Original Article

The relationship between abnormal cortical activity in the anterior cingulate gyrus and cognitive dysfunction in patients with end-stage renal disease: a fMRI study on the amplitude of low-frequency fluctuations

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Background: End-stage renal disease (ESRD) patients often have cognitive dysfunction. The abnormal changes in the brains of ESRD patients are difficult to detect with routine imaging examination. Cognitive performance scales are also not an ideal tool because assessments using these scales can be subjective and might be difficult to administer in some ESRD patients. Functional magnetic resonance has the advantages of non-radiation, multidirectional imaging, good repeatability. Using resting-state functional magnetic resonance imaging (rs-fMRI) and an amplitude of low-frequency fluctuation (ALFF) algorithm, this study characterized spontaneous brain activity and explored its relationship with cognitive function in ESRD patients. The aim of this study was to provide objective functional imaging evidence to reveal the pathophysiological mechanism of cognitive dysfunction in ESRD patients.

Methods: This study recruited 35 ESRD patients and 25 healthy controls (HC) who were matched to the ESRD group by age, sex, and years of education. All study subjects were examined by Montreal Cognitive Assessment (MoCA) and rs-fMRI. Data Processing & Analysis of Brain Imaging (DPABI) V4.3 software was used to preprocess the data to obtain ALFF maps. The ALFF value of the cingulate gyrus was compared between the ESRD and HC groups. Subsequently, the correlation between the ALFF value of the cingulate gyrus and the MoCA score was analyzed in ESRD patients.

Results: Compared with the HC group, the ESRD group had a significantly lower MoCA score ($P<0.05$). The ALFF values of the anterior and middle cingulate gyri were significantly lower in the ESRD patients (Gaussian random field (GRF) corrected, voxel-level significance: $P<0.001$, cluster-level significance: $P<0.05$). No increased ALFF was observed in any brain regions. The ALFF values of the bilateral anterior cingulate gyri were positively correlated with the MoCA scores ($r=0.768$, 0.625, GRF corrected, voxel-level significance: $P<0.01$, cluster-level significance: $P<0.05$).

Conclusions: Patients with ESRD showed impaired spontaneous brain activity in the bilateral anterior and middle cingulate gyri, suggesting that ALFF of the anterior cingulate gyrus may be an imaging indicator of cognitive dysfunction in ESRD patients.

Keywords: End-stage renal disease (ESRD); cognitive function; cingulate gyrus; magnetic resonance imaging; amplitude of low frequency fluctuations

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Introduction

End-stage renal disease (ESRD) is the last stage of chronic kidney disease. In recent years, research has found that ESRD can cause functional abnormalities of the central nervous system, especially cognitive dysfunction (1), which may affect the diagnosis and treatment of ESRD (2,3). The cingulate gyrus is a key brain structure that regulates emotional information, learning, and memory (4). Using functional magnetic resonance imaging (fMRI), a few studies have revealed that the abnormal function of the cingulate gyrus may play a significant role in cognitive dysfunction in ESRD patients (5,6). The amplitude of low-frequency fluctuations (ALFF) in fMRI reflects the energy of signal fluctuations in the low-frequency range (0.01–0.1 Hz) at the voxel level in blood oxygen level-dependent functional magnetic resonance imaging (BOLD-fMRI) (7). Therefore, ALFF can be used to evaluate regional spontaneous neuronal activity in the brain (8). In this study, we attempted to characterize the neural activity in the cingulate gyrus that is related to cognitive dysfunction in ESRD patients by using an ALFF algorithm, with the hope of providing objective functional imaging evidence for exploring the pathophysiological mechanism underlying ESRD-associated cognitive dysfunction. We present the following article in accordance with the MDAR checklist (available at http://dx.doi.org/10.21037/apm-20-2138).

Methods

General information

The ESRD group

This study included 41 ESRD patients who were treated in our hospital from April 2017 to June 2019. The inclusion criteria were as follows: (I) meting the diagnostic criteria of the American Society of Nephrology for ESRD (9); (II) age between 18 and 60 years old; (III) having undergone dialysis for more than six months; and (IV) right-handedness. The exclusion criteria were (I) a history of neurological or psychiatric diseases, including brain tumors, brain trauma, stroke, schizophrenia, and epilepsy; (II) a history of drug or alcohol dependence; (III) a history of diabetes or cirrhosis; (IV) head motion artifacts interfering experimental data acquisition or measurement; and (V) contraindications for MRI. According to the above exclusion criteria, six ESRD patients were excluded, including one patient with a history of cerebral hemorrhage, one patient with a history of brain trauma, one patient with diabetes, and three patients with motion artifacts that affected experimental data measurement. Finally, the ESRD group comprised 35 patients, including 15 males and 20 females aged 35 to 58 years old, with an average age of 47.60±6.05 years.

The healthy control (HC) group

During the same period, 26 healthy individuals who matched the ESRD patients by age, sex, and years of education were recruited as controls. The inclusion criteria were as follows: (I) age between 18 and 60 years old; (II) physical examination report within the recent six months and no obvious abnormalities in laboratory indicators, electrocardiogram, and B-ultrasound examination; and (III) right-handedness. The exclusion criteria for the HC group were the same as those for the ESRD group. One case was excluded due to the excessive interference of motion artifacts with data measurement. Finally, the HC group consisted of 25 individuals, including 13 males and 12 females aged 38 to 55 years, with an average age of 47.68±5.15 years.

There were no statistically significant differences in sex, age, or years of education between the two groups (P>0.05). This study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University (research number 2017010), and all subjects signed the informed consent form. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Examinations

Neuropsychological tests

The Montreal Cognitive Assessment (MoCA) was used to evaluate the cognitive function of all subjects within one hour before MRI scanning was performed.

MRI

All MRI examinations were performed using a Philips Achieva 3.0T MRI system equipped with a 16-channel phased-array head coil. Conventional cross-sectional T1-, T2-weighted imaging and coronal T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging were performed first to rule out brain structural lesions. High-resolution brain structure images were obtained using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time 8.0 ms, echo time 3.9 ms, field of view 250 mm × 250 mm, matrix 256×256, slice thickness 1.0 mm, no gap). Resting-state fMRI (rs-fMRI) was

performed with a gradient-echo echo-planar imaging (GRE-EPI) sequence (repetition time 2,000 ms, echo time 30 ms, slice thickness 4.0 mm, slice spacing 0.4 mm, field of view 240 mm × 240 mm, matrix 120 ×117, flip angle 90°, 250 time points, and 30 slices). During MRI scanning, the patients were asked to remain quiet and close their eyes but stay awake.

Image processing and analysis

rs-fMRI image preprocessing

The rs-fMRI image data were preprocessed by using the DPABI V4.3 (http://rfmri.org/dpabi) software package on the MATLAB 2013b platform. The main steps were as follows: (I) format conversion: the DICOM images were converted to the NIFIT format. (II) The data at the first 10 time points were discarded to eliminate interference associated with patients' adaptation to the environment and machine instability. (III) The image data were corrected for slice timing. (IV) The image data were corrected for head motion: Data with a head motion translation greater than 2 mm or rotation greater than 2° were discarded. (V) Spatial normalization: The original data were registered with the Montreal Neurological Institute (MNI) template, and the resampling voxel size was set as 3 mm × 3 mm × 3 mm. (VI) The data were treated with linear drift removal and band-pass filtering (frequency 0.01–0.1 Hz). (VII) The covariate factors were removed. (VIII) Spatial smoothing: Gaussian smoothing was performed with a full-width at half-maximum (FWHM) value of 4 mm to reduce spatial noise.

Calculation of ALFF

The fast Fourier transform (FFT) algorithm was used to transform the preprocessed time series into the frequency domain to obtain a power spectrum. The ALFF value was obtained by calculating the square root of the power spectrum.

Statistical analysis

General clinical data were statistically analyzed using SPSS 16.0 software. Age, years of education, and MoCA scores were expressed as $\bar{x}\pm s$, and the differences between the ESRD and HC groups were tested with two-sample t tests. The difference in the sex ratio between the two groups was tested with χ^2 tests, and P<0.05 indicated that the difference was statistically significant. Using the DPABI software, the standardized ALFF data were compared with two independent samples t tests and corrected by Gaussian random field (GRF), with P<0.001 at the voxel level and P<0.05 at the cluster level indicating a significant difference. The ALFF values of the cingulate gyrus and the MoCA scores of the ESRD patients were analyzed with *Pearson* correlation analysis and were GRF corrected, with P<0.01 at the voxel level and P<0.05 at the cluster level indicating a significant difference. Age, sex, and years of education were regarded as covariate factors, and their influence was removed.

Results

Comparison of general information and cognitive function between the two groups

There were no statistically significant differences in sex, age, and years of education between the two groups (P>0.05). The MoCA score of the ESRD group was lower than that of the HC group, and the difference between the two groups was statistically significant (P<0.05) (*Table 1*).

Comparison of the ALFF map of the cingulate gyrus between the ESRD and HC groups

Compared with the HC group, the ALFF value of the bilateral anterior and middle cingulate gyri was significantly lower in the ESRD group (GRF corrected, voxel-level significance P<0.001 and cluster-level significance P<0.05). The ALFF value of the posterior cingulate gyrus did not differ significantly between the two groups (P>0.05). No detectable increase in the ALFF value was observed in any brain region in the ESRD group (*Figure 1* and *Table 2*).

Correlation analysis between the ALFF value of the cingulate gyrus and cognitive function in ESRD patients

The ALFF values of the bilateral anterior cingulate gyri were positively correlated with the MoCA score (r=0.768, 0.625, GRF corrected, voxel-level significance P<0.01, cluster-level significance P<0.05) (*Figure 2*, *Table 3*).

Discussion

In rs-fMRI studies, ALFF reflects the intensity of neuronal activity in the brain by directly displaying the magnitude change in brain BOLD signals relative to the baseline, and it has been widely used to measure spontaneous functional abnormalities in the brain areas associated with mental

Table 1 General information and cognitive function of the ESRD and HC groups

Item	ESRD group	HC group	t/χ^2 value	P value
Sex (male/female)	15/20	13/12	0.490	0.484
Age (years)	47.60±6.05	47.68±5.15	−0.054	0.957
Years of education (years)	9.97±2.65	11.16±2.98	−1.625	0.110
MoCA (score)	24.06±3.86	26.96±1.34	−3.604	0.001

ESRD, end-stage renal disease; HC, healthy controls; MoCA, Montreal Cognitive Assessment.

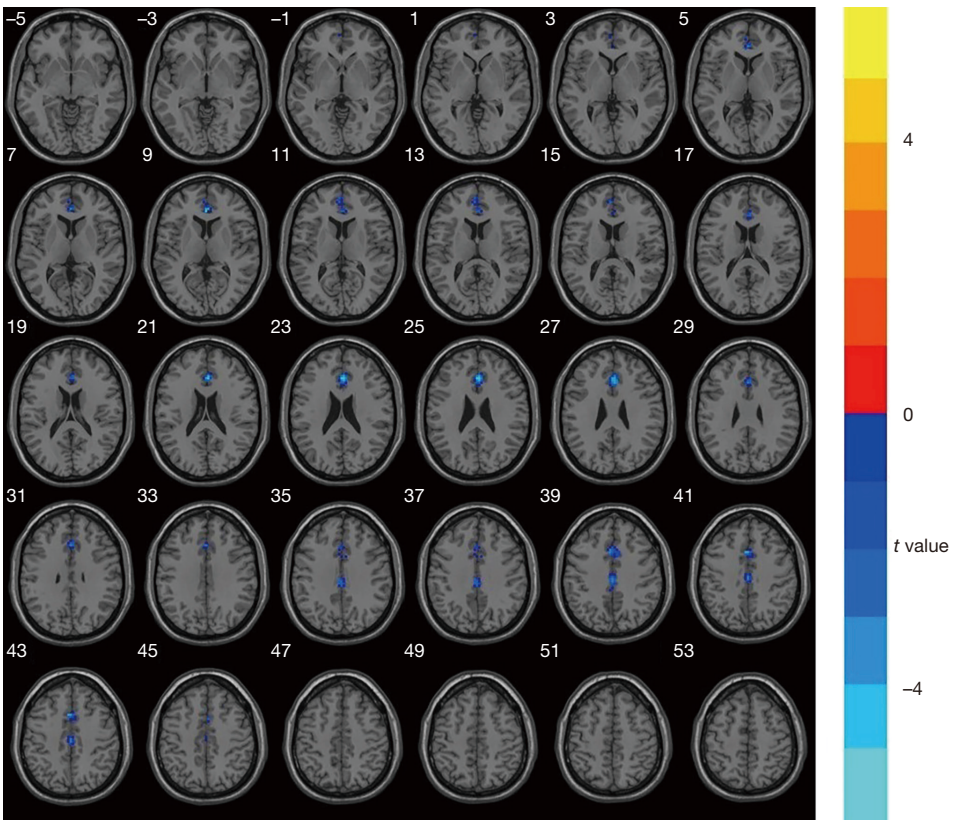

Figure 1 Regions of the anterior and middle cingulate gyri (blue areas) showing decreased ALFF in ESRD patients compared with the HCs. ESRD, end-stage renal disease; HC, healthy controls; ALFF, amplitude of low-frequency fluctuations.

Table 2 Areas in the cingulate gyrus with a decreased mean ALFF in the ESRD group compared with the HC group

Brain area	AAL subregion	Peak coordinates (MNI)			Number of voxels	*t* value	P value
		x	y	z			
Left anterior cingulate gyrus	31	0	36	9	54	−4.780	<0.001
Right anterior cingulate gyrus	32	3	30	24	42	−4.819	<0.001
Left middle cingulate gyrus	33	0	−21	39	29	−4.289	<0.001
Right middle cingulate gyrus	34	3	9	45	20	−3.841	<0.001

ESRD, end-stage renal disease; HC, healthy controls; ALFF, amplitude of low-frequency fluctuations; AAL, anatomical automatic labeling; MNI, Montreal Neurological Institute.

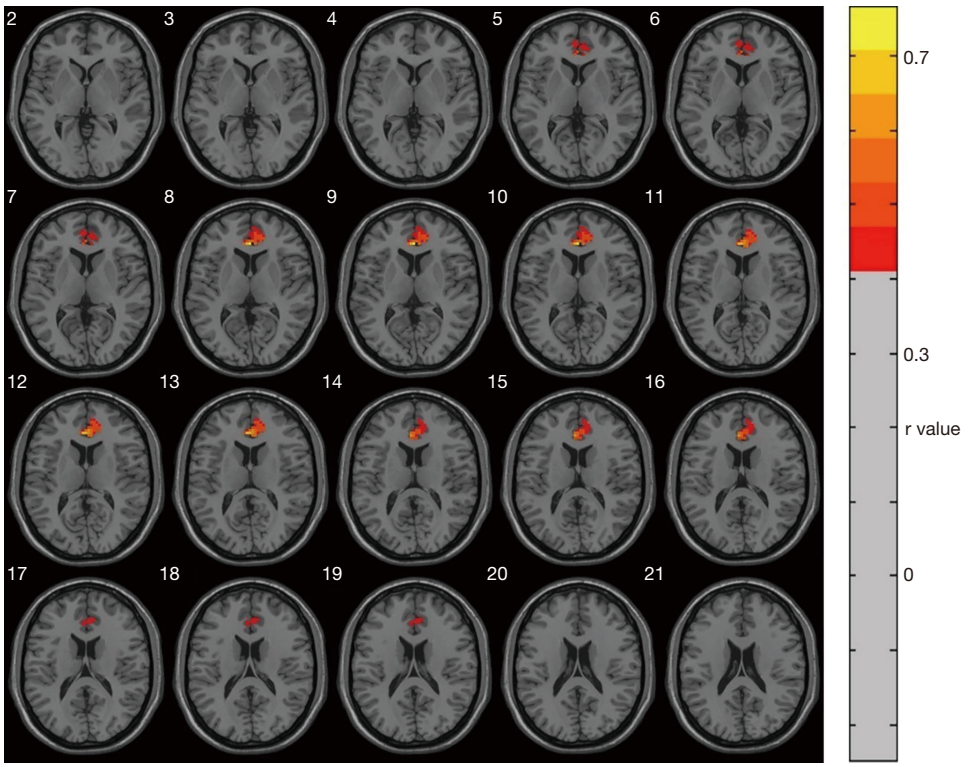

Figure 2 Regions of the anterior cingulate gyrus (red and yellow regions) with ALFF positively correlated with the MoCA score in the ESRD group. ALFF, amplitude of low-frequency fluctuations; MoCA, Montreal Cognitive Assessment; ESRD, end-stage renal disease;

Table 3 Correlation analysis of the ALFF of the cingulate gyrus and the MoCA score in the ESRD group

Brain area	AAL subregion	Peak coordinates (MNI)			Number of voxels	r value	P value
		x	y	z			
Left anterior cingulate gyrus	31	0	36	9	24	0.768	<0.01
Right anterior cingulate gyrus	32	3	36	12	74	0.625	<0.01

ESRD, end-stage renal disease; ALFF, amplitude of low-frequency fluctuations; MoCA, Montreal Cognitive Assessment; AAL, anatomical automatic labeling; MNI, Montreal Neurological Institute.

illness (10,11). Using the ALFF algorithm of rs-fMRI, this study revealed that compared with the HC group, the ESRD group had significantly lower ALFF values in the bilateral anterior and middle cingulate gyri. This indicates that ESRD patients had decreased spontaneous neural activity in the anterior and middle cingulate gyri, suggesting that these brain areas experienced functional damage of the neurons.

In our previous study, independent component analysis of rs-fMRI revealed that ESRD patients exhibited abnormalities in the default-mode network of the brain and had decreased functional connectivity of the posterior cingulate gyrus (12). The finding from the present study that the ALFF values of the bilateral anterior and middle cingulate gyrus were significantly decreased in ESRD patients further supports previous findings. The anterior cingulate gyrus is one of the important structures responsible for the executive function of the brain, and it mainly monitors ongoing directional behaviors and coordinates cognitive processes (13). The present study found that the ALFF of the anterior cingulate gyrus was decreased in the ESRD group, suggesting that ESRD

patients had weaker spontaneous brain activity in the anterior cingulate gyrus, which is consistent with the findings of Li *et al.* (14). In addition, correlation analysis showed that the decrease in ALFF values in the anterior cingulate gyrus was significantly positively correlated with the MoCA score, indicating that the impaired spontaneous activity of neurons in the anterior cingulate gyrus resulted in a gradual decline of cognitive function. The results suggest that the ALFF of the anterior cingulate gyrus may be an objective indicator that can be used to monitor the severity of cognitive dysfunction in ESRD patients. However, there was no significant correlation between the ALFF of the middle cingulate gyrus and cognitive function scores, a finding that may be attributable to the relatively small sample size or the cognitive function scale used. The middle cingulate gyrus is associated with episodic memory and executive function (15,16), and there are close connections between different parts of the cingulate gyrus and between the cingulate gyrus and other brain regions (17,18). Therefore, we speculate that the decreased ALFF value of the middle cingulate gyrus may contribute to cognitive dysfunction in ESRD.

In this study, the ALFF of the posterior cingulate gyrus did not show a significant decrease in ESRD patients, which may be associated with two factors. The first is the severity of disease. One possibility is that damage to the posterior cingulate gyrus occurs later than damage to the anterior and middle cingulate gyri in ESRD patients. Another possibility is that the neural functional impairment in the posterior cingulate gyrus is a manifestation of other factors resulting from the decline of nonspontaneous neural activity in ESRD patients, such as the decrease in functional connectivity found in previous study (12). The second factor is the interference of other diseases. Patients with diabetic nephropathy were excluded from this study. Previous studies have confirmed that the posterior cingulate gyrus is an important structure in the central nervous system that can be impaired in diabetes mellitus (19,20). Therefore, it is likely that the functional impairment of the posterior cingulate gyrus in ESRD patients was caused by confounding factors of both ESRD and diabetes in some existing studies. The question of whether there are any changes in the ALFF of the posterior cingulate gyrus in ESRD patients remains to be further clarified.

This study has some limitations. (I) The sample size was small, and the subjects were not followed up, which might lead to statistical errors in some data. (II) The dialysis methods were not classified and evaluated; as a result, the impact of dialysis methods on brain function may be neglected. Therefore, large-sample longitudinal studies are needed to provide more experimental evidence in the future.

In conclusion, using ALFF analysis of fMRI, this study revealed abnormal spontaneous activity in neurons in the cingulate gyrus of ESRD patients. The results suggest that ALFF analysis can provide an objective imaging basis for investigating abnormal spontaneous neural activity in the brain areas of interest in ESRD, which can improve our understanding of the pathological mechanism underlying ESRD-associated cognitive dysfunction. In addition, the new finding that patients with ESRD have abnormal ALFF values in the middle cingulate gyrus is a supplement to previous research findings.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-2138). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was reviewed and approved by The Third Affiliated Hospital of Soochow University ethical review board (research number 2017010), and all patients signed informed consent before enrollment. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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