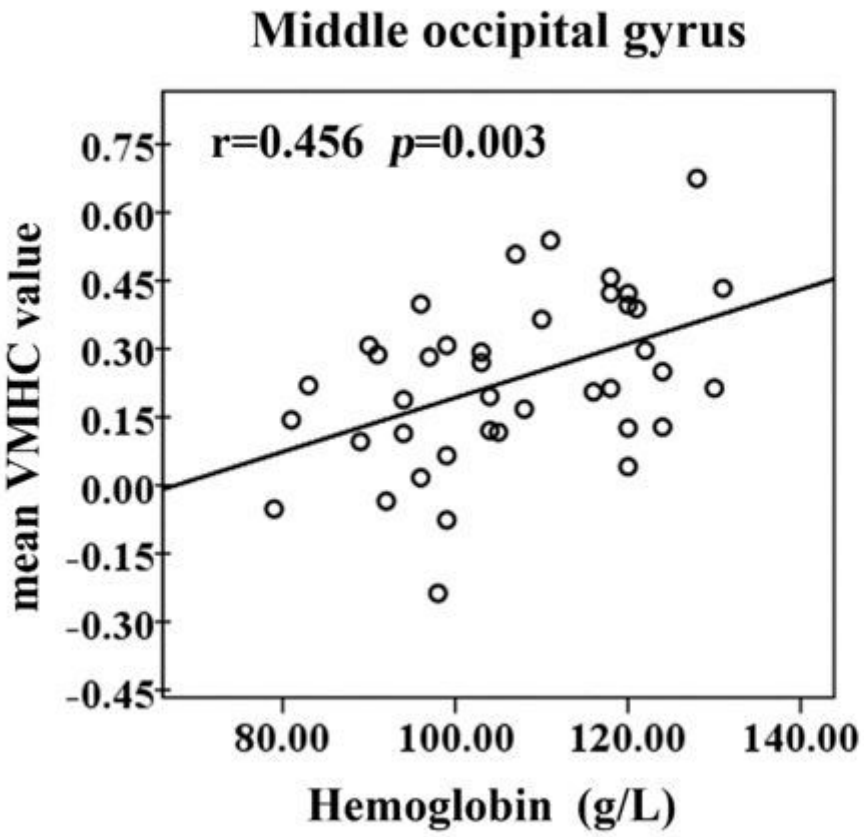

Figure 2

Scatterplot shows a positive correlation between the VMHC values in the middle occipital gyrus (MOG) and hemoglobin levels in patients with ESRD. VMHC, voxel-mirrored homotopic connectivity; ESRD, end-stage renal disease

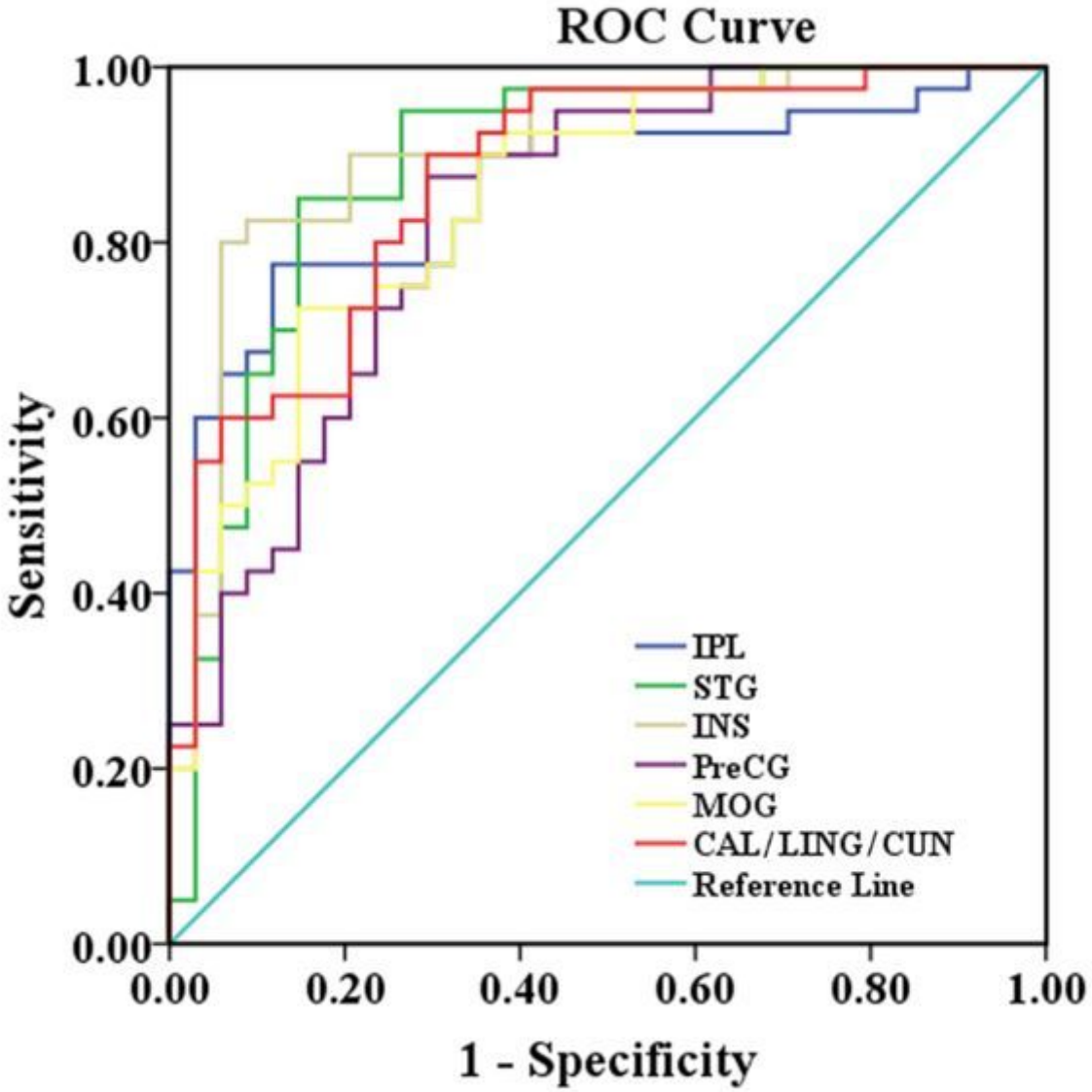

Figure 3

ROC curve analysis in altered mean VMHC values of different brain regions in patients with ESRD. The AUCs of the IPL, STG, insula, PreCG, MOG and calcarine/lingual/cuneus were 0.863, 0.887, 0.904, 0.829, 0.849 and 0.869, respectively. ROC, receptive operation characteristic; AUC, area under the curve; VMHC, voxel-mirrored homotopic connectivity; IPL, inferior parietal lobule; STG, superior temporal gyrus; INS, insula; PreCG, precentral gyrus; MOG, middle occipital gyrus; CAL/LING/CUN, calcarine/ lingual/ cuneus.