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Original Article

Disruptions of brain structural network in end-stage renal disease patients with long-term hemodialysis and normal-appearing brain tissues

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ABSTRACT

Objective. – End-stage renal disease (ESRD) patients on hemodialysis were demonstrated to exhibit silent and invisible white-matter alterations which would likely lead to disruptions of brain structural networks. Therefore, the purpose of this study was to investigate the disruptions of brain structural network in ESRD patients.
Materials and methods. – Thiry-three ESRD patients with normal-appearing brain tissues and 29 age- and gender-matched healthy controls were enrolled in this study and underwent both cognitive ability screening instrument (CASI) assessment and diffusion tensor imaging (DTI) acquisition. Brain structural connectivity network was constructed using probabilistic tractography with automatic anatomical labeling template. Graph-theory analysis was performed to detect the alterations of node-strength, node-degree, node-local efficiency, and node-clustering coefficient in ESRD patients. Correlational analysis was performed to understand the relationship between network measures, CASI score, and dialysis duration.
Results. – Structural connectivity, node-strength, node-degree, and node-local efficiency were significantly decreased, whereas node-clustering coefficient was significantly increased in ESRD patients as compared with healthy controls. The disrupted local structural networks were generally associated with common neurological complications of ESRD patients, but the correlational analysis did not reveal significant correlation between network measures, CASI score, and dialysis duration.
Conclusion. – Graph-theory analysis was helpful to investigate disruptions of brain structural network in ESRD patients with normal-appearing brain tissues.

Introduction

End-stage renal disease (ESRD) is defined as the final stage of chronic kidney disease with a permanent loss of > 90% of normal renal function and was usually characterized as an estimated glomerular filtration rate < 15 mL/min/1.73 m^2. The accumulated urea and toxic metabolites in the blood and tissues may lead to multiple organ dysfunctions in ESRD patients, and patients with lower renal functions were demonstrated to have more white-matter lesions or small-vessel diseases [1,2]. In modern societies, there was increasing number of patients undergoing hemodialysis in recent years [3,4]. However, ESRD patients on dialysis may develop uremic neuropathies such as osmotic demyelination syndrome, dialysis disequilibrium syndrome, and cerebrovascular diseases [5–7]. Although the continued dialysis helped resolve cerebral edema [8,9], the uremic neuropathies may have already caused permanent, invisible, and irreversible damage on the brain tissues in the patients.

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Diffusion tensor imaging (DTI) was demonstrated capable of detecting white-matter alterations caused by various brain diseases [10–12]. Recent studies further performed DTI to detect subtle white-matter alterations in ESRD patients without visible white-matter lesions [13,14], and showed that fractional anisotropy (FA) was significantly decreased and diffusivity was significantly increased in multiple white-matter regions. As subtle white-matter alterations might lead to disruptions of structural network and cognitive decline, a previous study performed diffusion tensor tractography to evaluate the abnormalities of fiber tracts in ESRD patients with visible white-matter lesions [15]. However, it remains unclear how the global structural connectivity network was altered in ESRD patients with normal-appearing brain tissues. Recently, some studies performed diffusion tractography to obtain structural connectivity between cortical regions and analyzed the network using graph-theory analysis [16,17]. Such an approach has been widely utilized to reveal the network alterations in patients with neurological or psychological disorders [18–21], but has not been utilized in ESRD patients.

Although previous studies performed functional magnetic resonance imaging (MRI) to understand the changes of functional connectivity between brain regions [22,23], the changes of structural connectivity network and their associations with cognitive function and dialysis duration have not been well understood in ESRD patients. Therefore, the purpose of this study was to investigate the alterations of brain structural network in ESRD patients with normal-appearing brain tissues using graph-theory analysis.

Materials and methods

Subjects

This study was approved by local Institutional Review Board. Thirty-three ESRD patients with normal-appearing brain tissues and 29 age- and gender-matched healthy controls with no history of neurological disorders were successfully recruited, and informed consent was obtained from each participant. Exclusion criteria were diagnosis of diabetes mellitus, major neurological and psychiatric disorders, substance abuse, pregnancy, metal implant, and claustrophobia. Prior to MRI acquisition, the cognitive functions of each participant were evaluated using the cognitive abilities screening instrument (CASI) which takes about 30 minutes to assess overall cognitive functions [24].

MRI acquisition

All brain magnetic resonance imaging data were acquired using a 1.5-T MR scanner (Signa Excite, GE Medical Systems). After tri-planar scans, 20 axial T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images were sequentially obtained from each participant, and whole brain DTI data were acquired using a single-shot, twice-refocused, spin-echo, echo-planar diffusion-weighted pulse sequence with an 8-channel phased array neurovascular coil. Other imaging parameters for DTI acquisition were: TR/TE = 8000/82.8 milliseconds, matrix size = 128×128, $b = 1000\ s/mm^2$, number of slice = 30, number of diffusion direction = 33, number of $b_0 = 1$, field of view = 240×240 mm, number of excitation = 1, acceleration factor = 2.0, and slice thickness = 4.4 mm. The scan time was 4 minutes and 48 seconds.

Structural connectivity network

All brain DTI data were transferred to a standalone workstation and processed using FSL (FMRIB Software Library, Oxford) and MATLAB (Mathworks, Natick, MA, USA). First, the eddy current distortions were corrected using affine registration with the b0 image as the reference. Second, Brain Extraction Tool was applied to DTI datasets to remove non-brain background signals. Third, the international consortium of brain mapping-FA template images, which share the same coordinate with 3D T1-weighted template image defining the 116 automatic anatomical labeling (AAL) brain regions, were spatially transformed to match the individual FA images using linear affine and non-linear demon registrations [25]. In this step, the cerebral cortices of individual brain were divided into 116 AAL brain regions. Subsequently, a Bayesian estimation of crossing fibers (BEDPOSTX, FMRIB, Oxford, UK) was performed to estimate multiple fiber orientations of each voxel in the whole brain, and then probabilistic tractography (PROBTRACKX, FMRIB, Oxford, UK) was performed with 5000 seeding points per voxel to estimate structural connectivity between two AAL regions of individual brains. Because the total number of fiber tracts was related to the size of seeding region, the structural connectivity between two AAL regions was defined as the number of fiber tracts normalized by a factor of $5000 \times$ (total number of seeding voxels). Finally, a 116×116 connectivity matrix that contains information on the normalized number of fiber tracts between the 116 AAL regions was obtained for statistics. In addition, four network measures including node-strength, node-degree, node-local efficiency, and node-clustering coefficient were calculated using the Brain Connectivity Toolbox (https://www.sites.google.com/site/bctnet/). Among them, node-strength and node-degree represent weighted and binarized density of a network that help briefly understand the integrity of a network; whereas the node-local efficiency and node-clustering coefficient indicate the inverse of shortest path length and the degree of segregation of a local network respectively that provide in-depth insight into how the network was altered. The results of network comparisons were displayed using BrainNet Viewer (https://www.nitrc.org/projects/bnv/) for better visualization.

Statistical analysis

In order to minimize the influence of noise, this study performed statistical analysis only on the structural connectivity with mean normalized tract number > 0.1 and removed those with zero mean tract number from statistics. In this study, a two-sample *t*-test was performed to show the difference of clinical data between the two groups. Pearson's correlational analysis was performed to understand the relationship between age, gender, CASI scores, and dialysis duration. For graph-theory analysis, the structural connectivity, node-strength, node-degree, node-local efficiency, and node-clustering coefficient between the two groups were statistically compared using a two-sample *t*-test with false discovery rate correction (Benjamini-Hochberg procedure) [26] in order to reduce false positive (type I error) in multiple comparisons. In regions with statistical significance, the post-hoc partial correlation coefficient was performed to show the associations between the network measures and dialysis duration in ESRD patients by nulling age and gender effects. The statistical results were reported if $P < 0.05$.

Results

Demographic characteristics of participants

In this study, sex and age were not significantly different between ESRD patients and healthy controls. The two-sample *t*-test showed that the CASI scores were significantly lower in the ESRD patients than control subjects. However, the correlational analysis did not show any significant correlation between the CASI scores,

Table 1
Demographic characteristics of ESRD patients and healthy controls enrolled in this study.

	ESRD patients	Healthy controls
Gender (M/F)	16/17	14/15
Age (y/o)	39.7 ± 7.8	38.1 ± 7.1
Dialysis Duration (y)	6.6 ± 4.7	N/A
CASI score	94.6 ± 6.2*	97.2 ± 2.9*

* Statistically significant difference ($P < 0.05$) between the two groups.

age, sex, or dialysis duration in both ESRD patients and normal controls. The demographic characteristics of ESRD patients and healthy controls are listed in Table 1.

Structural network analysis

The comparison of structural connectivity showed that ESRD patients exhibited significantly less fiber connections between brain regions mainly located in the frontal and temporal lobes, as shown in Fig. 1. The AAL regions with significant difference of structural connectivity are listed in Table 2. However, the partial correlation analysis did not reveal significant correlations between structural connectivity, CASI score, and dialysis duration in ESRD patients.

In node strength, the comparisons demonstrated significantly decreased nod-strength in both supra- and infra-tentorial regions in ESRD patients, as shown in Fig. 2. Regions with statistical significance were mainly located in bilateral insula, bilateral cingulum, bilateral hippocampus, bilateral caudate, bilateral putamen, and cerebellum in ESRD patients, as listed in Table 3. However, no significant correlation was noted between node-strength, CASI score, and dialysis duration in ESRD patients.

In node degree, the comparisons also demonstrated significant decrease of node-degree in both supra- and infra-tentorial brain regions of ESRD patients, as shown in Fig. 3. The regions with statistical significance were mainly located in bilateral cingulum, bilateral caudate, bilateral putamen, and cerebellum, as listed in Table 4. No significant correlation was noted between node-degree, CASI score, and dialysis duration in ESRD patients.

In node-local efficiency, significant decrease of local efficiency was found in vermis in ESRD patients, but no significant correlation was noted between the local efficiency, CASI score, and dialysis duration. In node-clustering coefficient, the comparison demonstrated significant increased clustering coefficient the right thalamus, but no significant correlation was noted between clustering coefficient, CASI score, and dialysis duration in ESRD patients. The AAL regions with significant difference of local efficiency and clustering coefficient are listed in Table 5.

Discussion

To the best of our knowledge, this is the first study using graph-theory analysis to investigate the disruptions of brain structural network in ESRD patients who exhibited normal-appearing brain tissues and cognitive decline after long-term hemodialysis. The graph-theory analysis demonstrated significant disruptions of brain structural network, including decrease in structural connectivity, node-strength, node-degree, and node-local efficiency, and increase in node-clustering coefficient in various brain regions of ESRD patients.

The statistical comparisons demonstrated significantly decreased brain structural connectivity in both supra- and infra-tentorial brain areas especially in frontal area. In graph-theory, the structural connectivity of two brain regions indicates the number of fiber tracts connecting to each other, so the decreased structural connectivity denotes impaired connection between the two brain regions. The results suggested that ESRD patients with long-term hemodialysis exhibited decreased structural connections between cortical regions.

In network measures, the decreased node-strength was found in both supra- and infra-tentorial regions of ESRD patients. The supra-tentorial regions included superior frontal gyrus, cingulum, caudate, insula, hippocampus, and thalamus, which were known to play roles in cognitive functions, such as decision-making, memory, emotion, and etc. Other regions, such as putamen, thalamus, cerebellum, and vermis, were associated with functions of motor control, posture, and locomotion. In graph-theory, the node-strength represents the weighted sum of connections that link to the node, so the decreased node strength of a region may imply fewer fiber tracts coming from other brain regions to this region. The findings suggested that the overall fiber connections towards those brain regions were impaired to cause cognitive decline and motion problem in ESRD patients.

Second, the significantly decreased node-degree was also found in both supra- and infra-tentorial regions of ESRD patients, including cingulum, precuneus, caudate nucleus, putamen, and cerebellum, which are associated with cognitive and motor functions as mentioned above. In graph-theory, the node-degree indicates the number of connections that link to the node, so the decreased node-degree denoted that fewer connections linking to those regions might alter associated brain functions in ESRD patients. The results may indicate that the functions of cognition, memory, and locomotion were altered in the ESRD patients after long-term hemodialysis.

Third, the node-local efficiency was significantly decreased in vermis only which was related to the functions of posture and locomotion. In graph-theory, the node-local efficiency is defined as the average inverse of shortest path length in a regional network, so the decreased local efficiency might suggest that local brain networks of those regions were deteriorated in communication. The findings speculated that the information transferring from neighboring regions to the vermis were less efficient and the motor functions were altered in ESRD patients.

Fourth, the node-clustering coefficient was significantly increased in the thalamus, which was associated with the functions motor, sensory, consciousness, sleep, and alertness. In graph-theory, the node-clustering coefficient is defined as the degree to which nodes tend to cluster together in a regional network. In normal brain, higher clustering coefficient indicates high efficiency of information transfer for specialized processing; however in ESRD patients, the increased clustering coefficient was likely associated with the reorganization of local networks and may influence thalamus-associated brain functions, such as motor, sensory, consciousness, sleep, and alertness.

However, the factors that caused disruptions of brain structural network in ESRD patients were complex and the underlying pathophysiological processes in ESRD patients with dialysis remain unclear. It was previously shown that patients with lower renal functions had more white-matter lesions or small-vessel diseases [1,2] and ESRD patients before hemodialysis may have uremic neuropathy and exhibit abnormal T2 hyper intensity in brain tissues [5–7]. After undergoing the first hemodialysis, patients were found to exhibit hyper T2 signal and elevated diffusivity in brain tissues [8,9,27], suggesting that the first dialysis induced high concentration gradient of urea between brain tissues and vessels and resulted in osmotic demyelination and vasogenic edema. Nevertheless, the continued dialysis helped normalize T2 signals [8,9], which was likely as the result of decreased concentration gradient of urea between brain tissues and vessels. After undergoing hemodialysis for longer than 1 year, invisible white-matter alterations characterized as decreased FA and increased MD were detected in ESRD

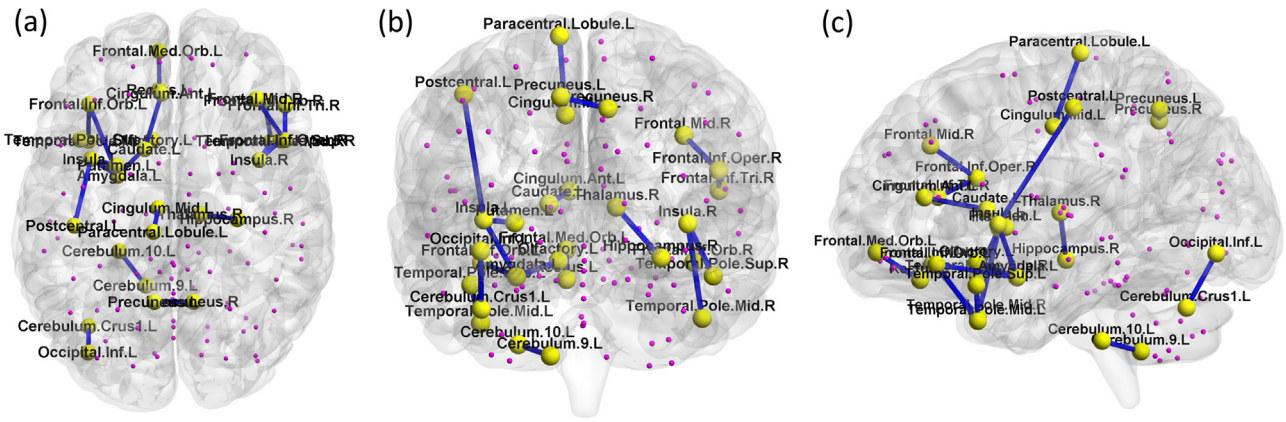

Fig. 1. The statistical results of brain structural connectivity between the ESRD and healthy controls in axial (a), coronal (b), and sagittal (c) views. The blue edges indicate significantly lower structural connectivity in ESRD patients than healthy controls. The spheres indicate the center of gravity of 116 AAL regions.

Table 2
The significant difference of structural connectivity between the two groups with corrected $P < 0.05$.

Structural connectivity	ESRD patients	Healthy controls
Frontal_Inf_Oper_R ↔ Frontal_Mid_R	0.19 ± 0.02	0.22 ± 0.02
Frontal_Inf_Oper_R ↔ Frontal_Inf_Tri_R	0.45 ± 0.05	0.50 ± 0.06
Frontal_Inf_Orb_L ↔ Amygdala_L	0.16 ± 0.05	0.22 ± 0.06
Olfactory_L ↔ Amygdala_L	0.21 ± 0.03	0.25 ± 0.05
Frontal_Med_Orb_L ↔ Rectus_L	0.69 ± 0.04	0.73 ± 0.05
Insula_L ↔ Amygdala_L	0.42 ± 0.08	0.49 ± 0.07
Insula_L ↔ Putamen_L	0.68 ± 0.06	0.75 ± 0.06
Cingulum_Ant_L ↔ Caudate_L	0.23 ± 0.03	0.27 ± 0.05
Occipital_Inf_L ↔ Cerebellum_Crus1_L	0.18 ± 0.03	0.22 ± 0.04
Postcentral_L ↔ Insula_L	0.18 ± 0.04	0.21 ± 0.03
Precuneus_L ↔ Precuneus_R	0.26 ± 0.04	0.30 ± 0.04
Paracentral_Lobule_L ↔ Cingulum_Mid_L	0.33 ± 0.04	0.37 ± 0.04
Thalamus_R ↔ Hippocampus_R	0.26 ± 0.03	0.28 ± 0.02
Temporal_Pole_Sup_R ↔ Insula_R	0.32 ± 0.03	0.35 ± 0.03
Temporal_Pole_Mid_L ↔ Frontal_Inf_Orb_L	0.17 ± 0.02	0.19 ± 0.02
Temporal_Pole_Mid_L ↔ Temporal_Pole_Sup_L	0.58 ± 0.04	0.61 ± 0.03
Temporal_Pole_Mid_R ↔ Frontal_Inf_Orb_R	0.15 ± 0.01	0.17 ± 0.02
Temporal_Pole_Mid_R ↔ Insula_R	0.15 ± 0.02	0.18 ± 0.02
Cerebellum_9_L ↔ Cerebellum_10_L	0.73 ± 0.07	0.81 ± 0.10

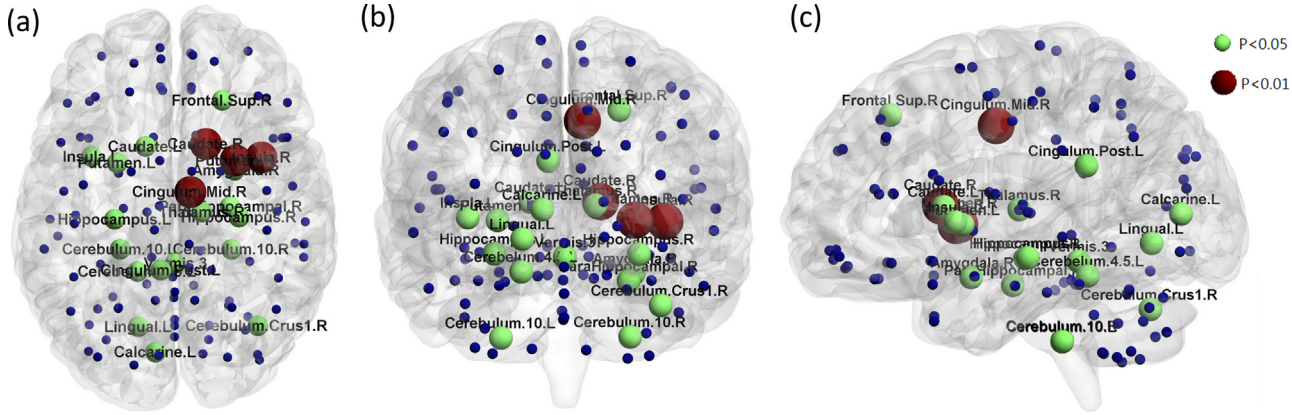

Fig. 2. The statistical results of node-strength of 116 AAL regions between the two groups in axial (a), coronal (b), and sagittal (c) views. The spheres indicate AAL regions with significantly lower node-strength in ESRD patients than healthy controls.

patients [13,14], indicating that white-matter alterations persisted in the brain and correlated with dialysis duration. Additionally, this study demonstrated that structural connectivity was decreased mainly in frontal lobe and network measures were altered in various brain regions with functions of cognition, sleep, alertness, consciousness, emotion, memory, decision-making, and motor, further speculating that invisible white-matter alterations resulted in disruptions of brain structural networks in certain brain regions which were generally overlapped with the alterations of functional connectivity found in previous functional MRI studies [22,23]. Therefore, the disrupted structural networks detected in this study were likely associated with the altered functional connectivity observed in the previous studies [22,23].

In neurological complications, previous studies reported that ESRD patients with dialysis commonly exhibited cognitive impairments [28,29], depression [30,31], anxiety [32], fatigue [33,34],

Table 3
The significant difference of node-strength between the two groups with corrected $P < 0.05$.

Node strength	Functions	ESRD patients	Healthy controls
Frontal_Sup_R	Executive, spatial cognition	3.76 ± 0.23	3.88 ± 0.18
Insula_L	Motor control, interoceptive	5.64 ± 0.43	5.90 ± 0.34
Insula_R**	awareness, emotion	5.06 ± 0.29**	5.31 ± 0.25**
Cingulum_Mid_R**	Emotion, cognition	4.33 ± 0.31**	4.67 ± 0.28**
Cingulum_Post_L		7.27 ± 0.94	7.83 ± 1.00
Hippocampus_L	Memory, emotion	6.92 ± 0.67	7.27 ± 0.49
Hippocampus_R		6.09 ± 0.54	6.37 ± 0.46
ParaHippocampal_R	Memory encoding and retrieval	4.60 ± 0.25	4.76 ± 0.26
Amygdala_R	Memory, decision-making, emotion	6.13 ± 0.45	6.45 ± 0.41
Calcarine_L	Visual	5.43 ± 0.40	5.68 ± 0.44
Lingual_L	Vision, word processing	5.52 ± 0.37	5.76 ± 0.43
Caudate_L	Motor, memory, learning, sleep,	5.13 ± 0.66	5.53 ± 0.44
Caudate_R**	emotion, language	4.81 ± 0.55**	5.25 ± 0.36**
Putamen_L	Motion	5.83 ± 0.62	6.26 ± 0.42
Putamen_R**		5.12 ± 0.42**	5.52 ± 0.31**
Thalamus_R	Motor, sensory, consciousness, sleep, alertness	4.08 ± 0.50	4.36 ± 0.34
Cerebulum_Crus1_R	Motor control	4.45 ± 0.18	4.55 ± 0.17
Cerebelum_4_5_L		5.56 ± 0.24	5.76 ± 0.40
Cerebulum_10_L		5.67 ± 0.71	6.11 ± 0.73
Cerebulum_10_R		5.53 ± 0.66	6.04 ± 0.69
Vermis_3	Posture, locomotion	7.00 ± 0.71	7.39 ± 0.64
Vermis_9		6.59 ± 0.44	6.93 ± 0.47
Vermis_10		6.77 ± 0.55	7.07 ± 0.46

** Indicates corrected $P < 0.01$.

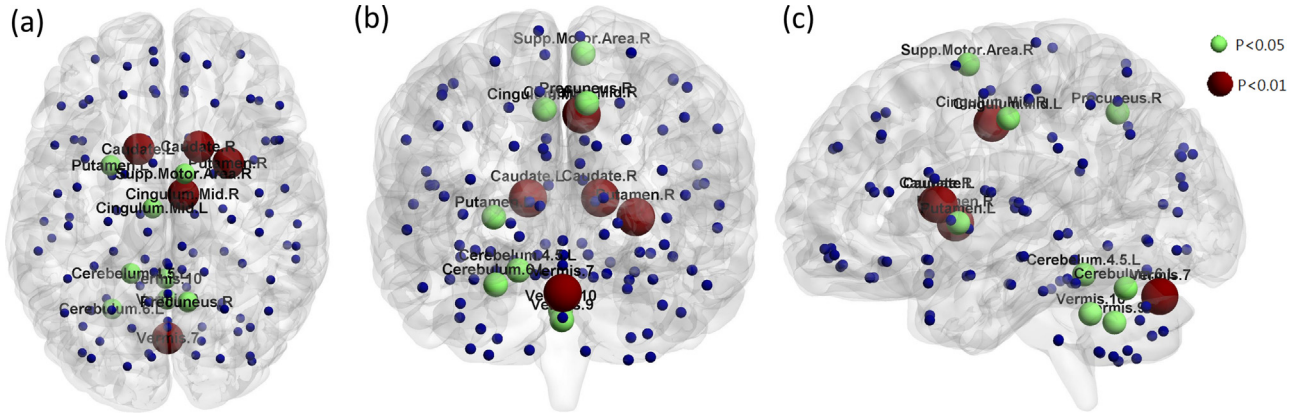

Fig. 3. The statistical results of node-degree in 116 AAL regions between the two groups in axial (a), coronal (b), and sagittal (c) views. The spheres indicate the AAL regions with significantly lower node-degree in ESRD patients than healthy controls.

Table 4
The significant difference of node-degree between the two groups with corrected $P < 0.05$.

Node degree	Functions	ESRD patients	Healthy controls
Supp_Motor_Area_R	Control of movement	7.79 ± 0.60	8.26 ± 0.59
Cingulum_Mid_L	Emotion, cognition	11.55 ± 1.25	12.63 ± 1.33
Cingulum_Mid_R**		12.03 ± 1.49**	13.52 ± 1.31**
Precuneus_R	Episodic memory, visuospatial processing, and consciousness	12.73 ± 1.77	13.78 ± 1.12
Caudate_L**	Motor, memory, learning, sleep,	15.58 ± 2.62**	17.59 ± 1.93**
Caudate_R**	emotion, language	14.24 ± 2.54**	16.33 ± 2.06**
Putamen_L	Motion	15.97 ± 3.15	17.96 ± 2.21
Putamen_R**		13.55 ± 2.44**	15.63 ± 1.88**
Cerebelum_4_5_L	Motor control	14.42 ± 1.44	15.52 ± 1.58
Cerebelum_6_L		12.06 ± 1.17	12.89 ± 1.22
Vermis_7**	Posture, locomotion	17.15 ± 1.20**	18.33 ± 1.54**
Vermis_9		15.12 ± 0.70	15.59 ± 0.75
Vermis_10		14.21 ± 1.76	15.33 ± 1.57

** Indicates corrected $P < 0.01$.

Table 5
The significant difference of node-local efficiency and clustering coefficient between the two groups with corrected $P < 0.05$.

	Functions	ESRD patients	Healthy controls
Local efficiency			
Vermis_6	Posture, locomotion	0.87 ± 0.01	0.89 ± 0.01
Clustering coefficient			
Thalamus_R	Motor, sensory, consciousness, sleep, alertness	0.55 ± 0.10	0.46 ± 0.12

and restless legs syndrome [35], which were intimately associated with functional alterations in memory, executive, emotion, sleep, consciousness, and motion, respectively. In this study, although no significant correlation between structural network and cognitive functions was found in ESRD patients due likely to very subtle cognitive impairments, the graph-theory analysis helped reveal several disrupted local structural networks in brain regions whose functions were related to those neuropsychiatric disorders commonly seen in patients with dialysis. Therefore, graph-theory analysis might be helpful to early detect disruptions of brain structural network and predict the prognosis of ESRD patients after long-term hemodialysis. However, follow-up study will be needed to further demonstrate the association between disrupted networks and neurological complications in ESRD patients.

We acknowledged some limitations of this study. First, the study population was small because the enrolled subjects have to be young and have no visible brain lesion. Second, this study assessed the overall cognitive functions by CASI, so it was unable to elaborate the relationship between the disrupted structural networks and specific functional domains. Besides, this study did not obtain education level from each participant, so the comparison of CASI score may have been affected by the difference of education level between patients and healthy controls. Third, this study did not evaluate functions of sleep, alertness, consciousness, emotion, memory, decision-making, and motor from patients, so it was unable to understand the relationship between the disrupted networks and neurological complications in ESRD patients. Fourth, the DTI data were acquired with lower spatial resolution in slice thickness, so it was expected to have more partial volume effects in the through-plane direction and possibly affect the tracking results. Finally, the DTI data were acquired with single-shot echo-planar imaging sequence, and hence the susceptibility distortions may have already affected the results of structural connectivity especially in regions near frontal and brain stem areas [36].

Conclusions

ESRD patients on long-term hemodialysis would exhibit cognitive decline even if they exhibit normal-appearing brain tissues. The comparisons of brain structural connectivity and network measures demonstrated disruptions of brain structural networks intimately associated with common neurological complications in ESRD patients. Therefore, we conclude that the graph-theory analysis is helpful to investigate disruptions of brain structural networks in ESRD patients with normal-appearing brain tissues.

Disclosure of interest

The authors declare that they have no competing interest.

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