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 reduced 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. Cognitive function was assessed using the Montreal Cognitive Assessment. The WM structural network was constructed by diffusion tensor imaging and a deterministic tractography method, and then we used graph theoretical approaches to investigate alterations in the global and regional properties of the WM networks in these participants. **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 a substantial public health concern worldwide. 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, normal or low calcium levels and low vitamin D 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 for assessing 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]. Recent studies have

revealed that whole brain white matter (WM) connectivity can be reconstructed through the diffusion tensor imaging (DTI) technique [16, 17]. Graph theoretical analysis suggested that WM networks characterize many important topological organizations, such as small-worldness [18]. To our knowledge, no studies have compared the topological differences of WM networks between SHPT and non-SHPT ESRD patients.

In this study, we hypothesized that the topological organization of the WM structural 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 this hypothesis, we included various physiological data from 50 patients with ESRD and 25 healthy controls, including cognitive tests, laboratory examinations and DTI data. We detected the changes in the topological organization of the WM structural networks in ESRD patients with and without SHPT and healthy controls by DTI tractography and graph theory methods. Then, correlation analyses among network topographical organizations, global cognitive scores and clinical biomarkers were conducted.

Methods And Materials

Participants

This study was approved by the Ethics Committee of the Second Hospital of Anhui Medical University and all participants provided written informed consent. 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 at the Second hospital of Anhui Medical University between January 2017 and July 2018. All subjects were right-handed and completed the neuropsychological test. The inclusion criteria were as follows: (1) clinically diagnosed ESRD (estimated glomerular filtration rate less than $15 \text{ mL/min/1.73 m}^2$), (2) receiving regular hemodialysis three times a week in our hospital, and (3) more than 18 years old. Exclusion criteria were as follows: (1) obvious encephalopathy revealed by clinical or imaging, (2) neurologic complications of ESRD treatment, (3) any history of drug/alcohol abuse, (4) leukoencephalopathy on a previous MRI, and (5) MRI contraindications.

In addition, 25 healthy right-handed controls (HC group, 12 males and 13 females, mean age 41.80 ± 7.15 years) without a history of neurologic, psychiatric, or traumatic diseases were selected from the local community. All healthy controls had no kidney disease and did not undergo laboratory tests.

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

Laboratory tests were conducted in all patients to evaluate their renal function, urea levels, and serum creatinine within 24 h prior to the MRI scan.

MRI Acquisition

MR imaging data were acquired in a 3.0T MRI scanner in our hospital. All participants were examined with an 8 channel head coil and foam padding to reduce head motion. We obtained 3D high resolution T1 weighted structural images (TE=2.98 ms, TR=1900 ms, slice thickness=1 mm, voxel size=1×1×1 mm³, FOV=256×256, number of slices=176) and diffusion weighted images (TE=84 ms, TR=8400 ms, slice thickness=3 mm, FOV=256×256, slice gap=0, b=0, 1000 s/mm², direction=30) in all subjects. All subjects were told to keep their eyes closed and stay awake during the MRI scan.

Data Processing

The data preprocessing and network construction were performed by PANDA (www.nitrc.org/projects/panda), which is a pipeline toolbox for diffusion MRI analysis [20]. Briefly, the image preprocessing steps were: format conversion of original data (DICOM), BET (skull removal), extract brain tissue and structure, eddy current and head motion correction, fractional anisotropy (FA) calculation, and diffusion tensor tractography.

WM network construction

Network node definition. The structural images of each subject were first coregistered to their first b0 images. Then, the images were resliced to DTI space through linear transformation. After that, the resliced images were normalized to the MNI space. Finally, the derived deformation parameters were inverted and employed to warp the automated anatomical labeling (AAL) atlas [21] from the MNI space to the diffusion image native space. After this procedure, 90 cortical and subcortical regions (45 for each hemisphere) were obtained, each representing a network node [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 end-points in both nodes during the fiber tracking). To reduce false positive connections due to the limited resolution of DTI a minimum of three fibers was used as a threshold [22]. The fiber number (FN) of the connected fibers between two regions was taken as the weights of the network edges. Finally, the FN weighted structural networks were constructed for each participant, which was represented by a symmetric 90×90 matrix[23] (Figure 1).

Network analysis

The WM network topological properties were analyzed using graph theory by GREYNA (www.nitrc.org/projects/gretna). To characterize the topological organization of the WM structural network, several key measures were considered. They are the clustering coefficient (Cp), shortest path length (Lp), small-worldness (σ) (normalized clustering coefficient (γ) and normalized shortest path length (λ)), local efficiency (Eloc), and global efficiency (Eg). The Cp 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.

To examine the γ and λ in this study, we generated 100 matched random networks that had the same number of nodes, edges, and degree distribution, but preserved 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.

E_g 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. E_{loc} 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 structural networks are essential nodes that are identified in various ways. In the present study, we applied regional efficiency to identify the hubs of the network. A node is considered as a hub if its regional efficiency is at least one SD greater than the mean nodal efficiency of the network.

Statistical analysis

Demographic and clinical data were analyzed using SPSS 23.0 (SPSS, Chicago, IL, USA). We used mean $\pm$ SD for continuous variables, and frequencies for categorical variables in descriptive analysis. Group differences in 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. 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 shown in Table 2. There were no significant differences in age, sex, or education among the three groups ($p > 0.05$). 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 C_p ($p=0.011$). 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 E_{loc} ($p=0.010$). No group difference was found for E_g (Figure 2).

Nodal characteristics

Identification of network hubs

The regions were defined as network hubs if their nodal efficiency was 1 SD greater than the average of the network. The 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 the bilateral precentral gyrus (PreCG), bilateral supplementary motor area (SMA), 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 altered nodal efficiency in the ESRD patients (Figure 4, Table 3). Among the three groups, we found the regions that were the most significantly decreased were 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). 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

We calculated the correlations between network metrics and global cognition scores 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). We did not find any correlations between nodal efficiency and global cognition scores or clinical index in these regions.

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 main findings are as follows: 1) decreased Cp in the SHPT group, 2) lower Eloc 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 showed a typical small-world organization, although there were differences of γ and λ between the SHPT and Non-SHPT group, which were consistent with previous studies in healthy people[24, 25]. However, several topological properties, including Cp, Lp and Eloc, were significantly altered in the SHPT group compared with the HC group. The fact that the WM network in SHPT patients had a lower Cp and a higher Lp compared to healthy controls indicated ineffective information transmission in SHPT patients. From the perspective of network efficiency, we demonstrated a lower Eloc 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 hub was weakened, likely related 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. First, the employment of deterministic tractography to define the WM network edges, which is insufficient in resolving fiber crossing, may result in a loss of existing fibers. Second, 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 evaluate global cognitive, and a detailed battery of neuropsychological tests of cognitive function is needed in future studies.

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 be 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.

References

- [1] Bugnicourt JM, Godefroy O, Chillon JM, Choukroun G, Massy ZA. Cognitive disorders and dementia in CKD: the neglected kidney-brain axis. *Journal of the American Society of Nephrology : JASN* 2013;24(3):353-63.
- [2] Liu ZH. Nephrology in china. *Nature reviews Nephrology* 2013;9(9):523-8.

- [3] Kurella M, Chertow GM, Luan J, Yaffe K. Cognitive impairment in chronic kidney disease. *Journal of the American Geriatrics Society* 2004;52(11):1863-9.
- [4] Jorde R, Waterloo K, Saleh F, Haug E, Svartberg J. Neuropsychological function in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D levels. The Tromso study. *Journal of neurology* 2006;253(4):464-70.
- [5] Seifter JL, Samuels MA. Uremic encephalopathy and other brain disorders associated with renal failure. *Seminars in neurology* 2011;31(2):139-43.
- [6] Theofilou P. Quality of life in patients undergoing hemodialysis or peritoneal dialysis treatment. *Journal of clinical medicine research* 2011;3(3):132-8.
- [7] Lee SY, Lee HJ, Kim YK, Kim SH, Kim L, Lee MS, et al. Neurocognitive function and quality of life in relation to hematocrit levels in chronic hemodialysis patients. *Journal of psychosomatic research* 2004;57(1):5-10.
- [8] Drueke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, et al. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *The New England journal of medicine* 2006;355(20):2071-84.
- [9] Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, et al. Correction of anemia with epoetin alfa in chronic kidney disease. *The New England journal of medicine* 2006;355(20):2085-98.
- [10] Chou FF, Chen JB, Hsieh KC, Liou CW. Cognitive changes after parathyroidectomy in patients with secondary hyperparathyroidism. *Surgery* 2008;143(4):526-32.
- [11] Kim SM, Zhao D, Schneider ALC, Korada SK, Lutsey PL, Guallar E, et al. Association of parathyroid hormone with 20-year cognitive decline: The ARIC study. *Neurology* 2017;89(9):918-26.
- [12] Lee CB, Yu SH, Kim NY, Kim SM, Kim SR, Oh SJ, et al. Association Between Coffee Consumption and Circulating Levels of Adiponectin and Leptin. *Journal of medicinal food* 2017;20(11):1068-75.
- [13] Pi HC, Xu YF, Xu R, Yang ZK, Qu Z, Chen YQ, et al. Cognitive Impairment and Structural Neuroimaging Abnormalities Among Patients with Chronic Kidney Disease. *Kidney & blood pressure research* 2016;41(6):986-96.
- [14] Kuriyama N, Mizuno T, Ohshima Y, Yamada K, Ozaki E, Shigeta M, et al. Intracranial deep white matter lesions (DWLs) are associated with chronic kidney disease (CKD) and cognitive impairment: a 5-year follow-up magnetic resonance imaging (MRI) study. *Archives of gerontology and geriatrics* 2013;56(1):55-60.
- [15] Luo S, Qi RF, Wen JQ, Zhong JH, Kong X, Liang X, et al. Abnormal Intrinsic Brain Activity Patterns in Patients with End-Stage Renal Disease Undergoing Peritoneal Dialysis: A Resting-State Functional MR

Imaging Study. *Radiology* 2016;278(1):181-9.

[16] Kim JH, Choi NK, Kim SM. A Retrospective Study of Association between Peg-shaped Maxillary Lateral Incisors and Dental Anomalies. *The Journal of clinical pediatric dentistry* 2017;41(2):150-3.

[17] Kalaitzidis RG, Karasavvidou D, Tatsioni A, Balafa O, Pappas K, Spanos G, et al. Risk factors for cognitive dysfunction in CKD and hypertensive subjects. *International urology and nephrology* 2013;45(6):1637-46.

[18] Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature reviews Neuroscience* 2009;10(3):186-98.

[19] Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;53(4):695-9.

[20] Cui Z, Zhong S, Xu P, He Y, Gong G. PANDA: a pipeline toolbox for analyzing brain diffusion images. *Frontiers in human neuroscience* 2013;7:42.

[21] Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 2002;15(1):273-89.

[22] Zou L, Su L, Qi R, Bao F, Fang X, Wang L, et al. Abnormal topological organization in white matter structural networks in survivors of acute lymphoblastic leukaemia with chemotherapy treatment. *Oncotarget* 2017;8(36):60568-75.

[23] Zhao T, Cao M, Niu H, Zuo XN, Evans A, He Y, et al. Age-related changes in the topological organization of the white matter structural connectome across the human lifespan. *Human brain mapping* 2015;36(10):3777-92.

[24] Gong G, He Y, Concha L, Lebel C, Gross DW, Evans AC, et al. Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography. *Cerebral cortex* 2009;19(3):524-36.

[25] Gong G, Rosa-Neto P, Carbonell F, Chen ZJ, He Y, Evans AC. Age- and gender-related differences in the cortical anatomical network. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 2009;29(50):15684-93.

[26] Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. *PLoS computational biology* 2007;3(2):e17.

[27] Siddarth P, Burggren AC, Eyre HA, Small GW, Merrill DA. Sedentary behavior associated with reduced medial temporal lobe thickness in middle-aged and older adults. *PloS one* 2018;13(4):e0195549.

- [28] Deshpande AK, Tan L, Lu LJ, Altaye M, Holland SK. fMRI as a Preimplant Objective Tool to Predict Children's Postimplant Auditory and Language Outcomes as Measured by Parental Observations. *Journal of the American Academy of Audiology* 2018;29(5):389-404.
- [29] Puschmann S, Thiel CM. Changed crossmodal functional connectivity in older adults with hearing loss. *Cortex; a journal devoted to the study of the nervous system and behavior* 2017;86:109-22.
- [30] Nilakantan AS, Voss JL, Weintraub S, Mesulam MM, Rogalski EJ. Selective verbal recognition memory impairments are associated with atrophy of the language network in non-semantic variants of primary progressive aphasia. *Neuropsychologia* 2017;100:10-7.
- [31] Crossley NA, Mechelli A, Scott J, Carletti F, Fox PT, McGuire P, et al. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain : a journal of neurology* 2014;137(Pt 8):2382-95.
- [32] Van der Werf YD, Jolles J, Witter MP, Uylings HB. Contributions of thalamic nuclei to declarative memory functioning. *Cortex; a journal devoted to the study of the nervous system and behavior* 2003;39(4-5):1047-62.
- [33] Smith R, Lane RD, Alkozei A, Bao J, Smith C, Sanova A, et al. Maintaining the feelings of others in working memory is associated with activation of the left anterior insula and left frontal-parietal control network. *Social cognitive and affective neuroscience* 2017;12(5):848-60.
- [34] Heinen K, Feredoes E, Ruff CC, Driver J. Functional connectivity between prefrontal and parietal cortex drives visuo-spatial attention shifts. *Neuropsychologia* 2017;99:81-91.
- [35] Mastroberardino S, Santangelo V, Macaluso E. Crossmodal semantic congruence can affect visuo-spatial processing and activity of the fronto-parietal attention networks. *Frontiers in integrative neuroscience* 2015;9:45.
- [36] Raphael KL, Wei G, Greene T, Baird BC, Beddhu S. Cognitive function and the risk of death in chronic kidney disease. *American journal of nephrology* 2012;35(1):49-57.
- [37] Giang LM, Weiner DE, Agganis BT, Scott T, Sorensen EP, Tighiouart H, et al. Cognitive function and dialysis adequacy: no clear relationship. *American journal of nephrology* 2011;33(1):33-8.
- [38] Fazekas G, Fazekas F, Schmidt R, Flooh E, Valetitsch H, Kapeller P, et al. Pattern of cerebral blood flow and cognition in patients undergoing chronic haemodialysis treatment. *Nuclear medicine communications* 1996;17(7):603-8.
- [39] Liang X, Wen J, Ni L, Zhong J, Qi R, Zhang LJ, et al. Altered pattern of spontaneous brain activity in the patients with end-stage renal disease: a resting-state functional MRI study with regional homogeneity analysis. *PloS one* 2013;8(8):e71507.

[40] Zheng G, Wen J, Zhang L, Zhong J, Liang X, Ke W, et al. Altered brain functional connectivity in hemodialysis patients with end-stage renal disease: a resting-state functional MR imaging study. Metabolic brain disease 2014;29(3):777-86.

Figures

Figure 1

Flowchart for the construction of WM structural network by DTI. 1) The rigid coregistration from T1-weighted image to the DTI native space. 2) The nonlinear registration from the resultant T1 image to the ICBM152 T1 template 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, resulting in the subject-specific AAL mask in the DTI native space. 4) The whole brain WM fibers were reconstructed 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, Lp and Eloc between HC and SHPT group. Significant group effects were found in σ by two indexes (γ and λ) between Non-SHPT and SHPT group. * $P < 0.05$.

Figure 3

The global network hubs with nodal efficiency in HC, Non-SHPT and SHPT group. HC, healthy control, Non-SHPT, end-stage renal disease (ESRD) without secondary hyperparathyroidism (SHPT) patients, SHPT, ESRD with SHPT patients.

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.