Re-Establishing Brain Networks in Patients with ESRD after Successful Kidney Transplantation

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Abstract

Background and objectives Cognition in ESRD may be improved by kidney transplantation, but mechanisms are unclear. We explored patterns of resting-state networks with resting-state functional magnetic resonance imaging among patients with ESRD before and after kidney transplantation.

Design, setting, participants, & measurements Thirty-seven patients with ESRD scheduled for kidney transplantation and 22 age-, sex-, and education-matched healthy subjects underwent resting-state functional magnetic resonance imaging. Patients were imaged before and 1 and 6 months after kidney transplantation. Functional connectivity of seven resting-state subnetworks was evaluated: default mode network, dorsal attention network, central executive network, self-referential network, sensorimotor network, visual network, and auditory network. Mixed effects models tested associations of ESRD, kidney transplantation, and neuropsychological measurements with functional connectivity.

Results Compared with controls, pretransplant patients showed abnormal functional connectivity in six subnetworks. Compared with pretransplant patients, increased functional connectivity was observed in the default mode network, the dorsal attention network, the central executive network, the sensorimotor network, the auditory network, and the visual network 1 and 6 months after kidney transplantation (P=0.01). Six months after kidney transplantation, no significant difference in functional connectivity was observed for the dorsal attention network, the central executive network, the auditory network, or the visual network between patients and controls. Default mode network and sensorimotor network remained significantly different from those in controls when assessed 6 months after kidney transplantation. A relationship between functional connectivity and neuropsychological measurements was found in specific brain regions of some brain networks.

Conclusions The recovery patterns of resting-state subnetworks vary after kidney transplantation. The dorsal attention network, the central executive network, the auditory network, and the visual network recovered to normal levels, whereas the default mode network and the sensorimotor network did not recover completely 6 months after kidney transplantation. Neural resting-state functional connectivity was lower among patients with ESRD compared with control subjects, but it significantly improved with kidney transplantation. Resting-state subnetworks exhibited variable recovery, in some cases to levels that were no longer significantly different from those of normal controls.

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Introduction

CKD is a major global health problem. In the United States, approximately 8% of the population suffers from CKD, and 571,000 patients receive treatment for ESRD (1). Cognitive impairment is prevalent in patients with ESRD, with an estimated prevalence of 30%–60% (2–5). This is particularly true among those receiving hemodialysis. Cognitive impairment is associated with adverse outcomes, such as disability, hospitalization, and death. It is also related to increased cost of medical care (6,7).

Recent studies showed that successful kidney transplantation can lead to improvement in the cognitive performance of patients with ESRD (8–10). However, it has also been shown that not all cognition domains recover simultaneously after successful kidney transplantation (8,11). Harciarek *et al.* (8) reported that psychomotor speed, visual planning, retrieval of learned material, and abstract thinking were improved in patients 1 month after kidney transplantation, whereas memory function improvement was generally not observed until 1 year after kidney transplantation. However, possible neural mechanism remains unclear.

Recently, resting-state functional magnetic resonance imaging (MRI) has provided evidence for spontaneous neuronal activity by measuring blood oxygen level–dependent signal in the absence of a prompted task. Brain activity in the resting state is spatially distributed into sets of functionally coherent patterns, namely resting-state networks (12–15). As a model-free analysis technique, independent component analysis can be used

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to separate a set of spatially independent components from mixed blood oxygen level–dependent signals (12). The resting-state network includes seven main subnetworks (*i.e.*, default mode network, dorsal attention network, central executive network, self-referential network, sensorimotor network, visual network, and auditory network) that have been consistently identified in human brains (16). These networks could facilitate investigation into the neural basis for behavioral improvement patterns after kidney transplantation.

To our knowledge, default mode network is the most widely investigated resting-state subnetwork in patients with ESRD (17–19). Default mode network regions are involved in visual and auditory attention, language processing, memory, and motoric activity. Recently, Zhang *et al.* (18) reported that functional connectivity recovered earlier than structural connectivity after changes to the default mode network. However, this study only focused on the structural and functional connectivity changes in the default mode network 1 month after kidney transplantation. The effects of ESRD may be more global (20), and the potential involvement of other resting-state subnetworks warrants investigation. Thus, the purpose of this investigation is to examine the recovery patterns of seven resting-state subnetworks in patients with ESRD after kidney transplantation.

For the purpose of our investigation, we used the independent component analysis algorithm to examine the temporal and spatial change patterns of the functional connectivity of resting-state networks in patients with ESRD 1 and 6 months after successful kidney transplantation. Additionally, we investigated the correlation between changes in the resting-state subnetworks and the neuropsychological test results and clinical biomarkers of patients with ESRD.

Materials and Methods

Subjects

This prospective study was approved by our Medical Research Ethics Committee, and written informed consent was obtained from each subject before enrollment. From June of 2012 to July of 2015, 37 patients with ESRD scheduled to undergo kidney transplantation (27 patients received hemodialysis, six patients received peritoneal dialysis, and four patients did not receive any replacement therapy during baseline examinations) were included. The average dialysis vintage was 1.4±1.7 years (0–8.3 years). The patients on hemodialysis received hemodialysis three times a week, whereas the patients on peritoneal dialysis received peritoneal dialysis four times per day. They were enrolled from the National Clinical Research Center of Kidney Disease, Jinling Hospital, Medical School of Nanjing University if they were diagnosed with eGFR<15 ml/min per 1.73 m^2 or receiving chronic dialysis treatment and scheduled for kidney transplantation. Patients with ESRD who completed all necessary laboratory examinations, neuropsychological tests, and MRI before and 1 and/or 6 months after kidney transplantation were included. The following additional exclusion criteria were applied: (*1*) history of drug or alcohol abuse, (*2*) noticeable brain lesions on MRI, (*3*) history of or current psychiatric disorders, (*4*) other systemic diseases, (*5*) clinically relevant visual or hearing impairment, (*6*) previous kidney transplantation or other organ transplantation, (*7*) dropout, (*8*) severe complications after kidney transplantation, and (*9*) head motion of >1.0 mm or 1.0° during MRI. The flowchart of this study can be found in Figure 1.

Twenty-two age- and sex-matched healthy control subjects were also recruited from the community. No control subjects had systemic diseases or history of psychiatric or neurologic diseases. All control subjects self-identified as right handed and had normal eyesight.

Neuropsychological Tests

All patients and healthy controls underwent a number of neuropsychological tests, including the number connecting test type A (NCT-A), the digit symbol test, the line tracing test, and the serial dotting test, within 1 hour before MRI. These examinations were performed at 24 hours after dialysis. Depression and anxiety were also measured using the Hospital Anxiety and Depression Scale (*i.e.*, self-rating anxiety and depression scales: the Zung Self-Rating Anxiety Scale [SAS] and the Zung Self-Rating Depression Scale) (21,22). NCT-A assesses the domain of psychomotor speed. Digit symbol test is associated with the domains of psychomotor speed, attention, and visual memory. The line tracing test is a test of motor speed and accuracy, and the serial dotting test examines the pure motor speed. SAS and the Zung Self-Rating Depression Scale evaluate the subjective anxiety and depression levels, respectively. Less time in the NCT-A, the line tracing test, and the serial dotting test and lower scores on the SAS and the Zung Self-Rating Depression Scale reflect better performance, whereas higher digit symbol test scores indicate better performance.

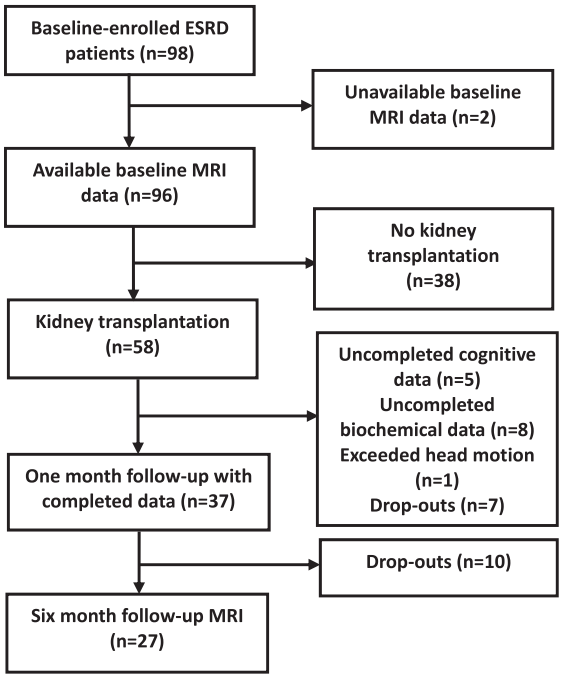

Figure 1. | **The flowchart of this study.** MRI, magnetic resonance imaging.

Laboratory Tests

All patients with ESRD completed laboratory tests to determine serum creatinine, urea, hematocrit, hemoglobin, and calcium levels within 24 hours before MRI at three time points: before and 1 and 6 months after kidney transplantation. No blood laboratory tests were performed for the healthy control subjects.

MRI Data Acquisition

MRI data were acquired using a 3T MR system (TIM Trio; Siemens Medical Solutions, Erlangen, Germany). All subjects were instructed to be still, keep their eyes closed, and stay awake during MRI. Foam padding was used to reduce head motion. T1-weighted and T2 fluid–attenuated inversion recovery anatomic images were obtained for each subject for the detection of silent lesions using the following two sequences. Functional data were obtained using a gradient echo echo-planar sequence. Each functional MRI sequence contained 250 volumes, and each volume included 30 axial sections placed approximately along the anterior-posterior commissure line. Detailed MRI sequences and acquisition protocols can be found in Supplemental Material.

Data Preprocessing

Data were preprocessed and analyzed using statistical parametric mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm/) with a software platform (Matlab; MathWorks, Natick, MA) as we described in our previous study (17). Detailed data preprocessing can be found in Supplemental Material.

Independent Component Analyses and Identification of Resting-State Networks

Group spatial independent component analysis was conducted using the GIFT software (http://icatb.sourceforge.net/; Vision 2.0d), and the method of identification of resting-state networks was the same as we used in our previous study (17). Seven resting-state network templates were used in this study: dorsal attention network, central executive network, default mode network, self-referential network, sensorimotor network, visual network, and auditory network, and they can be found in previous studies (23,24). The details can be found in Supplemental Material.

Group Statistical Maps

The independent components corresponding to seven resting-state networks were extracted from all subjects; then, a second-level random effects statistical analysis was performed for each resting-state network in each group using a one-sample t test. Significant thresholds were corrected to $P<0.05$ using the AlphaSim program. The group-level resting-state networks maps were then visualized with the BrainNet Viewer (http://www.nitrc.org/projects/bnv/). To compare the resting-state networks between the patient and control groups, random effects analysis two-sample t tests were applied. Paired t tests were used to examine differences between Z values before and after kidney transplantation. The t map of the two-sample t test was corrected using the AlphaSim program (25) in the REST software (26). We used a masking procedure to generate seven group maps of all 37 subjects corresponding to each resting-state network (significant thresholds defined as the one-sample t test above) and constrained the group comparison result to the voxels within these combined group maps.

Mixed Effects Model Analyses

To investigate the relationship between resting-state networks and the clinical indicators of patients with ESRD, we examined the regions within each resting-state network that differed significantly between patient and control groups. These differences were extracted as a mask consisting of several regions of interest (16). The mean Z values within these regions of interest were extracted for each patient. Differences between pre- and post-transplant values for Z values, clinical markers, and NCT-A/digit symbol test/line tracing test/serial dotting test/SAS/Zung Self-Rating Depression Scale scores are expressed as $\triangle$Z values, $\triangle$clinical markers, and $\triangle$NCT-A/$\triangle$digit symbol test/$\triangle$line tracing test/$\triangle$serial dotting test/$\triangle$SAS/$\triangle$Zung Self-Rating Depression Scale, respectively. The relationship between the changes of psychological tests (*e.g.*, $\triangle$NCT-A) and $\triangle$Z values was calculated by crossing subjects. A mixed effects model was performed using Statistical Analysis System software (SAS, version 9.3; SAS Institute Inc.), and the threshold was set at a significance level of $P<0.05$.

Results

Demographics and Clinical Data

There were no significant differences in sex, age, or education level between patients with ESRD and control subjects (Table 1). Worse neuropsychological performance was found in pretransplant patients compared with controls. After kidney transplantation, patients showed an increased trend in digit symbol test scores and a decreased trend in NCT-A scores compared with scores of pretransplant patients (Table 2), indicating better performance. There were no differences for other psychological scores between groups.

With regard to anxiety and depressed mood levels, the depressed and anxious mood levels was higher in pretransplant patients compared with controls. After kidney transplantation, patients showed decreased trends in SAS and Zung Self-Rating Depression Scale scores, suggesting mood improvement.

Spatial Pattern of Resting-State Networks in Each Group

The one-sample t tests showed the typical spatial patterns of each resting-state network for both patient and control groups as illustrated in Figure 2. Among these resting-state networks, default mode network involved posterior cingulate cortex/precuneus, bilateral angular gyrus, superior frontal gyrus, parahippocampal gyrus, and medial frontal gyrus. Dorsal attention network primarily involved middle and superior occipital gyri, parietal gyrus, inferior and superior parietal gyri, and middle and superior frontal gyri. Central executive network comprised the dorsal lateral prefrontal cortices and the posterior parietal cortices. Sensorimotor network included pre- and postcentral gyri, the primary sensorimotor cortices, and the

Table 1. Demographics, clinical characteristics, and cognitive tests of patients with ESRD before kidney transplantation and healthy controls

Protocols	Before Kidney Transplantation	Normal Controls
No. of subjects	37	22
Sex	25M/12W	16M/6W
Age, yr	32±9	34±14
Education, yr	13±3	14±3
Hemodialysis	27	
Peritoneal dialysis	6	
Nondialysis	4	
Dialysis vintage, yr	1.4±1.7	
Chronic GN	31	
IgA nephropathy	5	
Henoch–Schonlein purpura nephritis	1	
Number connecting test type A, s	41.9±16.0	33.0±12.7
Digital symbol test, score	56.8±12.5	66.6±14.1
Line tracing test, s	55.1±15.9	58.1±25.5
Serial dotting test, s	47.3±10.8	45.4±13.8
Zung Self-Rating Anxiety Scale, score	31.8±6.4	26.6±4.8
Zung Self-Rating Depression Scale, score	34.3±9.7	27.8±6.6

Continuous data are expressed as means and SD. Less time in the number connecting test type A, the line tracing test, and the serial dotting test and lower scores on the Zung Self-Rating Anxiety Scale and the Zung Self-Rating Depression Scale reflect better performance, whereas higher digital symbol test scores indicate better performance. M, men; F, women.

supplementary motor area. Self-referential network included the ventromedial prefrontal cortex, medial orbital prefrontal cortex, rectus gyrus, and pregenual anterior cingulate gyrus. Auditory network primarily included the bilateral middle and superior temporal gyri, Heschl gyrus, and temporal pole. Visual network included the inferior,

Table 2. Clinical characteristics of patients with ESRD before and after kidney transplantation

Protocols	Before Kidney Transplantation	1 mo after Kidney Transplantation	6 mo after Kidney Transplantation	*P* Value
Participants	37	37	27	—
Number connecting test type A, s	41.9±16.0	38.4±13.4	37.8±19.3	0.05
Digital symbol test, score	56.8±12.5	59.2±13.4	62.6±12.3	<0.001
Line tracing test, s	55.1±15.9	55.1±15.3	50.0±9.6	0.13
Serial dotting test, s	47.3±10.8	50.1±11.4	48.4±13.4	0.77
Zung Self-Rating Anxiety Scale, score	31.8±6.4	29.1±6.4	27.0±6.8	<0.01
Zung Self-Rating Depression Scale, score	34.3±9.7	28.3±6.6	27.6±7.5	<0.001
Total protein, g/dl	6.7±0.8	7.0±0.7	6.6±0.6	0.63
Serum albumin, g/dl	4.4±0.5	5.0±0.6	4.7±0.4	0.001
ALT, U/L	15±11	43±44	22±14	<0.01
AST, U/L	14±7	21±9	20±8	0.002
Urea, mg/dl	63±20	21±6	19±6	<0.001
Serum creatinine, mg/dl	11.2±3.4	1.3±0.4	1.2±0.4	<0.001
Uric acid, mg/dl	6.9±2.0	5.5±1.7	6.5±1.8	<0.001
Calcium, mg/dl	9.1±1.1	9.8±0.8	9.7±0.3	0.02
Sodium, mEq/L	136±22	140±2	142±3	0.06
Potassium, mEq/L	4.7±0.6	4.3±0.5	4.1±0.3	<0.001
Chloride, mEq/L	99±5	106±3	105±3	<0.001
Red blood cell count, $\times 10^{12}$	3.4±0.7	3.8±0.7	4.5±0.7	<0.001
Hemoglobin, g/dl	10.4±2.2	11.8±2.0	13.4±2.1	<0.001
Hematocrit, %	32±7	36±6	41±6	<0.001

Continuous data are expressed as means and SD. Less time in the number connecting test type A, the line tracing test, and the serial dotting test and lower scores on the Zung Self-Rating Anxiety Scale and the Zung Self-Rating Depression Scale reflect better performance, where higher digital symbol test scores indicate better performance. The *P* values were obtained by using repeated measures. —, no comparison; ALT, alanine aminotransferase; AST, aspartate transaminase.

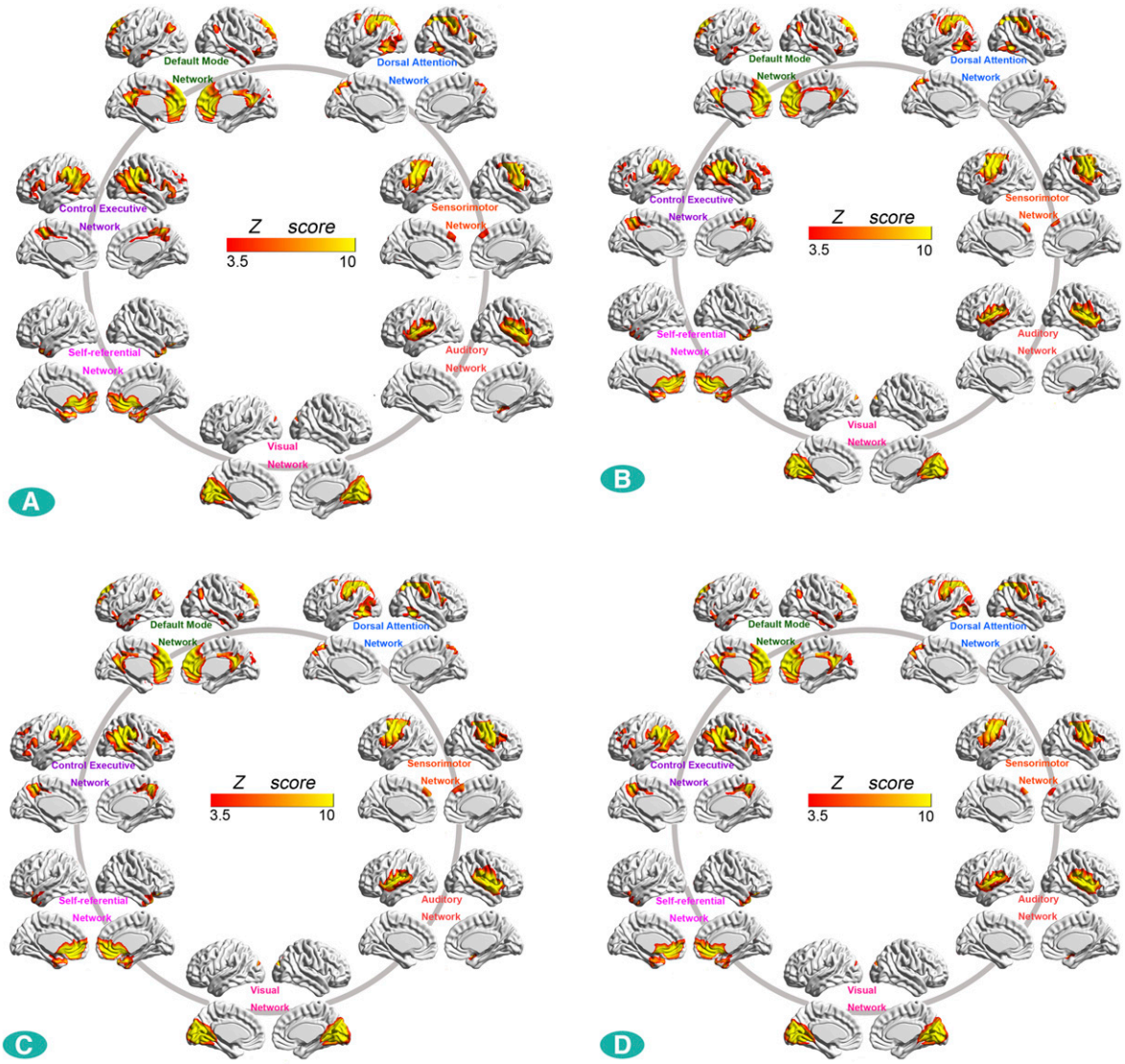

Figure 2. | Cortical representation of the seven group-level resting-state networks in controls and patient groups by one sample *t* test. Lateral and medial views of the left hemisphere and lateral and medial views of the right hemisphere are shown for each group. The color scale represents Z value in each resting-state subnetwork (maps are thresholded at $P<0.05$, AlphaSim corrected). (A) Control group. (B) Prekidney transplantation group. (C) One-month postkidney transplantation group. (D) Six-month postkidney transplantation group.

middle, and superior occipital gyri and the temporal-occipital regions along with superior parietal gyrus (Figure 2).

Aberrant Resting-State Networks in Patients with ESRD

The two-sample/paired *t* test results showed significant differences in functional connectivity between the patients and controls (Figures 3 and 4, Supplemental Table 1). Except for self-referential network, pretransplant patients (including patients on hemodialysis) showed abnormal (mostly decreased) functional connectivity in the other six networks compared with healthy controls. Particularly, pretransplant patients (including patients on hemodialysis) showed decreased functional connectivity in these brain regions, such as the default mode network, including anterior cingulate cortex, posterior cingulate cortex, superior frontal gyrus, inferior frontal gyrus, and other five subnetworks regions listed in Supplemental Table 1. Compared with controls, patients after kidney transplantation showed decreased functional connectivity in the default mode network, the dorsal attention network, the central executive network, the sensorimotor network, and the auditory network 1 month after surgery. Both increased and decreased functional connectivity were observed in the visual network. Six months after kidney transplantation, patients still showed decreased functional connectivity for the default mode network and showed both increased and decreased functional connectivity in the sensorimotor network compared with controls, indicating that these two networks were still under dynamic reorganization. No differences were observed for the dorsal attention network, the central executive network, the auditory network, and the visual network, which suggests that these resting-state subnetworks returned to normal. These networks showed gradual improvement from pretransplant to 1 month after

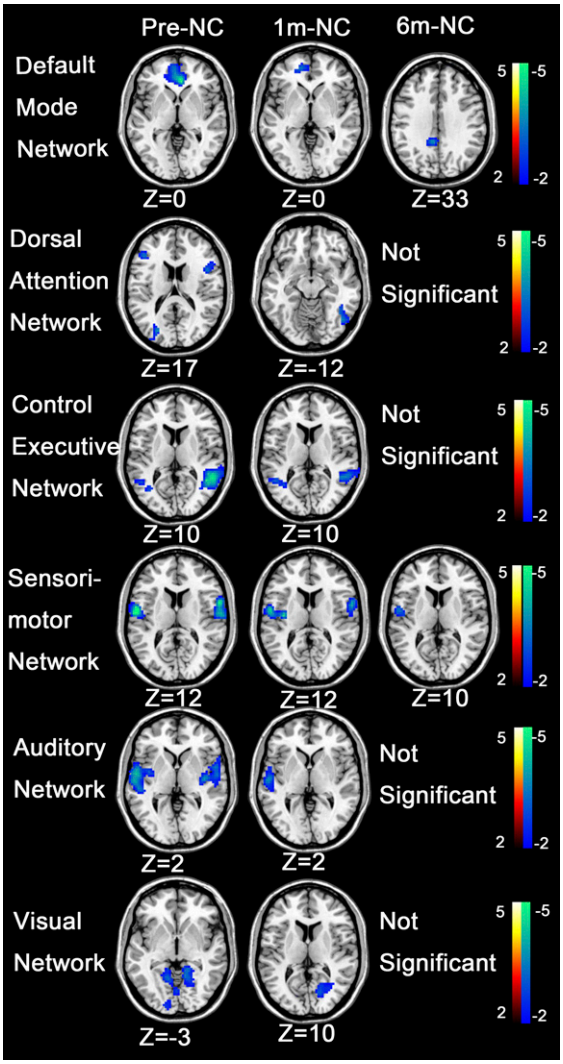

Figure 3. | Abnormal functional connectivity in six resting-state networks in the patients group compared with normal controls (NCs). Except for in the self-referential network, pretransplantation patients with ESRD show abnormal (mostly decreased) functional connectivity in six subnetworks compared with healthy controls. Compared with controls, patients in the 1-month kidney transplantation group show decreased functional connectivity in the default mode network, the dorsal attention network, the control executive network, the sensorimotor network, and the auditory network. Both increased and decreased functional connectivity were found for the visual network. Six months after kidney transplantation, patients showed both increased and decreased functional connectivity for the sensorimotor network compared with controls. No differences are found for the dorsal attention network, the control executive network, the auditory network, and the visual network. These networks show a gradually improving tendency from prekidney transplantation to 1 month after kidney transplantation to 6 months after kidney transplantation. *Z* represents Montreal Neurologic Institute coordinates of brain regions. Blue indicates decreased functional connectivity, and red indicates increased functional connectivity, with the amount of blue or red proportional to the magnitude of the difference. Not significant indicates no statistical difference. Pre, prekidney transplantation; 1 m, 1 month after kidney transplantation; 6 m, 6 months after kidney transplantation.

kidney transplantation to 6 months after kidney transplantation.

Patients showed significantly increased functional connectivity in the default mode network, the dorsal attention network, the central executive network, the sensorimotor network, the auditory network, and the visual network 1 and 6 months after kidney transplantation compared with that in pretransplant patients.

Six months after kidney transplantation, patients showed only significantly increased functional connectivity for the default mode network, the central executive network, and the auditory network compared with 1 month after kidney transplantation. No difference in functional connectivity for the dorsal attention network, the sensorimotor network, and the visual network was observed.

Mixed Effects Model Analyses of Regions of Resting-State Networks with Neuropsychological Tests Scores

Supplemental Table 2 illustrates the analysis results between *Z* scores and psychological tests scores. A mixed effects model analysis revealed that the functional connectivity changes of the left middle frontal gyrus in the dorsal attention network were associated with improvements in digit symbol test scores and SASs during the pretransplant and 1-month follow-up periods, respectively. The functional connectivity changes of the left triangular inferior frontal gyrus associated with improvement in the NCT-A. The functional connectivity changes of the left triangular inferior frontal gyrus and the left superior parietal gyrus were associated with improvement in SASs. The functional connectivity changes of the left inferior parietal gyrus were associated with improvement in the line tracing test. The changes in functional connectivity of the right opercular inferior frontal gyrus within the dorsal attention network were associated with improvements in the Zung Self-Rating Depression Scale. The functional connectivity changes of the right middle frontal gyrus were associated with improvements in the NCT-A and the digit symbol test.

During the pretransplant and 6-month follow-up periods, the functional connectivity of the posterior cingulate cortex within the default mode network was associated with improvement in the serial dotting test. The functional connectivity of the right postcentral gyrus within the dorsal attention network was associated with improvement in the NCT-A. Change in functional connectivity of the right superior temporal gyrus within the central executive network was associated with improvement in the digit symbol test scores. Changes in functional connectivity of the right inferior parietal lobule within the central executive network were associated with improvement in self-rating anxiety scale scores. Changes in functional connectivity of the left supplementary motor area within the sensorimotor network were associated with improvement in the Zung Self-Rating Depression Scale. The functional connectivity changes of the right precentral gyrus and left precentral gyrus within the sensorimotor network were associated with improvement in the NCT-A score.

Discussion

This longitudinal study shows that the recovery patterns of resting-state subnetworks vary in patients with ESRD

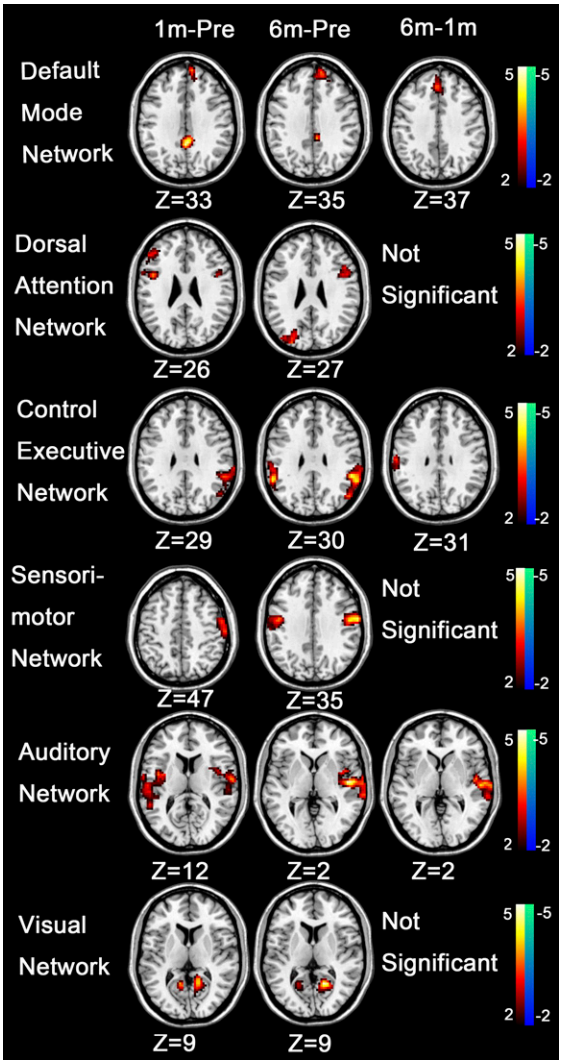

Figure 4. | Increased functional connectivity in patients after kidney transplantation compared with prekidney transplantation. Compared with prekidney transplantation, 1 and 6 months after transplantation, patients showed significantly increased functional connectivity in the default mode network, the dorsal attention network, the control executive network, the sensorimotor network, the auditory network, and the visual network. Compared with 1 month postkidney transplantation, the patients 6 months after kidney transplantation showed significantly increased connectivity for the default mode network, the control executive network, and the auditory network (all P=0.01). For the dorsal attention network, the sensorimotor network, and the visual network, no significant functional connectivity changes are shown between 1 and 6 months after kidney transplantation. Z represents Montreal Neurologic Institute coordinates of brain regions. Blue indicates decreased functional connectivity, and red indicates increased functional connectivity, with the amount of blue or red proportional to the magnitude of the difference. Not significant indicates no statistical difference. Pre, prekidney transplantation; 1 m, 1 month after kidney transplantation; 6 m, 6 months after kidney transplantation.

after successful kidney transplantation, which might be the neural basis of different cognitive function recovery patterns after kidney transplantation. The better cognition performance after kidney transplantation might be associated with the brain's resting-state network recovery.

The decrease in functional connectivity reflects impairment in brain function, whereas increased functional connectivity might be a compensatory mechanism. In patients with ESRD, six resting-state subnetworks (default mode network, sensorimotor network, visual network, dorsal attention network, central executive network, and auditory network) showed decreased functional activity, three subnetworks (dorsal attention network, central executive network, and auditory network) also showed increased functional connectivity, and only the self-referential network remained unchanged. This suggests that patients with ESRD had selective impairment rather than diffuse impairment of resting-state subnetworks. This pattern has not previously been reported, and therefore, our results may contribute to better understanding the cognitive impairment of patients with ESRD.

This study found different recovery patterns for resting-state network in patients with ESRD after kidney transplantation. Functional connectivity of the default mode network, the dorsal attention network, the central executive network, the sensorimotor network, the auditory network, and the visual network showed improvement 1 month after kidney transplantation, but only improvements in the dorsal attention network, the central executive network, the auditory network, and the visual network were statistically indistinguishable from controls 6 months after kidney transplantation. The default mode network and the sensorimotor network remained statistically different from controls even 6 months after kidney transplantation. These findings provide neural substrates for different brain cognition function recovery patterns in accordance with previously reported results (8,11). Different networks are responsible for distinct domains of brain function. As aforementioned, the disruptions and reconstruction in these intrinsic networks may relate to parallel patterns of cognitive impairment and recovery pretransplantation and post-transplantation. The digit symbol test and the NCT-A examine the domains of psychomotor speed, attention, and visual memory. Significant improvements in digit symbol test and NCT-A scores shortly after kidney transplantation suggest better performance in cognitive function. Importantly, the mixed effects model analyses showed that change in cognitive test was associated with change in functional connectivity, thus suggesting cognitive changes along with functional connectivity changes in our patients. It is speculated that better performance in cognitive function after kidney transplantation may be associated with the successful removal of toxins (11). Moreover, kidney transplantation is associated with restoration of a normal biochemical milieu and the removal of dialytic stress, which may be beneficial for the cognition improvement. The hemodynamic may maintain at a relatively stable level after cessation of dialysis, which may contribute to cognitive improvement.

Interestingly, the default mode network and the sensorimotor network in patients with ESRD did not return to normal when evaluated 6 months after kidney transplantation. Previous studies showed that some domains of cognition function, especially memory, did not fully return to normal until 1 year after successful kidney transplantation (8). The default mode network is involved in numerous brain functions, including memory, visual and

auditory attention, motor activity, and language processing (27). The posterior cingulate cortex is an important component of the default mode network, and it is closely associated with integrated tasks, such as regulation of visual-spatial episodic memory (28). This finding builds a bridge between clinical cognitive impairment and its pathophysiologic basis. The memory problems in patients with ESRD on dialysis are likely indirectly linked to the effects of CKD-related neurotoxicity and cerebrovascular disease. However, more time is needed for the enhancement of cerebrovascular factors. Thus, it can require longer time for memory improvement after kidney transplantation with patients' general functional and medical recovery (29).

We acknowledge that the study has several limitations. The small sample size and young age of the patient population may limit the generalization of the results. Also, not all patients received the same treatment before transplantation. Additionally, although we dynamically observed the functional connectivity changes in patients with ESRD after kidney transplantation, the 6-month follow-up period may have been insufficient to observe all potential benefits of kidney transplantation for brain function. Thus, future studies should involve longer follow-up periods to further improve our understanding of the dynamic reorganization of resting-state networks in patients with ESRD after kidney transplantation. The same scales were used to assess cognitive status in our follow-up study, and learning effects due to repeated administration of cognitive tasks could not be avoided. We did not perform the follow-up study on healthy controls, which should be considered in our future study. We did not perform the multiple hypothesis testing when analyzing the resting-state subnetworks, because they are regarded as independent. Also, the average time interval between baseline examination and kidney transplantation varied, which may have an effect on our results. Finally, the high rate of dropouts might have biased our results; thus, a prospective cohort study with a large sample size is needed in the future.

In conclusion, our study found that recovery patterns of resting-state subnetworks differ in patients with ESRD after successful kidney transplantation. Specifically, functional connectivity of the dorsal attention network, the central executive network, the default mode network, the sensorimotor network, the auditory network, and the visual network was improved 1 and 6 months after kidney transplantation. The dorsal attention network, the central executive network, the auditory network, and the visual network were statistically indistinguishable from controls, but the default mode network and the sensorimotor network remained statistically different from controls at the 6-month point after kidney transplantation. These findings provide the neural basis of cognitive function recovery patterns after kidney transplantation.

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Disclosures

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Expression of Concern

Expression of Concern: Re-Establishing Brain Networks in Patients with ESRD after Successful Kidney Transplantation

Hui Juan Chen, Jiqiu Wen, Rongfeng Qi, Jianhui Zhong, U. Joseph Schoepf, Akos Varga-Szemes, Virginia W. Lesslie, Xiang Kong, Yun Fei Wang, Qiang Xu, Zhe Zhang, Xue Li, Guang Ming Lu, and Long Jiang Zhang. Re-establishing brain networks in patients with ESRD after successful kidney transplantation. *Clin J Am Soc Nephrol* 13: 109–117, 2018.

Regarding the above article, *CJASN* is issuing an "Expression of Concern". *CJASN* publishes research work that adheres to internationally accepted ethical standards and is committed to upholding the Declaration of Helsinki and Declaration of Istanbul. The Editors have been troubled by the recent report of the widespread practice of using organs harvested from executed prisoners in China (1). The Editors are unable to determine if this report violated the code of ethics followed by *CJASN*.

We obtained the following additional information from the authors of this publication:

- This report describes 37 transplant recipients. These individuals underwent kidney transplantation between July 2012 and July 2015 and enrolled in the study between June 2012 and July 2015.
- Of the 37 transplant recipients, 24 received a living donor kidney transplant and 13 received a deceased donor transplant.
- The authors certify that the transplant organs were procured with the consent of the donors or their families, as appropriate.
- The authors certify that none of the transplant organs for the 37 organ recipients were obtained from executed prisoners.
- The study was undertaken under the auspices of Medical Research Ethics Conference (2012-GJJ-057).

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