Clinical Kidney Journal, 2024, vol. 18, no. 1, sfae283

https://doi.org/10.1093/ckj/sfae283
Advance Access Publication Date: 10 September 2024
Original Article

ORIGINAL ARTICLE

Cerebral white matter damage in patients with end-stage kidney disease associates with cognitive impairment

Yi-Chou Hou[1,2], Chih-Chien Tsai[3], Ruei-Ming Chen[4,5,6], Yi-Chien Liu[2,7], Kuo-Cheng Lu[8,9], Yao-Liang Chen[10,11,12], Ting-Wen Shen[13,14] and Jiun-Jie Wang[3,10,12,15]

[1]Department of Internal Medicine, Cardinal Tien Hospital, New Taipei City, Taiwan, [2]School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan, [3]Healthy Aging Research Center, Chang Gung University, Taoyuan City, Taiwan, [4]TMU Research Center of Cancer Translational Medicine, Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei City, Taiwan, [5]Cell Physiology and Molecular Image Research Center, Wan Fang Hospital, Taipei Medical University, Taipei City, Taiwan, [6]Anesthesiology and Health Policy Research Center, Taipei Medical University Hospital, Taipei City, Taiwan, [7]Department of Neurology, Cardinal Tien Hospital, New Taipei City, Taiwan, [8]Department of Nephrology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan, [9]Division of Nephrology, Department of Medicine, Fu Jen Catholic University Hospital, School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan, [10]Department of Medical Imaging and Radiological Sciences, Chang Gung University, Taoyuan City, Taiwan, [11]Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital, Linkou, Taoyuan City, Taiwan, [12]Department of Diagnostic Radiology, Chang Gung Memorial Hospital, Keelung City, Taiwan, [13]Department of Medical Imaging and Intervention, New Taipei Municipal TuCheng Hospital, Chang Gung Medical Foundation, New Taipei City, Taiwan, [14]College of Medicine, Chang Gung University, Taoyuan City, Taiwan and [15]Department of Chemical Engineering, Ming-Chi University of Technology, New Taipei City, Taiwan

Correspondence to: Ruei-Ming Chen; E-mail: rmchen@tmu.edu.tw, Jiun-Jie Wang; jwang@mail.cgu.edu.tw

ABSTRACT

Background. Damage to brain white matter often occurs in individuals with chronic kidney disease, which might be related to their cognitive decline. This study aims to investigate tract-specific white matter damage in patients with end-stage kidney disease by using fixel-based analysis.

Methods. Images of 31 end-stage kidney disease patients and 16 normal controls (aged: 61.1 ± 10.4 years; 11 men) were acquired from a 1.5T magnetic resonance scanner. The patients were subsequently divided into with normal cognition ($N = 17$, aged: 66.9 ± 7.2 years; 10 men) and cognitive impairment ($N = 14$, aged: 72.4 ± 9.4 years; 7 men). Cognitive assessment, and neurologic, hematologic and biochemical samples were collected. Fixel-based analysis was used to examine the tract-specific damage within white matter. Differences between groups were evaluated through connectivity-based fixel enhancement and non-parametric permutation testing. Correlation with biomarkers was conducted through general linear model. Significance was determined with family-wise error-corrected P-value $<.05$.

Received: 29.3.2024; Editorial decision: 4.9.2024

Results. Reduced fixel-based metrics were observed in specific tract located the cerebral peduncle, internal capsule, corpus callosum, fornix and superior corona radiata in patients when compared with normal controls, indicating a reduction in fiber content. The fibers crossing the corpus callosum and the fornix/stria terminalis are particularly vulnerable sites, which can be associated with the decrease in both Mini-Mental State Examination (R^2 ranged between 0.420 and 0.556) and Montreal Cognitive Assessment (R^2 ranged between 0.425 and 0.509), as well as the plasma concentration of calcium (R^2 ranged between 0.207 and 0.322). The plasma concentration of indoxyl sulfate was associated with the descending tracts from right posterior limb of internal capsule to cerebral peduncle (R^2 ranged between 0.262 and 0.335).
Conclusions. Tract-specific white matter damage can be noticed in the patients with end-stage kidney disease, and could be associated with their cognitive decline.

Keywords: cognitive impairment, corpus callosum, end-stage kidney disease, fixel-based analysis, leukoarariosis

KEY LEARNING POINTS

What was known:

- Patients with end-stage kidney disease often experience cognitive impairment, marked by a chronic decline in memory, learning and concentration abilities.
- White matter damage was linked to cognitive impairment in patients.
- Quantifying white matter lesion in patients with end-stage kidney disease are crucial for monitoring cognitive decline.

This study adds:

- Reduced fixel-based metrics in patients, compared with normal controls, were observed in specific tracts including cerebral peduncle, corpus callosum, fornix and superior corona radiata.
- Fibers crossing the corpus callosum and fornix/stria terminalis was positively correlated with Mini-Mental State Examination, Montreal Cognitive Assessment scores and plasma calcium concentration.

Potential impact:

- Fixel-based analysis identified tract-specific damage, essential for clinicians to understand the impact of end-stage kidney disease on white matter integrity.
- Further investigation into the mechanisms preserving these tracts from damage, as well as their role in cognitive decline and kidney disease progression, is warranted.

INTRODUCTION

Chronic kidney disease (CKD) is a condition characterized by the chronic loss of glomerular filtration rate, proteinuria or structural defects in the genitourinary tract [1]. The risk factors contributing to CKD are multifactorial, typically including metabolic disorders such as diabetes mellitus and hypertensive cardiovascular disease [1]. CKD patients may experience comorbidities, including renal osteodystrophy, anemia, vascular calcification, congestive heart failure and neurologic complications [2, 3]. The dysregulated homeostasis of electrolytes, accumulation of uremic toxins, anemia and increased risk of cerebrovascular disorder have been proposed to lead a higher incidence of neurodegenerative disorders such as cognitive impairment and dementia [3, 4].

Cognitive impairment is a common complication in patients with end-stage kidney disease (ESKD, the advanced CKD with maintenance renal replacement therapy) [5]. It is characterized by chronic decline in memory, learning or ability to concentrate [4]. Lesions in white matter could impair signal transmission in integrity or speed, thus negatively impacting the cognitive function [6]. Its damage might be linked to cognitive impairment in patients with CKD due to overlapping risk factors and causative pathogenesis. Exploration of the structural disturbances in white matter in patients with ESKD might shed new light on the understanding of their cognitive impairment.

White matter is a susceptible area for vascular disorders such as hypertension, cerebral small vessel disease or hypertensive arteriopathy. White matter lesions are a common radiological finding in ESKD patients. The severity of lesions, such as leukoaraiosis, is associated with future cognitive decline or other psychiatric disorders [7, 8]. The extent of lacunar infarction or white matter hyperintensity has been shown to be related to the severity of cognitive decline [9]. Identification of the white matter damage is crucial in preventing cognitive decline, especially in ESKD patients.

Diffusion magnetic resonance imaging (MRI) has been widely used in the study of white matter diseases [10]. Fixel-based analysis is a novel method for the processing of diffusion MRI, which measures the FIber population within a specific voXEL (FIXEL). Fixel-based metrics include fiber density (FD), which measures the volume of axons aligning with a specific fiber population; fiber cross-section (FC), which measures the macroscopic cross-sectional size of individual fiber bundles; and FDC, which represents the combination effect of FD and FC [11, 12]. The integrity of the structural connection of white matter can be assessed by using fixel-based analysis [11, 12].

Our study hypothesizes that a correlation exists between clinical assessment, biochemical parameters and white matter status in ESKD patients. The aim of our study is to use fixel-based analysis to identify the white matter integrity in the brain of ESKD patients.

Table 1: The demographic, neurologic biomarkers and biochemical result and cognitive scale in the study subjects.

		ESKD	ESKD	
	Normal control	Total	Cognition normal	Cognition impairment
Demographics				
Age (years)[a]	61.1 ± 10.4	68.7 ± 7.7	66.9 ± 7.2	72.4 ± 9.4
Sex (M/F)	11/5	17/14	10/7	7/7
Education (years)[a,b]	13.0 ± 1.8	9.4 ± 3.4	10.4 ± 2.9	7.8 ± 4.4
Hypertension (–/+)	8/8	6/25	4/13	2/12
Diabetes (–/+)	10/6	14/17	6/11	8/6
MMSE[a,c]	29.9 ± 0.3	25.4 ± 4.9	28.6 ± 2	20.4 ± 4.4
MoCA[a,c]	29.7 ± 0.9	23.5 ± 6.8	28.2 ± 2.6	15.6 ± 4.7
BDI-II	1.8 ± 2.7	4.6 ± 3.2	4.0 ± 2.7	5.1 ± 3.6
Neurologic biomarkers				
Tau protein (pg/mL)	21.54 ± 2.70	22.58 ± 3.55	26.57 ± 3.75	26.60 ± 3.37
Aβ1/42 (pg/mL)	16.42 ± 0.44	16.51 ± 0.42	16.56 ± 0.44	16.45 ± 0.41
NfL (pg/mL)	10.41 ± 2.94	9.53 ± 2.30	9.85 ± 2.48	9.82 ± 2.04
UCH-L1 (pg/mL)	61.55 ± 13.42	56.26 ± 11.87	55.40 ± 10.78	57.59 ± 13.71
GFAP (pg/mL)	32.71 ± 12.98	25.81 ± 10.16	27.08 ± 11.41	23.86 ± 7.89
BDNF (pg/mL)	63.37 ± 10.43	67.28 ± 13.58	67.92 ± 14.56	63.30 ± 12.44
Biochemical parameters				
BUN (U/L)[a,b,d]	20.94 ± 6.76	73.79 ± 17.10	77.78 ± 78.49	68.73 ± 14.15
Creatinine (mg/dL)[a,b,d]	1.06 ± 0.32	9.46 ± 1.93	10.07 ± 1.72	9.46 ± 1.93
Na (mEq/L)[a,c]	139.05 ± 2.18	137.79 ± 2.82	138.79 ± 2.55	136.53 ± 2.72
K (mEq/L)[a,b,d]	4.11 ± 0.40	4.86 ± 0.68	4.81 ± 0.54	4.53 ± 0.83
GOT (U/L)[b]	23.68 ± 11.64	17.08 ± 13.11	15.21 ± 9.30	19.46 ± 16.82
GPT (U/L)[a,b,d]	28.83 ± 18.33	12.58 ± 9.06	10.94 ± 4.63	14.66 ± 12.56
LDL (mg/dL)	102.20 ± 31.74	88.61 ± 33.20	96.36 ± 38.78	80.10 ± 24.99
TG (mg/dL)[c,d]	176.16 ± 40.21	142.42 ± 33.38	157.77 ± 35.53	131.20 ± 27.69
TC (mg/dL)	136.66 ± 54.34	146.58 ± 90.34	152.10 ± 92.29	139.60 ± 90.52
Ca (mg/dL)[d]	9.27 ± 0.29 (16/0)[e]	8.80 ± 0.79 (20/11)[e]	8.87 ± 0.68 (12/5)[e]	8.71 ± 0.93 (8/6)[e]
P (mg/dL)[a,b,d]	3.74 ± 0.59	5.60 ± 1.52	5.91 ± 1.34	5.20 ± 1.68
Indoxyl sulfate (μg/mL)[a,b,d]	3.99 ± 7.60	38.08 ± 15.03	43.04 ± 13.90	34.85 ± 15.36

[a]Normal control versus ESKD patients with cognition impairment.
[b]Normal control versus ESKD patients with cognition normal.
[c]ESKD patients with cognition normal versus cognition impairment.
[d]Normal control versus ESKD.
[e]Number of participants whose plasma calcium concentration was <8.5 mg/dL (–/+).
M, male; F, female; BUN, blood urea nitrogen; Ca, calcium; Cr, creatinine; GOT, glutamic oxaloacetic transaminase; K, potassium; LDL, low-density lipoprotein; Na, sodium; P, phosphorus; TC, total cholesterol; TG, triglyceride; UCH-L1: ubiquitin C-terminal hydrolase-L1; BDI-II: beck depression inventory-second edition.

MATERIALS AND METHODS

Ethics declaration

The prospective study, conducted in accordance with the Declaration of Helsinki, received approval from the Ethics Committee of Human Studies at Cardinal Tien Hospital (approval number CTH-109-2-1-068). All participants provided informed consent prior to participation.

Study subjects

Between August 2019 and December 2020, 35 patients with ESKD were recruited from a regional hospital in New Taipei City, Taiwan. Inclusion criteria were: (i) age between 45 and 80 years old; (ii) proficiency in Chinese or Taiwanese language; and both verbal and written (iii) diagnosis as ESKD status of CKD, defined by receiving hemodialysis for over 3 months. Exclusion criteria were: (i) age under 45 years; (ii) recent stroke, seizure, or brain tumor within 6 months; (iii) pregnancy; (iv) severe anemia (serum hemoglobin level <8.0 g/dL); (v) history of pacemaker implantation; and (vi) refusal to participate.

Blood sampling, cognitive assessments and MRI scans were conducted. Midday blood was sampled for patients preceded dialysis, while the normal control group received non-fasting venous blood sampling. Cognitive assessments were performed by using Mini-Mental Status Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR).

Additional 19 normal controls were recruited from local community. The normal control group was defined by an MMSE score between 25 and 30, with normal serum creatinine levels (male <1.3 mg/dL; female <1.0 mg/dL). Seven participants were excluded from the analysis for the following reasons: six did not complete the image acquisition; one had severe metal artefact in images. The final image analysis included 31 patients with ESKD (average age: 68.7 ± 7.7 years old; 17 men) and 16 normal controls (average age: 61.1 ± 10.4 years old; 11 men). The patients with ESKD were subsequently divided into two sub-groups based on MMSE score: (i) MMSE 25–30, indicating normal cognition ($n = 17$, aged 66.9 ± 7.2 years old; 10 men), and (ii) MMSE 10–24, indicating cognitive impairment ($n = 14$, aged 72.4 ± 9.4 years old; 7 men).

Demographic information, medical history and diagnoses were obtained from Cardinal Tien Hospital records (Table 1).

Measurement of peripheral neurologic biomarkers

Immunomagnetic reduction (IMR, MagQu in New Taipei City, Taiwan) was used to blindly measure peripheral biomarkers following Chiu *et al*. [13]. Whole blood (10 mL) was collected from the participants, which was then deposited into K2 EDTA tubes. The plasma was separated from the whole blood by centrifugation at 2500 × *g* for 15 min within 3 h of collection, and subsequently mixed with IMR reagents: glial fibrillary acidic protein (GFAP) IMR agents (MF-GFA-0060, MagQu) with anti-GFAP antibody (837 204, Biolegend); ubiquitin C-terminal hydrolase-L1 (UCH-L1) IMR agents (MF-UCH-0060, MagQu) with anti-UCH-L1 antibody (sc-271639, Santa Cruz); brain-derived neurotrophic factor (BDNF) IMR agents (MF-BND-0060, MagQu) with anti-BDNF antibody (DY248; R&D Systems); Amyloid beta (Aβ)1/42 with IMR agents (MF-AB2-0060, MagQu) with anti-Aβ1/42 antibody (ab34376, Abcam); tau protein with IMR reagents (MF-TAU-0060, MagQu) with anti-tau antibody (T9450, Sigma Aldrich); and neurofilament light chain (NfL) IMR agents (MF-NFL-0060, MagQu) with anti-NfL antibody (sc-20012, Santa Cruz). The superconducting quantum interference device–based alternating-current magnetosusceptometer (XacPro-S, MagQu Co., New Taipei City, Taiwan) was employed to determine the protein level. This analyzer quantified protein levels by detecting the magnetic signal changes resulting from the interactions between IMR reagents and target proteins.

Measurement of peripheral hematologic and biochemical parameters

The plasma hematologic and biochemical parameters included the following: hemoglobin, platelet count, white blood cell count, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase (GPT), albumin, blood sugar, uric acid, total cholesterol, triglyceride, sodium, potassium, calcium, phosphorus and indoxyl sulfate. Estimated glomerular filtration rate was determined by the Modification of Diet in Kidney Disease Study equation.

Imaging procedure

Acquisition of images was performed using a 1.5T MR scanner (GE HealthCare, Signa HDxt 1.5T, Germany), and included T1-weighted magnetization-prepared rapid acquisition gradient echo (T1-MPRAGE) and diffusion-weighted images. The total acquisition time for both sequences was approximately 45 min. The imaging parameters for the T1-weighted images were: repetition time/echo time of 7242/3.052 ms, 180 slices, voxel size of 1 mm × 1 mm × 1 mm, inversion time of 900 ms, flip angle of 15° and matrix size of 224 × 256.

Diffusion-weighted images were acquired using a spin-echo echo-planar Imaging sequence with the following parameters: repetition time/echo time/flip angle of 12 000 ms/91.9 ms/90°, field of view of 192 × 192 mm, matrix size of 256 × 256 and diffusion-weighting gradients applied along 64 non-collinear directions. A b-value of 1000 s/mm^2 was used.

Image analysis

Fixel-based analysis was performed in accordance with the recommended protocol as implemented in MRtrix3 [12] using single-tissue constrained spherical deconvolution. Preprocessing included denoising (Marchenko-Pastur principal component analysis) [14], Gibbs ringing removal [15], and correction for motion, distortion and bias field [16]. Diffusion-weighted images were resampled to an isotropic voxel size of 1.3 mm, followed by non-linear co-registration. Finally, fixel-based metrics, including FD, FC and the combination of both (FDC), were computed for each voxel.

Analysis of region of interest was performed after statistical analysis of group difference or regression. The brain from each subject was parcellated, followed the procedures described by Lo *et al*. [17]. Specific white matter tracts in each parcellated region were identified using the Johns Hopkins University DTI-based white matter atlas (ICBM-DTI-81), which includes 48 tracts [18]. For each parcellated region of interest, significant fixels were extracted according to the results of statistical analysis. We then calculated the mean values of the fixel-based metrics for each parcellated white matter region.

Statistics

The one-way analysis of variance was employed to compare continuous variables between the three groups, and the chi-square test was used to analyze the association between categorical variables. All statistical analyses were performed using SPSS for Windows (Version XVII; SPSS, Inc., Chicago, IL, USA). A two-sided *P*-value of $<.05$ was considered statistically significant.

Statistical analyses on images was performed in MRtrix3, where age, sex, hypertension and diabetes mellitus were regarded as covariates. Differences in fixel-based metrics (FDC, FD and FC) were evaluated through connectivity-based fixel enhancement and non-parametric permutation testing [19]. This was involved in comparing normal control group, patients with normal cognition and patients with cognitive impairment.

Fixel-based metrics were analyzed for their correlation with biomarkers using linear regression through general linear model. In all analyses, single group averages of age, sex, hypertension and diabetes mellitus were regarded as covariates. Significance was determined using nonparametric permutation testing with family-wise error-corrected *P*-value $<.05$. In the subsequent region of interest analysis, adjusted R^2 values from linear fitting were used to express the goodness-of-fit between fixel-based metrics and clinical parameters. The F-test was regarded as statistically significant if $P < .05/n$ after correction for multiple comparisons, where n is the number of the regions that contain significant fixels in each metric.

RESULT

Demographic characteristics

Table 1 presents a group comparison of demographics, hematologic and biochemical parameters, and neurologic biomarkers. ESKD patients with cognition impairment had a higher mean age than the normal control ($P < .05$). Among MMSE-based groupings, the MoCA score was lowest in ESKD patients with cognition impairment. Regarding neurologic biomarkers, no significant differences were found in peripheral concentrations. However, ESKD patients exhibited higher plasma levels of blood urea nitrogen, creatinine, potassium, indoxyl sulfate and phosphate ($P < .05$). Conversely, triglyceride and GPT levels were lower in ESKD patients compared with the normal control ($P < .05$). When comparing ESKD patients with cognition impairment versus the normal control, lower

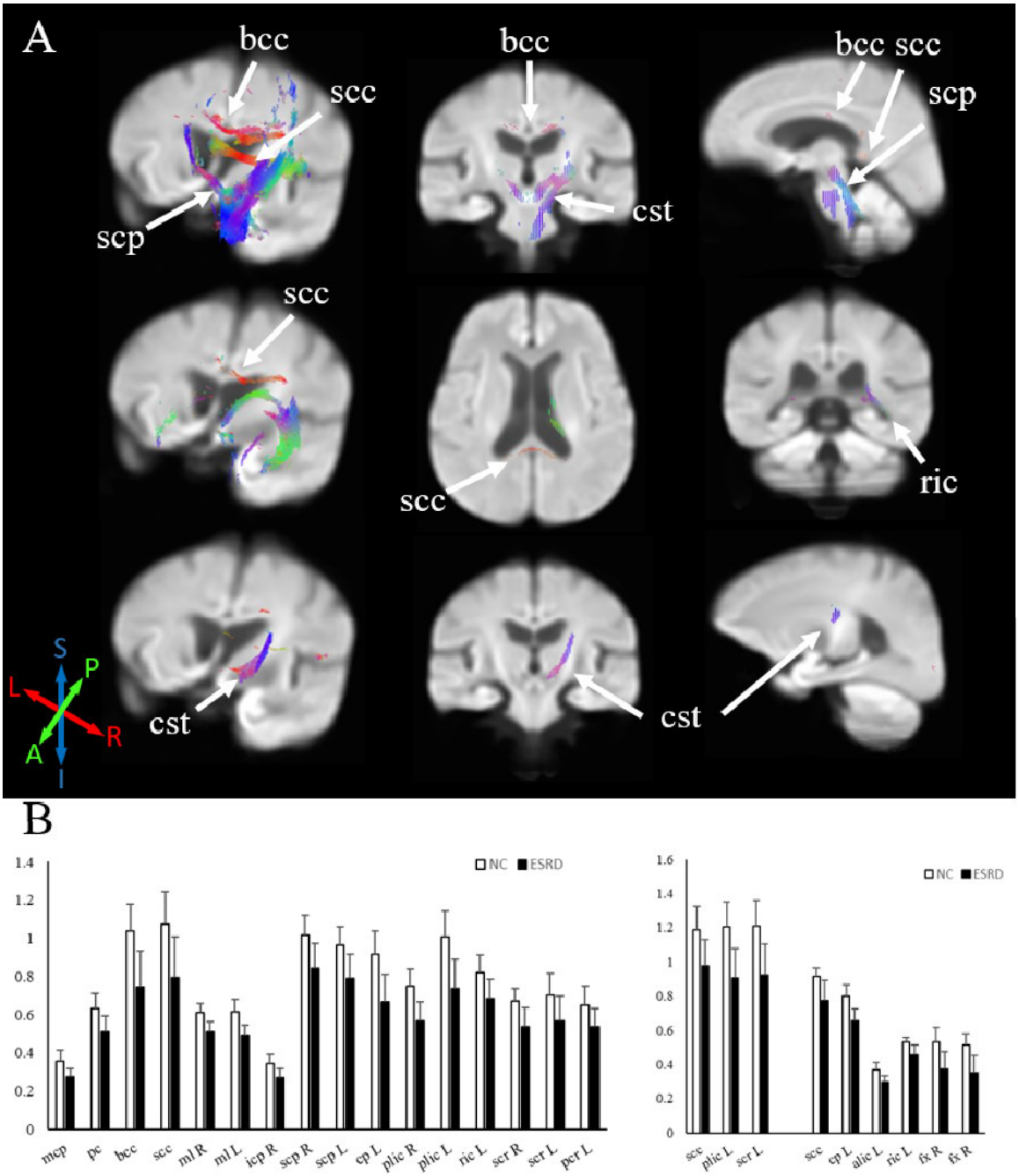

Figure 1: Group comparisons between patients with ESKD and normal controls. (**A**) Significant fixel-based metrics between ESKD patients and normal control were displayed. Left column: figures displayed stereoscopically in the superior left frontal view. Middle and right column: figures displayed in the axial/sagittal/coronal view. Fixel-based metrics with significance (family-wise error-corrected $P < .05$) were illustrated with color encoded according to the fiber direction. Upper row, FDC; middle row, FD; lower row, FC. Green: anterior (A)-to-posterior (P); blue, superior (S)-to-inferior (I); and red: left (L)-to-right (R). (**B**) The average values of fixel-based metrics were presented from parcellated brain regions for the normal control (blank bar) and the ESKD patient group (solid bar). Left panel, FDC; right panel, FD and FC. R, right; L, left; alic, anterior limb of internal capsule; bcc, body of corpus callosum; cp, cerebral peduncle; cst, corticospinal tract; fx, fornix; mcp, middle cerebellar peduncle; ml, medial lemniscus; pc, pontine cross tract; pcr, posterior corona radiata; plic, posterior limb of internal capsule; ric, retrolenticular part of internal capsule; scc, splenium of corpus callosum; scp, superior cerebellar peduncle; scr, superior corona radiata; slf, superior longitudinal fasciculus.

concentrations of sodium, calcium, GPT and triglyceride were observed. Additionally, ESKD patients with cognitive impairment showed lower levels of sodium, calcium and triglyceride compared with ESKD patients with normal cognition.

The decrease of fiber content in ESKD patients

Figure 1 shows decreased fixel-based metrics in several brain regions as observed in ESKD patients when compared with normal control (Fig. 1A). Specifically, changes in the splenium of

the corpus callosum was found in each metric. Decreased FDC was observed in the cerebral peduncle and retrolenticular part of the internal capsule, associated solely with FD. Both FDC and FC reductions were found in the posterior limb of the internal capsule and superior corona radiata. Furthermore, regions with decreased FDC only included the cerebellar peduncle (superior, middle and inferior) and corticospinal tract. The fornix also exhibited reduced FD. The corresponding value of fixel-based metrics from these regions with significant changes is shown in Fig. 1B.

The decrease of fiber content in comparisons of cognitive impairment

Figure 2 shows the white matter involvement in the comparison of ESKD patients with normal cognition (Fig. 1A)/cognitive impairment (Fig. 2B) and normal controls. The affected regions in FC include the splenium of corpus callosum and posterior thalamic radiation (Fig. 1A). No changes in FDC and FD were found. In the analysis of ESKD patients with cognitive impairment versus normal controls, the affected regions in FDC include the corpus callosum (body and splenium), corticospinal tract, fornix, cerebellar white matter and superior corona radiata (Fig. 2B, upper row). Similar patterns were observed in both FDC and FD (Fig. 2B, middle row), with a notable extension of FD into the genu of the corpus callosum. In contrast, FC changes were localized to the body of the corpus callosum, corticospinal tract and superior longitudinal fasciculus (Fig. 2B, lower rows).

Figure 3 illustrates the fixel-based analysis to compare the fiber between ESKD patients with cognitive impairment and normal cognition (Fig. 3A) and the corresponding results from region of interest analysis (Fig. 3B). Both FDC and FD reduction were noticed in the corpus callosum (body and splenium) and fornix. Decreased FD was found in the genu of corpus callosum, internal capsule (anterior limb, posterior limb and retrolenticular part), corona radiata (anterior, superior and posterior), and posterior thalamic radiation. No changes in FC were found. The value of metrics in regions with significant changes were plotted in Fig. 3B.

Supplementary data, Fig. S1A and S1B depicts sequential cross-sectional slices in regions with significant difference of ESKD/normal control and ESKD cognitive impairment/normal cognition in the axial view, respectively.

The correlation of fixel-based metrics with the cognitive scores

Figure 4 shows positive correlations were found between fixel-based metrics and scores on the MMSE (Fig. 4A) and MoCA (Fig. 4B). Correlations of fixel-based metrics with both cognitive scores were located in overlapping regions. These tracts include the superior cerebellar peduncle, body and splenium of the corpus callosum, cerebral peduncle, superior and posterior corona radiata, external capsule, cingulum and superior longitudinal fasciculus. For FDC, the goodness-of-fit ranges (R^2) are 0.313–0.477 for MMSE and 0.241–0.461 for MoCA, respectively. Additional correlations were observed with FD, located in the fornix head and fornix stria terminalis. The goodness-of-fit ranged between 0.441 and 0.465 for MMSE and 0.433 and 0.472 for MoCA, respectively. Supplementary data, Fig. S2 showed slices in cross-sectional view with significant correlations of MMSE and MoCA respectively. Table 2 summarizes the goodness-of-fit for fixel-based metrics with significant correlations in regions.

The association between the fiber content and peripheral hematologic/biochemical parameters

Figure 5 shows the associations between fixel-based metrics and plasma calcium (Fig. 5A), as well as indoxyl sulfate (Fig. 5B), respectively. In Fig. 5A, plasma calcium levels have a positive association with each metric in the corpus callosum, as well as FD of the fornix head/stria terminalis. Additional regions included the cerebral peduncle, posterior limb of the internal capsule, external capsule and superior corona radiata. The goodness-of-fit (R^2) ranges between 0.143 and 0.322.

Figure 5B demonstrates that plasma indoxyl sulfate concentration was negatively associated with FDC and FD in regions located in the corticospinal tract ($R^2 = 0.313$) and fornix/stria terminalis ($R^2 = 0.275$), respectively. The goodness-of-fit between fixel-based metrics and plasma concentrations is summarized in Table 3.

No significant correlations were found with other peripheral hematologic, biochemical parameters and peripheral neurologic biomarkers.

DISCUSSION

Main finding

The primary goal of our study was to investigate white matter changes in ESKD patients compared with an age range-matched group of healthy subjects. Our findings showed that white matter damage can be observed in the brains of ESKD patients. We subsequently divided the ESKD patients into two groups based on their cognitive performance, as assessed by the MMSE. We found that white matter damage was more extensive in patients with cognitive impairment.

Our study identified subtle alterations in white matter in ESKD patients, which highlighted the impact of CKD on the brain. Tract-specific white matter damage was observed in patients when compared with the normal controls, indicating a reduction in fiber content. Decreased fixel-based metrics were identified in various brain regions, including the corpus callosum, fornix, cerebral and cerebellar peduncle, internal capsule, corona radiata and corticospinal tract. Our study suggests that the white matter alteration in ESKD patients may reflect an accelerated neurodegenerative process. To identify the damage in specific tracts and regions is therefore of important interest to clinicians.

The findings suggest that the structural integrity in white matter can be relevant to the cognitive status. Positive correlations were observed between fixel-based metrics and cognitive scores as measured by MMSE and MoCA, which indicated an association between white matter status and cognitive function. The fibers crossing the corpus callosum and the fornix/stria terminalis are particularly vulnerable sites. Correlations were also found between fiber content and plasma calcium and indoxyl sulfate levels in regions such as the corpus callosum, fornix and corticospinal tract, which might suggest potential links between these biochemical parameters and white matter integrity. This might lead to further interest in research to investigate the mechanisms in preserving these tracts from damage, as well as their role in cognitive decline and kidney disease progression.

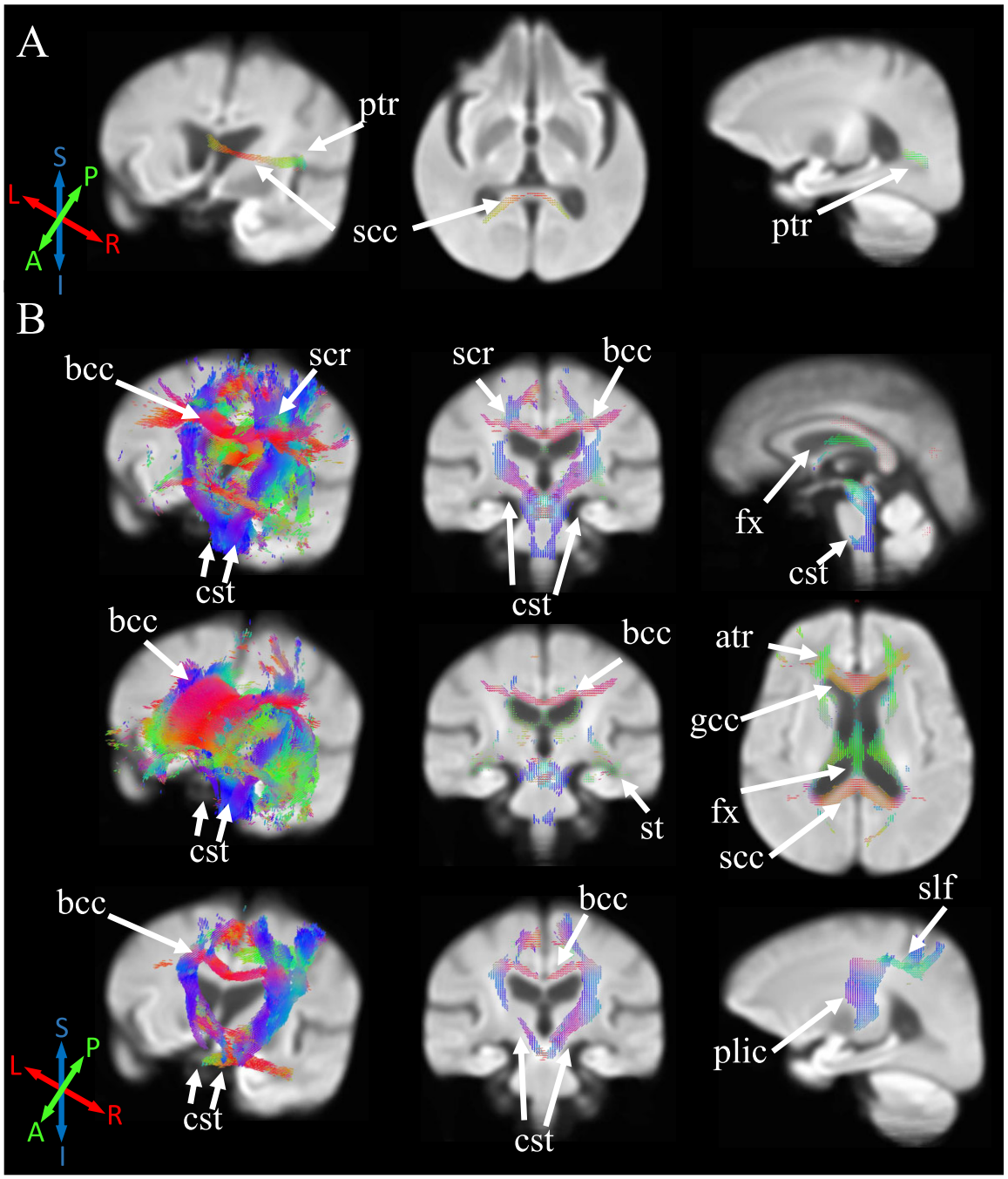

Figure 2: Comparison of patients with ESKD with and without cognitive impairment, and normal controls. Significant fixel-based metrics were displayed for comparisons in (**A**) between ESKD patients with normal cognition and normal control, as well as (**B**) between ESKD patients with cognitive impairment and normal control. Left column: figures displayed stereoscopically in the superior left frontal view. Middle and right column: figures displayed in the axial/sagittal/coronal view. Fixel-based metrics with significance (family-wise error-corrected $P < .05$) were illustrated with color encoded according to the fiber direction. Row for (A): FC; Rows for (B): upper row, FDC; middle row, FD; lower row, FC. Green: anterior (A)-to-posterior (P); blue, superior (S)-to-inferior (I); and red: left (L)-to-right (R). atr, anterior thalamic radiation; bcc, body of corpus callosum; cst, corticospinal tract; fx, fornix; gcc, genu of corpus callosum; mcp, middle cerebellar peduncle; plic, posterior limb of internal capsule; ptr, posterior thalamic radiation; scc, splenium of corpus callosum; scr, superior corona radiata; slf, superior longitudinal fasciculus; st, stria terminalis.

White matter damage and cognitive impairment in ESKD patients

Our study revealed subtle alteration in the corpus callosum and fibers over the fornix/stria terminalis in ESKD patients, which can be linked to their cognitive decline [20, 21]. The decreased white matter integrity, reflected as the reduction in FD, may be attributed to alterations in intra-axonal volume [12]. The finding highlighted the significant influence of integrity in corpus callosum on cognition in ESKD patients. The corpus callosum plays a vital role in connecting the two hemispheres of the brain, facilitating various cognitive functions such as learning,

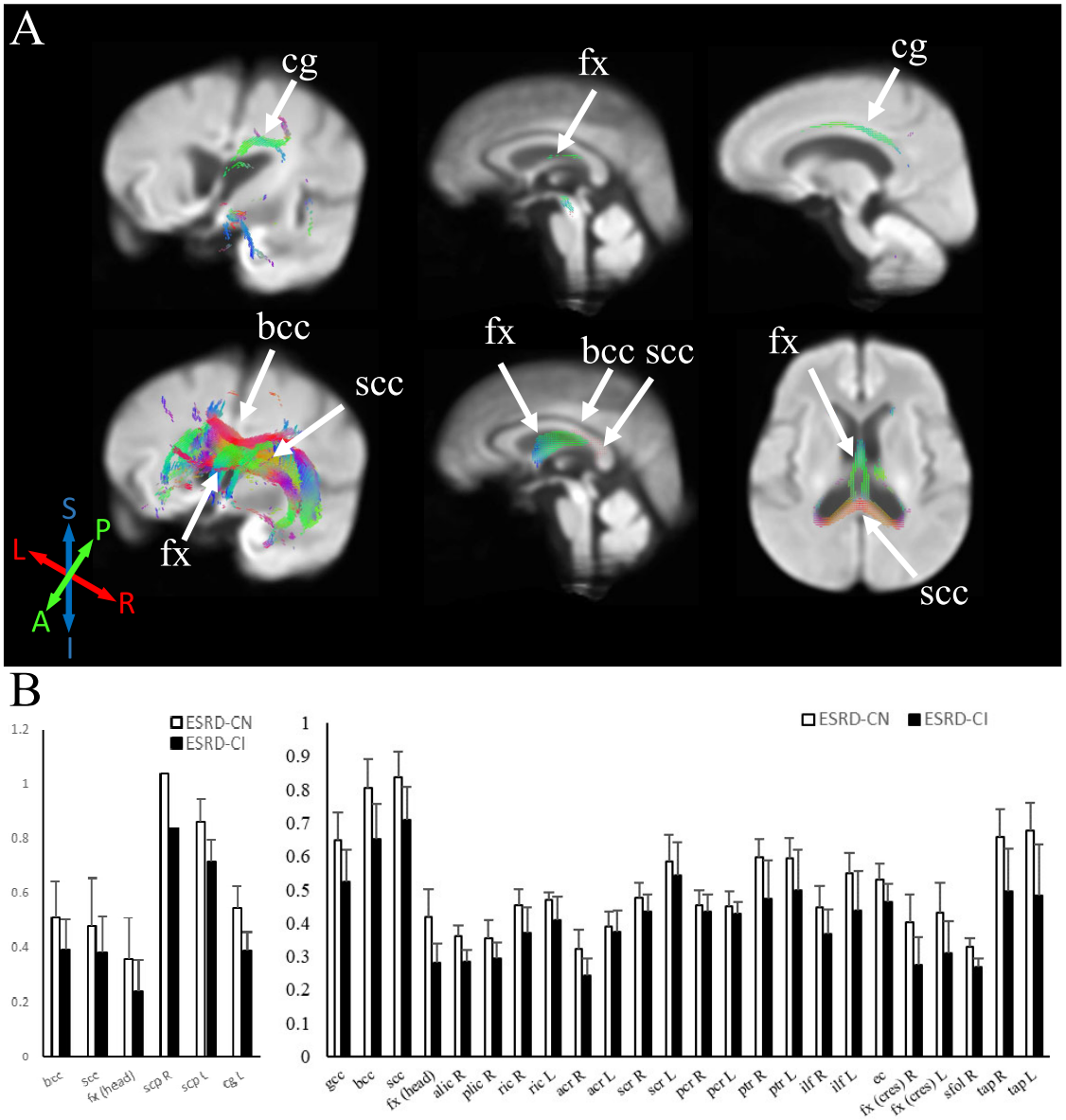

Figure 3: Group comparisons between ESKD patients with and without cognitive impairment. (**A**) Significant fixel-based metrics between ESKD patients with and without cognitive impairment were displayed. Left column: figures displayed stereoscopically in the superior left frontal view. Middle and right column: figures displayed in the axial/sagittal/coronal view. Fixel-based metrics with significance (family-wise error-corrected $P < .05$) were illustrated with color encoded according to the fiber direction. Upper row, FDC; middle row, FD. Green: anterior (A)-to-posterior (P); blue, superior (S)-to-inferior (I); and red: left (L)-to-right (R). (**B**) The average values of fixel-based metrics from parcellated brain regions were presented for the ESKD patients with normal cognition (blank bar) and the ESKD patients with cognition impairment (solid bar). Left panel, FDC; right panel, FD. R, right; L left; acr, anterior corona radiata; alic, anterior limb of internal capsule; bcc, body of corpus callosum; cg, cingulum; cp, cerebral peduncle; ec, external capsule; sfol, fx, fornix; pcr, posterior corona radiata; plic, posterior limb of internal capsule; ptr, posterior thalamic radiation; ilf, inferior longitudinal fasciculus; ric, retrolenticular part of internal capsule; scc, splenium of corpus callosum; scp, superior cerebellar peduncle; scr, superior corona radiata; sfol, superior frontal-occipital fasciculus; tap, tapetum.

memory and executive functions. Microvascular damage to the corpus callosum and the associated corona radiata can occur in the early stages of subclinical vascular cognitive decline [22]. The decrease fiber in the corpus callosum was associated with the cognitive decline [23], which is consistent with our study.

The fiber crossing the bed nucleus of the stria terminalis (BNST)/fornix terminalis, as well as the BNST itself, has been associated with cognitive decline [24]. BNST is an extended part of the amygdala [25], which connects with the anterior commissure, while its caudal ends connect with the septal and dorsal preoptic area through GABAergic and glutamatergic efferent interneurons [26]. The BNST plays a crucial role in mediating responses to anxiety, stress and behavioral disorders [27, 28]. Given that ESKD patients often experience higher emotional stress due to their underlying illness [29], we believed that

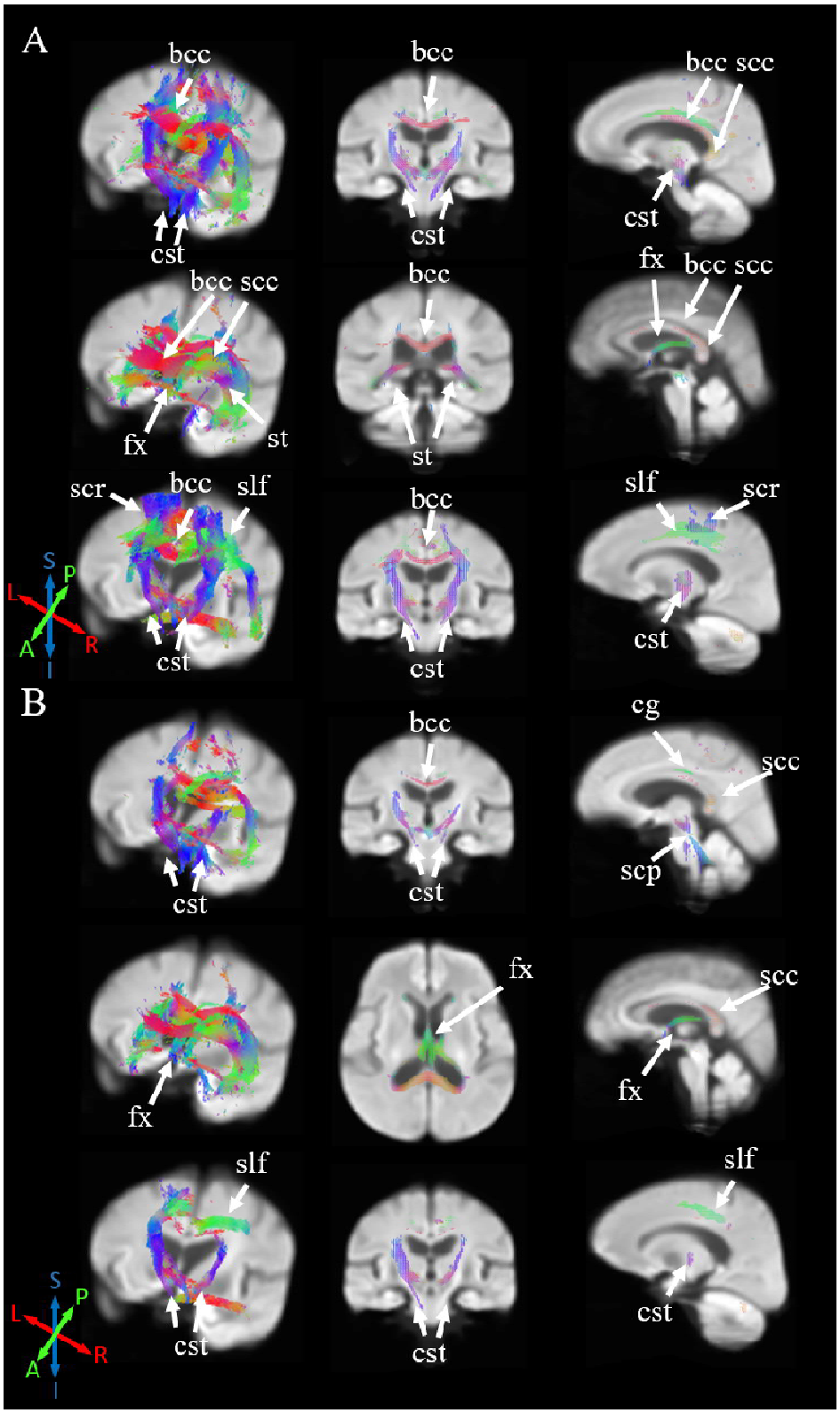

Figure 4: Results of regression analysis between fixel-based metrics and cognitive tests. (**A**) MMSE; (**B**) MoCA. Left column: figures displayed stereoscopically in the superior left frontal view. Middle and right column: figures displayed in the axial/sagittal/coronal view. Fixel-based metrics with significance (family-wise error-corrected $P < .05$) were illustrated with color encoded according to the fiber direction. Upper row, FDC; middle row, FD; lower row, FC. Green: anterior (A)-to-posterior (P); blue, superior (S)-to-inferior (I); and red: left (L)-to-right (R). bcc, body of corpus callosum; fx, fornix; gcc, genu of corpus callosum; ric, retrolenticular part of internal capsule; scc, splenium of corpus callosum; scr, superior corona radiata; scp, superior cerebellar peduncle; slf, superior longitudinal fasciculus; st, stria terminalis.

Table 2: The goodness-of-fit for involved tracts with association between fixel-based metrics and cognitive scores.

	MMSE			MoCA		
	FDC	FD	FC	FDC	FD	FC
Cerebellum peduncle						
Sup.	0.365/0.368	–/0.443	0.376/0.342	0.345/0.361	–/0.424	0.383/–
Inf.	0.234/–	–/–	–/–	0.209/–	–/–	–/–
Pontine crossing tract	0.222			0.250		
Corpus callosum						
Genu		0.542			0.466	
Body	0.442	0.556	0.477	0.409	0.509	0.453
Splenium	0.352	0.471	0.313	0.292	0.416	0.241
Fornix						
Head		0.441			0.472	
Stria terminalis	–/0.459	0.465/0.42	–/–	–/–	0.433/0.425	–/–
Corticospinal tract	0.190/0.140	–/–	0.163/0.137	0.221/–	–/–	0.175/–
Medial lemniscus	0.349/0.321	–/–	–/–	0.320/0.336	–/–	–/–
Cerebral peduncle	0.335/0.327	0.237/0.394	0.315/0.307	0.308/0.317	–/0.237	0.293/0.326
Ant. limb of internal capsule	0.210/0.310	0.516/0.477	–/0.371	–/–	0.537/–	–/0.387
Post. limb of internal capsule	0.392/0.372	0.465/0.401	0.391/0.383	0.369/0.341	–/–	0.374/0.387
Ant. corona radiata	–/–	0.480/0.209	0.152/–	–/–	–/–	–/–
Sup. corona radiata	0.347/0.310	0.520/–	0.372/0.374	0.319/0.216	0.470/0.196	0.336/0.349
Post. corona radiata	0.319/0.334	0.241/0.231	0.266/0.317	0.246/0.304	–/0.265	0.287/0.276
Post. thalamic radation	0.268/0.434	0.506/0.398	0.362/0.284	–/–	0.374/0.300	–/–
External capsule	0.339/0.402	0.245/0.374	0.385/0.379	0.271/0.367	0.179/0.253	0.379/–
Ant. cingulum	–/0.480	–/0.361	0.465/0.394	–/0.466	–/–	0.461/0.405
Sup. longitudinal fasciculus	0.352/0.298	–/–	0.364/0.323	0.219/–	–/–	0.300/–
Sup. fronto-occipital fasciculus	–/–	0.539/–	–/–	–/–	0.527/–	–/–
Tapetum	0.279/0.256	0.475/0.440	–/–	0.200/0.199	0.367/0.346	–/–

The goodness-of-fit (adjusted R^2) was presented for tracts in the left hemisphere/right hemisphere.
Ant., anterior; post., posterior; sup., superior; inf., inferior; retro., retrolenticular part.

BNST may serve as a vulnerable site for stress-related cognitive decline in ESKD patients.

Ageing and cognitive impairment

ESKD patients with cognitive impairment in our study were significantly older than the normal control group. The observed white matter changes in the comparison between ESKD patients with cognitive impairment and normal control subjects (Fig. 2B) can be related to both cognitive impairment and ESKD. Since we did not include a group of cognitively impaired subjects without ESKD, it is challenging to determine the primary cause for whether the white matter changes are primarily due to ESKD, cognitive impairment, or aging. However, we did find that white matter changes were more widespread in patients with cognitive impairment compared with those without (Fig. 3A).

The decline in cognitive performance in ESKD patients likely results from multiple causes. Because the age difference between ESKD patients with cognitive impairment and normal cognition was not significant, it is less likely that aging alone accounts for the cognitive decline. The observed white matter changes, as shown in Fig. 3B, might be attributed to cognitive impairment in the context of ESKD.

Our study indicates that ESKD is associated with damage in specific white matter regions. This white matter damage appears to be more extensive in ESKD patients with cognitive impairment compared with those without. Although cognitive impairment is more common in older individuals, the white matter damage observed in patients with cognitive impairment in our study is less likely to be related to aging alone. These findings suggest the need for further exploration of the interplay between ESKD, cognitive impairment and aging in future prospective, age-matched studies.

Comorbidity of hypertension and diabetes mellitus

In this study, the control group consisted of 16 subjects. Among them, eight participants suffered from hypertension and six from diabetes. Although neither diabetes mellitus nor hypertension is part of the inclusion/exclusion criteria, both conditions *per se* may cause structural changes in the brain. In the results as presented in our analysis, both diseases were set as a covariate in order to minimize its contribution.

Hypertension or diabetes by itself can result in structural changes in the brain of the subjects. Hypertension was linked to the white matter hyperintensity [30], and can potentiate hyperintensity in white matter along with the cognitive decline [31]. The extent of white matter hyperintensity can be associated with hypertensive disease in the brain [32]. Similarly, severe diabetes mellitus can be associated with the severity of white matter hyperintensity [33], and induced brain atrophy [34]. In order to clarify the contribution from the comorbidity and its influences on CKD, additional non-ESKD subjects but with hypertension or diabetes as well as CKD subjects without hypertension or diabetes mellitus should be recruited. This will lead to new interest in the future study.

Peripheral neurologic biomarkers: calcium and decrease in fixel

Extracellular calcium concentration may negatively impact neuronal excitability, as it can inhibit spontaneous network

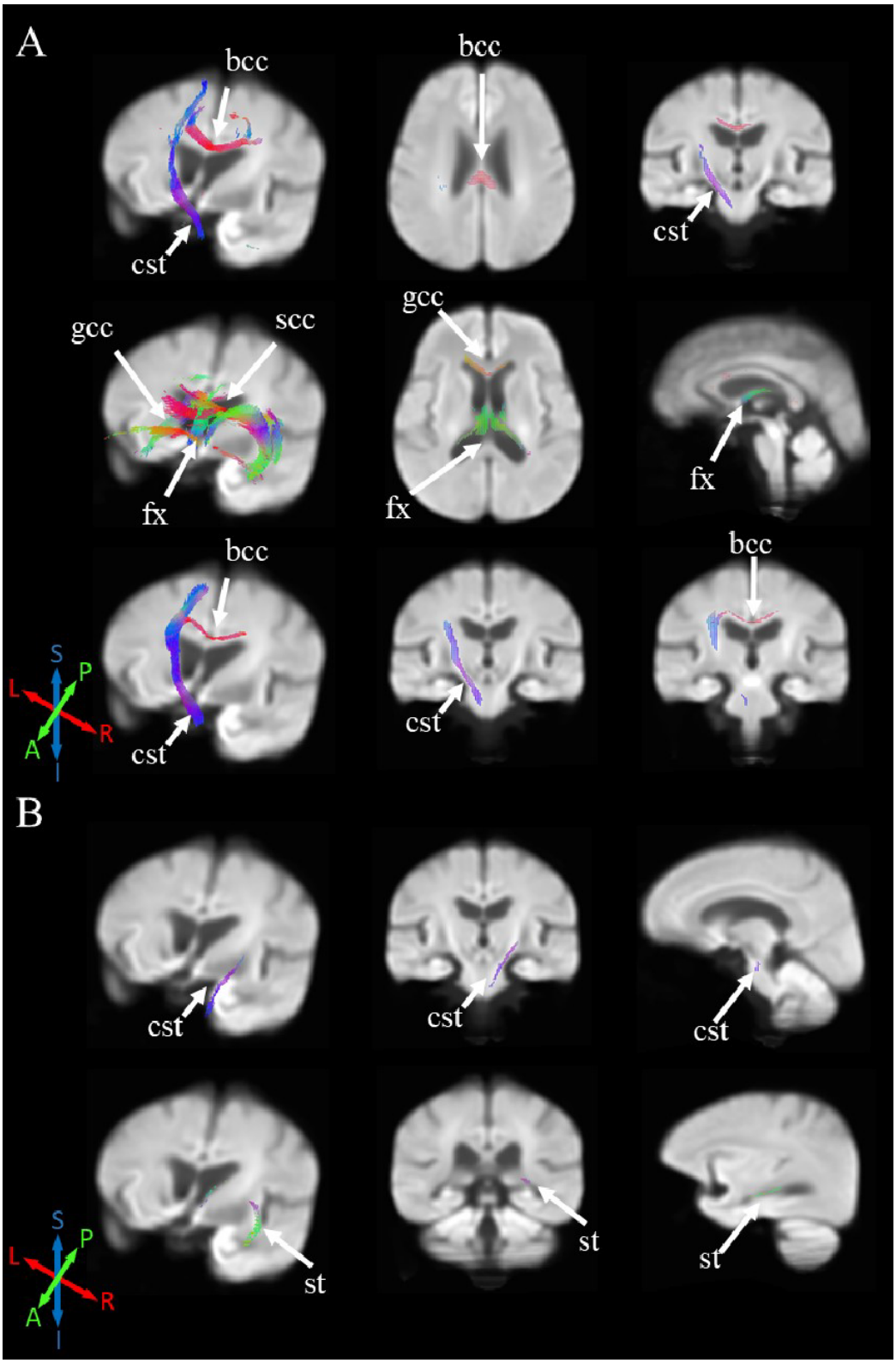

Figure 5: Correlation between the peripheral hematologic/biochemical parameters and fixel-based metrics. (**A**) plasma calcium (**B**) indoxyl sulfate. Left column: figures displayed stereoscopically in the superior left frontal view. Middle and right column: figures displayed in the axial/sagittal/coronal view. Fixel-based metrics with significance (family-wise error-corrected $P < .05$) were illustrated with color encoded according to the fiber direction. Rows for (A): upper row, FDC; middle row, FD; lower row, FC. Row for (B): upper row, FDC; lower row, FD. Green: anterior (A)-to-posterior (P); blue, superior (S)-to-inferior (I); and red: left (L)-to-right (R). acr, anterior corona radiata; bcc, body of corpus callosum; cst, corticospinal tract; fx, fornix; gcc, st, stria terminalis.

Table 3: The goodness-of-fit for involved tracts with association between fixel-based metrics and plasma biomarkers.

	Ca			IS		
	FDC	FD	FC	FDC	FD	FC
Pontine crossing tract				0.359		
Corpus callosum						
Genu		0.215				
Body	0.187	0.322	0.156			
Splenium		0.209				
Fornix						
Head		0.151				
Stria terminalis	–/–	–/0.207	–/–	–/–	–/0.275	–/–
Corticospinal tract	0.151/–	–/–	–/–	–/0.313	–/–	–/–
Cerebral peduncle	0.149/–	–/–	–/–	–/0.335	–/–	–/–
Ant. limb of internal capsule	–/–	–/0.177	–/–	–/–	–/–	–/–
Post. limb of internal capsule	–/–	–/–	0.143/–	–/0.262	–/–	–/–
Ant. corona radiata	–/–	0.189/–	–/–	–/–	–/–	–/–
Sup. corona radiata	0.230/–	–/–	0.184/–	–/–	–/–	–/–
Post. thalamic radation	–/–	0.188/–	–/–	–/–	–/–	–/–
External capsule	–/–	–/0.318	0.176/–	–/–	–/–	–/–

The goodness-of-fit (adjusted R^2) was presented for tracts in the left hemisphere/right hemisphere.
Ca, plasma calcium; IS, indoxyl sulfate; ant., anterior; post., posterior; sup., superior; mid., middle; retro., retrolenticular part.

hypersynchrony at physiological levels. Hypocalcemia has been linked to compromised white matter integrity in CKD patients [35]. In our study, the number of subjects with hypocalcemia (plasma calcium <8.5 mg/dL) was 0 in the control group, 29.4% (5 out of 17) in the ESKD with normal cognition group and 42.8% (6 out of 14) in the ESKD with cognitive impairment group. Our study suggests that hypocalcemia may influence cognitive function by affecting white matter integrity.

In CKD patients, hypocalcemia is often due to hyperparathyroidism and vitamin D deficiency. Vitamin D facilitates intestinal calcium absorption [36], and hyperparathyroidism exacerbates vitamin D degradation [37]. Vitamin D supplementation may also enhance nerve myelination following injury [38, 39]. The correlation between plasma calcium concentration and white matter alterations in our results supports the clinical guideline that maintaining adequate vitamin D levels should be encouraged in ESKD patients [40]. Although our study did not record hyperparathyroidism and vitamin D deficiency among participants, our results underscore the importance of maintaining plasma calcium levels in ESKD patients [40]. The potential contribution of hypocalcemia to the cognitive decline in ESKD patients may spark new research interests.

Peripheral biochemical biomarkers: indoxyl sulfate and decrease in fixel

In our study, fixel-derived metrics in the strial terminalis were negatively correlated with indoxyl sulfate levels. Indoxyl sulfate concentration was associated with the cognitive decline in early CKD [41] and in ESKD patients [42]. As the indoxyl sulfate concentration in plasma elevated, the permeability of blood brain barrier increased in ESKD patients and potentially induced neurologic damage [43]. A possible explanation is that indoxyl sulfate induces oxidative stress, potentially leading to neurotoxicity or mediating astrogliosis and microgliosis [44]. The study findings might suggest that indoxyl sulfate can be related to neuroinflammation and thus contribute to white matter alterations. The relationship to the oxidative stress and the underlying mediating pathways could open up new avenues for research into therapeutic strategies targeting indoxyl sulfate and its effects on the brain, particularly in conditions associated with CKD.

Limitations

Our study has several limitations. First, the small sample size may have compromised the reliability of our findings, warranting the need for a larger sample to establish a stronger association between white matter lesions and cognitive function in ESKD patients. Secondly, as a cross-sectional study, we were unable to track changes in white matter fiber integrity over time. Additionally, we did not analyze the correlation between fiber deficits and corresponding MMSE/MoCA categories, which could guide future *in vivo* neuropsychiatric studies.

CONCLUSION

White matter damage was observed in ESKD patients using diffusion MRI and could be associated with their cognitive decline. Hypocalcemia and indoxyl sulfate are correlated with the white matter integrity as detected by fixel-based analysis.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

ACKNOWLEDGEMENTS

The authors would like to thank the Leadgene Biomedical, Inc. Tainan, Taiwan, for their technical support in measuring indoxyl sulfate by ELISA method.

FUNDING

This study was supported by grants from the National Science and Technology Council (grants NSTC 109-2221-E-182-009-MY3, 109-2314-B-182-021-MY3, 112-2321-B-182A-004, and 112-2314-B-

182-052-MY3, preparation of the manuscript), the Healthy Aging Research Center (grants EMRPD1M0451, EMRPD1M0431, and EMRPD1N0151, preparation of the manuscript), and Cardinal Tien Hospital (CTH-112-AK-NDMC-2223, participant collection and CTH-113-AK-NDMC-2225, measurement of biomarkers).

AUTHORS' CONTRIBUTIONS

Y.-C.H. executed this study and drafted the manuscript. C.-C.T. performed image and statistical analysis of the study, and revised the draft of manuscript. R.-M.C., Y.-C.L. and K.-C.L. assisted in collecting clinical samples and provided assistance with manuscript drafting. Y.-L.C., T.-W.S. and J.-J.W. supervised the study and edited the draft and the revision of manuscript.

DATA AVAILABILITY STATEMENT

Image data could be available under reasonable request and with approval from appropriate ethical committee. The code that was used can be obtained at GitHub (https://github.com/MRtrix3/mrtrix3/tree/master/docs/fixel_based_analysis).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Levey AS, Eckardt K-U, Tsukamoto Y *et al*. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2005;**67**:2089–100. https://doi.org/10.1111/j.1523-1755.2005.00365.x
2. Bello AK, Alrukhaimi M, Ashuntantang GE *et al*. Complications of chronic kidney disease: current state, knowledge gaps, and strategy for action. *Kidney Int Suppl* 2017;**7**:122–9. https://doi.org/10.1016/j.kisu.2017.07.007
3. Kelly DM, Rothwell PM. Disentangling the relationship between chronic kidney disease and cognitive disorders. *Front Neurol* 2022;**13**:830064. https://doi.org/10.3389/fneur.2022.830064
4. Sarnak MJ, Tighiouart H, Scott TM *et al*. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. *Neurology* 2013;**80**:471–80. https://doi.org/10.1212/WNL.0b013e31827f0f7f
5. Sarnak MJ, Tighiouart H, Scott TM *et al*. Frequency of and risk factors for poor cognitive performance in hemodialysis patients. *Neurology* 2013;**80**:471–80.
6. Smith E, Salat D, Jeng J *et al*. Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology* 2011;**76**:1492–9.
7. Polinder-Bos HA, García DV, Kuipers J *et al*. Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. *J Am Soc Nephrol* 2018;**29**:1317. https://doi.org/10.1681/ASN.2017101088
8. Miglinas M, Cesniene U, Janusaite MM *et al*. Cerebrovascular disease and cognition in chronic kidney disease patients. *Front Cardiovasc Med* 2020;**7**:96. https://doi.org/10.3389/fcvm.2020.00096
9. Ye S, Dong S, Tan J *et al*. White-matter hyperintensities and lacunar infarcts are associated with an increased risk of Alzheimer's disease in the elderly in China. *J Clin Neurol* 2019;**15**:46–53. https://doi.org/10.3988/jcn.2019.15.1.46
10. Horsfield MA, Jones DK. Applications of diffusion-weighted and diffusion tensor MRI to white matter diseases–a review. *NMR Biomed* 2002;**15**:570–7.
11. Dhollander T, Clemente A, Singh M *et al*. Fixel-based analysis of diffusion MRI: methods, applications, challenges and opportunities. *Neuroimage* 2021;**241**:118417. https://doi.org/10.1016/j.neuroimage.2021.118417
12. Raffelt DA, Tournier J-D, Smith RE *et al*. Investigating white matter fibre density and morphology using fixel-based analysis. *Neuroimage* 2017;**144**:58–73. https://doi.org/10.1016/j.neuroimage.2016.09.029
13. Chiu M-J, Chen Y-F, Chen T-F *et al*. Plasma tau as a window to the brain—negative associations with brain volume and memory function in mild cognitive impairment and early Alzheimer's disease. *Hum Brain Mapp* 2014;**35**:3132–42. https://doi.org/10.1002/hbm.22390
14. Veraart J, Novikov DS, Christiaens D *et al*. Denoising of diffusion MRI using random matrix theory. *Neuroimage* 2016;**142**:394–406. https://doi.org/10.1016/j.neuroimage.2016.08.016
15. Kellner E, Dhital B, Kiselev VG *et al*. Gibbs-ringing artifact removal based on local subvoxel-shifts. *Magn Reson Med* 2016;**76**:1574–81. https://doi.org/10.1002/mrm.26054
16. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. *Neuroimage* 2016;**125**:1063–78. https://doi.org/10.1016/j.neuroimage.2015.10.019
17. Lo CY, Wang PN, Chou KH *et al*. Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer's disease. *J Neurosci* 2010;**30**:16876–85. https://doi.org/10.1523/JNEUROSCI.4136-10.2010
18. Mori S, Oishi K, Jiang H *et al*. Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage* 2008;**40**:570–82. https://doi.org/10.1016/j.neuroimage.2007.12.035
19. Raffelt DA, Smith RE, Ridgway GR *et al*. Connectivity-based fixel enhancement: whole-brain statistical analysis of diffusion MRI measures in the presence of crossing fibres. *Neuroimage* 2015;**117**:40–55. https://doi.org/10.1016/j.neuroimage.2015.05.039
20. Qiu Y, Yu L, Ge X *et al*. Loss of integrity of Corpus callosum white matter hyperintensity penumbra predicts cognitive decline in patients with subcortical vascular mild cognitive impairment. *Front Aging Neurosci* 2021;**13**:605900. https://doi.org/10.3389/fnagi.2021.605900
21. Kamal S, Park I, Kim YJ *et al*. Alteration of the corpus callosum in patients with Alzheimer's disease: deep learning-based assessment. *PLoS One* 2021;**16**:e0259051. https://doi.org/10.1371/journal.pone.0259051
22. Tuladhar AM, van Norden AGW, de Laat KF *et al*. White matter integrity in small vessel disease is related to cognition. *Neuroimage Clin* 2015;**7**:518–24. https://doi.org/10.1016/j.nicl.2015.02.003
23. Wei YC, Kung YC, Lin CP *et al*. White matter alterations and their associations with biomarkers and behavior in subjective cognitive decline individuals: a fixel-based analysis. *Behav Brain Funct* 2024;**20**:12. https://doi.org/10.1186/s12993-024-00238-x

24. Chiu Y-L, Tsai H-H, Lai Y-J *et al*. Cognitive impairment in patients with end-stage renal disease: accelerated brain aging? *J Formos Med Assoc* 2019;**118**:867–75. https://doi.org/10.1016/j.jfma.2019.01.011
25. Stamatakis AM, Sparta DR, Jennings JH *et al*. Amygdala and bed nucleus of the stria terminalis circuitry: implications for addiction-related behaviors. *Neuropharmacology* 2014;**76**:320–8. https://doi.org/10.1016/j.neuropharm.2013.05.046
26. Ju G, Swanson LW. Studies on the cellular architecture of the bed nuclei of the stria terminalis in the rat: I. Cytoarchitecture. *J Comp Neurol* 1989;**280**:587–602. https://doi.org/10.1002/cne.902800409
27. Walker DL, Toufexis DJ, Davis M. Role of the bed nucleus of the stria terminalis versus the amygdala in fear, stress, and anxiety. *Eur J Pharmacol* 2003;**463**:199–216. https://doi.org/10.1016/S0014-2999(03)01282-2
28. Miles OW, Maren S. Role of the bed nucleus of the stria terminalis in PTSD: insights from preclinical models. *Front Behav Neurosci* 2019;**13**:68. https://doi.org/10.3389/fnbeh.2019.00068
29. Raff H, Trivedi H. Circadian rhythm of salivary cortisol, plasma cortisol, and plasma ACTH in end-stage renal disease. *Endocr Connect* 2013;**2**:23–31. https://doi.org/10.1530/EC-12-0058
30. de Leeuw FE, de Groot JC, Oudkerk M *et al*. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain* 2002;**125**:765–72. https://doi.org/10.1093/brain/awf077
31. Hajjar I, Quach L, Yang F *et al*. Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: the Cardiovascular Health Study. *Circulation* 2011;**123**:858–65. https://doi.org/10.1161/CIRCULATIONAHA.110.978114
32. Allan CL, Zsoldos E, Filippini N *et al*. Lifetime hypertension as a predictor of brain structure in older adults: cohort study with a 28-year follow-up. *Br J Psychiatry* 2015;**206**:308–15. https://doi.org/10.1192/bjp.bp.114.153536
33. Schweitzer N, Son SJ, Aizenstein H *et al*. Higher HbA1c is associated with greater 2-year progression of white matter hyperintensities. *Diabetes* 2024;**73**:604–10. https://doi.org/10.2337/db23-0303
34. Zhang T, Shaw M, Cherbuin N. Association between type 2 diabetes mellitus and brain atrophy: a meta-analysis. *Diabetes Metab J* 2022;**46**:781–802. https://doi.org/10.4093/dmj.2021.0189
35. Liu M, Wu Y, Wu X *et al*. White matter microstructure changes and cognitive impairment in the progression of chronic kidney disease. *Front Neurosci* 2020;**14**:559117. https://doi.org/10.3389/fnins.2020.559117
36. Christakos S, Dhawan P, Porta A *et al*. Vitamin D and intestinal calcium absorption. *Mol Cell Endocrinol* 2011;**347**:25–9. https://doi.org/10.1016/j.mce.2011.05.038
37. Zierold C, Mings JA, DeLuca HF. Regulation of 25-hydroxyvitamin D3-24-hydroxylase mRNA by 1,25-dihydroxyvitamin D3 and parathyroid hormone. *J Cell Biochem* 2003;**88**:234–7. https://doi.org/10.1002/jcb.10341
38. Chabas JF, Alluin O, Rao G *et al*. Vitamin D2 potentiates axon regeneration. *J Neurotrauma* 2008;**25**:1247–56. https://doi.org/10.1089/neu.2008.0593
39. Chabas J-F, Stephan D, Marqueste T *et al*. Cholecalciferol (Vitamin D3) improves myelination and recovery after nerve injury. *PLoS One* 2013;**8**:e65034. https://doi.org/10.1371/journal.pone.0065034
40. Kidney Disease: Improving Global Outcomes CKDMBDUWG. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl (2011)* 2017;**7**:1–59.
41. Yeh YC, Huang MF, Liang SS *et al*. Indoxyl sulfate, not p-cresyl sulfate, is associated with cognitive impairment in early-stage chronic kidney disease. *Neurotoxicology* 2016;**53**:148–52. https://doi.org/10.1016/j.neuro.2016.01.006
42. Hou YC, Chueh TI, Lu KC *et al*. The ratio of plasma amyloid-beta 1-42 over serum albumin can be a novel biomarker signature for diagnosing end-stage renal disease-associated cognitive impairment. *J Alzheimers Dis* 2024;**97**:1393–405. https://doi.org/10.3233/JAD-230747
43. Bobot M, Guedj E, Resseguier N *et al*. Increased blood-brain barrier permeability and cognitive impairment in patients with ESKD. *Kidney Int Rep* 2024; in press. https://doi.org/10.1016/j.ekir.2024.07.021
44. Lin YT, Wu PH, Tsai YC *et al*. Indoxyl sulfate induces apoptosis through oxidative stress and mitogen-activated protein kinase signaling pathway inhibition in human astrocytes. *J Clin Med* 2019;**8**:191. https://doi.org/10.3390/jcm8020191

Received: 29.3.2024; Editorial decision: 4.9.2024