Abnormal rich club organization in end-stage renal disease patients before dialysis initiation and undergoing maintenance hemodialysis

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Abstract:

Background: End-stage renal disease (ESRD) patients are at substantially higher risk for developing cognitive impairment compared with the healthy population. Dialysis is an essential way to maintain the life of ESRD patients. Based on previous research, there did not provide an uncontested result whether cognition was improved or worsened during dialysis.

Methods: To explore the impact of dialysis treatment on cognitive performance, we recruited healthy controls (HCs), ESRD patients before dialysis initiation (bESRD) and those undergoing maintenance hemodialysis (mESRD). All ESRD patients performed a serious of blood biochemistry tests (hemoglobin, urea, cystatin C, Na+, K+ and parathyroid hormone). Neuropsychological tests were used to measure cognitive function. By using diffusion tensor imaging and graph-theory approaches, the topological organization of the whole-brain structural network was investigated. Generalized linear models (GLMs) were performed to investigate blood biochemistry predictors of the neuropsychological tests and the results of graph analyses in mESRD and bESRD groups.

Results: Neuropsychological analysis showed mESRD exhibited greater cognitive function than bESRD, but both were worse than HCs. Whole-brain graph analyses revealed that increased global efficiency and normalized shortest path length remained in the bESRD and mESRD than the HCs. Besides, lower normalized clustering coefficient was in bESRD relative to the HCs and mESRD. For the GLMs analysis, only the Cystatin C level was significantly associated with the average fiber length of rich club connections in bESRD.

Conclusions: Our study revealed that dialysis had a limited effect on cognitive improvement. Cystatin C may be a risk feature of cognitive decline of bESRD.
Keywords: end-stage renal disease, dialysis initiation, graph analyses, Cystatin C
**Background**

End-stage renal disease (ESRD) is known as the glomerular filtration rate of <15 mL/min/1.73 m², or continuous dialysis therapy is essential [1, 2]. It is often found in those with altered central nervous system function [3] and various neuropsychiatric troubles [4], which are closely related to reducing quality of life. One neuropsychological study documented that the partial metabolites and excessive toxins could be removed undergoing dialysis to retain effective basic life support [5]. Although some researchers pointed out that ESRD patients who are undergoing dialysis have universally been discovered to perform better than non-dialysis patients with ESRD on neuropsychological tests [6-12], others observed the persistence of cognitive dysfunction in ESRD patients on dialysis [6, 7, 9, 11-23]. Hence, it is necessary to explore the effect of dialysis on the pathophysiology of cognitive dysfunction in patients with ESRD.

Reproducible results of evidence observed cognitive decline in patients with chronic kidney disease and individuals during their dialysis therapy [5, 24-26]. Sabrina et al. discovered a reversible part of low neuropsychological testing in patients with ESRD who are receiving a single dialysis session, particularly in the abilities of memory, execution and psychomotor speed [27]. However, regular dialysis treatment may abduct arterial hypoxemia, ephemeral hypotension, and undulations in electrolytes and brain water content, which may eventually result in the aberrant central nervous system [28]. Therefore, the effect of the dialysis therapy in ESRD patients on cognitive dysfunctions remains largely unclear.

Neuroimaging has proved to be a worthy tool to explore the neural mechanisms of whole brain cognitive impairments in continuous hemodialysis ESRD patients [29-31]. As we know,
cognitive impairment does not only have the appearance of one or more altered isolated areas, but is also compactly associated with the abnormality of the distributive brain circuits [32-34]. The human connectome is essential for research of basic neurobiology [35], which could help us to comprehensively and accurately describe the internal network connection pattern of the whole brain [36].

In our study, to explore the impact of dialysis treatment and kidney failure on cognitive performance, we recruited healthy controls (HCs), ESRD patients before dialysis initiation (bESRD) and those undergoing maintenance hemodialysis (mESRD). Diffusion tensor imaging (DTI) was employed to systematically analyze the microstructure of the brain white matter network in all subjects. We hypothesized that both bESRD and mESRD patients had aberrant topological organization of the brain anatomical network, and there was discrimination between the two groups. We further investigated the association among the resulting network abnormality, neuropsychological performance, and clinical blood tests of all participants.

Methods

All prospective research was approved by the Medical Ethics Committee of the First Affiliated Hospital of the Medical College in Xi’an Jiaotong University and was conducted in accordance with the Declaration of Helsinki. Each participant signed a written informed consent before the experimental procedures were conducted.

Participants

In our research, 27 mESRD patients (34.1±1.66 years old), 32 age-, education- and gender-matched bESRD (32.7±1.67 years old) and 33 healthy controls with normal sight
(35.0±1.72 years) underwent MR imaging. The dialysis duration was greater than 3 months in mESRD patients. The following exclusion criteria were employed: (1) macroscopic brain T2-visible lesions on MRI scans; (2) psychiatric disorders or major neurologic disorders; (3) ischemic diseases including acute ischemic cerebrovascular disease, acute peripheral arterial occlusion, and/or advanced liver or heart failure; (4) asymptomatic coronary ischemia by electrocardiogram testing; (5) a history of diabetes; (6) substance abuse including drugs, alcohol and cigarettes; (7) color blindness, and (8) claustrophobia.

**Laboratory Examinations**

All patients with ESRD performed a series of blood biochemistry tests including hemoglobin, urea, cystatin C, Na⁺, K⁺ and parathyroid hormone before MR imaging to evaluate renal function. No blood indicator was measured in HCs.

**Neuropsychological tests**

All subjects underwent Auditory Verbal Learning Test–Huashan version (AVLT-H) to assess memory function, including immediate recall trial, short-term delayed recall trial, long-term delayed recall trial, and recognition trial. The neuropsychologic test contained 12 two-character spoken Chinese words from three diverse categories (occupations, apparel, flowers) with four words per category. The researcher read the list of words with one second between word intervals and asked each individual to remember as many words as possible [37]. AVLT-H scores were as follows: (1) immediate recall total score (IR-S), the total number of correct recollection of words in the first three learning tests; (2) short-term delayed recall score (SR-S), the total number of correct recollections of words when the researcher read the same word list 5 minutes after the first three learning tests; (3) long-term delayed recall score (LR-S), the total number of correct recollections of words when the researcher read the same word list 24 hours after the first three learning tests; (4) recognition score (RC), the number of correctly recognized words among those recalled in the three learning trials.
recall score(LR-S), the total number of correct recollections of words when the researcher read the same word list 5 minutes after the first three learning tests; and (4) recognition score (REC-S), the total number of correct recollections of words when the researcher read the same word list and 12 unrelated words (occupations, apparel, flowers).

*Image Acquisition*

All MRI imaging data were acquired with a 3.0 Tesla GE Excite scanner using an eight-channel coil (GE Medical System, Milwaukee, WI), including high-resolution T1-weighted image and diffusion tensor imaging (DTI) scans.

DTI sequences were obtained including 30 volume sequences with diffusion gradients applied along 30 non-collinear directions (b = 1000 sec/mm²) and one volume sequence with a b value of 0 sec/mm², and the following parameters were slice thickness, 4 mm; field of view (FOV), 240×240 mm²; matrix size, 128×128; repetition time (TR), 40,000 ms; and echo time (TE), 84 ms. Additionally, high-resolution anatomical images were also acquired by applying a T1-weighted three-dimensional MRI sequence with the following parameters: 140 axial slices; TR = 8.5 ms; TE = 3.4 ms; flip angle (FA) = 12°; slice thickness = 1.0 mm; no gap; matrix = 240×240; and FOV = 240×240 mm². Each participant was placed in a standard head coil to decrease head movement during the MRI data acquisition.

*Image Preprocessing*

Preprocessing of the DTI imaging data included three steps. Firstly, all raw DT imaging sequence quality was examined qualitatively. Then, the head motion and eddy current distortions were aligned by using an affine alignment of each diffusion-weighted image to the b=0 image. Finally, brain extraction and diffusion tensor elements
were evaluated by solving the Stejskal and Tanner equation [38, 39].

Network Construction

For each participant, a structural connectivity matrix was created by combining white matter tractography and cortical labels. In our study, we applied the Human Brainnetome Atlas [40] to extract the nodes of brain white matter connectivity, which segmented entire networks into 246 regions of interest. Additionally, the deterministic fiber tracking method [41] was employed to map white matter connections between brain regions. During the tracking procedure, we removed fibers which were less than 20 mm in length, as these may be false positive fibers [42]. For each participant, the two connectivity matrices described (1) unweighted networks (the number of fibers was greater than 3 between two brain regions), and (2) weighted networks along the average fibers strengths connecting a pair of ROIs.

Network Measures

The so-called rich club phenomenon of the brain network exists when the highly connected regions of a network are more intensively connected with each other than predicted on the basis of their high degree alone [43]. In recent studies, rich club organization of the brain structural connectome was discovered [30, 44–46]. In current research, we employed the graph theory approach to analysis the rich club organization of the brain binary networks in all subjects at the range of the nodal degree (k) cutoff, including rich club coefficient ($\varphi(k)$), normalized $\varphi(k)$ ($\varphi_{\text{norm}}(k)$), clustering coefficient ($C$), shortest path length ($L$), global efficiency ($E_{\text{gob}}$) and edge ($E$). The details and interpretations of these network measures are briefly described below.

The rich club coefficient, $\varphi(k)$, which was defined as a ratio of the number of connections among nodal degree $k$ or higher and the total probable number of connections if
these regions were completely connected [44, 45].

This is defined as the fraction of edges, E, that connects nodes, N, of degree k or higher over a range of k-values:

\[ \varphi(k) = \frac{2E_{\geq k}}{N_{\geq k}(N_{\geq k} - 1)} \]

where k is the number of connections of node i, N> k is the number of nodal degree > k and E> k is the number of remaining connections that delete the regions with connections less than k. \( \varphi_{\text{random}}(k) \) was calculated as the average on a set of 1000 random graphs within the equal size and similar connectivity distribution \( \varphi_{\text{norm}}(k) \), which was computed as the fraction of \( \varphi(k) \) and \( \varphi_{\text{random}}(k) \):

\[ \varphi_{\text{norm}}(k) = \frac{\varphi(k)}{\varphi_{\text{random}}(k)} \]

Therefore, \( \varphi_{\text{random}}(k) \) could be summed up as a rich club organization as usually being >1.

To better evaluate the effect of rich club organization, we added parameters at the same k-level range. By doing so, we could contrast and detect the global parameters if the supporting standard metrics were altered across elected k-values or the entire k-value regime.

At a specific k value, the clustering coefficient of a node \( i \), \( C_i \), which was defined as a ratio that is the proportion of possible connections that actually exist between the nearest neighbors of a node [47, 48]:

\[ C_i = \frac{2e_i}{k_i(k_i - 1)} \]

where \( k_i \) is the degree of node \( i \), and \( e_i \) is the number actually existing between the nearest neighbors of node \( i \).

The mean clustering coefficient of network C is the average of the clustering coefficient
over all nodes, which indicates the extent of local interconnectivity or cliquishness in a network [47]:

\[ C = \frac{1}{N} \sum_i C_i \]

*The shortest path length, \( L_{i,j} \),* defined as the minimal travel path for node \( i \) and node \( j \) in the network, is computed as follows [47]:

\[ L = \frac{1}{N(N-1)} \sum_{i \neq j} \min\{L_{i,j}\} \]

where \( N \) is the number of nodes in the network, and \( \min\{L_{i,j}\} \) is the shortest path length between any pair of nodes (e.g., node \( i \) and node \( j \)). The \( L \) of a network quantifies the ability for information propagation in parallel.

*The global efficiency\( (E_{glob}) \) of G that measures the capability of the parallel information transfer in the network [49] is defined as:

\[ E_{glob}(G) = \frac{1}{N(N-1)} \sum_{i,j \in G} \frac{1}{L_{i,j}} \]

where \( L_{i,j} \) is the shortest path length between node \( i \) and node \( j \) in G.

In order to normalize the parameters, we compared the actual values with the average calculated from 100 randomized networks of the same number of regions and nodal degree sequence. It can help to regulate these unstable graph theory indicators, such as \( C \) and \( L \), as their absolute values provided a restricted message about the integration of the brain network [50]. Statistically, we performed the same analyses as described above for the rich club effect and its factors, \( N \) and \( E \).

Additionally, we carried out the same analysis as described above for the number of the connections of the rich club organization across all k-levels, \( E \).
Network Nodes and Edges

In our study, we defined the rich club regions in three ways: on the basis of the group-average brain network which was calculated by the connections of all healthy subjects greater than 50%, on the individual level by ranking the degree value of the regions, and on the basis of the first 20% of most consistently interconnected regions in the HC groups [44].

Based on the definition of the rich club organization, we divided all nodes of the whole brain network into rich club and non-rich club nodes, and further divided the edges into three topological categories [45]: (1) the edges between two rich club regions were called rich club connections; (2) the edges between rich club regions and non-rich club regions were called feeder connections; and (3) the edges between two non-rich club regions were called local connections [45]. Additionally, for the brain weighted networks of the fiber length, we calculated the average value of the three types of connections for each participant.

Statistical Analysis

Software (SPSS version 16.0; SPSS, Chicago, Ill) was employed for the demographic and clinical characteristics among mESRD, bESRD and HC. To compare age, years of education and neuropsychological tests, the one-way analysis of variance (one-way ANOVA) was applied among the three groups, and the independent-sample t-test was used between pairs of individual groups (mESRD vs HC, bESRD vs HC, and mESRD vs bESRD). The χ² test was used to contrast gender distribution among the three groups. A significant difference was present if the p-value was less than 0.05.

To explore whether there were significant between-group differences in laboratory examinations (hemoglobin, urea, cystatin C, Na⁺, K⁺ and parathyroid hormone) between
mESRD and bESRD patients, we employed the independent-sample t-test after controlling age, gender and years of education. A p value of less than 0.05 was considered to show a significant difference.

For brain structural network connectivity (including $\varphi(k)$, $\varphi_{norm}(k)$, clustering coefficient (C), shortest path length (L), global efficiency ($E_{glob}$) and edge (E)), we employed a linear regression with coding controls as 0 and disease groups as 1 to test group differences for each group (HCs, mESRD and bESRD patients) after removing age, gender and education. The false discovery rate (FDR) approach was applied to correct for multiple comparisons across all k-level regimes. Additionally, we conducted the same method to analyze the differences of the average tract length of the rich club, feeder and local connections among the three groups in the selected k level.

Generalized linear models (GLMs) were performed separately to investigate blood biochemistry predictors of the neuropsychological test and average tract length results in the two groups (mESRD and bESRD patients) with gender, age and education imported as covariates. The threshold for a significant difference was set at an uncorrected p value of less than 0.05.

Results

Demographic, Laboratory Examinations and Memory Function comparisons

Demographic and laboratory examinations for the mESRD, bESRD and healthy control groups are summarized in Table 1. There was no significant difference in age ($p=0.532$), education level ($p=0.541$) and gender among the three groups (Table 1). Age, gender and education were employed as covariates in a subsequent statistical analysis.
Additionally, of all the results of blood indicator examinations between the two patient groups, hemoglobin, urea, Na⁺ and parathyroid hormone were thought to show significant differences (p<0.05), but no difference was indicated for Cystatin C and K⁺ (p>0.05) (Table 1).

Higher IR-S and SR-S were found in HCs compared with ESRD patients, and the mESRD compared with bESRD (Table 2, all p<0.05). LR-S and REC-S performed better in HCs compared with ESRD patients (p<0.05), while no difference was discovered between mESRD and bESRD patients (p>0.05) (Table 2).

After the GLMs analysis, we discovered a significant correlation between Cystatin C and IR-S, SR-S and LR-S in the bESRD group (uncorrected p<0.05) (Table 3).

**Global Topologic Organization of the Structural Network**

In the global brain network, \( \phi_{\text{norm}}(k) \) was increasingly higher than 1 over an increasing regime of k-levels among the three groups (HCs, mESRD and bESRD patients), which exhibited that a rich club phenomenon was detectable. The \( \phi_{\text{norm}}(k) \) was significantly greater in patients with ESRD than in the HC group, and bESRD patients was higher than mESRD patients for \( \phi_{\text{norm}}(k) \) at a steady range of k-values (p < 0.05, FDR corrected, Fig. 1). E, global efficiency, normalized shortest path length (normalized L) and normalized clustering coefficients (normalized C) were considered to show significant differences for each group (HCs, mESRD and bESRD patients) across high-degree k-levels respectively (p < 0.05, FDR corrected, Fig. 2). Additionally, compared with HCs, both mESRD and bESRD patients exhibited significantly increased normalized L at k=0, with no significant differences between mESRD and bESRD groups (p < 0.05, FDR corrected, Fig. 2c). There were evidently lower normalized C in bESRD patients relative to
the HCs and mESRD group, but no significant difference was discovered for normalized C between the HCs and mESRD individuals at k=0 ($p < 0.05$, FDR corrected, Fig. 2d). Here, graph analysis research recorded the differences of the rich club organization for the brain structural network.

*Regional Topologic Organization of the Structural Network*

The results of rich club regions were convergent on a group-level, on the individual level and across the group of participants, including the insular gyrus (INS), cingulate gyrus (CG), superior frontal gyrus (SFG), middle frontal gyrus (MFG), superior parietal lobule (SPL), inferior parietal lobule (IPL), superior temporal gyrus (STG), middle temporal gyrus (MTG), precentral gyrus (PrG), precuneus (Pcun), caudal cuneus gyrus (Cun), occipital polar cortex (OcG), superior occipital gyrus (sOcG), hippocampus (Hipp), basal ganglia (Str), and thalamus (Tha) (Fig. 3a).

In our results, we observed significantly increased average fiber length of the rich club, feeder, local connections in both the mESRD and bESRD groups relative to controls ($p < 0.05$, FDR corrected, Fig. 4). The average fiber length of the rich club connections of bESRD patients showed a significant increase relative to mESRD patients, with no differences for the average tract length of the feeder and local connections ($p < 0.05$, FDR corrected, Fig. 4).

*Relationships between Average Fiber Length and Laboratory Examinations*

GLMs analysis revealed that the Cystatin C level was significantly associated with the average fiber length of the rich club connections in patients with bESRD (uncorrected $p<0.05$), with no relationship for the average tract length of the feeder and local connections ($p>0.05$) (Table 4). There was no correlation between the Cystatin C level and the average
fiber length of the three types of brain structural connections in mESRD patients \((p>0.05)\) (Table 4).

**Discussion**

In our study, we detected the relationship between dialysis treatment, kidney failure and cognitive performance in ESRD patients. This study demonstrated that dialysis treatment has a limited protection effect on both cognitive performance and brain networks in ESRD patients, which can be summarized as follows: (i) The IR-S and SR-S comply with the order: HC > mESRD > bESRD; the LR-S and REC-S comply with the order: HC > mESRD = bESRD; (ii) For the global topologic organization of the structural network, both mESRD and bESRD have reduced the information transfer efficiency compared to HCs; and (iii) Cystatin C level was found to be correlated with the average fiber length of rich club connections in patients with bESRD.

We found that mESRD exhibited greater memory than bESRD, but both were worse than HCs. Based on previous research, there were not yet able to provide an uncontested result whether cognition was improved or worsened during dialysis [51-53]. Based on the results of the neuropsychological tests, our results seemed to indicate that ESRD patients who underwent long-term dialysis have better cognitive function than ESRD patients before dialysis initiation. Dialysis had an improvement effect for cognitive function. However, there are also many studies which found worse cognitive function over time for dialysis patients [6, 21]. The reason may be concerned with the time of dialysis. Because some report have indicated that the duration of dialysis was also an important feature for cognition [21]. The mean duration of dialysis for our subjects was 30 months, with the beneficial effect of
treatment on retaining cognition lasting only a limited amount of time. At some point in a longer duration, the gradient course of cognition might reach a plateau or even decline, but we cannot account for this in this study.

By using graphic metrics, such as efficiency and modularity, we found that all of the groups (HC, mESRD and bESRD) exhibited a rich club phenomenon. Increased global efficiency remained in the bESRD group and mESRD rather than the HC group. Global efficiency measures the ability of parallel information propagation with in a network. Higher global efficiency seems to indicate effective integrity and rapid information propagation between and across remote brain regions [54, 55]. For our earlier studies, decreased global efficiency has previously been reported in functional brain networks [56]. Here, the increased global efficiency in the structural network may suggest of self-regulation of the brain. A long tradition of research has clearly shown the brain's ability to learn volitional control of its own activity and effects on behavior [57]. The increased global efficiency in structural networks and decreased global efficiency in functional network synergy were used to maintain brain functioning. Besides, both mESRD and bESRD patients exhibited significantly increased normalized L at k=0 than healthy control subjects. It indicated that, to maintain brain function, the structural network of ESRD patients (no matter if undergoing dialysis) may show a network recombination to connect more distant brain regions. The dialysis seems to not have a protective effect for the brain network. Furthermore, for normalized C, we found lower normalized C in bESRD patients relative to the HCs and mESRD group, but no significant difference was discovered between the HCs and mESRD group. It suggested that patients undergoing long-term dialysis have better cognitive function than ESRD patients before
dialysis initiation. From the above, our findings have implications that dialysis has a limited protective effect for the brain network.

For the correlation analysis between the structural network and laboratory examinations, only the Cystatin C level was significantly associated with the average fiber length of rich club connections in patients with bESRD. Many studies have reported that Cystatin C is one of the early markers of chronic kidney disease which might serve as early and effective markers for cognitive decline in kidney patients [58, 59]. Besides, studies have shown that the Cystatin C concentration is also associated with the risk of dementia [60, 61]. For the neuropsychological tests, the difference between mESRD and bESRD mainly focuses on memory. Higher levels of Cystatin C may play a role in the worse memory scores, which is consistent with our results and previous studies [60, 61].

Our study had several limitations which need to be addressed in future studies. First, the sample size is relatively small in this study, which limits efforts in the statistical analysis. A large group of population samples is needed in the future to verify the relationships between dialysis treatment and cognitive performance. Second, blood biochemistry levels were only tested in ESRD patients, but blood biochemistry tests should be considered in healthy control subjects to investigate the relationship between the network and blood biochemistry in further studies. Finally, the neuropsychological tests in our study were all based on a scale test, and more comprehensive cognitive-ability tasks should be obtained in the further experiments.

Conclusion

To summarize, we conclude that cognitive function seems to improve in ESRD patients who underwent dialysis treatment. Dialysis treatment may predict better cognitive
performance, but the improvement effect is limited. Higher Cystatin C levels may be potential risk factors of cognitive function in ESRD patients before dialysis initiation. These results highlighted the need for a better understanding of dialysis treatment on cognition. In the future, the relationship between cognitive function and the different stage and duration of dialysis should be observed.

List of abbreviations

ESRD End-stage renal disease
bESRD ESRD patients before dialysis initiation
mESRD ESRD patients undergoing maintenance hemodialysis
HCs healthy controls
IR-S immediate recall total score
SR-S short-term delayed recall score
LR-S long-term delayed recall score
REC-S recognition score

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Declarations:

Ethics approval and consent to participate: All research procedures were approved by the Institutional Review Board of the First Affiliated Hospital of the Medical College at Xi'an Jiaotong University and were conducted in accordance with the Declaration of Helsinki. All
subjects gave written, informed consent after the experimental procedures had been fully explained.

**Consent for publication:** Written informed consent for publication was obtained from all participants.

**Availability of data and material:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** None declared.

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Authors' contributions: SM, MZ, YL, DD, PL, XM, HL, JM

SM: experiment design, data analysis, drafting of manuscript; MZ: experiment design, data analysis; YL: data analysis; DD: patient evaluation and selection; PL: patient evaluation and selection; HL: performed the experiment; JM: study conception/design. All authors read and approved the final manuscript.

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References

1. Luo S, Qi RF, Wen JQ, Zhong JH, Kong X, Liang X, Xu Q, Zheng G, Zhang Z, Zhang LJ: 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):181-189.

2. Kim HS, Park JW, Bai DS, Jeong JY, Hong JH, Son SM, Jang SH: Diffusion tensor imaging findings in neurologically asymptomatic patients with end stage renal disease. NeuroRehabilitation 2011, 29(1):111-116.

3. Deyn PPD, Saxena VK, Abts H, Borggreve F, Crols R: Clinical and pathophysiological aspects of neurological complications in renal failure. Acta Neurologica Belgica 1992, 92(4):191-206.

4. Brouns R, Deyn PPD: Neurological complications in renal failure: a review. Clinical Neurology & Neurosurgery 2004, 107(1):1-16.

5. Williams MA, Sklar AH, Burright RG, Donovick PJ: Temporal effects of dialysis on cognitive functioning in patients with ESRD. American Journal of Kidney Diseases 2004, 43(4):705-711.

6. Bo H: A prospective study of patients in chronic hemodialysis—III. Predictive value of intelligence, cognitive deficit and ego defence structures in rehabilitation. Journal of Psychosomatic Research 1974, 18(3):151-160.

7. Ginn HE, Teschan PE, Walker PJ, Hamel B: Neurotoxicity in uremia. Kidney International Supplement 1975, 7(3):357-360.

8. Murawski BJ: Psychological approaches to study the uremic state. Kidney International Supplement 1975(2):206-209.

9. Teschan PE, Ginn HE, Bourne JR, Ward JW, Hamel B, Nunnally JC, Musso M, Vaughn WK: Quantitative indices of clinical uremia. Kidney International 1979, 15(6):676-697.

10. Ryan JJ, Souheaver GT, Dewolfe AS: Halstead-reitan test results in chronic hemodialysis. Journal of Nervous & Mental Disease 1981, 169(5):311-314.

11. Mckee DC, Burnett GB, Raft DD, Batten PG, Bain KP: Longitudinal study of neuropsychological functioning in patients on chronic hemodialysis: A preliminary report. Journal of Psychosomatic Research 1982, 26(5):511-518.

12. Baker LRI, Brown AL, Byrne J, Charlesworth M, Warrington EK: Head scan appearances and cognitive function in renal failure. Clinical Nephrology 1989, 32(5):242-248.

13. Greenberg RP, Davis G, Massey R: The psychological evaluation of patients for a kidney transplant and hemodialysis program. American Journal of Psychiatry 1973, 130(3):274-277.

14. Teschan PE, Ginn HE, Walker PJ, Bourne JR, Ward JW: Quantified functions of the nervous system in uremic patients on maintenance dialysis. Trans Am Soc Artif Intern Organs 1974, 20A:388-392.

15. Spehr W, Sartorius H, Berglund K, Hjorth B, Kablitz C, Plog U, Wiedemann PH, Zapf K: EEG and haemodialysis. A structural survey of EEG spectral analysis, Hjorth’s EEG descriptors, blood variables and psychological data. Electroencephalogr Clin Neurophysiol 1977, 43(6):787-797.

16. English A, Savage RD, Britton PG, Ward MK, Kerr DN: Intellectual impairment in chronic renal failure. Br Med J 1978, 1(6117):888-890.

17. Alexander L, Hightower MG, Anderson RP, Snow NE: Suitability of vigilance test data as a neurobehavioral measure of uremic status. Perceptual & Motor Skills 1980, 50(1):131-135.

18. Harold, A., Ziesat, Jr., Patrick, E., Logue, Sarah, M., McCarty: Psychological measurement of
memory deficits in dialysis patients. *Percept Mot Skills* 1980, 50(1):311–318.

19. Gilli P., Bastiani P, De: Cognitive function and regular dialysis treatment. *Clinical Nephrology* 1983, 19(4):188-192.

20. Ratner DP, Adams KM, Levin NW, Rourke BP: Effects of hemodialysis on the cognitive and sensory-motor functioning of the adult chronic hemodialysis patient. *Journal of Behavioral Medicine* 1983, 6(3):291-311.

21. Wolcott DL, Wellisch DK, Marsh JT, Schaeffe J, Landsverk J, Nissenson AR: Relationship of dialysis modality and other factors to cognitive function in chronic dialysis patients. *American Journal of Kidney Diseases* 1988, 12(4):275-284.

22. Marsh JT, Brown WS, Wolcott D, Carr CR, Harper R, Schweitzer SV, Nissenson AR: rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. *Kidney Int* 1991, 39(1):155-163.

23. Churchill DN, Bird DR, Taylor W, Beecroft ML, Gorman J, Wallace JE: Effect of high-flux hemodialysis on quality of life and neuropsychological function in chronic hemodialysis patients. *American Journal of Nephrology* 1992, 12(6):412-418.

24. Kurella, M.: Chronic kidney disease and cognitive impairment in the elderly: the health, aging, and body composition study. *Journal of the American Society of Nephrology Jasn* 2005, 16(7):2127-2133.

25. Chilcot J, Wellsted D, Silva-Gane MD, Farrington K: Depression on dialysis. *Nephron Clinical Practice* 2008, 108(4):c256-c264.

26. Ma X, Jiang G, Li S, Wang J, Zhan W, Zeng S, Tian J, Xu Y: Aberrant functional connectome in neurologically asymptomatic patients with end-stage renal disease. *Plos One* 2015, 10(3):e0121085.

27. Schneider SM, Malecki AK, Katrin M, Robby S, Matthias G, Peter M, Marcus H, Heike K, Kristin J, Kielstein JT: Effect of a single dialysis session on cognitive function in CKD5D patients: a prospective clinical study. *Nephrology Dialysis Transplantation* 2015, 30(9):1551-1559.

28. Toyoda: Simultaneous onset of haemorrhagic and ischaemic strokes in a haemodialysis patient. *J Neurol Neurosurg Psychiatry* 2002, 72(5):673-674.

29. Prohovnik I, Post J, Uribarri J, Lee H, Sandu O, Langhoff E: Cerebrovascular effects of hemodialysis in chronic kidney disease. *Journal of Cerebral Blood Flow & Metabolism Official Journal of the International Society of Cerebral Blood Flow & Metabolism* 2007, 27(11):1861-1869.

30. Qiu Y, Lv X, Su H, Jiang G, Cheng L, Tian J, Satoru H: Structural and functional brain alterations in end stage renal disease patients on routine hemodialysis: a voxel-based morphometry and resting state functional connectivity study. *Plos One* 2014, 9(5):e98346.

31. Zhang R, Liu K, Yang L, Zhou T, Qian S, Li B, Peng Z, Li M, Sang S, Jiang Q: Reduced white matter integrity and cognitive deficits in maintenance hemodialysis ESRD patients: A diffusion-tensor study. *European Radiology* 2015, 25(3):661-668.

32. Liu J, Liang J, Qin W, Tian J, Yuan K, Bai L, Zhang Y, Wang W, Wang Y, Li Q: Dysfunctional connectivity patterns in chronic heroin users: An fMRI study. *Neuroscience Letters* 2009, 460(1):72-77.

33. Ling-Li Z, Hui S, Li L, Wang L, Li B, Peng F, Zhou Z, Li Y, Hu D: Identifying major depression using whole-brain functional connectivity: a multivariate pattern analysis. *Brain A Journal of Neurology* 2012, 135(5):1498-1507.
34. Nan J, Liu J, Li G, Xiong S, Yan X, Yin Q, Zeng F, Deneen KM, Liang F, Gong Q: Whole-brain functional connectivity identification of functional dyspepsia. Plos One 2013, 8(6):e65870.
35. W. TA, A. CK, M. TP, W. SD, Darrell VHJ: Mapping the human connectome. Neurosurgery 2012, 71(1):1-5.
36. Varela FJ, Lachaux JP, Rodriguez E, Martinerie JF: The brainweb: phase synchronization and large-scale integration. Nature Reviews Neuroscience 2001, 2(4):229-239.
37. Zhao Q, Lv Y, Yan Z, Zhen H, Guo Q, Sonia B: Short-term delayed recall of auditory verbal learning test is equivalent to long-term delayed recall for identifying amnestic mild cognitive impairment. Plos One 2012, 7(12):e51157.
38. P.J., Basser, and, J., Mattiello, and, D., LeBihan: MR diffusion tensor spectroscopy and imaging. Biophysical Journal 1994, 66(1):259-267.
39. Peter, J., Basser, and, Carlo, Pierpaoli: Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. Journal of Magnetic Resonance 1996, 111(3):209-219.
40. Fan L, Li H, Zhuo J, Zhang Y, Wang J, Chen L, Yang Z, Chu C, Xie S, Laird AR: The human brainnetome atlas: A new brain atlas based on connectional architecture. 2016, 26(8):3508-3526.
41. Fang-Cheng, Yeh, Timothy, D., Verstynen, Yibao, Wang, Juan, C., Fernández-Miranda: Deterministic diffusion fiber tracking improved by quantitative anisotropy. Plos One 2013, 8(11):e80713.
42. Daianu M, Mezher A, Mendez MF, Jahanshad N, Jimenez EE, Thompson PM: Disrupted rich-club network in behavioral variant frontotemporal dementia and early-onset Alzheimer’s disease. Hum Brain Mapp 2016, 37(3):868-883.
43. Colizza V, Flammini A, Serrano MA, Vespignani A: Detecting rich-club ordering in complex networks. Nature Physics 2006, 2(3):110-115.
44. van den Heuvel MP, Sporns O: Rich-club organization of the human connectome. J Neurosci 2011, 31(44):15775-15786.
45. van den Heuvel MP, Kahn RS, Goni J, Sporns O: High-cost, high-capacity backbone for global brain communication. Proc Natl Acad Sci U S A 2012, 109(28):11372-11377.
46. van den Heuvel MP, Sporns O: An anatomical substrate for integration among functional networks in human cortex. J Neurosci 2013, 33(36):14489-14500.
47. Watts DJ, Strogatz SH: Collective dynamics of small world networks. Nature 1998, 393(6684):440-442.
48. Liu J, Zhao L, Li G, Xiong S, Nan J, Li J, Yuan K, von Deneen KM, Liang F, Qin W: Hierarchical alteration of brain structural and functional networks in female migraine sufferers. Plos One 2012, 7(12).
49. Vito, Latora, Massimo, Marchiori: Efficient behavior of small-world networks. Physical Review Letters 2001, 87(19):198701.
50. Lock T: Networks of the brain. Journal of Developmental & Behavioral Pediatrics 2012, 33(3):213.
51. Investigators CS: Cognitive impairment in non–dialysis-dependent CKD and the transition to dialysis: findings from the chronic renal insufficiency cohort (CRIC) study. American Journal of Kidney Diseases 2018, 72(4):499-508.
52. Song M-K, Paul S, Ward SE, Gilet CA, Hladik GA: One-year linear trajectories of symptoms,
physical functioning, cognitive functioning, emotional well-being, and spiritual well-being among patients receiving dialysis. American Journal of Kidney Diseases 2018, 72(2):198-204.

53. Neumann D, Mau W, Wienke A, Girndt M: Peritoneal dialysis is associated with better cognitive function than hemodialysis over a one-year course. Kidney International 2017, 93(2):430-438.

54. Sporns O, Zwi JD: The small world of the cerebral cortex. Neuroinformatics 2004, 2(2):145-162.

55. He, Yi, Yu, Xin, Wang, Xiao, Huali, Jinhui, Yong: Apolipoprotein E epsilon 4 modulates functional brain connectome in alzheimer’s disease. Human brain mapping 2015, 36(5):1828-1846.

56. Mu J, Chen T, Liu Q, Ding D, Ma X, Li P, Li A, Huang M, Zhang Z, Liu J: Abnormal interaction between cognitive control network and affective network in patients with end-stage renal disease. Brain Imaging & Behavior 2017, 12(4):1099-1111.

57. Birbaumer N, Ruiz S, Sitaram R: Learned regulation of brain metabolism. Trends in Cognitive Sciences 2013, 17(6):295-302.

58. Wei Y, Wei YK, Zhu J: Early markers of kidney dysfunction and cognitive impairment among older adults. Journal of the Neurological Sciences 2017, 375(375):209-214.

59. Yaffe K, Kurella-Tamura M, Ackerson L, Hoang TD, Anderson AH, Duckworth M, Go AS, Krousel-Wood M, Kusek JW, Lash JP et al: Higher levels of cystatin C are associated with worse cognitive function in older adults with chronic kidney disease: the chronic renal insufficiency cohort cognitive study. J Am Geriatr Soc 2014, 62(9):1623-1629.

60. Yelena S, Peters KW, Areef I, Kristine Y, Fink HA, Stone KL, Michael S, Ensrud KE, Fractures ftSoO: Cystatin C and cognitive impairment 10 years later in older women. J Gerontol A Biol Sci Med Sci 2014, 70(6):771-778.

61. Yaffe K, Lindquist K, Shlipak MG, Simonsick E, Kurella-Tamura M: Cystatin-C as a marker of cognitive function in elders: findings from the health ABC study. Annals of Neurology 2008, 63(6):798-802.
**Figure legends**

Figure 1. The rich club phenomenon in HCs, mESRD and bESRD groups. (a). the rich club level of HCs. (b). the rich club level of mESRD. (c). the rich club level of bESRD. (d). The rich club phenomenon in HCs, mESRD and bESRD groups.

Figure 2. The difference of network properties among HCs, mESRD and bESRD groups. (a). the E values of three groups in difference k level. (b). the global efficiency of three groups in difference k level. (c). the normalized L of three groups in difference k level. (d). the normalized C of three groups in difference k level.

Figure 3. rich club node and edges. (a) The rich club node include: the insular gyrus (INS), cingulate gyrus (CG), superior frontal gyrus (SFG), middle frontal gyrus (MFG), superior parietal lobule (SPL), inferior parietal lobule (IPL), superior temporal gyrus (STG), middle temporal gyrus (MTG), precentral gyrus (PrG), precuneus (Pcun), caudal cuneus gyrus (Cun), occipital polar cortex (OcG), superior occipital gyrus (sOcG), hippocampus (Hipp), basal ganglia (Str), and thalamus (Tha). (b) the rich club edges

Figure 4. the difference of edges of rich club among HCs, mESRD and bESRD groups.