Structural network topology correlates to cognitive impairment and iPTH level in End-stage renal disease patients with peritoneal dialysis

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Abstract

Objective: The burden of cognitive impairment in patients with end-stage renal disease (ESRD) undergoing peritoneal dialysis has received more attention lately. It is associated with hospitalization, mortality and poorer quality of life. We aimed to assess the topological alterations of the brain white matter structural network in ESRD and the correlation between network metrics with Montreal Cognitive Assessment scores and clinical data. **Methods:** The study included 25 ESRD patients with secondary hyperparathyroidism (SHPT group), 25 patients without SHPT (Non-SHPT group) and 25 healthy controls (HC group) of comparable age and sex. Montreal Cognitive Assessment was used to assess the cognitive function. The WM structural network was constructed by DTI technique, and then we used graph theoretical approaches to detect changes in the global and regional properties of the WM networks in these participants through deterministic tractography method. **Results:** ESRD patients showed cognitive impairment compared to HC, and the SHPT patients had lower cognitive scores than the Non-SHPT patients. The global topological organization and local efficiency of the WM network was significantly disrupted in the SHPT but not in the Non-SHPT patients compared with the HC group. Moreover, lower regional efficiency was found in the ESRD patients, mainly distributed in the frontal and parietal cortices. In addition, an association was found between iPTH, shortest path length and cognitive impairment, and the iPTH level was negatively correlated with small-worldness by two indexes, the normalized clustering coefficient and the normalized shortest path length. **Conclusion:** The present study indicated that the brain structural connectome in ESRD patients with high iPTH levels was disrupted in association with cognitive impairment and it is a potential connectome-based biomarker for early detection.

Introduction

Chronic kidney disease (CKD) is an important issue that is of widespread public concern. There are approximately 571000 patients with end-stage renal disease (ESRD) receiving treatment in the United States, and nearly 270000 patients with ESRD undergo hemodialysis in China [1, 2]. Cognitive impairment has received more attention recently in ESRD patients because it has a prevalence of approximately 30%–60% [1, 3, 4]. Cognitive impairment is associated with adverse outcomes and a decreased quality of life [5, 6].

Cerebrovascular disease, anemia, uremic toxins, and secondary hyperparathyroidism (SHPT) have been reported to be major causes of cognitive impairment in CKD patients [7–10]. SHPT is characterized by high parathyroid hormone (PTH) levels, low vitamin D levels and normal or low calcium levels. There is some evidence that PTH levels may correlated with cognitive impairment and the risk of dementia [11, 12]. However, the pathophysiology of cognitive impairment in ESRD patients with SHPT is still unclear.

Neuroimaging has been established as a reliable tool to assess the neuropathologic mechanisms of cognitive impairment in ESRD patients [13, 14]. Resting-state functional magnetic resonance imaging (rs-fMRI) showed that ESRD patients have lower ALFF values and abnormal brain functional connectivity in default mode network (DMN) regions when compared with healthy controls [15]. Some studies have

found the diffusion tensor imaging (DTI) technique can reconstruct whole brain white matter (WM) connectivity [16, 17]. Graph theoretical analysis suggested that WM networks characterize many important topological organizations, like small-worldness [18]. To date, no studies have been conducted to compare topological differences in WM networks between SHPT and non-SHPT ESRD patients.

In current study, we hypothesized that the topological organization of the WM network was changed in ESRD patients undergoing peritoneal dialysis, and we further detected a relationship between the neurocognitive scores and clinical biomarkers with network metrics. To test the hypothesis, we included different physiological data from 50 patients with ESRD and 25 healthy controls, including cognitive tests, laboratory tests and DTI data. By using DTI traction diagram and graph theory, we compared the changes of WM network topology property in ESRD patients with or without SHPT and healthy controls. Then, correlation analyses among network topographical organizations, global cognitive scores and clinical biomarkers were conducted.

Methods And Materials

Participants

The present study was approved by the Ethics Committee of the Second Hospital of Anhui Medical University. Written informed consent was provided from all participants. Fifty hemodialysis ESRD patients (25 patients with SHPT, 14 males and 11 females, mean age 42.20 ± 7.53 years (SHPT group); 25 patients without SHPT, 15 males and 10 females, mean age 41.96 ± 6.17 years (Non-SHPT group)) were enrolled at the Nephrology Department in our hospital from January 2017 to July 2018. ESRD patients were diagnosed by (GRE (estimated glomerular filtration rate) ≤ 15 mL/min/1.73 m²). 25 healthy controls (HC group, 12 males and 13 females, mean age 41.80 ± 7.15 years) were recruited. The healthy controls had no kidney disease and did not undergo laboratory tests.

All subjects were right-handed, and more than 18 years old. All participants received the neuropsychological test and MRI examination on the same day, receiving regular hemodialysis three times a week in our hospital. Exclusion criteria were as follows: (1) obvious encephalopathy (cerebrovascular disease) revealed by clinical or imaging, (2) any history of drug/alcohol abuse, (3) leukoencephalopathy on a previous MRI, and (4) MRI contraindications.

Neuropsychological test

Before the MRI scan, we used the Montreal Cognitive Assessment (MoCA) to assess the participants' global cognitive abilities. A score less than 26 was defined as a diagnosis of cognitive impairment [19].

Laboratory test

Serum creatinine and urea levels within 24 hours prior to the MRI scan were conducted to evaluate renal function of all patients.

MRI Acquisition

MR imaging data were acquired in a Siemens Verio 3.0T MR scanner using an 8 channel coil. Use foam padding to reduce head motion. MRI sequence include 3D T1 weighted structural sagittal images (TE = 2.98 ms, TR = 1900 ms, thickness = 1 mm, voxel size = $1 \times 1 \times 1 \text{ mm}^3$, FOV = 256×256 , 176 slices) and diffusion weighted images (30 directions, TE = 84 ms, TR = 8400 ms, slice thickness = 3 mm, FOV = 256×256 , b = 0, 1000 s/mm^2 , no gap) in all subjects. All subjects were told to keep their eyes closed and remain awake within the MRI scanning process.

Data Processing

Data preprocessing and network construction are accomplished by using PANDA toolbox (www.nitrc.org/projects/panda) [20]. Briefly, the image preprocessing procedure included format conversion from DICOM to NIFTI format, BET (skull removal), extract brain tissue and structure, eddy current and motion artifact correction, and calculation of fractional anisotropy (FA).

WM network construction

Network node definition. The automated anatomical labeling (AAL) atlas [21] were used to parcel 90 cortical and subcortical regions (45 for each brain hemisphere) to define the network nodes [18] (Table 1, Figure 1).

Network edge definition. To define the edges of the structural network, we selected a threshold value for the fiber bundles with two end points located in both two regions. To remove spurious connections, we used a minimum of three fibers as a threshold [22]. We used fiber number (FN) of the connected fibers between two regions for the weights of the network edges. Finally, for each participant, the FN weighted 90×90 matrix structural networks were constructed [23] (Figure 1).

Network analysis

We performed by GREYNA (www.nitrc.org/projects/gretna) toolbox to analyze the WM network topological properties, included clustering coefficient (C_p), shortest path length (L_p), small-worldness (σ) (normalized clustering coefficient (γ) and normalized shortest path length (λ), local efficiency (E_{loc}), and global efficiency (E_g). The C_p of a network is the average of the clustering coefficient of each node in the network, which indicates the local efficiency for the transformation of the information. The L_p of the entire network refers to the average shortest travel distance across all nodes and indicates the most efficiency information transfer between the two nodes.

In order to test γ and λ in this study, 100 matched random networks are generated. These networks have the same number of nodes, edges and degree distributions, but retain the weighted distribution of the real network. We computed the γ ($\gamma = C_p/C_{p_{\text{random}}}$) and λ ($\lambda = L_p/L_{p_{\text{random}}}$), where $C_{p_{\text{random}}}$ and $L_{p_{\text{random}}}$ are the average clustering coefficient and shortest path length over the random network, respectively. A small world network should meet the γ if it is much larger than 1 and λ is close to 1.

Eg is the average of the inverse of the shortest path length of all node pairs in the network and usually reflects the ability of the network in parallel information processing. Eloc is the average of the global efficiency of the community neighboring all nodes in the network and represents the fault tolerance level of the network.

Identification of Hubs

Hubs of networks are key nodes that are estimated by different methods. In the present study, we identify the hub regions by regional efficiency. The hubs defined with regional efficiency at least one SD greater than the mean nodal efficiency of the network.

Statistical analysis

Demographic factors and clinical data were analyzed by SPSS 23.0 (SPSS, Chicago, IL, USA). We used mean $\pm$ SD for continuous variables, and frequencies for categorical variables in descriptive analysis. The differences among three groups including age, education and neuropsychological tests were analyzed with one-way analysis of variance (ANOVA). Post hoc pairwise comparisons were then performed using t tests. The sex data were analyzed by the chi-square test. In addition, two-sample t tests were used to compare the clinical data between two groups of patients.

For group effects in global and regional network metrics, comparisons were conducted among the three groups by one-way ANOVA and Nonparametric test (Kruskal-Wallis Test) for normal distribution and abnormal distribution, respectively. Levels of significance were set at $p < 0.05$ and a Bonferroni correction for multiple testing was applied for group differences ($\alpha = 0.05/3 = 0.017$). We also detected the relationship between network metrics, neuropsychological test scores and the clinical index by correlation analysis. To investigate the correlation between the neuropsychological test scores and specific brain regions, the nodes with significant group differences were taken.

Results

Neuropsychological and Clinical Assessments

The demographic, neuropsychological, and clinical data of the patients are summarized in Table 2. Differences in age, sex, and education level among groups were not significant ($p > 0.05$). No significant differences were found in disease duration or blood biochemistry between the two patient groups ($p > 0.05$) except for intact parathyroid hormone (iPTH) levels ($p < 0.01$). For the neuropsychological test, there were significantly decreased global cognition scores among both the SHPT and Non-SHPT patients compared with the healthy controls ($p < 0.01$).

Small-Worldness

All three groups showed a typical small-world organization of structural networks expressed as $\gamma > 1$ and $\lambda \approx 1$ (Figure 2). Compared with the healthy controls, the SHPT patients had a significantly decreased Cp

($p = 0.011$). Compared with the Non-SHPT patients, SHPT patients had a significantly lower γ ($p = 0.012$) and λ ($p = 0.006$).

Network Efficiency

Compared with healthy controls, only the SHPT patients had a significantly lower Eloc ($p = 0.010$). No group difference was found for Eg (Figure 2).

Nodal characteristics

Identification of network hubs

Network hub was defined if the nodal efficiency of a region was 1 SD greater than the average of the network. This study identified 12 hub nodes of the WM structural networks in the HC group and 14 hub nodes in both the SHPT and Non-SHPT groups. In three groups, 11 hub regions were identified in common, including bilateral supplementary motor area (SMA), the bilateral precentral gyrus (PreCG), bilateral precuneus (PCUN), right dorsolateral superior frontal gyrus (SFGdor), right middle frontal gyrus (MFG), right median cingulate and paracingulate gyri (DCG), left postcentral gyrus (PoCG) and right putamen (PUT). One hub region, the right middle temporal gyrus (MTG), was identified as a hub in the HC group. In addition, the left PUT was identified as a hub in both the SHPT and Non-SHPT groups. Two brain regions, the left middle frontal gyrus (MFG) and the right PoCG, were identified as hubs in the SHPT group but not in the Non-SHPT group. However, the left DCG and left middle occipital gyrus (MOG) were identified as hubs in the Non-SHPT group (Figure 3).

Between-group differences in regional efficiency

We further localized the regions with changed nodal efficiency in the ESRD patients (Figure 4, Table 3). Among the three groups, we found the regions which mainly distributed in the frontal and parietal cortices, including 5 frontal regions (bilateral SMA, left PreCG, left MFG and right ROL), 3 parietal regions (bilateral PoCG and right SMG), 2 temporal regions (bilateral MTG) and 2 subcortical regions (right THA and right PUT) were most significantly decreased. Post hoc tests showed that all of these regions had a reduced efficiency in both the SHPT and Non-SHPT group compared with the HC. Moreover, 8 of these regions, including 2 frontal regions (left PreCG and left MFG), 3 parietal regions (bilateral PoCG and right SMG), 1 temporal region (right MTG) and 2 subcortical regions (right THA and right PUT) showed significantly reduced efficiency in the Non-SHPT group compared with the SHPT group.

Correlations between network metrics and neuropsychological tests and clinical data

It was found that the iPTH and Lp were significantly negatively correlated with global cognition scores in the ESRD patients ($r = -0.531$, $p = 0.000$; $r = -0.289$, $p = 0.042$, respectively). For the clinical data, we found that the iPTH level was significantly negatively correlated with γ ($r = -0.351$, $p = 0.013$), λ ($r = -0.407$, $p = 0.003$) and σ ($r = -0.328$, $p = 0.020$) (Figure 5). For nodal efficiency, we conducted an analysis

only for the nodes in the abnormal regions (the 12 regions in Table 3). Correlations between nodal efficiency and global cognition scores or clinical index in these regions were not found.

Discussion

The present study showed the topological alterations of WM networks in ESRD patients with SHPT by using DTI tractography and graph theory methods. The major findings are summarized as follows: 1) decreased C_p in the SHPT group, 2) lower E_{loc} for SHPT patients, 3) alterations in γ , λ and σ between the two patient groups compared with HC, 4) alterations in nodal efficiency in the two patient groups compared with HC; and 5) a correlation between network metrics and neuropsychological tests and clinical data. These results will help us in understanding the neurophysiological mechanisms in ESRD patients with and without SHPT from a network perspective.

WM networks among the three groups displayed a typical small-world organization, although γ and λ were different between the SHPT and Non-SHPT group, which were in line with previous studies in healthy people[24, 25]. However, several topological properties, including C_p and E_{loc} , altered significantly between SHPT group and HC group. The fact that the WM network in SHPT patients had a lower C_p compared to healthy controls indicated ineffective information transmission in SHPT patients. From the perspective of network efficiency, we demonstrated a lower E_{loc} in SHPT patients compared to healthy controls, which suggests a loss of short-range connections throughout the brain network, likely attributable to changes in the modularized information processing ability and fault tolerance in the information transfers of the network[26].

Of the 12 brain regions identified as hubs from healthy controls, 11 brain regions were found in all three groups. We found both the SHPT and Non-SHPT group had added two more brain regions as hubs, the left MFG and the right PoCG, and the left DCG and MOG, respectively. On the other hand, the right MTG was no longer a hub in both the SHPT and Non-SHPT groups. The MTG is involved in several cognitive processes such as language and semantic memory processing and multimodal sensory integration[27–30]. Hubs play an important role in global information transfer and seem to be more vulnerable, since a stronger connection between hub regions leads to a higher probability of damage[31]. On the other hand, this result indicates that the weakened hub, likely relates to the cognitive impairment in the ESRD patients.

The spatial distribution of impaired brain regions by nodal efficiency was mainly located in the frontal and parietal cortices in ESRD patients. The node with the greatest disruption was the right THA, which is an intermediary for information processing, and the anterior and mediodorsal nucleus of THA influence memory storage and retrieval, respectively[32]. Frontal-parietal cortex lesions are considered to cause impairment of attention function, such as working memory, visuo-spatial attention and attention shift[33–35]. Some previous studies have demonstrated that ESRD patients have neuropsychological problems such as attention, learning and memory, speed and decision making[36, 37]. Moreover, ESRD patients had significantly decreased cerebral blood flow in the frontal cortex and thalamus in a perfusion

study[38]. In addition, several functional MRI studies have consistently shown ReHo and FC are decreased in the frontal and parietal cortex in ESRD patients[39, 40]. In short, the concurrent abnormalities found in functional studies and our disrupted WM connection in the same brain region could be specific metabolic brain disorders in ESRD patients.

We first found that the MoCA scores were negatively associated with Lp, and the iPTH level was also negatively correlated with small-world organization by two indexes (γ and λ) in ESRD patients. The small-worldness indicates an optimal balance between local specialization and global integration. The Lp and small-worldness changes reflect a possible disruption of WM connections in ESRD patients with increased iPTH levels. However, we did not find any relationships between neuropsychological tests and the clinical data with the global network measures in the SHPT and Non-SHPT group, which may be attributable to the small sample size.

There are several limitations of this study that should be addressed. Firstly, we define the WM network edges which is insufficient in resolving fiber crossing by using deterministic tractography. Secondly, we only constructed WM structural networks, and a combination of the functional and structural network is needed in future studies. Third, we only performed MoCA tests to evaluated global cognitive, and a detailed battery of neuropsychological tests of cognitive function is needed in future studies. Fourth, the sample size is quite limited and should cautiously interpreting the results. Finally, we did not collect information of anemia in healthy controls, which may affect our results.

In conclusion, our results indicated that the brain structural connectome in ESRD patients with SHPT was more disrupted than in without SHPT patients, which was correlated with cognitive impairment. The iPTH level may a risk factor for cognitive impairment in ESRD patients, and the WM structure network has the potential to be a connectome-based biomarker for early detection of cognitive impairment.

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Tables

Table 1. Cortical and subcortical regions of interest defined in the study.

Index	Regions	Abbreviation	Index	Regions	Abbreviation
(1,2)	Precentral gyrus	PreCG	(47,48)	Lingual gyrus	LING
(3,4)	Superior frontal gyrus, dorsolateral	SFGdor	(49,50)	Superior occipital gyrus	SOG
(5,6)	Superior frontal gyrus, orbital part	ORBsup	(51,52)	Middle occipital gyrus	MOG
(7,8)	Middle frontal gyrus	MFG	(53,54)	Inferior occipital gyrus	IOG
(9, 10)	Middle frontal gyrus, orbital part	ORBmid	(55,56)	Fusiform gyrus	FFG
(11,12)	Inferior frontal gyrus, opercular part	IFGoperc	(57,58)	Postcentral gyrus	PoCG
(13,14)	Inferior frontal gyrus, triangular part	IFGtriang	(59,60)	Superior parietal gyrus	SPG
(15,16)	Inferior frontal gyrus, orbital part	ORBinf	(61,62)	Inferior parietal, but supramarginal and angular gyri	IPL
(17,18)	Rolandic operculum	ROL	(63,64)	Supramarginal gyrus	SMG
(19,20)	Supplementary motor area	SMA	(65,66)	Angular gyrus	ANG
(21,22)	Olfactory cortex	OLF	(67,68)	Precuneus	PCUN
(23,24)	Superior frontal gyrus, medial	SFGmed	(69,70)	Paracentral lobule	PCL
(25,26)	Superior frontal gyrus, medial orbital	ORBsupmed	(71,72)	Caudate nucleus	CAU
(27,28)	Gyrus rectus	REC	(73,74)	Lenticular nucleus, putamen	PUT
(29,30)	Insula	INS	(75,76)	Lenticular nucleus, pallidum	PAL
(31,32)	Anterior cingulate and paracingulate gyri	ACG	(77,78)	Thalamus	THA
(33,34)	Median cingulate and paracingulate gyri	DCG	(79,80)	Heschl gyrus	HES
(35,36)	Posterior cingulate gyrus	PCG	(81,82)	Superior temporal gyrus	STG
(37,38)	Hippocampus	HIP	(83,84)	Temporal pole: superior temporal gyrus	TPOsup
(39,40)	Parahippocampal	PHG	(85,86)	Middle temporal gyrus	MTG

	gyrus				
(41,42)	Amygdala	AMYG	(87,88)	Temporal pole: middle temporal gyrus	TPOmid
(43,44)	Calcarine fissure and surrounding cortex	CAL	(89,90)	Inferior temporal gyrus	ITG
(45,46)	Cuneus	CUN			

Table 2. Demographic characteristics of study participants.

Characteristics	SHPT(n=25)	Non-SHPT(n=25)	Healthy Controls(n=25)	P-value
Age (year)	42.20±7.53	42.95±6.39	41.80±7.15	0.98a
Gender (M/F)	14/11	15/10	12/13	0.69b
Education(year)	9.36±2.86	9.44±3.23	11.12±2.54	0.06a
Disease duration(month)	40.76±18.28	38.44±16.84	-	0.64c
Urea(mmol/L)	26.14±7.08	26.01±8.06	-	0.95c
Creatinine(μmol/L)	962.96±212.19	914.48±274.11	-	0.49c
Uric acid(μmol/L)	447.04±38.42	463.00±52.40	-	0.23c
Calcium(mmol/L)	2.37±0.33	2.25±0.20	-	0.14 c
Phosphate (mmol/L)	1.26±0.12	1.27±0.10	-	0.74 c
Vitamin D (ng/ml)	8.75±4.62	11.14±4.09	-	0.06 c
iPTH(pg/mL)	1401±721.06	35.68±11.01	-	0.00c
MoCA(score)	22.92±2.22	24.96±1.59	28.00±1.22	0.00a*#

Note: a *p* value from one-way analysis of variance (ANOVA), b *p* value from chi-square test, c *p* value from t test. * means the post hoc analysis showed significant group difference between SHPT and Healthy controls. # means the post hoc analysis showed significant group difference between Non-SHPT and Healthy controls

Table3. Brain regions with significant group effects in nodal efficiency among SHPT, Non-SHPT patients and healthy controls.

Regions	F value of ANOVA(p value)	p value of post hoc test		
		SHPT versus healthy controls	Non-SHPT versus healthy controls	SHPT versus Non-SHPT
THA.R	26.51(0.000)	0.000	0.000	0.003
SMA.L	22.74(0.000)	0.000	0.000	0.341
SMA.R	22.66(0.000)	0.000	0.000	0.363
MTG.R	22.09(0.000)	0.000	0.000	0.039
PreCG.L	19.20(0.000)	0.002	0.000	0.004
PoCG.L	17.44(0.000)	0.005	0.000	0.004
SMG.R	16.67(0.000)	0.001	0.000	0.035
MFG.L	16.36(0.000)	0.008	0.000	0.004
ROL.R	15.57(0.000)	0.000	0.000	0.097
MTG.L	14.56(0.000)	0.000	0.000	0.285
PoCG.R	14.14(0.000)	0.044	0.000	0.002
PUT.R	13.99(0.000)	0.009	0.000	0.012

Figures

Figure 1

Flowchart for the construction of WM structural network by DTI. 1) The rigid coregistration from T1-weighted image (b) to the DTI native space (a). 2) The nonlinear registration from the resultant T1 image to the ICBM152 T1 template (c) in the MNI space resulting a transformation matrix (T). 3) The application of the inverse transformation (T') to the AAL template in the MNI space (e), resulting in the subject-specific AAL mask in the DTI native space (f). 4) The whole brain WM fibers were reconstructed (d) by DTI

deterministic tractography method. 5) The fiber number (FN) weighted networks of each subject were created by computing FN that connected each pair of brain regions. The matrices and 3D representations (lateral view) of the mean WM structural network of each group are shown in the bottom panel. The nodes and edges were mapped onto the cortical surfaces by BrainNet viewer software. HC, healthy controls, Non-SHPT, end-stage renal disease (ESRD) without secondary hyperparathyroidism (SHPT) patients, SHPT, ESRD with SHPT patients.

Figure 2

Boxplot shows the difference in global topological measures among the three group (medical, 50th percentile values, minimum and maximum). Significant differences were observed in Cp and Eloc between HC and SHPT group. Significant group effects were found γ and λ between Non-SHPT and SHPT group. * $P < 0.017$.

Figure 4

The distribution of brain regions with significant group difference in the nodal efficiency among three group. The node size represents the significance of between-group differences.

Figure 5

Scatterplots of correlation between network metrics and global cognition scores and clinical data. Negative correlation between MoCA scores with iPTH level and Lp. Negative correlation between network topological property (γ , λ and σ) and iPTH level.