Alterations in Structural and Functional Connectivities in Patients with End-Stage Renal Disease

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Background and Purpose The aim of this study was to evaluate the structural and functional connectivities of brain network using graph theoretical analysis in neurologically asymptomatic patients with end-stage renal disease (ESRD). We further investigated the prevalence of cognitive impairment (CI) in ESRD patients and analyzed the association between network measures of brain connectivity and cognitive function.

Methods We prospectively enrolled 40 neurologically asymptomatic ESRD patients, 40 healthy controls, and 20 disease controls. All of the subjects underwent diffusion-tensor imaging (DTI) and resting-state functional magnetic resonance imaging (rs-fMRI). We calculated measures of structural and functional connectivities based on DTI and rs-fMRI, respectively, and investigated differences therein between the ESRD patients and the healthy controls. We assessed cognitive function in the ESRD patients using the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery.

Results The ESRD patients exhibited decreased global structural and functional brain connectivities, as well as alterations of network hubs compared to the healthy controls and disease controls. About 70% of the ESRD patients had CI. Moreover, ESRD patients without CI exhibited decreased global connectivity and alterations of network hubs. Furthermore, there was a significant positive association between measures of brain connectivity and cognitive function.

Conclusions We found that ESRD patients exhibited decreased structural and functional brain connectivities, and that there was a significant association between brain connectivity and cognitive function. These alterations in the brain network may contribute to the pathophysiological mechanism of CI in ESRD patients.

Key Words kidney failure, brain, cognition.

INTRODUCTION

Chronic kidney disease (CKD) is defined as abnormalities of the structure or function of the kidney that last for more than 3 months.[1] A condition is diagnosed as CKD if the glomerular filtration rate (GFR) is decreased to <60 mL/min/1.73 m^2, structural abnormalities are detected in imaging, or there are abnormalities in urine tests such as proteinuria.[1] End-stage renal disease (ESRD) is an advanced stage of CKD that is characterized by a GFR of <15 mL/min/1.73 m^2. ESRD patients should prepare for and then undergo renal replacement therapy, such as kidney transplantation and dialysis. About 50% of ESRD cases are due to diabetes, with other important causative conditions being hypertension and glomerulonephritis. ESRD patients can have numerous complications and higher mortality rates than the general population. Cardiovascular complications are the most common, and are the most-important cause of death among ESRD patients.[1] ESRD patients are also frequently affected by various neurological complications, such as peripheral polyneuropathy, auto-

nomic dysfunction, stroke, uremic encephalopathy, and cognitive impairment (CI),[2] with CI being the most common nowadays. Many studies with cross-sectional and longitudinal designs have shown that CI is more common in ESRD patients than in the general population even in the early stage of CKD, and that ESRD is an independent risk factor for CI.[3] The prevalence of CI is inversely proportional to the deterioration of renal function.[4]

Recent studies on quantitative analyses of the brain have shown reduced total cortical and subcortical volumes—which are associated with CI—in ESRD patients.[5] In addition, ESRD patients have shown smaller cortical thicknesses than healthy controls, especially in the frontal cortex.[6] Other studies applying a method of tract-based spatial statistical analysis to diffusion-tensor imaging (DTI) data to investigate the microstructural changes in the white matter over the whole brain in ESRD patients have revealed that lower fractional anisotropy (FA) and higher mean diffusivity in the white matter are more widespread in ESRD patients than in healthy controls.[7,8] In these DTI studies, correlation analysis revealed a significant positive correlation between the Mini Mental State Examination (MMSE) scores and the FA values in several regions of the white matter.[7,8] All of these quantitative brain magnetic resonance imaging (MRI) analyses suggest that CI is related to these structural abnormalities in the brain.

Studying brain connectivity and its relation to cognition is an emerging field in neuroscience. Many neuroimaging studies have elucidated alterations in the brain network related to CI in various neurological disorders.[9,10] Graph theoretical analysis is one of the common methods used to investigate brain connectivity.[11] This is a branch of mathematics concerned with how networks can be encoded and their properties measured. It has an advantage in that it simplifies the complex brain connectivity as a simple model in order to improve clinical interpretability.[11] A previous study using graph theoretical analysis in healthy subjects found significant correlations between IQ and various network measures derived from graph theoretical analysis, such as the mean clustering coefficient, global efficiency, local efficiency, small-worldness index, and characteristic path length, thus indicating that brain connectivity is related to cognitive function.[12]

The aim of this study was to identify alterations in structural and functional connectivities using graph theoretical analysis based on DTI and resting-state functional MRI (rs-fMRI) in neurologically asymptomatic ESRD patients compared to healthy controls. We additionally investigated the prevalence of CI in the ESRD patients and analyzed the association between the network measures of brain connectivity and cognitive function.

METHODS

Subjects

This study was approved by the Institutional Review Board (IRB) of Inje University Haeundae Paik Hospital (IRB number: 2018-09-015-003). A written informed consent form was completed by all participants. The study was prospectively performed in a single tertiary hospital. We enrolled 40 neurologically asymptomatic ESRD patients from October 2018 to March 2019. These patients were defined[1] as 1) having a GFR of <15 mL/min/1.73 m^2 where renal replacement therapy is required, 2) receiving dialysis for more than 3 months, and 3) having no previous history of neurological or psychiatric disorders.

We also enrolled an age- and sex-matched control group of 40 healthy subjects who had no significant past medical, neurological, or psychiatric history. The mean age and proportion of males did not differ significantly between the ESRD patients and the healthy controls (62.9 years vs. 61.9 years, p=0.6529; and 45% vs. 42%, p=0.8228; respectively). In addition, we enrolled 20 patients with diabetes or hypertension as a disease-control group, comprising subjects with no medical, neurological, or psychiatric history except for diabetes or hypertension. The 20 disease-control group included 16 patients (80%) with hypertension and 11 (55%) with diabetes as their underlying disease. The mean age and proportion of males did not differ significantly between the ESRD patients and the disease controls (62.9 years vs. 64.6 years, p=0.2737; and 45% vs. 45%, p=1.000; respectively). All of the subjects (ESRD patients, healthy controls, and disease controls) had normal brain MRI findings on visual inspection.

Brain MRI

All subjects underwent MRI using the same imaging protocol. The scans were performed using a 3.0-T MRI scanner equipped with an eight-channel head coil (Achieva, Philips Healthcare, Best, The Netherlands), and included sagittal-oriented three-dimensional T2- and T1-weighted images and coronal-oriented three-dimensional fluid-attenuated inversion recovery images to evaluate structural lesions in the brain. Moreover, all subjects underwent DTI and rs-fMRI to obtain data for use in graph theoretical analysis. DTI was performed using spin-echo single-shot echo-planar pulse sequences with 32 different diffusion directions [echo time (TR)/repetition time (TE)=8,620/85 ms, flip angle=90°, slice thickness=2.25 mm, acquisition matrix=120×120, field of view (FOV)= 240×240 mm^2, and b value=1,000 s/mm^2]. rs-fMRI was performed using multislice echo-planar imaging sequences (TR/ TE=3,000/30 ms, flip angle=65°, slice thickness=4.4 mm, acquisition matrix=128×128, FOV=220×220 mm^2, and scan

time=7.5 min).

Image processing and analysis

We analyzed most of the DTI data for evaluating structural connectivity using DSI Studio software (http://dsi-studio.lab-solver.org). The following procedures were used in the graph theoretical analysis. The first step was to create a tractography map from the DTI data, which included reading and parsing digital imaging and communications in medicine files, reconstructing to characterize the main diffusion directions of the fibers, and fiber tracking. The next step was to generate a connectivity matrix, which was calculated using the counts of the connecting tracts. The automated anatomical labeling template was used for brain parcellation, and every white-matter fiber was evaluated for extreme points. This step included obtaining the whole-brain fiber tracks, placing seeding regions in the whole brain, spatial normalization, defining the region of interest, and creating a connectivity matrix. The graph theoretical network measures were then calculated from the connectivity matrix.

The rs-fMRI data were analyzed using Statistical Parametric Mapping software packages (version 12, Functional Imaging Laboratories, London, UK), as well as the CONN functional connectivity toolbox (version 17, Cognitive and Affective Neuroscience Laboratory, Massachusetts Institute of Technology, Cambridge, MA, USA) running under MATLAB (MathWorks, Sherborn, MA, USA). The rs-fMRI data were preprocessed using the standard spatial preprocessing steps of realignment, slice-time correction, coregistration, normalization in Montreal Neurological Institute space, and smoothing with a 6-mm Gaussian kernel. Functional connectivity analysis was then performed using the CONN toolbox.

We used an undirected network and a weighted version of the matrix. When we calculated the edges, we controlled for the effects of age and sex as covariates. We used data from the structural and functional connectivity matrix based on DTI and rs-fMRI to calculate the following network measures: global efficiency, local efficiency, mean clustering coefficient, characteristic path length, and small-worldness index. We used a fixed-cost threshold value of 0.15.

Neuropsychological tests

We assessed cognitive function in the ESRD patients. All of the patients underwent a standardized neuropsychological test called the assessment packet of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K),[13] which includes measures of frontal/executive, language, memory, and visuospatial functions. Tests that were scored contained the following items: MMSE in the CERAD-K (MMSE-KC), immediate recall and 15-min delayed recall

and recognition of a 10-word list, delayed figure recall, the Korean version of the Boston Naming Test (BNT-K), word fluency (animal names), Trail-Making test type B, Stroop test of reading colored words, and figure copying. These tests were performed to assess the function in the following cognitive domains: 1) frontal/executive function (word fluency, Trail-Making test type B, and Stroop test of reading colored words), 2) language (BNT-K), 3) memory (immediate recall and 15-min delayed recall and recognition of a 10-word list, and delayed figure recall), 4) visuospatial function (figure copying), and 5) global cognition (MMSE-KC). Scores that were more than -1.5 standard deviations below the mean for the age- and education-adjusted norms were considered to be abnormal. CI was defined when more than one cognitive domain was impaired in CERAD-K. These tests were implemented by a board-certified clinical neuropsychologist.

Statistical analysis

Data were compared using the chi-squared test for categorical variables and *t*-test or the Mann-Whitney test for numerical variables. We quantified correlations between the global and local network measures and cognitive function using Pearson's correlation test. Categorical variables are presented as frequency and percentage values, while numerical variables are presented as mean and standard-deviation values. A *p* value of <0.05 was considered to indicate statistical significance in all calculations. However, when analyzing the global and functional structural or functional connectivities, multiple corrections with Bonferroni correction were applied to control for the familywise error rate ($p<0.01$ for global connectivity and $p<0.001$ for local connectivity). All of the statistical tests were performed using MedCalc® (version 18.6, MedCalc Software, Ostend, Belgium).

RESULTS

Demographic and laboratory characteristics of the subjects

The ESRD patients comprised 20 hemodialysis patients and 20 peritoneal dialysis patients. Their mean dialysis period was 3.8 years, and the male-to-female ratio was 0.8 (18 males and 22 females). All 40 patients had hypertension, and 17 of them (42.5%) had diabetes as their underlying disease. The other demographic and laboratory characteristics are presented in Table 1.

Neuropsychological tests

In the function tests for cognitive domains, the ESRD patients performed worse in the frontal/executive function test than in the other tests. Twenty-nine of the 40 participants (72.5%)

were classified as patients with CI. The distributions of age, years on dialysis, dialysis types, underlying diseases such as diabetes mellitus, and hypertension did not differ significantly between patients with or without CI. There were also no significant differences in the laboratory data across the groups. In the neuropsychological tests, the patients with CI showed

Table 1. Demographic, laboratory, and neuropsychological data in patients with ESRD

Variable	Patients with ESRD (n=40)	Patients without CI (n=11)	Patients with CI (n=29)	p^*
Demographic data				
Age, years	62.90±6.59	61.60±8.30	63.30±5.90	0.511
Sex, male	18 (45.0)	8 (72.7)	10 (34.4)	0.040
Dialysis duration, months	46.50±52.53	34.80±21.20	50.93±60.00	0.976
Dialysis type (hemodialysis/peritoneal)	20 (50.0)/20 (50.0)	4 (36.3)	16 (55.1)	0.480
Education, years	10.40±4.10	9.80±3.20	10.50±4.30	0.530
Hypertension	40 (100)	11 (100)	29 (100)	1.000
Diabetes mellitus	17 (42.5)	7 (73.6)	16 (55.1)	0.730
Laboratory data				
Hemoglobin, g/dL	10.41±1.17	10.80±0.93	10.20±1.22	0.166
Hematocrit, %	31.91±3.68	33.30±2.92	31.30±3.83	0.131
Protein, g/dL	6.55±0.63	6.30±0.51	6.60±0.66	0.166
Albumin, g/dL	3.80±0.34	3.60±0.28	3.80±0.36	0.157
Aspartate aminotransferase, U/L	21.10±6.89	19.70±5.67	21.60±7.33	0.455
Alanine aminotransferase, U/L	20.13±10.70	19.70±6.13	20.20±12.08	0.591
Blood urea nitrogen, mg/dL	58.84±16.72	55.80±11.30	59.90±18.41	0.385
Creatinine, mg/dL	9.00±2.50	10.00±2.75	8.60±2.32	0.079
Sodium, mmol/L	138.78±3.25	139.10±3.65	138.60±3.14	0.385
Potassium, mmol/L	4.81±0.65	4.80±0.62	4.80±0.67	0.811
Chloride, mmol/L	99.23±4.16	98.80±4.37	99.30±4.14	0.788
Calcium, mg/dL	8.49±0.68	8.30±0.81	8.50±0.63	0.492
Phosphate, mg/dL	4.85±0.94	4.70±1.09	4.90±0.89	0.743
Parathyroid hormone, pg/mL	286.63±209.31	311.30±259.33	277.20±191.50	0.976
Total CO_2 content, mmol/L	24.68±2.62	25.70±2.78	24.20±2.49	0.028
Neuropsychological data (z score)				
Frontal/executive function				
Verbal fluency test	-0.67±0.94	-0.47±0.84	-0.75±0.98	0.415
Trail-making test type B	-1.22±1.11	-1.12±0.92	-1.26±1.19	0.722
Stroop test (reading colored words)	-1.03±1.10	-0.46±0.98	-1.15±1.16	0.040
Language				
Modified BNT-K score	0.25±0.86	0.88±1.14	0.01±0.89	0.003
Verbal memory				
Word-list memory	-0.03±1.08	-0.16±0.88	0.02±1.16	0.638
Word-list recall	-0.16±1.12	0.36±0.72	-0.35±1.19	0.070
Word-list recognition	0.11±0.93	0.41±0.46	-0.00±1.04	0.217
Visual memory				
Constructional recall	-0.37±0.95	0.12±0.94	-1.20±1.33	0.005
Visuospatial function				
Figure copying	-0.83±1.31	0.16±0.49	-1.20±1.33	0.002
Global cognition				
MMSE-KC score	0.24±0.89	0.40±0.75	0.17±0.94	0.470
MMSE-KC, raw score	26.90±2.80	27.30±2.00	26.80±3.00	0.606

Data are n (%) or mean±standard-deviation values.
*Significant difference between the patients with and without CI in the chi-squared test, t-test, or the Mann-Whitney test.
BNT-K: Korean version of the Boston Naming Test, CI: cognitive impairment, ESRD: end-stage renal disease, MMSE-KC: Mini Mental State Examination in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease.

worse performances in the Stroop test of reading colored words, BNT-K, visual-memory tasks, and figure copying, but not in the verbal memory and global cognition tests compared to the patients without CI.

Structural connectivity

The measures of global structural connectivity differed significantly between the ESRD patients and the healthy controls.

The global efficiency was significantly lower in the ESRD patients than in the healthy controls. However, there were no significant differences in the local efficiency, mean clustering coefficient, characteristic path length, or small-worldness index between these two groups (Table 2). There was also a significant difference in the measures of local structural connectivity between the two groups. The betweenness centrality of the right and left postcentral gyrus and the left superior
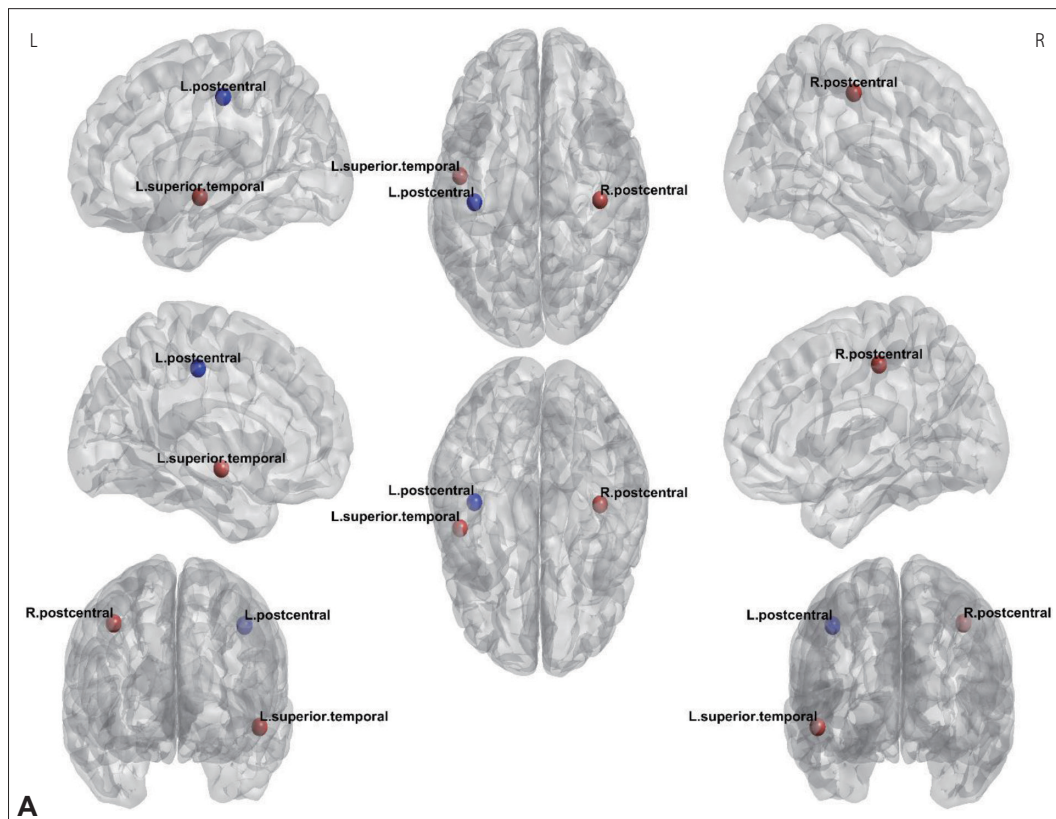
Table 2. Measures of global structural connectivity in patients with ESRD, healthy controls, and disease controls

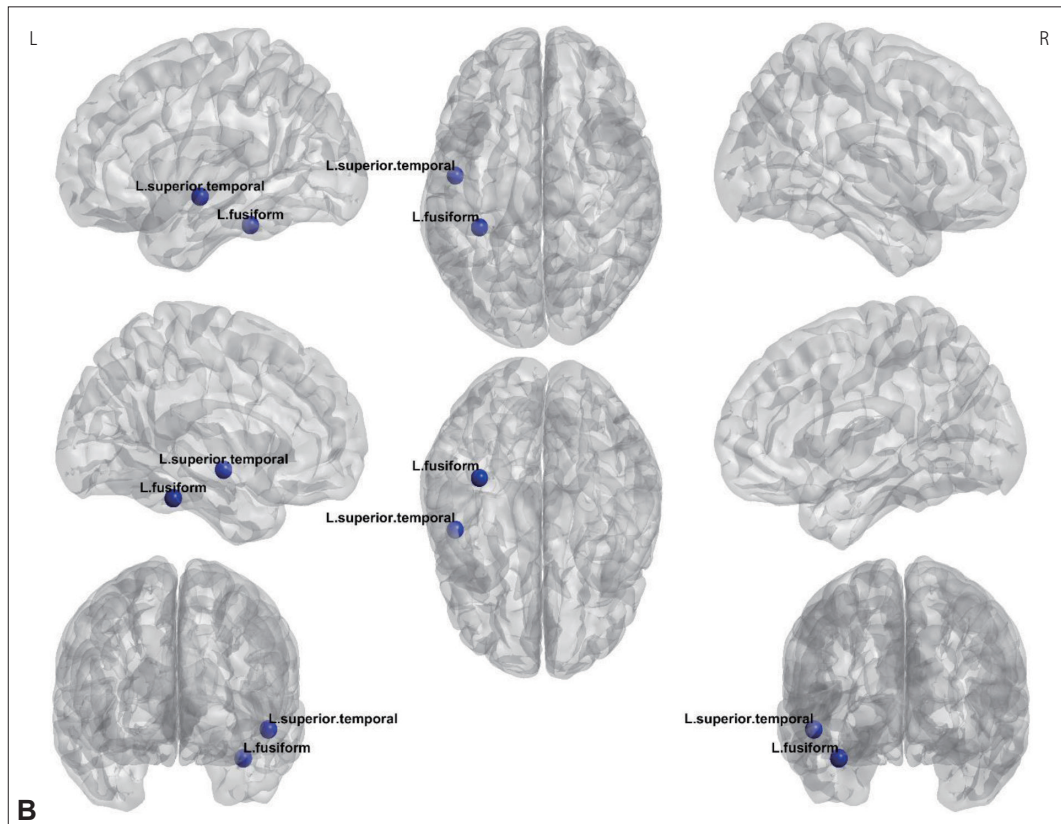| Variable	Patients with ESRD (*n*=40)	*p**	*p*†	Patients without CI (*n*=11)	*p*†	*p*§	Healthy controls (*n*=40)	Disease controls (*n*=20)
Global efficiency	0.871±0.078	<0.001	<0.001	0.847±0.101	0.004	0.002	0.938±0.082	1.525±0.136
Local efficiency	1.113±0.157	0.047	<0.001	1.032±0.107	0.009	0.004	1.191±0.183	2.451±0.286
Mean clustering coefficient	0.133±0.047	0.538	<0.001	0.128±0.047	0.914	0.179	0.126±0.056	0.248±0.087
Characteristic path length	3.946±0.343	0.761	0.004	4.160±0.453	0.179	0.476	3.972±0.388	4.250±0.404
Small-worldness index	0.088±0.032	0.809	<0.001	0.081±0.026	0.523	0.041	0.090±0.044	0.267±0.090

Data are mean±standard-deviation values.
*Significant difference between ESRD patients and healthy controls in *t*-test, †Significant difference between ESRD patients and disease controls in *t*-test, ‡Significant difference between ESRD patients without CI and healthy controls in *t*-test, §Significant difference between ESRD patients without CI and disease controls in *t*-test.
CI: cognitive impairment, ESRD: end-stage renal disease.

Fig. 1. Differences in local structural connectivity between the ESRD patients and the healthy controls. There were alterations in the local structural connectivity in many regions in the ESRD patients. Red and blue dots (A) indicate nodes with increased and decreased betweenness centrality, respectively, in the ESRD patients with CI (A) and without CI (B) compared to the healthy controls. CI: cognitive impairment, ESRD: end-stage renal disease, L: left, R: right.

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Table 3. Measures of global functional connectivity in patients with ESRD, healthy controls, and disease controls

Variable	Patients with ESRD (n=40)	p^*	$p^†$	Patients without CI (n=11)	$p^‡$	$p^§$	Healthy controls (n=40)	Disease controls (n=20)
Global efficiency	0.493±0.021	0.174	0.040	0.491±0.022	0.165	0.093	0.499±0.016	0.506±0.025
Local efficiency	0.730±0.022	0.723	0.138	0.736±0.021	0.514	0.113	0.732±0.020	0.719±0.030
Mean clustering coefficient	0.532±0.035	0.679	0.010	0.540±0.035	0.336	0.032	0.528±0.035	0.500±0.050
Characteristic path length	2.356±0.153	0.041	0.005	2.378±0.152	0.033	0.007	2.296±0.093	2.241±0.103
Small-worldness index	0.226±0.012	0.105	0.426	0.227±0.009	0.410	0.399	0.230±0.010	0.222±0.014

Data are mean±standard-deviation values.
*Significant difference between ESRD patients and healthy controls in t-test, †Significant difference between ESRD patients and disease controls in t-test, ‡Significant difference between ESRD patients without CI and healthy controls in t-test, §Significant difference between ESRD patients without CI and disease controls in t-test.
CI: cognitive impairment, ESRD: end-stage renal disease.

temporal gyrus differed significantly between the two groups (Fig. 1A).

Eleven of the ESRD patients did not have CI. However, the measures of global structural connectivity also differed significantly between the ESRD patients without CI and the healthy controls. The global efficiency and local efficiency were significantly lower in the ESRD patients without CI than in the healthy controls, whereas the mean clustering coeffi-

cient, characteristic path length, and small-worldness index did not differ between these two groups (Table 2). The measures of local structural connectivity also differed significantly between the ESRD patients without CI and the healthy controls. The betweenness centrality of the left fusiform gyrus and the left superior temporal gyrus differed significantly between the ESRD patients without CI and the healthy controls (Fig. 1B).

There were also significant differences in global connectivity between the patients with ESRD and the disease controls, with the global efficiency, local efficiency, mean clustering coefficient, characteristic path length, and small-worldness index being lower in the patients with ESRD. Moreover, the betweenness centrality of the right amygdala and right caudate differed significantly between the ESRD patients and the disease controls.

Comparisons of the ESRD patients without CI and the disease controls revealed that the global efficiency and local efficiency were significantly lower in the ESRD patients without CI than in the disease controls. The betweenness centrality of the left supplementary area and left superior temporal gyrus differed significantly between the ESRD patients without CI and the disease controls.
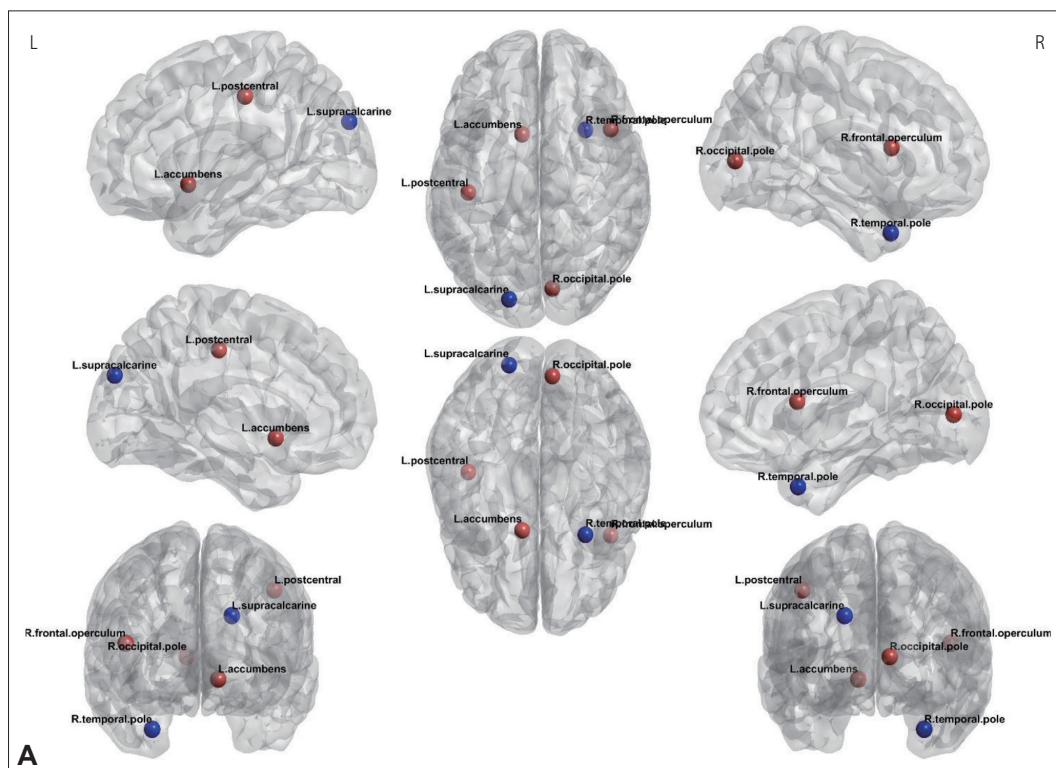
Functional connectivity

None of the five measures of global functional connectivity (global efficiency, local efficiency, mean clustering coefficient, characteristic path length, and small-worldness index) differed significantly between the patients with ESRD and the healthy controls after applying multiple corrections (Table 3). However, the measure of local functional connectivity (be-

tweenness centrality) of the left accumbens, right frontal operculum cortex, right occipital pole, left supra-calcarine cortex, right temporal pole, and left postcentral gyrus differed significantly between the two groups (Fig. 2A).
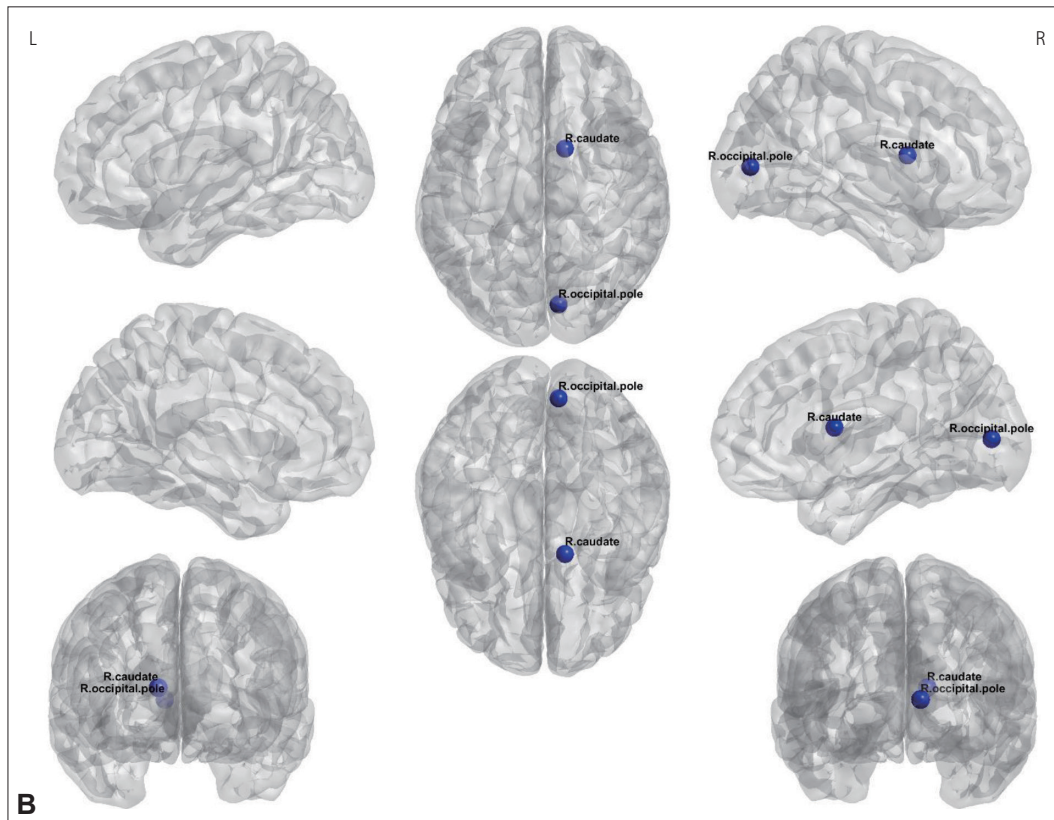
The five measures of global functional connectivity also did not differ significantly between the ESRD patients without CI and the healthy controls after applying multiple corrections (Table 3). However, the measure of local functional connectivity (betweenness centrality) of the right caudate nucleus and right occipital pole differed significantly between the ESRD patients without CI and the healthy controls (Fig. 2B).

There were significant differences in global connectivity between the patients with ESRD and the disease controls. The characteristic path length was significantly longer in the patients with ESRD than in the disease controls. The betweenness centrality of the left accumbens differed significantly between the patients with ESRD and the disease controls.

Comparisons of the ESRD patients without CI and the disease controls revealed that the characteristic path length was significantly longer in the ESRD patients without CI than in the disease controls. The betweenness centrality of the left accumbens, right caudate, and left pars opercularis of the inferior frontal gyrus also differed significantly between the

Fig. 2. Differences in local functional connectivity between the ESRD patients and the healthy controls. There were alterations in the local functional connectivity in many regions in the ESRD patients. Red and blue dots (A) indicate nodes with increased and decreased betweenness centrality, respectively, in the ESRD patients with CI (A) and without CI (B) compared to healthy controls. CI: cognitive impairment, ESRD: end-stage renal disease, L: left, R: right.

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ESRD patients without CI and the disease controls.

Analysis of the correlation between the measures of neuropsychological tests and connectivity

Some measures of the global structural and functional connectivities were strongly correlated with the neuropsychological tests. Among the measures of global structural connectivity, global efficiency and characteristic path length were correlated with word-list recall ($r=0.344$, $p=0.032$; and $r=-0.357$, $p=0.025$; respectively). Among the measures of global functional connectivity, global efficiency was correlated with word-list memory, word-list recall, and word-list recognition ($r=0.469$, $p=0.002$; $r=0.405$, $p=0.018$; and $r=0.367$, $p=0.023$; respectively), while the mean clustering coefficient was correlated with word-list memory ($r=0.357$, $p=0.027$). There were also significant correlations between the local connectivity of some cortex and cognitive functions. The measure of local structural connectivity (betweenness centrality) of the right superior occipital cortex was correlated with the modified BNT-K score ($r=0.56$, $p<0.001$). The local betweenness centrality of the left superior temporal gyrus was correlated with word-list recognition ($r=0.50$, $p<0.001$), and that

of the left frontal operculum cortex was correlated with constructional recall ($r=0.51$, $p<0.001$).

DISCUSSION

The main findings of this study were that ESRD patients exhibited decreased global structural and functional brain connectivities as well as significant alterations in the network hubs compared to the healthy controls. In addition, we found that about 70% of the neurologically asymptomatic ESRD patients had CI. However, even the ESRD patients without CI exhibited decreased global structural and functional connectivities and alterations in the network hubs. Furthermore, there were significant positive correlations between the measures of brain connectivity and cognitive function, especially global efficiency and verbal memory.

Additionally, to confirm that our results were not produced by risk factors for ESRD, including diabetes or hypertension, we also enrolled patients with diabetes or hypertension as a disease-control group, and found that they exhibited alterations of structural and functional brain connectivities compared to the ESRD patients.

The graph theoretical analysis revealed that the global efficiency of structural connectivity was significantly lower in the patients with ESRD than in the healthy controls, while the global efficiency, local efficiency, mean clustering coefficient, and small-worldness index of structural connectivity were lower in the patients with ESRD than in the disease controls. We additionally found that the characteristic path length of functional connectivity was longer in the patients with ESRD than in the disease controls. In graph theory, the global efficiency corresponds to the efficiency of transferring information from one region to the whole network, and is simply calculated as the average nodal efficiency across all nodes.[11,14] Meanwhile, the local efficiency corresponds to the efficiency of transferring information from each region to the neighboring regions, and this is conventionally defined as the average of the local efficiencies of all nodes in a network.[11,14] In this study we used the measure of betweenness centrality to investigate the local connectivity. We found widespread alterations in the structural and functional hubs in the ESRD patients compared to both the healthy controls and the disease controls. The betweenness centrality is defined as the ratio of the shortest path between any pair of nodes through a node, and it can be used to identify the hubs of a brain network.[11,14] Hubs are the nodes for which the number of links greatly exceeds the average, and they provide valuable information about the configuration of a network.[11,14]

The clustering coefficient is a measure of the degree to which nodes tend to cluster together, and the characteristic path length is the average of the shortest path length between nodes. The global efficiency and the characteristic path length represent the degree of integration of the brain network, whereas the mean clustering coefficient and local efficiency indicate the degree of segregation in the brain.[11,14] Higher values of these network measures indicate that the brain network is more effective, and so the present findings of decreased network measures in the ESRD patients are suggestive of disruptions in the brain network and indicate decreased integration and segregation in those patients. Moreover, these findings were consistently found even in the ESRD patients without CI.

Few studies have investigated functional connectivity based on rs-fMRI with graph theoretical analysis in ESRD patients. Li et al.[15] investigated functional connectivity in ESRD patients, and found decreased functional connectivity in the regions of the default-mode network. Another study found widespread weakening of cortical and subcortical network connectivities in ESRD patients.[16] Both of these studies found that brain networks were disrupted in ESRD patients compared to healthy controls, which is consistent with the present study. Conversely, Chou et al.[17] is the only study to have previously analyzed structural connectivity based on DTI, and found that this was decreased in patients on hemodialysis. However, those authors did not apply detailed neuropsychological tests to the patients. Moreover, all of the previous studies analyzing connectivity in ESRD patients investigated structural and functional connectivities independently of each other. Since structural connectivity has an effect on the functional organization, given that brain plasticity shapes structural connectivity, brain connectivity can be analyzed more accurately if structural and functional connectivities are taken into account simultaneously.

The present study prospectively investigated both structural and functional connectivities in ESRD patients. As in several previous studies that have investigated structural and functional relationships in various brain networks using healthy subjects, the present findings show a general agreement that functionally connected regions are also structurally well connected.[18,19] Therefore, the present results validate the presence of a relationship between the structural and functional connectivities in ESRD patients, as also seen in healthy controls. However, this relationship is very complex and has not been well defined.[20] The anatomical alignment of the structural and functional connectivities appeared to be restricted to specific networks and tracts, and some changes in structural and functional connectivities were not strongly correlated.[21] In addition, structural deficits were not directly related to functional abnormalities.[22] Some of these discrepancies was also identified in the present study. Several previous studies have demonstrated that clinical presentations of many neuropsychiatric diseases, especially schizophrenia, are more weakly correlated with structural connectivity of the brain, and more strongly correlated with functional connectivity with behavioral performance and emotional measures.[23,24] Furthermore, a study of patients with spastic diplegic cerebral palsy found that the motor network had a significantly lower functional connectivity efficiency over the areas with intact structural connectivity and a lower structure-function coupling compared to the control group.[25] All of these studies suggest that clinical manifestations are reflected more closely by functional connectivity than by structural connectivity in various neuropsychiatric diseases.

Previous studies have found a high prevalence of CI in ESRD patients.[4,26-28] Our results confirm that ESRD is associated with an increased prevalence of CI, and suggest that CI is more common than previously recognized. The etiology of CI in ESRD patients is thought to be multifactorial, including in sharing common risk factors such as old age, diabetes, hypertension, and dyslipidemia between ESRD and CI, with the occurrence of retention of uremic solutes, chronic inflammation, vascular calcification, and anemia being due to im-

paired renal function.[29]

It was particularly interesting that we found that the ESRD patients performed worse in the frontal/executive and visuospatial function tests than in the tests for other cognitive domains. Among the 29 ESRD patients with CI, 14 and 16 patients exhibited decreased frontal/executive and visuospatial functions, respectively, whereas 2 and 10 patients exhibited decreased language and memory function, respectively. A high prevalence of cardiovascular risk factors is a strong risk factor for the development of CI, and decreased frontal/executive function is often observed in cardiovascular disease. Most of the ESRD patients had cardiovascular risk factors, and ESRD itself might be a surrogate marker of accelerated atherosclerosis. Thus, the ESRD patients had a high prevalence of CI, especially regarding frontal/executive function. This is also supported by previous reports of the Montreal Cognitive Assessment (MoCA) being a more-appropriate test than MMSE for detecting CI in ESRD patients,[30,31] since the MoCA is more sensitive to conditions involving frontal/executive function.[32] In addition, this finding could be consistent with a previous study finding progressively decreased regional homogeneity in the default-mode network of the frontal and parietal lobes in patients with ESRD.[33]

We found that some measures of the global structural and functional connectivities were strongly correlated with the findings of the neuropsychological tests, especially between global efficiency and memory. Although both segregation and integration in brain networks are critical for cognitive function, the findings of several studies support our results.[34] A previous study found that individual differences in global efficiency during the working-memory task were significant predictors (in addition to age) of the working-memory performance.[35] Furthermore, another study suggested that segregation (reflected by the local efficiency and mean clustering coefficient) was critical for motor execution, whereas integration (reflected by the global efficiency and characteristic path length) was critical for word-list memory.[36] All of these findings suggest that brain connectivity patterns as measured using brain MRI techniques such as DTI and rs-fMRI are associated with cognitive function.

One strength of our study was that we only enrolled neurologically asymptomatic patients with normal brain MRI findings on visual inspection, in order to exclude other factors that affect brain connectivity. Furthermore, we simultaneously investigated the structural and functional connectivities, and we included detailed neuropsychological evaluations and analyzed the associations between the network measures of brain connectivity and cognitive function. However, this study was also subject to several limitations. First, due to its cross-sectional design, we only observed the connectivity and cognitive function in the ESRD patients at a single time point. Follow-up longitudinal studies may provide further insight into the time course of alterations in brain connectivity and cognitive function. Second, the sample was relatively small, and so further researches involving large samples may be needed to confirm the present results.

In conclusion, we found that ESRD patients exhibited decreased global structural and functional brain connectivities, as well as significant alterations in the network hubs compared to healthy controls. We additionally found that about 70% of neurologically asymptomatic ESRD patients had CI, and that there were significant positive correlations between the measures of brain connectivity and cognitive function. These alterations in the brain network may contribute to the pathophysiological mechanism of CI in ESRD patients.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Acknowledgements

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