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# Abnormal degree centrality in neurologically asymptomatic patients with end-stage renal disease: A resting-state fMRI study

Shumei Li [a], Xiaofen Ma [a], Ruiwang Huang [b], Meng Li [a], Junzhang Tian [a], Hua Wen [a], Chulan Lin [a], Tianyue Wang [a], Wenfeng Zhan [a], Jin Fang [a], Guihua Jiang [a,*]

[a] Department of Medical Imaging, Guangdong No. 2 Provincial People's Hospital, No. 466 Xingang Road, Haizhu Distinct, Guangzhou 510317, PR China
[b] Center for the Study of Applied Psychology, Key Laboratory of Mental Health and Cognitive Science of Guangdong Province, School of Psychology, South China Normal University, Guangzhou, PR China

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HIGHLIGHTS

- Abnormal intrinsic dysconnectivity pattern of whole-brain functional networks occurs in end-stage renal disease (ESRD) patients using resting-state fMRI.
- ESRD patients have decreased functional connectivity in the left inferior parietal and left precuneus within the brain network.
- ESRD patients have increased connectivity in depression-related regions including bilateral inferior frontal gyrus and right superior temporal gyrus.

ABSTRACT

*Objective:* End-stage renal disease (ESRD), characterized by multi-organ dysfunction, has been shown to co-occur with abnormal brain function. Previous resting-state fMRI studies suggested that regional brain spontaneous activity and functional connectivity within the default mode network are abnormal in ESRD patients. The current study aimed to depict intrinsic dysconnectivity pattern of whole-brain functional networks in voxel level in neurologically asymptomatic patients with ESRD.
*Methods:* fMRI datasets were acquired from 22 ESRD patients (without clinical neurological disease) and 29 healthy control (HC) subjects. We investigated the degree centrality for a given element in a network to reveal the changes of functional connectivity throughout the huge human functional network. In the brain regions showing a difference between the HC and ESRD groups, we further conducted receptive operation characteristic (ROC) analyses to confirm the accuracy, sensitivity and specificity of our results.
*Results:* ESRD patients showed decreased functional connectivity in the left inferior parietal and left precuneus within the brain network; both regions are important components of the default-mode network (DMN). In contrast, patients showed increased connectivity in depression-related regions including bilateral inferior frontal gyrus and right superior temporal gyrus. These regions showed an acceptable accuracy (0.68–0.75), sensitivity (0.64–0.70) and high specificity (0.82–0.96) in distinguishing between the two groups.
*Conclusions:* Our findings reveal abnormal intrinsic dysconnectivity pattern of whole-brain functional networks in ESRD patients.
*Significance:* Our results could lead to a better understanding of the intrinsic dysconnectivity patterns of default-mode network-related regions in ESRD patients from the whole brain network perspective.


## 1. Introduction

End-stage renal disease (ESRD), an increasingly prevalent problem with multi-organ dysfunctions (Foley and Collins, 2007), has been shown to occur when glomerular filtration rate (GFR) is less

* Corresponding author. Tel./fax: +86 20 8916 8071.
*E-mail address:* GH.jiang2002@163.com (G. Jiang).

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than 15 mL/min/1.73 $m^2$ or when chronic renal failure progresses to the point at which the kidneys are permanently functioning at less than 10% of their capacity (Brouns and De Deyn, 2004; Foley and Collins, 2007). As a result, patients with ESRD usually suffer regular hemodialysis 3 times per week to remove excess urea and other toxic metabolites from the body. Prior studies have reported that ESRD patients with hemodialysis not only have central nervous system abnormalities, such as white matter lesions, cerebral atrophy, and myelinoclasis (De Deyn et al., 1992), but also various neurological problems of the brain, such as wernicke's encephalopathy, uremic encephalopathy, and dialysis encephalopathy (Brouns and De Deyn, 2004). These neurologic complications may be related to ESRD itself or to dialysis. Moreover, ESRD patients are at higher risk for developing cognitive impairments (Hsieh et al., 2009; Lux et al., 2010; Zhang et al., 2013) and ultimately an increased risk of death (Altmann et al., 2007; Madero et al., 2008; Raphael et al., 2012). Therefore, early assessment of brain abnormalities in neurologically asymptomatic patients with ESRD is crucial for the prompt treatment of these patients and the improvement of their prognosis.

The development of neuroimaging techniques has provided a new avenue of research on detecting early brain changes. Diffusion-tensor imaging (DTI), an available non-invasive tool for probing the microanatomical organization of human brain white matter *in vivo*, has been used to investigate the property of white matter in ESRD. Evidence from previous DTI studies showed that not only the local microstructure of white matter integrity (Hsieh et al., 2009; Chou et al., 2013) but also the interregional fiber tractography (Kim et al., 2011) is altered in patients with ESRD compared with normal controls. Voxel-based morphometry (VBM) (Zhang et al., 2013; Qiu et al., 2014) and magnetic resonance spectroscopy(MRS) (Tryc et al., 2011) and arterial spin-labeling MR perfusion imaging (Prohovnik et al., 2007) have also been used in investigating ESRD, and these techniques provide measures of cerebral metabolic, brain structural and functional changes in ESRD patients. Recently, resting-state functional magnetic resonance imaging (R-fMRI) related studies have shown that the brain functional alterations induced by the ESRD patients are not limited to regional changes but also exhibited at a level of functional integration within the default-mode network related regions (Liang et al., 2013; Li et al., 2014; Ni et al., 2014). The default-mode network is a well-established network that includes brain regions such as the posterior cingulated cortex (PCC), precuneus, medial prefrontal cortex (MPFC), inferior parietal cortex, and medial temporal cortex (Buckner et al., 2008; Broyd et al., 2009). Using R-fMRI and the regional homogeneity (ReHo) analysis method, Liang et al. found that ESRD patients showed decreased ReHo values in the default-mode network-related regions including the bilateral frontal, parietal and temporal lobes (Liang et al., 2013). In addition, Li et al. also found that ESRD patients showed significantly abnormal ReHo values in the left medial prefrontal gyrus, bilateral superior temporal gyrus, and right medial temporal gyrus (Li et al., 2014). Using R-fMRI and Independent Component Analysis (ICA), Ni et al. investigated the functional connectivity of the DMN network in ESRD and found that ESRD showed significantly less functional connectivity in the posterior cingulate cortex, precuneus, and medial prefrontal cortex (MPFC) (Ni et al., 2014). Moreover, our study related to the aberrant functional connectome in ESRD patients indicated decreased connectivity strength within the default-mode network (Ma et al., 2015). Regional analysis in our study showed that the disease disproportionately weakened nodal efficiency of the default mode components and tended to preferentially affect central or hub-like regions (Ma et al., 2015). Based on these findings from previous studies, we hypothesized that these observed changes in the default-mode network-related regions may be a disease biomarker for ESRD patients.

Recently, characterization of functional networks of the human brain becomes more popular in various diseases (Wang et al., 2010; Zhang et al., 2011). Among the graph-based measures, degree centrality is recently gaining great attention because it is the most reliable metric among several nodal network metrics (Wang et al., 2011) and measures the centrality or importance of individual elements in the brain (e.g., brain regions) by capturing their relationship with the entire brain network in the voxel level (Zuo et al., 2012). Many previous studies using the metric "degree centrality" in graph theory have indicated that the default-mode network-related regions are the main hubs of our human brain (Buckner et al., 2009; Li et al., 2013; van den Heuvel and Sporns, 2013; Wang et al., 2013). Thus, we speculate that the metric "degree centrality" may be related to ESRD pathology, and we used it to explore whether the default-mode network-related regions exhibit intrinsic disconnectivity patterns in this study.

Currently, the calculation of degree centrality can reach the voxel-based level. It counts the number of direct connections for a given voxel in a network and reflects its functional connectivity within the brain network. Voxel-wise centrality maps provide novel insights into the patterns and complexity of functional connectivity throughout the huge human functional network and have been widely used in brain network studies (Buckner et al., 2009; Tomasi and Volkow, 2010; Di Martino et al., 2013). In our above published study (Ma et al., 2015), the degree centrality measure was not calculated. In addition, whole-brain functional networks in our above published study were obtained by calculating the interregional correlation of low-frequency fluctuations in spontaneous brain activity among 1024 parcels that cover the entire cerebrum. Thus, all the analysis level in our recently published paper is regional. However, the analysis level in this study using degree centrality is based on voxel. Therefore, focusing on network architecture, the current study aimed to depict intrinsic dysconnectivity pattern of whole-brain functional networks in voxel level in neurologically asymptomatic patients with ESRD. In addition, we also correlated the degree centrality changes to clinical biomarkers and dialysis of duration of the ESRD patients. In order to identify the optimal cut-off degree values and the accuracy/sensitivity/specificity characteristics of each region showing difference between ESRD and HC groups, ROC curve analysis was used in this study.

## 2. Materials and methods

### 2.1. Participants

This study was approved by the Ethics Committee of the Guangdong No. 2 Provincial People's Hospital. Each subject completed informed written consent prior to the MR scanning. We enrolled 25 ESRD patients in this study from August 2011 to July 2012. All the patients were recruited from the renal transplantation department at Guangdong No. 2 Provincial People's Hospital, Guangzhou, China. ESRD patients were excluded if they had a history of diabetes, alcoholism, drug abuse, psychiatric disorders or major neurologic disorders (e.g., severe head injury, stroke, epilepsy or visible lesions). Conventional MR images were checked by an experienced radiologist who was blinded to whether the images were from the patient or control group. Three patients were excluded due to abnormal hyper-intensities in their T2-FLAIR MR images. Therefore, 22 right-handed neurologically asymptomatic ESRD patients (16 males, 6 females; mean age 38 ± 10.5 years, range 18–61 years) included in this study. The subjects here are the same as the subjects in our previous study (Ma et al., 2015) and partly included the subjects in our another previous study (Li et al., 2014). All ESRD patients completed biochemical tests, including urea level, hemoglobin level, serum creatinine, serum

kalium, and serum calcium within 24 h before the MR imaging. In this study, each ESRD patient underwent mini-mental state examination (MMSE) (Schultz-Larsen et al., 2007) and scored $\geqslant$28, which indicated normal global neurocognition.

In addition, we also recruited twenty-nine healthy controls matched on age, handedness and gender (HC) (all right handed; 19 males, 10 females; mean age 42.1 ± 8.4 years, range 28–61 years) from the local community by means of advertisements. None of the control subjects had diseases of the renal system or other organ systems, or any history of psychiatric or neurological diseases.

### 2.2. Data acquisition

All MRI datasets were scanned using a 1.5-T MR scanner (Achieva Nova-Dual; Philips, Best, the Netherlands) at the Department of Medical Imaging, Guangdong No. 2 Provincial People's Hospital. The MRI datasets include T1-weighted images, T2-FLAIR images and R-fMRI dataset. The conventional T2-FLAIR images were gained to detect brain lesions. The R-fMRI dataset was acquired using a gradient-echo echo planar imaging (EPI) sequence. During the R-fMRI data acquisition, the subjects were asked to lie quietly with their eyes closed and to avoid eye movement (Pierrot-Deseilligny et al., 2004), thinking of anything specific, or falling asleep while in the scanner. The R-fMRI acquisition parameters were as follows: 33 axial slices; repetition time (TR)/echo time (TE) = 3000 ms/50 ms, matrix = 128 × 128, field of view (FOV) = 230 × 230 $mm^2$, slice thickness = 4.5 mm without gap; flip angle = 90°, interleaved scanning, 22 axial slices covering the whole brain. The R-fMRI data were scanned approximately along the AC-PC line, and 160 volumes were acquired in approximately 8 min. The parameters of the T1-weighted images are as follows: 160 axial slices; TR = 25 ms; TE = 4.1 ms; FA = 30°; slice thickness = 1.0 mm; no gap; matrix = 256 × 256; and FOV = 230 × 230 $mm^2$.

### 2.3. Data processing

All fMRI data preprocessing was performed using DPARSF Advanced Edition V2.2 (Harley and Loftus, 2000; Gispert et al., 2003; Chao-Gan and Yu-Feng, 2010). Before the preprocessing, the first 10 volumes for each subject were discarded to keep the stability of the remaining MRI signal, and to allow subjects' adaptation to the scanning noise. Then the remaining 150 fMRI images were performed with slice time correction for intra-volume acquisition time delay and realignment for inter-volume geometrical displacements owing to head movement. Subjects with head motion lower than 1 mm of maximal translation or 1° of maximal rotation were included for further analysis. All realigned images were normalized to the standard Montreal Neurological Institute (MNI) template by applying the EPI template at a 3 × 3 × 3 $mm^3$ resolution. The resulting normalized functional images were subjected to spatial smoothing [6-mm full width at half maximum (FWHM) Gaussian kernel)] and removal of linear trends. Lastly, fMRI dataset was filtered using typical temporal bandpass (0.01–0.08 Hz) to reduce the low-frequency drift and high-frequency respiratory and cardiac noise.

### 2.4. Degree centrality calculation

According to previous studies, degree centrality represents the number of direct connections for a given voxel in the voxel-based graphs. It has been widely used to represent the node characteristic of large-scale brain intrinsic connectivity networks. Specifically, the preprocessed fMRI data were used to compute the voxel-based whole-brain correlation analysis. The time course of each voxel in each brain was correlated to every other voxel time course in the gray matter mask. As a result, we can acquire an $n \times n$ matrix of pearson correlation coefficients between any pair of voxels, where $n$ is the voxel number of the whole-brain mask. To obtain each subject's graph, a binary undirected adjacency matrix was formed by thresholding each correlation at $r > 0.25$. The threshold is the default setting in the calculation of the degree centrality map and was chosen to eliminate counting voxels that had low temporal correlation attributable to signal noise. Buckner et al. indicated that different threshold selections did not qualitatively change the results (Buckner et al., 2009). Only positive pearson correlation coefficients were considered in the study for the uncertain interpretation of negative correlations. Based on the voxel-based graph, degree centrality was calculated by counting the number of functional connections (significant positive correlations) at the individual level (Buckner et al., 2009; Zuo et al., 2012). In order to confirm if the degree measure can distinguish between ESRD group and NC group, receiver operating characteristic (ROC) curve analysis was used to summarize the accuracy/sensitivity/specificity characteristics of significant different regions between two groups, and the optimal cut-off degree values was determined.

### 2.5. Statistical analysis

The differences in age, education, and dialysis duration between the ESRD and control groups were assessed with a two-sample two-tailed t-tests using SPSS statistics software (version 13.0). A two-tailed Pearson chi-square test was performed to determine the difference in sex between the two groups. For the degree centrality difference between the two groups, a second level two-sample $t$-test was performed on the individual degree maps in a voxel-by-voxel manner. All results were presented at the statistical threshold of $P < 0.05$ using AlphaSim correction, as determined by monte carlo simulations (Ledberg et al., 1998). Moreover, a partial correlation analysis was adopted to assess the relationship between the mean degree values in all the regions showing significant differences and clinical variables (dialysis duration, hemoglobin level, creatinine level, calcium level, kalium level, and urea level) in the ESRD group after controlling for age, gender, and summary measures of head motion.

## 3. Results

### 3.1. Demographics and clinical characteristics

The demographics and clinical data of the participants in this study are shown in Table 1. The HC and ESRD group showed no significant between-group differences in gender ($P = 0.583$), age ($P = 0.127$), and education ($P = 0.27$). The average duration of hemodialysis for the patients was 7.4 ± 2.2 months. The mean calcium, kalium, hemoglobin, creatinine, and urea levels for the patients were 2.3 ± 0.2 mmol/L, 4.0 ± 0.6 mmol/L, 93.3 ± 22.4 g/L, 965.2 ± 212.620 μmol/L, and 22.3 ± 6.4 mmol/L, respectively.

### 3.2. Alterations of region brain intrinsic dysconnectivity pattern in ESRD patients

Results of the two-sample $t$-test showed significant degree centrality alterations for several related brain regions in ESRD patients compared to the HC groups ($P < 0.05$, Alphasim corrected) (Table 2). We found that the ESRD patients showed a decreased degree centrality value, with a peak difference in left inferior parietal (Parietal_Inf_L) and left precuneus (Precuneus_L) (Fig. 1), while the ESRD patients showed increased degree centrality in

**Table 1**
Demographics and clinical characteristics of all participants.

| | ESRD ($S$ = 22) | HC ($S$ = 29) | $P$-value |
|---|---|---|---|
| Gender (M/F) | 16/6 | 19/10 | 0.583[a] |
| Age (yrs) | 38 ± 10.5 (18–61) | 42.1 ± 8.4 (28–61) | 0.127[b] |
| Education (yrs) | 11.4 ± 3.7 | 12.5 ± 3.4 | 0.27[b] |
| Dialysis duration (mths) | 7.4 ± 2.2 (2–10) | | |
| Serum calcium (mmol/L) | 2.3 ± 0.2 (1.6–2.5) | | |
| Serum kalium (mmol/L) | 4.0 ± 0.6 (2.8–5.6) | | |
| Hemoglobin (g/L) | 93.3 ± 22.4 (51–147) | | |
| Serum creatinine (μmol/L) | 965.2 ± 212.6 (670–1359) | | |
| Blood urea nitrogenurea (mmol/L) | 22.3 ± 6.4 (12.2–36.4) | | |

Values are represented as mean ± SD (min–max). ESRD, end-stage renal disease; HC, healthy control. $S$: Subjects.
[a] The $P$-value was obtained by chi-square test.
[b] The $P$-value was obtained by two-sided two-sample $t$ test.

**Table 2**
Brain regions showing differences in the degree between controls and patients with ESRD.

| Brain regions | MNI coordinates | | | Voxels | $T$ value |
|---|---|---|---|---|---|
| | $x$ | $y$ | $z$ | | |
| Temporal_Sup_R _R | 34 | 8 | −30 | 83 | 3.81 |
| Frontal_Inf_R | 39 | 23 | −5 | 170 | 3.43 |
| Frontal_Inf_L | −35 | 23 | −7 | 130 | 3.40 |
| Parietal_Inf_L | −39 | −66 | 33 | 95 | −3.04 |
| Precuneus_L | 0 | −66 | 36 | 139 | −3.36 |

A negative $T$ value represents decreased degree in ESRD group. L, R: Left and Right.

bilateral inferior frontal gyrus (Frontal_Inf_L, Frontal_Inf_R) and right superior temporal gyrus (Temporal_Sup_R) (Fig. 2).

### 3.3. Relationship between imaging changes and clinical variables

No significant correlations were found for the mean degree values in all the regions showing significant differences with any of the clinical variables (dialysis duration, hemoglobin level, creatinine level, calcium level, kalium level, and urea level) in the ESRD group after controlling for age, gender, and summary measures of head motion.

### 3.4. Accuracy, sensitivity and specificity measures of the significant regions

As shown in Table 3, among the 5 regions showing significant differences between the two groups, all of them showed an acceptable accuracy (0.68–0.75), sensitivity (0.64–0.70) and high specificity (0.82–0.96) at the optimal cutoff point in distinguishing between the two groups. The right superior temporal gyrus showed relatively higher accuracy, sensitivity and specificity (0.71/0.70/0.96).

## 4. Discussion

The study examined for the first time the characteristic of the intrinsic dysconnectivity pattern of whole-brain functional networks in patients with ESRD by combining R-fMRI and degree approaches from the voxel-level. The results revealed that ESRD patients had a decreased functional connectivity in the left inferior parietal and left precuneus within the brain network; both regions are important components of the default-mode network (DMN) (Greicius et al., 2003; Long et al., 2008). In addition, we found an increased connectivity in bilateral inferior frontal gyrus and right superior temporal gyrus. The ROC analysis demonstrated the degree values in these regions have acceptable accuracy and high specificity in distinguishing the two groups. Thus it seems promising that degree centrality measures in these regions could be the neuroimaging biomarkers in some extent for characterizing ESRD patients.

An important finding in the current study is that ESRD patients showed decreased degree values in the left inferior parietal and left precuneus, which reflects that the number of direct connections of the two brain regions decreased within the brain network. The results in our study can be supported in some extent by previous studies related to ESRD patients focused on neuroimaging techniques, such as diffusion tensor imaging (Hsieh et al., 2009), fMRI (Liang et al., 2013; Li et al., 2014) and MR spectroscopy (Tryc et al., 2011). Many previous studies have shown that the parietal or the frontal lobes have structural, functional or metabolic abnormalities in neurologically asymptomatic patients with ESRD (Fazekas et al., 1996; Harciarek et al., 2012). Ni et al. demonstrated that ESRD patients without nephrotic encephalopathy showed decreased intrinsic functional connectivity in the precuneus and posterior cingulate cortex (PCC) and medial prefrontal cortex (MPFC) (Ni et al., 2014). Parietal cortex lesions are considered to be related to distinct attention functions such as attention shift, working memory, and visuo-spatial attention (Lynch et al., 1977; Mesulam, 1981; Posner et al., 1984). The precuneus dysfunction is considered to be engaged in decreased self-consciousness, visuo-spatial attention, and episodic and source memory (Lundstrom et al., 2003, 2005; Wenderoth et al., 2005). These abnormal cognitive functions are common in the chronic kidney disease long before any obvious neurological symptoms can be observed (Tryc et al., 2011). Although the results in our study and the study by Ni et al. (2014) both demonstrate decreased functional connectivity in the ESRD patients mainly located in the DMN network regions, the concrete DMN network regions are not entirely the same. In our study, decreased intrinsic functional connectivity in the precuneus and posterior cingulate cortex (PCC) and medial prefrontal cortex (MPFC) was not detected. The reasons may be due to the different analysis methods and the ESRD patients: the functional connectivity in the study by Ni (Ni et al., 2014) using the correlation coefficient elucidates synchronous ultra-slow frequency oscillation between brain areas from an integrated perspective. However, the degree centrality in our study is not only simple correlation coefficient between regions but quantitative analysis of complex brain networks, based largely on graph theory. In addition, the mean dialysis duration time for ESRD patients in our study is different with the study by Ni (Ni et al., 2014).

In addition, the decreased regions are both located in the left brain. The left-side of the brain is considered to be adept at tasks that involve logic, language, and analytical thinking. Our results here may indicate that the degree values in the brain regions

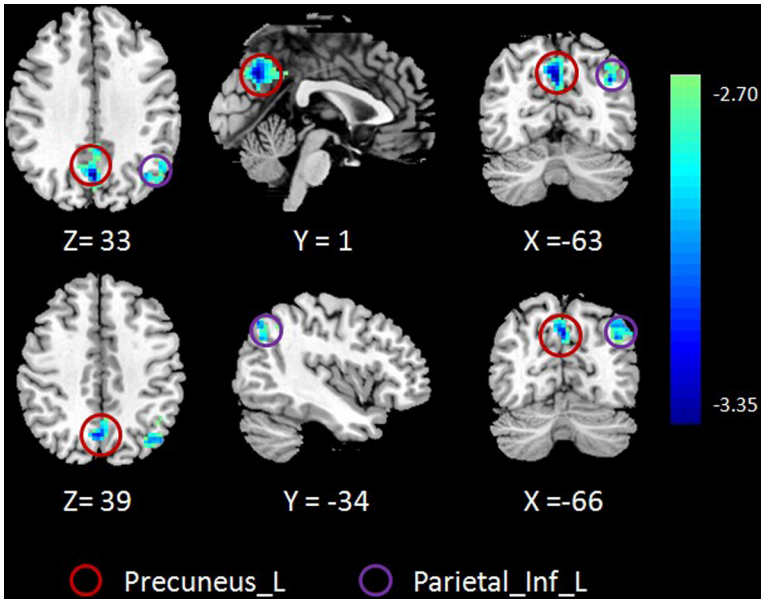


**Fig. 1.** Brain regions showing decreased degree differences in ESRD group compared to HC group. The regions showing decreased degree differences in axial ($Z = 33$, $Z = 39$ mm), coronal ($X = -63$, $X = -66$) and sagittal map ($Y = 1$, $Y = -34$).

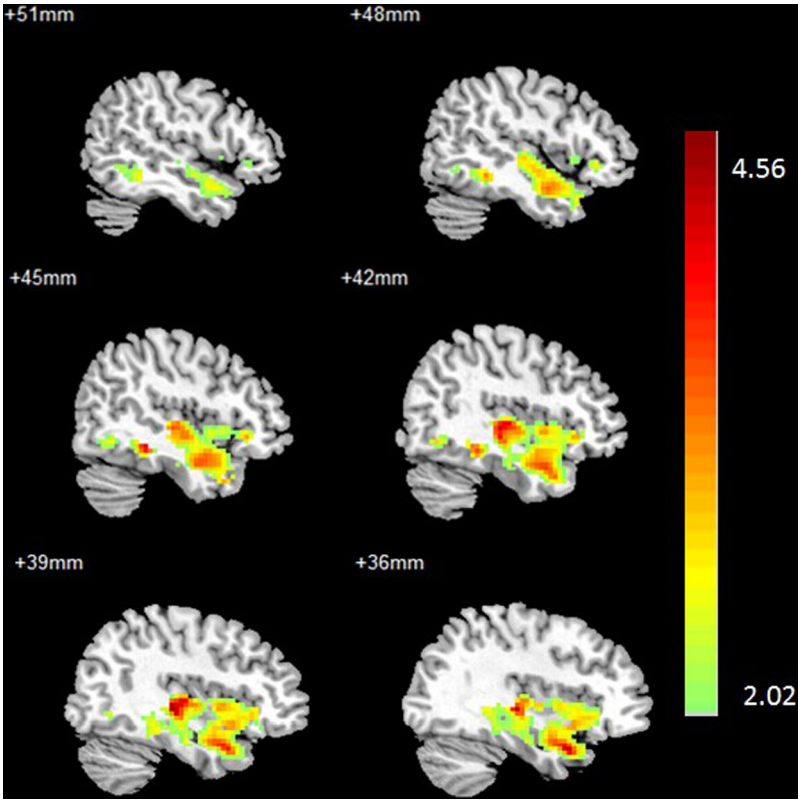


**Fig. 2.** Brain regions showing increased degree differences in ESRD group compared to HC group. The regions showing increased degree differences in axial map from $Z = +36$ to $Z = +51$ mm (every 3 mm) at the given threshold.

related to memory, language, and visuospatial processing have decreased. However, the global cognitive function is normal on the MMSE tests. Thus, our findings of decreased degree values in both the regions in ESRD patients provide further evidence from the functional network integrity view that the function of cognitive related regions is weakening. In this study, all the ESRD patients have clinically normal global cognitive function, which does not mean that these patients are totally free of cognitive deficits. Previous study showed that hemodialysis patients have a high probability of mild cognitive impairment despite normal global cognitive function (Post et al., 2010). In addition, the regions in default-mode networks of the mild cognitive impairment patients tend to show structural and functional abnormalities.

**Table 3**
The characteristics of the ROC curve in the significant brain regions.

| Brain regions | MNI coordinates | | | Accuracy | Sensitivity | Specificity | Cut-off |
|---|---|---|---|---|---|---|---|
| | *x* | *y* | *z* | | | | |
| Temporal_Sup_R | 34 | 8 | −30 | 0.71 | 0.70 | 0.96 | 485 |
| Frontal_Inf_R | 39 | 23 | −5 | 0.69 | 0.68 | 0.83 | 99 |
| Frontal_Inf_L | −35 | 23 | −7 | 0.68 | 0.69 | 0.85 | 233 |
| Parietal_Inf_L | −39 | −66 | 33 | 0.68 | 0.66 | 0.82 | 397 |
| Precuneus_L | 0 | −66 | 36 | 0.75 | 0.64 | 0.82 | 616 |

ROC: receiver operating characteristic.

We also found increased degree values in bilateral inferior frontal gyrus and right superior temporal gyrus in the ESRD patients. The regions we detected in the present study are supported by many previous brain imaging studies in pre-dialysis patients or the ESRD patients. Using R-fMRI and ReHo method, Li et al. found that compared to healthy controls, ReHo values were increased in the bilateral superior temporal gyrus and left medial frontal gyrus in ERSD patients (Li et al., 2014). Using the Tc-99m ethylcysteinate dimer brain single photon emission tomography, Song et al. found that chronic kidney disease (without beginning dialysis) patients have significant hypoperfusion in the right superior and middle temporal gyrus and inferior frontal gyrus (Song et al., 2009). Additionally, Qiu et al. reported that ESRD patients have significantly enhanced functional connectivity between the medial prefrontal cortex and the left temporal cortex (Qiu et al., 2014). Previous studies have reported that the superior temporal gyrus and the inferior frontal gyrus were related to depression (Kim et al., 2008; Grieve et al., 2013). In addition, depression is the most common psychological disorder in ESRD patients (Kimmel et al., 2007). Thus, the increased degree values in bilateral inferior frontal gyrus and right superior temporal gyrus may be related to the depression complications in the ESRD patients.

In this study, we studied ESRD patients and observed that in spite of these patients exhibiting clinically normal global cognitive function, they have abnormal intrinsic disconnectivity pattern of whole-brain functional networks at the voxel level compared with the healthy controls. Our results suggest that such abnormal intrinsic connectivity may be specific to ESRD patients, which is different from other patients who already have cognitive deficits. There are several possible reasons why this abnormal intrinsic connectivity may be specific to ESRD patients. First, all the ESRD patients have clinically normal global cognitive function. Thus, this abnormal intrinsic connectivity is not caused by the obvious cognitive defects. Second, the white matter abnormalities in patients with ESRD who showed no specific lesions on conventional brain MRI are found mainly in the parietal and frontal lobes using the DTI technique (Hsieh et al., 2009; Kim et al., 2011; Zhang et al., 2015). In addition, these white matter defects are known to be related to many different kinds of cognitions, including attention, memory or visuospatial function. Third, all the ESRD patients in this study underwent hematodialysis. There is increasing evidence suggesting that a long-term hemodialysis can result in significantly cerebral abnormalities of oxygenation (Prohovnik et al., 2007) and cerebral blood flow (Holzer et al., 1981; Stefanidis et al., 2005; Regolisti et al., 2013) in ESRD patients, which can remarkably affect the cerebral circulation and brain function (Gottlieb et al., 1987; Postiglione et al., 1991; Hata et al., 1994). Fourth, many previous studies have also shown that the clinical biochemical indexes (serum urea, hemoglobin, blood urea nitrogen urea, etc.), in the ESRD patients are significantly correlated to the imaging findings (Liang et al., 2013; Zheng et al., 2014; Ma et al., 2015). Therefore, we speculate that such abnormal intrinsic connectivity in our study may reflect the specificity of the neurologically asymptomatic patients with ESRD, which is helpful for the early diagnosis and treatment of the possible neurologic complications in ESRD patients.

However, in the current study, we did not find significant correlations for the mean degree values in all the regions showing significant differences with any of the clinical variables. This result is consistent with two previous studies (Li et al., 2014; Qiu et al., 2014). The potential reasons are as follows. First, the relatively small sample size may lead to insufficient statistical power. Second, 20–25% of the ESRD patients are depressed and the increased degree values in the depression-related regions were found in the study. Therefore, the abnormal brain activity observed in this study may result from this complication (depression) and not from the ESRD itself. Further study should add the depression evaluation to exclude this confound. Although no significant correlations were found between the regions showing significant differences with any of the clinical variables, the ROC analysis demonstrated the degree values in these regions have acceptable accuracy and high specificity in distinguishing the two groups. According to the previous study (Dai et al., 2012), the cause of the specificity much more than the mean sensitivity might be the small-size sample and the imbalanced IBS and healthy control datasets. To optimize the present findings and make the method as a practical clinical tool, larger and balanced datasets would be required to determine sensitivity/specificity using the cut-off degree values reported here.

Because the causes of neurologic complications associated with ESRD are complex, the exact mechanisms underlying these changes are not known. Thus future studies with more rigorous experimental design are needed. Several limitations need to be considered in the further study. Firstly, degree centrality can only find brain regions showing abnormal functional connectivities. Thus it will be interesting for future studies to trace the brain sites to which the abnormal functional connectivities were linked. Secondly, the sample size was relatively small in the present study. Additional studies in a large sample of ESRD patients are needed to improve the power of the statistical analysis of our findings and to provide comprehensive interpretation of the results. Thirdly, the abnormal functional connectivies in the present study may be related to ESRD itself or to hemodialysis dialysis. Further study is needed to collect data from patients with chronic kidney disease (stage 4–5) without hemodialysis to be able to tell whether and how hemodialysis itself can affect the brain activity. Finally, we only tested the global cognitive function of the ESRD patients using the MMSE test ($\geqslant$28). It might be better to use a battery of neuropsychological tests (e.g., digit-symbol test, line-tracing test, serial-dotting test) and the Self-Rating Depression Scale (SDS) to comprehensively understand the specific cognitive functions and emotional status in ESRD patients.

## 5. Conclusion

In the current study, we applied the resting-state fMRI technique and degree approach to examine the intrinsic

dysconnectivity pattern of whole-brain functional networks in neurologically asymptomatic patients with ESRD. Our results found decreased functional connectivities in DMN-related regions including the left inferior parietal and left precuneus. Moreover, we found an increased connectivity in depression/mood-related regions in bilateral inferior frontal gyrus and right superior temporal gyrus. Our results suggest a new approach to explore the potential cognitive deficits or emotional problems of neurologically asymptomatic ESRD patients. The resting-state fMRI study suggests that the abnormal intrinsic dysconnectivity pattern of whole-brain functional networks may serve as early biomarkers for further obvious cognitive deficits and emotional problems in ESRD patients.

## Conflict of interest

The authors have no relevant conflicts of interest to disclose.

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