RESEARCH ARTICLE

Altered white matter microstructure mediates the relationship between hemoglobin levels and cognitive control deficits in end-stage renal disease patients

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Abstract

The brain–kidney crosstalk theory suggested that the brain and kidneys may be considered end organs on parallel trajectories and subject to shared risk factors, which are receiving increasing attention. Cognitive control deficits were frequently presented in patients with end-stage renal disease (ESRD). Whether or not cognitive control impairment is concerned with brain–kidney crosstalk is in need of further research. To detect the relationship between ESRD and cognitive control impairment, diffusion tensor imaging was collected in 64 healthy controls (HCs) and 64 patients with ESRD. Tract-based spatial statistics and fixel-based analysis were used to detect the difference of white matter (WM) microstructure and morphology between ESRD patients and HCs in the whole brain. Tractography atlas-based analysis was also used to investigate the difference of diffusional characteristics along fiber bundles of interest between the two groups. For the whole-brain analysis, ESRD patients showed WM microstructural alteration and fiber density variation in the cingulum. In addition, ESRD patients exhibited higher MD and RD than HCs along the anterior cingulum. Among all of the blood biochemistry tests that represent kidney disease to a degree, the stepwise regression analysis showed that only hemoglobin significantly contributed to the cognitive control deficits in ESRD patients. Mediation analysis proved that the relationship between hemoglobin and cognitive control deficits of ESRD patients was mediated by WM microstructural alteration of the cingulum. Our results indicated that the anterior cingulum was correlated with cognitive control deficits and mediated the impact of hemoglobin on cognitive control.

KEYWORDS

cognitive control, end-stage renal disease, fixel-based analysis, hemoglobin level, tractography atlas-based analysis

1 | INTRODUCTION

End-stage renal disease (ESRD) is defined as chronic renal disease deteriorating to the point where renal functions permanently decrease to <10% of their normal capacity (Lu, Kiernan, Murray, Rosner, & Ronco, 2015; Luo et al., 2016; Zhang et al., 2016). Patients with ESRD often have central nervous system abnormalities reported up to approximately 60% of ESRD patients who had cognitive function impairments, such as cognitive control (Kalirao et al., 2011; Kurella,

Mapes, Port, & Chertow, 2006; Madero, Gul, & Sarnak, 2007). Cognitive control is the ability of flexible allocation of mental resources in the behavior of goal-driven decision-making (Mackie, Van Dam, & Fan, 2013; Solomon et al., 2009). Cognitive control deficits would contribute to poor executive control and may decrease adherence of medication regimens, decrease the quality of life, and decrease the survival rate of patients with ESRD (Condé et al., 2010; Theofilou, 2011). However, relatively little is known about the potential relationship between cognitive control deficits and ESRD.

Brain–kidney crosstalk may be a possible explanation for cognitive control deficits in ESRD patients. Due to similar hemodynamics in vascular supply, the kidneys and brain influence each other by shared anatomic and vasoregulatory systems and bidirectional humoral pathways (Buchman et al., 2009; Davenport, 2008; Murray, 2009; Non-gnuch, Panorchan, & Davenport, 2014). Kidney function impairment could affect extracellular fluid homeostasis, with the accumulation of risk factors (such as albuminuria or anemia), which will also impair cerebral functions (Davenport, 2008; Lu et al., 2015). This indicated that cognitive control deficits of ESRD patients may be concerned with the alteration of the brain which is affected by damaged kidney function.

Despite the link between ESRD and cognitive control deficits, relatively little is known about its neuroanatomic basis. For ESRD patients, blood–brain barrier disruption is frequently presented; an increase in the expression of aquaporin channels facilitated an influx of water into the brain by osmosis causing cerebral edema (Ishida et al., 1999). WM, as nerve fibers that connect neurons in different brain regions into functional circuits, was sensitive to the change in brain water content (Pierpaoli et al., 2001). Moreover, uremic toxins may have a direct neurotoxic effect on glial cells that form the myelin sheath (Lu et al., 2015). Structural neurologic imaging studies showed reproducible findings that widespread and symmetrical white matter (WM) microstructural change existed in ESRD patients, including the cognitive control-related pathway (Chou et al., 2013; Zhang et al., 2015). Hence, WM abnormalities may be associated with cognitive control deficits in patients with ESRD.

Diffusion tensor imaging (DTI), as an important neuroscience technology, can noninvasively probe the structure and properties of brain WM tissue in vivo (Basser, Mattiello, & LeBihan, 1994). The analysis of diffusion tensor-derived values has been used extensively for investigating WM alteration (Basser & Pierpaoli, 1996). Tract-based spatial statistics (TBSS) is a common method for studying WM, providing evidence of WM microstructural variability by detecting differences in the whole-brain WM skeleton (Smith et al., 2006). Fixel-based analysis (FBA) is a method based on the analysis of DTI data, which can compare measures related to the total intra-axonal volume of WM axons, providing a method that can be used to detect degeneration within WM tracts (Raffelt et al., 2017). Combining these two methods, the WM microstructural and morphology alteration could be investigated in the whole brain in ESRD patients. In addition, tractography atlas-based analysis (TABS), which combines spatial normalization of tensor images with a voxel-wise statistical framework for tract-oriented statistics for a single hypothesis test per tract (Liu et al., 2017), is also an important method to detect altered microstructural properties of cerebral WM. Exploring the information from multiple methods to search WM microstructural alterations can detect more comprehensive WM changes, which will advance scientific understanding of brain changes due to disease.

In this study, we hypothesized that brain WM microstructure and morphology was altered in ESRD patients, and we further investigated the relationship among ESRD, WM measurements and cognitive control performance in the patient group. To test this hypothesis, we collected various pathopsychophysiological data from 64 patients with ESRD and 64 healthy controls, including laboratory examinations and

DTI data. TBSS and FBA were used to explore regions with diffusion measurement alteration without a hypothesis of an affected location from the whole brain. Furthermore, based on the results of TBSS and FBA, TABS method was used to quantify WM microstructural characterization along with fiber tracts of interest. The color-words Stroop task was employed to detect cognitive control in ESRD patients. Finally, mediation analysis modeling, which could examine the direct and mediating links between multiple risk factors of ESRD and brain crosstalk, was used to detect the underlying relationship among cognitive control performance, fiber tracts of interest, and ESRD.

2 | MATERIALS AND METHODS

All research procedures were approved by the Institutional Review Board of the First Affiliated Hospital of the Medical College in 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.

2.1 | Participants

Sixty-four patients with ESRD (32 males, 32 females, [mean $\pm$ SE: 33.9 ± 1.6 years of age]) and 64 healthy age-, education-, and gender-matched, right-handed healthy controls (HCs) were recruited (32 males, 32 females, [mean $\pm$ SE: 32.8 ± 2.0 years of age]). The main underlying cause of ESRD in our patient group was glomerulonephritis. All ESRD patients were on maintenance hemodialysis and the dialysis duration was longer than 3 months. The exclusion criteria were: (a) macroscopic brain T2-visible lesions on MRI scans, (b) existence of a neurological disease, (c) physical deformities, (d) alcohol, nicotine, or drug abuse, (e) diabetic nephropathy or primary hypertensive nephropathy, (f) color blindness, or (g) claustrophobia.

2.2 | Laboratory examinations

Blood biochemistry tests including those to measure serum urea, serum creatinine, phosphate, calcium, hematocrit, cystatin, and hemoglobin (Hb) levels were conducted in all patients with ESRD 3 days before MR imaging. No biochemistry tests were conducted in HCs.

2.3 | Cognitive control measurements

The original color-words Stroop task comprised of a number of color-words employed for the cognitive control measurements of ESRD patients (Stroop, 1992). Stimuli were Chinese language color words (red, blue, or green) with the colors red, blue, and green presented centrally on a gray background on a computer monitor. Congruent stimuli (word meaning and color presentation matched each other) and incongruent stimuli (word meaning and color presentation did not match each other) trials were displayed in randomized order, separated by an interstimulus interval with a cross at the center of the screen. Participants were required to report the color presentation, regardless of the word meaning, by pressing one of the buttons on the keypad which was mapped to a specific color (button 1 = red, button 2 = blue, and button 3 = green). All stimuli consisted of two runs

with congruent and incongruent blocks and were counterbalanced in order across participants. Each run was programmed as 5 congruent, 5 incongruent, and 11 interval blocks and each stimulus was presented for 1 s with an interstimulus interval of 0.5 s. There were seven trials in each task block, and each trial was separated with a rest block which lasted 17 s with the instructions to "Rest." The command "Identify the Color" was presented before each trial. All instructions lasted 2 s. During the task, we collected five parameters for the cognitive control measurements, that is, reaction time and errors in the congruent condition, reaction time and errors in the incongruent condition, and reaction delay measured by reaction time during the incongruent condition minus the congruent condition.

2.4 | Data acquisition

All subjects were scanned on a 3.0 Tesla GE Excite scanner using an eight channel coil (GE Medical Systems, Milwaukee, WI). DTI was obtained with a single-shot echo-planar imaging sequence. The diffusion sensitizing gradients were applied along two repeats of 30 noncollinear directions ($b = 1,000 \text{ s/mm}^2$) with five repeats of b_0 (no diffusion weighted image). The imaging parameters were 75 continuous axial slices with a slice thickness of 2 mm and no gap; field of view (FOV) = 256; TR = 9,400 ms; TE = 84 ms; and matrix size = 128×128 , resulting in 2 mm isotropic voxels.

2.5 | Whole-brain TBSS analysis

For DTI data, the correction of eddy current distortion, subject motion, and brain extraction was performed using FMRIB's software library FSL (<https://fsl.fmrib.ox.ac.uk/fsl>). Then, a series of metric maps: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and mode of anisotropy (MO) were yielded using dtifit. The crossing-fiber measures (F1 and F2) were estimated using bedpostX which automatically determines the number of crossing fibers per voxel (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). FA, MD, RD, and AD are specific biomarkers which can describe WM microstructural changes (Jones, Knosche, & Turner, 2013). MO provides measures corresponding to WM fiber complexity (single fiber orientations, multiple fiber orientations or crossings; Douaud et al., 2011). F1, defined as the major or primary fiber population, and F2, defined as the minor or secondary fiber population, correspond to specific tracts within each voxel (Panagiotaki et al., 2012).

TBSS analysis was carried out using FSL software (Smith et al., 2006). FA image of each subject was aligned into common space by using FNIRT, which is a nonlinear registration tool. Then, a mean FA image was created by averaging the aligned FA images. An FA skeleton was derived from the mean FA image with a threshold of 0.2. Subsequently, all aligned FA images of each subject were projected into the skeleton and a four-dimensional (4D) skeletonized FA image was created for voxel-wise statistics. For the non-FA image (MD, AD, RD, MO, and F1 and F2), the nonlinear warp and skeleton projection generated from the FA image-based TBSS were applied to other images. The 4D projected skeleton data of non-FA images were obtained for statistical analysis.

2.6 | FBA analysis

FBA analysis is a whole-brain analysis method which enables characterization of multiple fiber orientations within voxels (Raffelt et al., 2017). Using this approach, we can compare measures related to the total intra-axonal volume of WM axons in any particular direction, thus providing a method that can be used to detect degeneration within specific WM tracts.

Fiber density (FD), fiber cross-section (FC), and combined measure of fiber density and cross-section (FDC) which are the common measures of FBA were computed using Mrtrix3 software package (www.mrtrix.org). Detailed methodology for FBA has been described by Raffelt et al. (2017). In brief, to increase anatomical contrast and improve downstream spatial normalization and statistics, DW images were up-sampled to a voxel size of 1.25 mm. To estimate the fiber orientation distribution (FOD), we used the group average response function to perform constrained spherical deconvolution. Then, a study-specific unbiased FOD template was created using all of the participants. Subsequently, all FOD images of subjects were registered to the FOD average template, with an intersection template mask obtained for each subject. FD can be derived from transformed FOD images based on the Jacobian matrix at each voxel. FD was sensitive to alterations at a microstructural, within-voxel level. FC was estimated from the warp field that maps from the template to subject space, describing the atrophy of a fiber pathway. FDC is combined with FC and FD which manifest the changes in within-voxel fiber density and macrostructural changes in a fiber-bundle cross-section.

2.7 | TABS method

TABS is a DTI statistical analysis method attracting attention for detecting tract microstructural properties and understanding voxel-wise WM properties along a fiber tract as described in our previous study (Liu et al., 2017). This method facilitates an easy interpretation of the results by directly reporting the resulting statistics on the fiber tracts. The main parts of TABS consist of diffusion tensor template construction (Supporting Information Figure S1a,b) and voxel-wise statistical spatial framework building (Supporting Information Figure S1c–g; Liu et al., 2017). In the pipeline of the TABS method, altered microstructural properties of WM were embodied by analyzing the anisotropy value along a fiber tract (Supporting Information Figure S1h).

According to the TBSS and FBA analysis results, the regions of between-group differences were mainly concentrated in the cingulum (see Results). The cingulum consists of frontal association tracts that play a critical role in cognitive control (Holroyd & Yeung, 2012; Metzler-Baddeley et al., 2012). To further confirm the results of TBSS and FBA, we selected the cingulum as the fiber of interest for the TABS analysis to detect the voxel-wise difference in WM properties along a fiber tract.

2.8 | Statistical analysis

The group differences in the subjects' basic information (age, years of education) and cognitive control performance (errors rates, reaction time, and reaction delay) were analyzed using one-way ANOVAs. Post

hoc comparisons were performed using *t* tests and $p < .05$ was considered statistically significant.

The difference in FA, MD, RD, AD, MO, and F1 and F2 were detected between ESRD patients and HCs. The randomize tool implemented in FSL was applied with 5,000 permutations and threshold-free cluster enhancement (TFCE) with the family-wise error (FWE) correction for multiple comparison corrections; $p < .05$ was considered statistically significant. To correct for multiple comparisons in these values, a Bonferroni correction was applied to account for the seven measurements ($p = .05/7$, corresponding to $p = .007$).

The differences in FD, FC, and FDC metrics were detected independently using connectivity-based fixel enhancement (Raffelt et al., 2015) with 5,000 permutations and TFCE with the FWE correction for multiple comparison corrections; $p < .05$ was considered statistically significant. To correct for multiple comparisons in these values, a Bonferroni correction was applied to account for the three measurements ($p = .05/3$, corresponding to $p = .017$).

To study the between-group differences in subjects' diffusion properties along the fiber tracts, permutation-based nonparametric inferences were used (5,000 random permutations). The threshold for statistical significance was $p < .05$ using TFCE with the FWE correction for multiple comparison corrections. To correct for multiple comparisons in these values, a Bonferroni correction was applied to

account for the four measurements ($p = .05/4$, corresponding to $p = .0125$).

2.9 | Mediation analysis

To examine the effects of clinical variables on cognitive control deficits and WM microstructural alteration of the cingulum in ESRD patients, we performed mediation analyses to identify if the WM microstructural changes could mediate the role of biological indicators in cognitive control behaviors (Hayes, 2013).

To study the relationship between cognitive control deficits and blood biochemistry tests, a stepwise regression model was used to calculate the odds ratio of the biochemical indices for ESRD patients' cognitive control measurements. Before the regression analysis, the Kolmogorov–Smirnov (K–S) test for normality was performed on ESRD patients' cognitive control measurements using SPSS 20.0 (SPSS Statistics, IBM, Armonk, NY).

Based on the results of the stepwise regression analysis, correlation analyses were performed to detect the relationship between resulting blood biochemistry tests and cognitive control measurements and WM microstructural changes.

Based on the results of the correlation analysis, biological indicators constituted the independent variable, cognitive control measurements indicated the dependent variable and WM microstructural changes consisted of the mediator variable. The mediation analyses were performed with SPSS software. The significance threshold for the Sobel test was set at $p < .05$.

TABLE 1 Demographic and clinical characteristics of healthy controls and patients with end-stage renal disease

Variables	ESRD (<i>n</i> = 64)	Controls (<i>n</i> = 64)	<i>p</i>
<i>Demographic</i>			
Gender, female (%)	32 (50)	32 (50)	–
Age, mean (SE), years	33.3 (8.75)	34.7 (9.1)	.249
Educational, mean (SE), years	11.6 (4.5)	12.05 (2.9)	.1
Dialysis duration, mean (SE), months	31.19 (21.14)	–	–
<i>Laboratory examinations</i>			
Urea, mean (SE), $\mu\text{mol/L}$	23.5 (8.14)	–	–
Creatine, mean (SE), $\mu\text{mol/L}$	921.41 (250.33)	–	–
Phosphate, mean (SE), mmol/L	1.83 (0.39)	–	–
Calcium, mean (SE), mmol/L	2.16 (0.20)	–	–
Hematocrit, mean (SE)	32.84 (6.16)	–	–
Cystatin, mean (SE), mg/L	4.41 (1.28)	–	–
Hemoglobin, mean (SE), g/L	103.67 (20.10)	–	–
<i>Stroop(ms)</i>			
<i>Congruent</i>			
Reaction time, mean (SE)	579.92 (12.50)	573.07 (15.90)	.227
Errors rates, mean (SE)	0.17 (0.27)	0.13 (0.24)	.957
<i>Incongruent</i>			
Reaction time, mean (SE)	703.59 (18.48)	657.74 (14.53)	.062
Errors rates, mean (SE)	0.31 (0.04)	0.22 (0.04)	.224
<i>Incongruent–congruent</i>			
Reaction delay, mean (SE)	123.69 (13.91)	84.66 (8.03)	.017*

The group differences in subjects' basic information (age, years of education) were analyzed using one-way ANOVAs. Post hoc comparisons were performed using *t* tests.

* $p < .05$.

3 | RESULTS

3.1 | Demographic characteristics and cognitive control measurements

Demographic and clinical data for patients with ESRD and HCs are summarized in Table 1. There were no significant differences in age and years of education between the two groups. During the Stroop task, both groups showed a significant Stroop effect, where the reaction time was longer during the incongruent than the congruent condition (ESRD: 703.59 ± 18.48 ms vs. 579.92 ± 12.50 ms; HCs: 657.74 ± 14.53 ms vs. 573.07 ± 15.90 ms). There were no significant differences between the two groups during the congruent or incongruent time and error rate during the congruent ($p = .227$) or incongruent condition ($p = .062$). In addition, reaction delay measured by the reaction time during the incongruent condition minus the congruent condition was longer in ESRD patients than HCs (123.69 ± 13.91 ms vs. 84.66 ± 8.03 ms, $p = .017$).

3.2 | Whole-brain analysis

Whole-brain TBSS analysis results of differences between HCs and ESRD patients are shown in Figure 1. Compared with HCs, significantly lower FA and F1, higher MD and RD were observed in WM tracts in ESRD patients ($p < .007$). No significant differences were observed in AD, F2, and MO values between ESRD patients and HCs.

FIGURE 1 Tract-based spatial statistics analyses between ESRD patients and healthy controls. ESRD patients showed lower FA and F1, and higher MD and RD. this figure is layered on an FMRIB58_FA_1mm image. Color bar represents the p value. Abbreviations: ESRD = end-stage renal disease; FA = fractional anisotropy; MD = mean diffusivity; RD = radial diffusivity; F1 = crossing-fiber measures [Color figure can be viewed at wileyonlinelibrary.com]

The location of the TBSS results of the group difference was mainly focused on the cingulum.

Whole-brain FBA analyses yielded significant between-group differences in FD in the left cingulum at a significance threshold of ($p < .017$; Figure 2). However, no significant differences were found in FC and FDC between ESRD patients and HCs.

3.3 | Along-tract statistical analysis

As compared with the HCs, significantly higher MD (Figure 3a, $p < .0125$) and RD (Figure 3b, $p < .0125$) were found in patients with ESRD in the anterior section of the cingulum. There were no

significant between-group differences in FA and AD along the atlas-normalized arc length. The conjoint analysis of the between-group difference is shown in Figure 3c, which mainly focuses on the anterior part of the left cingulum.

3.4 | Mediation analysis

For the results of the K-S test, cognitive control measurements of the Stroop task can be considered to have a normal distribution, and can be dealt with as normally distributed variables during calculation. All biochemical indices were used to build a stepwise regression model with cognitive control measurements, where only Hb significantly contributed to the reaction delay ($p = .006$, effect size = 0.528) (Table 2). Our results seemed to indicate that Hb is an important factor in affecting the cognitive control performance of ESRD patients.

Moreover, the RD in the anterior section of the left cingulum showed a negative correlation with Hb levels (Figure 4a1) in ESRD patients, but no significant association was found between MD and Hb levels in ESRD patients.

Correlation analysis results revealed that the RD in the anterior section of the left cingulum was positively associated with reaction delay in ESRD patients (Figure 4a2), no significant association was found between MD and reaction delay in ESRD patients.

In the mediation analysis, the independent factor was Hb and dependent variables were cognitive control measures that were reflected by the reaction delay, with the mean value of RD in the anterior section of the left cingulum as the proposed mediator. As shown in Figure 4b, the mediation analysis indicated that higher RD of the anterior section of the left cingulum mediated the effect of Hb on the cognitive control deficits (Figure 4b, $b = 0.5$, $p = .021$, 95% confidence interval) in ESRD patients.

4 | DISCUSSION

In the current study, we aimed to explore the relationship among ESRD, WM abnormalities, and cognitive control deficits. For the whole-brain analysis, TBSS results showed microstructural alteration in the WM skeleton in ESRD patients, which mainly focused on the

FIGURE 2 Fixel-based analysis between ESRD patients and healthy controls. Fixels that were significantly decreased in ESRD patients compared to healthy controls for the FD metric, with fixels colored by the p value. Abbreviations: ESRD = end-stage renal disease; FD = Fiber density [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Tractography atlas-based analysis between ESRD patients and healthy controls. The group-difference in diffusion measurements is shown in (a) and (b). Significantly higher MD (a, $p < .0125$) and RD (b, $p < .0125$) were found in patients with ESRD in the anterior section of the cingulum. The conjoint analysis of the between-group differences is shown in (c). Abbreviations: ESRD = end-stage renal disease; MD = mean diffusivity; RD = radial diffusivity [Color figure can be viewed at wileyonlinelibrary.com]

cingulum. FBA analysis showed FD reduction in ESRD patients which was also located in the cingulum. For the ROI-based analysis, the results of TABS showed WM microstructural alteration in the anterior section of the cingulum in ESRD patients. Mediation analysis supported the model that the low level of Hb was an important risk factor for cognitive control deficits in ESRD patients, and the relationship was mediated by the WM microstructural changes in the anterior section of the cingulum. Our findings may enhance our understanding of the possible reason for cognitive control deficits in ESRD patients and provide support for the interaction among kidney failure, brain WM pathways, and cognitive decline.

4.1 | Whole-brain WM analysis

From the application of the TBSS analysis and FBA method, ESRD patients showed diffusion characteristic alteration and WM morphology variation which mainly focused on the cingulum. For the TBSS results, the diffusion characteristics difference between ESRD patients and HCs was mainly focused on lower FA and F1, and higher MD and RD. FA is a value that describes the degree of anisotropy of the diffusion process. MD is the mean of all three axes of the diffusion ellipsoid reflecting the rate of water diffusion within a voxel. RD reflects diffusivity perpendicular to the major axis of the tensor (Benedetti et al., 2011; Madden et al., 2012; Thomason & Thompson, 2011). The changes of FA, MD, and RD in our study reflect the alteration of WM microstructural changes. F1 is concerned with the fiber complexity and reflect the primary fiber population (Panagiotaki et al.,

2012). Lower F1 in our results indicated primary fiber population reduction in voxels. This may also be the reason for the WM microstructural property changes. Moreover, with the FBA method, reduced FD was found in the cingulum in ESRD patients. FD is used to describe the intra-axonal volume (Mito et al., 2018; Raffelt et al., 2017). FD variation may suggest substantial axonal loss occurring at the microstructural level in the presence of morphological alterations in WM structures in ESRD. Furthermore, changes in the axonal diameters or density may also influence WM characteristics which coincided with the TBSS results (Alexander et al., 2011; Feldman, Yeatman, Lee, Barde, & Gaman-Bean, 2010).

4.2 | WM microstructural alteration along the cingulum of ESRD patients

Higher MD and RD in the anterior section of the cingulum were observed in patients with ESRD, which demonstrated that patients with ESRD showed WM microstructural alteration along the cingulum. The cingulum is a collection of WM fibers projecting from the cingulate gyrus to the entorhinal cortex in the brain, playing a critical role because it connects sites implicated in cognitive control (Metzler-Baddeley et al., 2012). In our results, the main WM microstructural properties variation of the cingulum differentiating patients with ESRD from HCs was observed in the anterior part of the cingulum. Previous work focused on the role of the prefrontal cortex, notably the anterior cingulate cortex, which is a key node of a distributed cognitive control network (Holroyd & Yeung, 2012). It had reported that

TABLE 2 Stepwise multiple regression analysis

Biochemical indices	Correlation coefficient	T	p	Partial correlation	Collinearity statistics	
					Tolerance	VIF
Hemoglobin ^a	−0.528 ^a	−3.049	.006*	−0.528	1.000	1.000
Ca ²⁺ ^b	0.041 ^b	0.231	.819	0.048	0.995	1.005
Urea ^b	−0.137 ^b	−0.757	.457	−0.156	0.932	1.073
Creatine ^b	−0.302 ^b	−1.630	.117	−0.322	0.821	1.219
Hematocrit ^b	0.073 ^b	0.265	.793	0.055	0.412	2.426
Cystatin c ^b	0.178 ^b	1.018	.319	0.208	0.987	1.013
Phosphate ^b	0.100 ^b	0.570	.574	0.118	0.998	1.002

^a Entered variables.^b Excluded variables.* $p < .05$.

the anterior cingulate cortex was implicated in the networks for top-down attentional control and goal-directed behavior was connected via the anterior cingulum (Metzler-Baddeley et al., 2012). Many studies suggested that the dysfunction of the anterior cingulate cortex predicted impaired performance in Stroop tasks reflecting cognitive control deficits (Apps, Rushworth, & Chang, 2016; McTeague, Goodkind, & Etkin, 2016; Tolomeo et al., 2016). Moreover, several kidney

studies had found there was dysfunction of the anterior cingulate cortex in ESRD patients (Ni et al., 2014; Papoiu et al., 2014). As the WM properties may be linked to gray matter changes, the anterior part of the cingulum in our results was consistent with the above findings which may further indicate the effects of the kidneys on WM.

4.3 | The relationship between WM alteration, cognitive control deficits, and Hb

Another important finding in our study was the significant correlation between Hb and RD in the anterior section of the cingulum in ESRD patients. As validated by many studies, low levels of Hb always result in loss of integrity of the blood–brain barrier which was regarded as induced brain edema (Lu et al., 2015). WM was sensitive to the change in brain water content (Pierpaoli et al., 2001). Low levels of Hb-induced compensatory mechanisms resulting in cerebral arteriolar dilatation and brain blood flow increase could be detrimental for those with cerebral edema (Kramer & Zygun, 2009; Roberts & Zygun, 2012). This indicated that low levels of Hb are an important factor that could lead to cerebral edema. Cerebral edema that results from breakdown of the blood–brain barrier, as plasma constituents cross the barrier caused by vascular permeability increase, occurs when water moves extracellularly along fiber tracts and can affect WM microstructural properties (Adachi & Feigin, 1966; Lu et al., 2015). The significant correlation between Hb and RD in our study may provide evidence that low levels of Hb could affect the loss of myelin of the anterior section of the cingulum in ESRD patients.

In our study, RD in the anterior section of the cingulum was correlated with reaction delay of the Stroop task in ESRD patients. The original color-words Stroop task comprises of a number of color-words employed for the cognitive control measurements (Stroop, 1992). Longer reaction delay suggested there were cognitive control deficits in patients with ESRD (Stroop, 1992). The relationship between RD in the anterior section of the cingulum and reaction delay demonstrated that the microstructural properties alteration of the anterior part of the cingulum may be concerned with cognitive control deficits in ESRD patients. Moreover, some DTI studies suggested that WM microstructural properties were related to neural activity, and that these neural activities were associated with cognitive function (Stretton et al., 2013; Winston et al., 2013). It may be indicated that the alteration of the cingulum would affect neuron function under

FIGURE 4 Mediation analysis. Negative correlation between RD, which was extracted from white matter of the conjoint analysis and Hb is shown in (a). Positive correlation between reaction delay and RD, which was extracted from white matter of the conjoint analysis is shown in (b). The relationship among Hb, the mean RD in the white matter of the conjoint analysis, and reaction delay are shown in (b). Alteration of white matter diffusion measurements in the anterior part of the cingulum mediated the relationship between Hb and reaction delay. Abbreviations: ESRD = end-stage renal disease; RD = radial diffusivity, Hb, hemoglobin [Color figure can be viewed at wileyonlinelibrary.com]

normal circumstances, thereby affecting information processing and performance during cognitive control.

4.4 | WM microstructural properties mediate the effects of Hb on cognitive control

The relationships between low level of Hb and longer reaction delay were found within ESRD patients, with higher RD interactions constituting the compelling finding, demonstrating that WM microstructural alteration of the cingulum can be an important mediator of the relationship between low levels of Hb and cognitive control deficits in ESRD patients. Many studies have shown that WM microstructural property variation in the left anterior cingulum was extremely sensitive to performance of cognitive control tasks (Metzler-Baddeley et al., 2012; Soeda et al., 2005). Furthermore, low levels of Hb have well-known adverse effects on physical and cognitive performance of individuals (Chen et al., 2013; Granthamcgregor & Ani, 2001). Some studies also suggested that low levels of Hb might be an independent risk factor for executive function impairment (Chaves et al., 2006; Evans, 2002). However, it is unclear whether WM or Hb primarily influences cognitive control in ESRD patients. Elaborating the relationships among Hb, WM, and reaction delay is very helpful to understand the neural mechanism of cognitive control deficits in ESRD patients. Our mediation model suggested that Hb levels might be an indicator of ESRD predisposed to altering WM microstructural properties, thereby affecting the underlying cognitive function.

4.5 | Limitations and future considerations

There are some limitations that should be noted in our studies. In our study, the HCs had no biochemistry tests done. Hence, we cannot detect the potential relationship between biochemistry tests and cognitive control measurements in the HCs. However, many studies reported that patients with ESRD exhibited tremendously high levels of anemia (Lu et al., 2015; Luo et al., 2016; Nissenson et al., 2002; Zhang et al., 2016). In addition, the Hb level of patients in our study was 103.67 g/L (range from 80 g/L to 123 g/L). The normal range of Hb was 120–160 g/L. Only two patients had a marginal value of a normal Hb level. Hence, the patients in our study were associated with anemia. In further research, we will try to obtain the biochemistry tests from the HCs and validate the results. Second, the DTI scan was applied along 30 noncollinear directions with five acquisitions without diffusion weighing in our study. The limitation of DTI is the delineation of crossing and touching fibers due to insufficient anisotropy and angular separation (Meng & Zhang, 2014). Diffusion spectrum imaging (DSI) was increasingly applied and explored in neuroimaging studies with a higher angular resolution and more diffusion weighted directions than DTI (Bilgic et al., 2012; Chiu et al., 2011; Nezamzadeh et al., 2010). In further research, the use of DSI could be a means of image scanning to get more accurate tractography. Third, only the cingulum was taken into consideration in our study, which had a correlation with cognitive control. Further studies are needed to select more fiber tracts which were connected to the cingulum and to investigate whether WM microstructural properties of these fiber tracts would lead to cognitive control deficits.

5 | CONCLUSION

In summary, our study indicated that a low level of Hb was an important risk factor for cognitive control deficits in ESRD patients, and the relationship was mediated by the WM microstructural properties in the anterior part of the cingulum. These findings may enhance our understanding of the underlying pathophysiological mechanisms of cognitive control deficits in ESRD patients and provide support for the interaction between the kidneys and the brain. In addition, neuroimaging is a sensitive technique used to detect the changes in brain structure and function, and the use of neuroimaging would be helpful to clarify the underlying mechanisms of cognitive control deficits in ESRD patients.

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CONFLICT OF INTEREST

None declared.

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