White-matter functional network dysfunction associated with cognitive deficits and clinical phenotypes in patients with end-stage renal disease

Supplementary Materials

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Supplementary Methods

MRI data acquisition

The T1-FLAIR was scanned before the rs-fMRI protocol to adapt to the MR environment and exclude intracranial lesions(echo time/repetition time = 24/1750 ms, matrix = 256 × 256, flip angle = 111°, inversion time = 780 ms, slice thickness = 6 mm, slice gap = 0.6 mm) .The T1-weighted structural data were obtained with a three-dimensional brain volume imaging sequence (echo time/repetition time = 3.2/8.2, flip angle = 15°, matrix = 256 × 256, slice thickness = 1 mm, slice gap = 0 mm, slices number = 140).The rs-fMRI data were collected with an echo-planar imaging sequence (TE/TR = 50/2000 ms, matrix = 64 × 64, FA = 90°, field-of-view FOV = 240 × 240 mm^2, slice thickness = 4 mm, slice gap = 0 mm, slices = 45, voxel size = 3 × 3 × 3 mm^3). Each rs-fMRI acquisition lasted for 6 min 10 s and included 185 functional volumes.

FC and FCC of WM networks

It is important to emphasize that the FCC and FC of WM functional networks are complementary and contribute to the interpretation of rs-fMRI studies. FC refers to the correlation between BOLD signals from two regions, so it can only reflect information from two limited regions (i.e., one-to-one information flow). In contrast, by integrating information from multiple regions, the FCC carries complex information interactions (i.e., one-to-many-to-one information flow). The FC strength between WM functional networks reflects their inherent interactions, while the FCC strength balances the influence of gray matter on WM functional networks[1,2]. Therefore, in this study, we use both FC and FCC to characterize the relationships between WM functional networks.

Supplementary Results

Between-group differences of the FC in WM functional networks

Compared with HCs, ESRD patients exhibited widespread reductions in FC among 11 WM functional networks (Figure 3a and Supplementary Table 2, $p < 0.05$, FDR corrected), including between corona radiata network and frontal, middle temporal, orbitofrontal, cerebellar, frontoparietal, and deep networks; between frontal network and middle temporal, orbitofrontal, occipital, cerebellar, frontoparietal, and deep networks; between pre/post-central network and middle temporal, cerebellar, occipital, frontoparietal, and deep networks; between middle temporal network and orbitofrontal, frontoparietal, and deep networks; between cerebellar network and orbitofrontal, frontoparietal, and deep networks; between occipital network and frontoparietal network; between orbitofrontal network and frontoparietal network; and between deep network and frontoparietal, middle temporal, cerebellar, and orbitofrontal networks.

Between-group differences of the FCC in WM functional networks

Compared with HCs, ESRD patients exhibited widespread reductions in FCC among WM functional networks (Figure 3b and Supplementary Table 3, $p < 0.05$, FDR corrected), including reduced FCC between corona radiata network and frontal, middle temporal, orbitofrontal, cerebellar, frontoparietal, and deep networks; between frontal network and middle temporal, orbitofrontal, occipital, cerebellar, frontoparietal, and deep networks; between pre/post-central network and middle temporal, cerebellar, occipital, and deep networks; between middle temporal network and orbitofrontal, frontoparietal, and deep networks; between cerebellar network and orbitofrontal, frontoparietal, and deep networks;

between orbitofrontal network and deep network; and between deep network and frontoparietal, middle temporal, cerebellar, and orbitofrontal networks. In addition, compared with HCs, ESRD patients also exhibited localized increased in FCC among WM functional networks ($p < 0.05$, FDR corrected), including the middle temporal network and occipital network, as well as between cerebellar network and occipital network.

Clinical and neuropsychological variables associated with FC and FCC alterations in ESRD patients

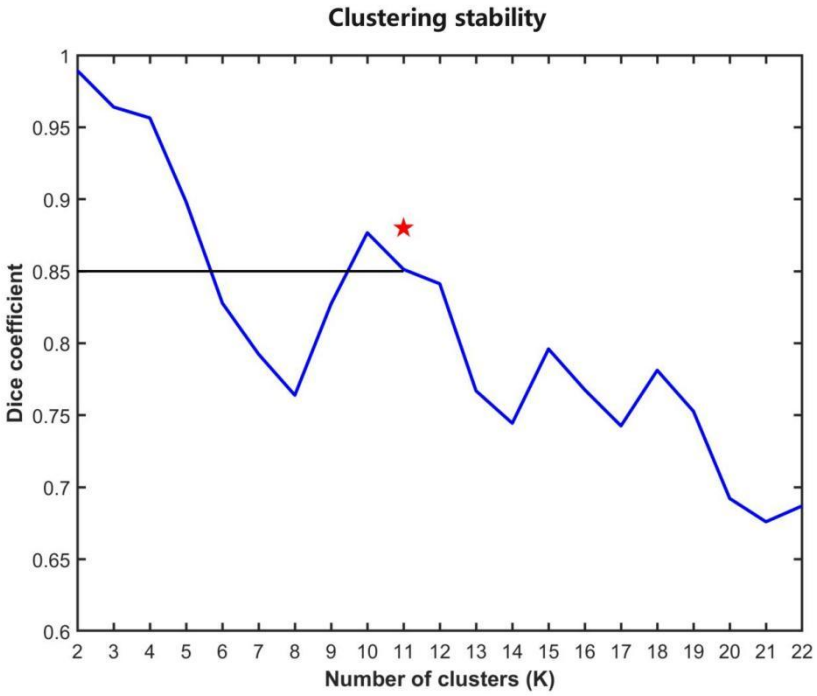
As shown in Supplementary Figure 2, neuropsychological scores in ESRD patients showed significant correlations with the FCC strength of WM networks. Specifically, the greater the cognitive deficits (short-term memory and long-term memory) and mood disorder (depression), the weaker the FCC strength (frontal-middle temporal network, middle temporal-frontparietal network, corona radiate-deep network, frontal-deep network, and middle temporal-deep network). Similarly, clinical indictors in ESRD patients were significantly correlated with FCC strength of WM network. Specifically, the lower the hematocrit and haemoglobin level, the weaker the FCC strength (corona radiate-middle temporal network, pre/post-central-cerebellar network, and cerebellar-occipital network). The severe the uremia toxins (creatinine) and calcium-phosphorus metabolism disorders (calcium, phosphorus, parathormone), the weaker the FCC strength (corona radiate-middle temporal network, pre/post-central-cerebellar network, cerebellar-occipital network, middle temporal-deep, corona radiate-deep network, and deep-middle temporal network). All significant correlations were identified using Spearman or Pearson correlation analyses ($p < 0.05$, FDR-corrected).

Neuropsychological scores in ESRD patients showed significant correlations with the FC strength of WM networks (Supplementary Figure 3). Specifically, the greater the cognitive deficits, the weaker the FC strength (corona radiate-frontal network, corona radiate-deep network, middle temporal-deep network, cerebellar-deep network, frontal-frontoparietal network, and frontal-deep network). Similarly, clinical indictors in ESRD patients were significantly correlated with FC strength of WM network. Specifically, the lower the hematocrit level, the weaker the FC strength (corona radiate-middle temporal network, pre/post-central-cerebellar network, and cerebellar-occipital network). The longer the dialysis vintage and cystatin C level, the weaker the FC strength (middle temporal-orbitofrontal network, corona radiate-middle temporal network, pre/post-central-cerebellar network, coronaradiate-frontoparietaln network, pre/post-central-deep network, and corona radiate-deep network). All significant correlations were identified using Spearman or Pearson correlation analyses ($p < 0.05$, FDR-corrected).

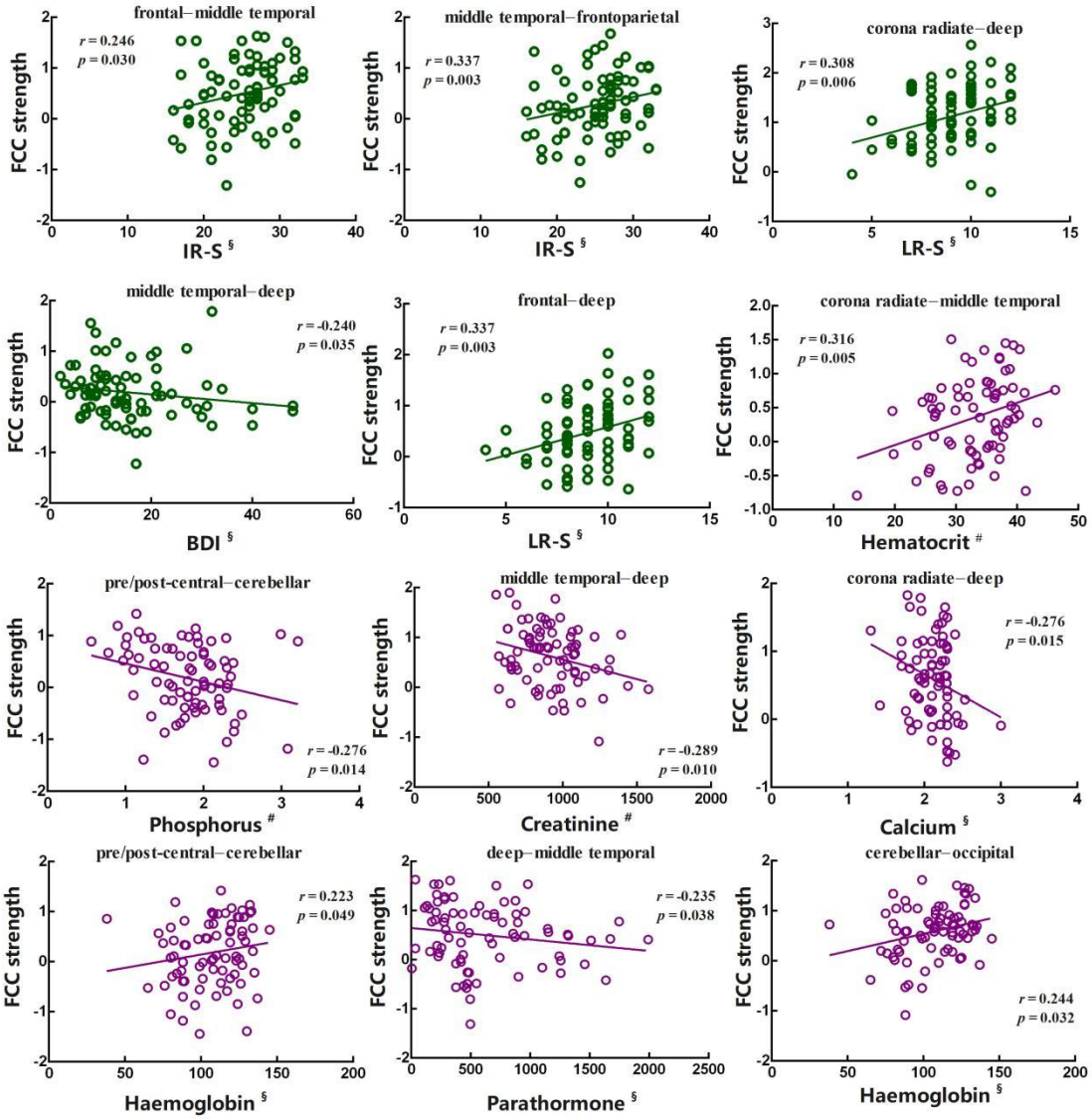
Supplementary References

1 Zhang, H. *et al.* Topographical Information-Based High-Order Functional Connectivity and Its Application in Abnormality Detection for Mild Cognitive Impairment. *J Alzheimers Dis* **54**, 1095-1112 (2016).

2 Jiang, Y. *et al.* Dysfunctional white-matter networks in medicated and unmedicated benign epilepsy with centrotemporal spikes. *Hum Brain Mapp* **40**, 3113-3124, doi:10.1002/hbm.24584 (2019).



Supplementary Figure 1. Stability of clustering for different numbers of clusters. This graph provides the Dice's coefficient for each number of clusters, and shows that the most stable segregation number was eleven.



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126 **Supplementary Figure 2. Clinical and neuropsychological variables associated with FCC**

127 **alterations in ESRD patients.** Green circles denote correlations between the FCC strength of

128 WM functional networks and neuropsychological variables. Purple circles denote correlations

129 between the FCC strength of WM functional networks and clinical indicators,. Pearson (#) or

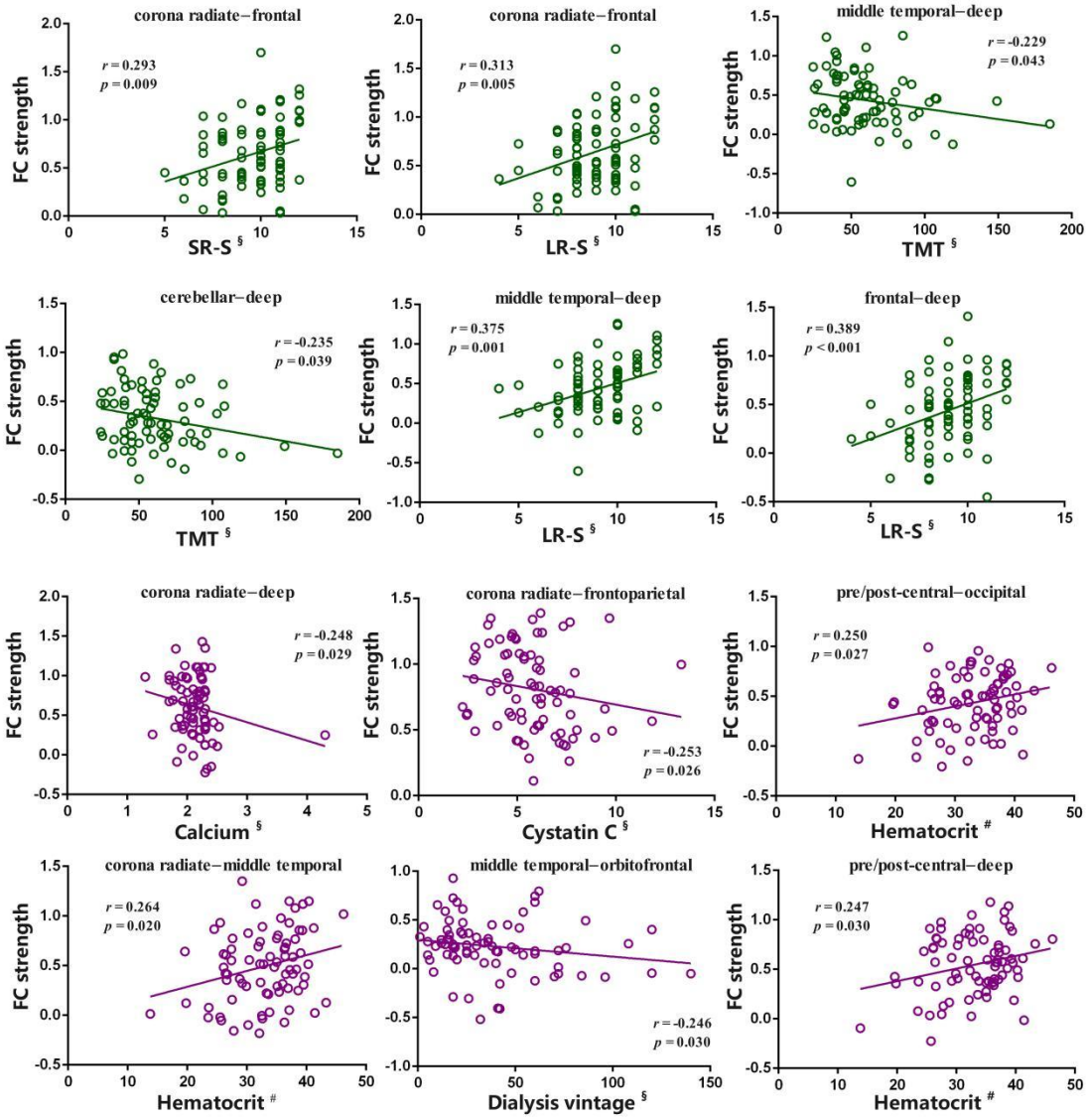
130 Spearman (§) correlation analyses was used to assess relationships between FCC alterations

131 and both clinical indicators and neuropsychological variables. The significance threshold was

132 set to *p* values of <0.05 after FDR correction. FCC, functional covariance connectivity; ESRD,

133 end-stage renal disease; IR-S, immediate recall score; LR-S, long-term recall score; BDI,

Beck depression inventory.



Supplementary Figure 3. Clinical and neuropsychological variables associated with FC alterations in ESRD patients. Green circles denote correlations between the FC strength of WM functional networks and neuropsychological variables. Purple circles denote correlations between the FC strength of WM functional networks and clinical indicators. Pearson (#) or Spearman (§) correlation analyses was used to assess relationships between FC alterations and both clinical indicators and neuropsychological variables. The significance threshold was set to p values of <0.05 after FDR correction. ESRD, end-stage renal disease; SR-S, short-

143 term recall score; LR-S, long-term recall score; TMT, trail-making test.

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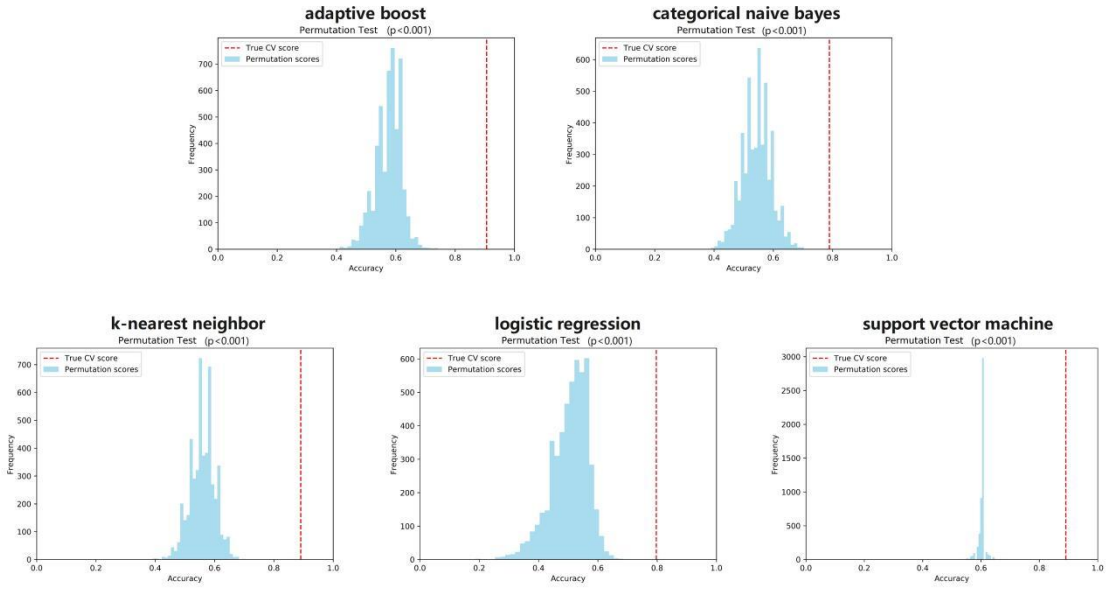

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146 **Supplementary Figure 4. Permutation test results for multiple classification models (repeated**

147 **5,000 times).**

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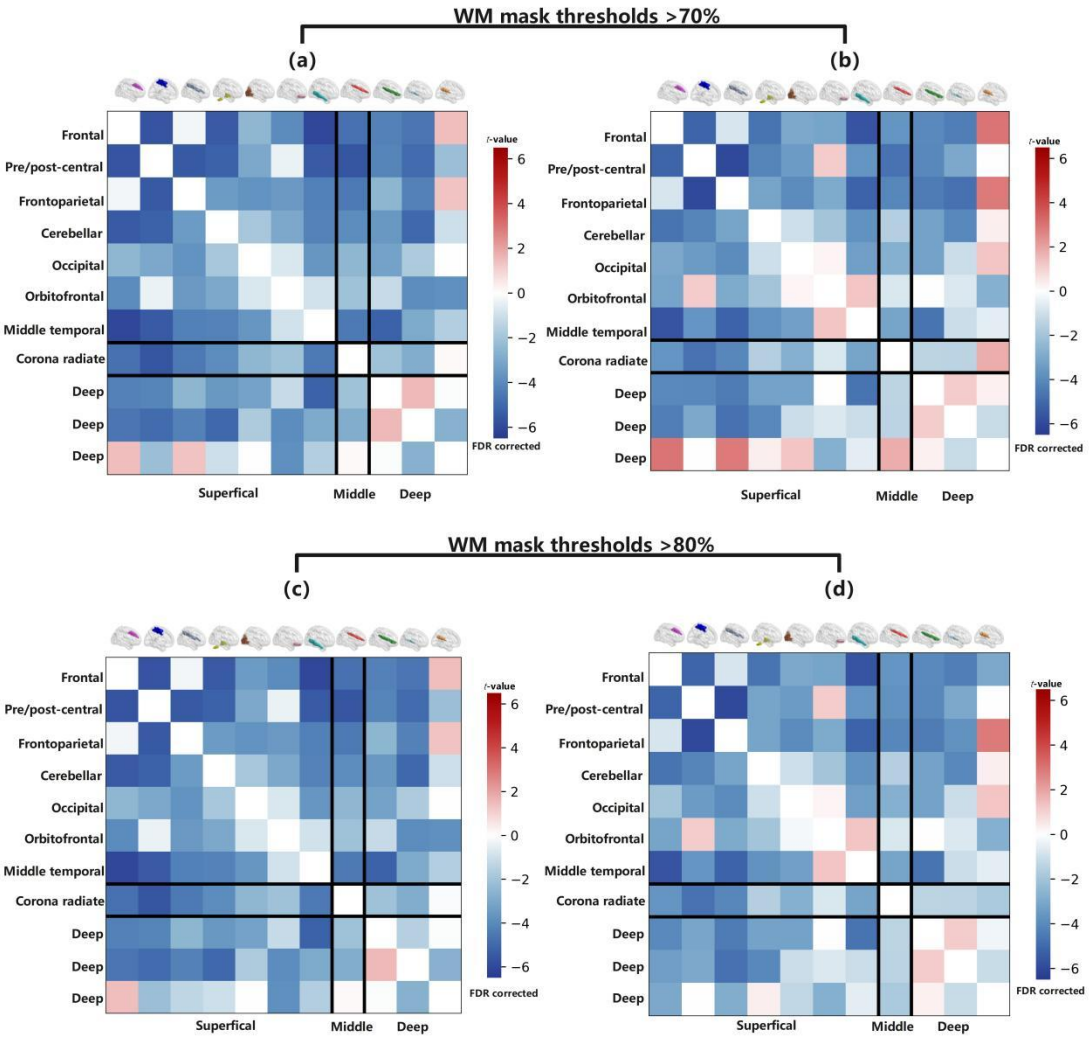
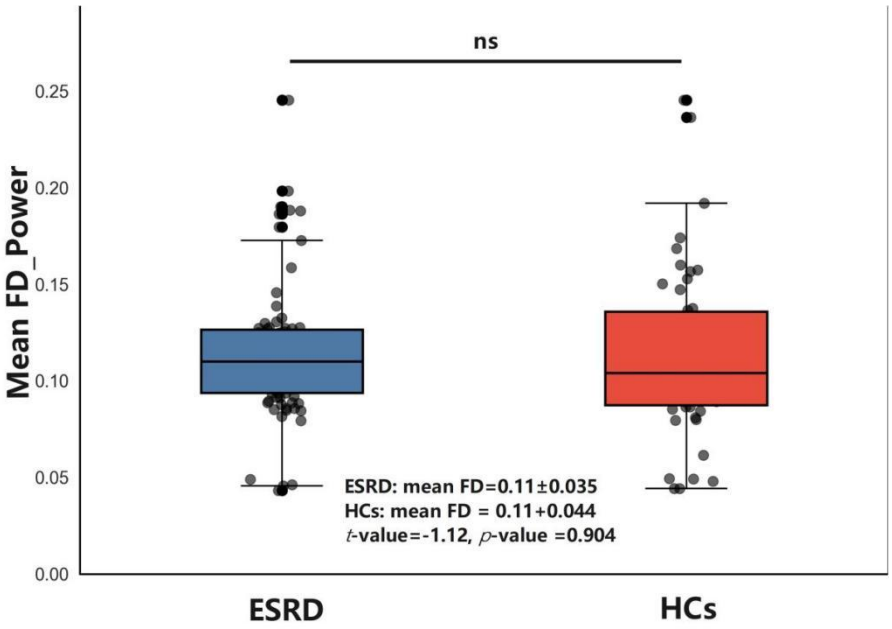


Supplementary Figure 5. Between-group differences of FC and FCC among WM functional networks in ESRD patients and HCs (threshold > 70% and 80%, $p < 0.05$, FDR-corrected). (a) and (b) respectively show the between-group differences in FC and FCC of 11 WM networks under WM mask threshold > 70%. (c) and (d) respectively show the between-group differences in FC and FCC of 11 WM networks under WM mask threshold > 80%. Both the main results of 70 and 80% group-level masks were consistent with the main results of 60% masks. Thus, the main results were still stable even with stricter masks. ESRD, end-stage renal disease; HCs, healthy controls; WM, white matter; FC, functional connectivity; FCC, functional covariance connectivity.



Supplementary Figure 6. Box plots of the mean framewise displacement (FD) values. No significant differences in the mean FD values between ESRD patients and HCs.

Supplementary Table 1. White-matter functional networks

White-matter functional network	Network-tract correspondence	Layer
Frontal network	Frontopontine tract and superior longitudinal fasciculus	Superficial
Pre/post-central network	Corticospinal tract and cingulum tracts	Superficial
Middle temporal network	Uncinate and middle temporal lobe tracts	Superficial
Cerebellar network	Inferior corticospinal and posterior cerebellar tracts	Superficial
Occipital network	Forceps major system	Superficial
Orbitofrontal network	Forceps minor system and anterior thalamic radiation	Superficial
Frontoparietal network	Cingulum and associated tracts	Superficial
Corona radiate network	Anterior corona radiata and superior corona radiata	Middle
Deep network	Superior longitudinal fasciculus and uncinate fasciculus	Deep
Deep network	Posterior thalamic radiation and internal capsule	Deep
Deep network	Inferior longitudinal fasciculus	Deep

Note: The network-tract correspondences were estimated based on the overlap between white-matter functional networks and two white-matter tractography atlases provided by Susumu Mori.

Supplementary Table 2. Between-group differences of the FC in WM functional network between ESRD patients and HCs (FDR corrected)

WM functional network	WM functional network	*t*-value	*p*-value
Corona radiate network	Frontal network	-5.452	<0.001
	Pre/post-central network	-0.904	0.368
	Deep network	-5.287	<0.001
	Middle temporal network	-6.060	<0.001
	Cerebellar network	-4.351	<0.001
	Occipital network	-1.614	0.109
	Orbitofrontal network	-3.667	<0.001
	Deep network	-4.268	<0.001
	Deep network	-4.536	<0.001
	Frontoparietal network	-2.912	0.004
	Pre/post-central network	-0.429	0.669
	Deep network	-4.186	<0.001
	Middle temporal network	-5.662	<0.001
	Cerebellar network	-5.497	<0.001
Frontal network	Occipital network	-2.182	0.031
	Orbitofrontal network	-3.027	0.003
	Deep network	-5.228	<0.001
	Deep network	-5.630	<0.001
	Frontoparietal network	-4.910	<0.001
	Deep network	-1.179	0.241
	Middle temporal network	-4.035	<0.001
	Cerebellar network	-3.495	0.001
Pre/post-central network	Occipital network	-3.797	<0.001
	Orbitofrontal network	-0.816	0.416
	Deep network	-3.020	0.003
	Deep network	-2.130	0.035
	Frontoparietal network	-3.954	<0.001
	Middle temporal network	-4.334	<0.001
Deep network	Cerebellar network	-2.514	0.013
	Occipital network	-0.071	0.943

	Orbitofrontal network	-3.171	0.002
	Deep network	-3.584	<0.001
	Deep network	-2.108	0.037
	Frontoparietal network	1.670	0.098
	Cerebellar network	-0.338	0.736
	Occipital network	1.463	0.146
Middle temporal network	Orbitofrontal network	-2.545	0.012
	Deep network	-5.516	<0.001
	Deep network	-4.774	<0.001
	Frontoparietal network	-4.672	<0.001
	Occipital network	1.376	0.171
Cerebellar network	Orbitofrontal network	-3.808	<0.001
	Deep network	-3.341	0.001
	Deep network	-4.558	<0.001
	Frontoparietal network	-4.242	<0.001
Occipital network	Orbitofrontal network	0.007	0.995
	Deep network	-0.978	0.330
	Deep network	0.109	0.914
	Frontoparietal network	-2.710	0.008
Orbitofrontal network	Deep network	-1.954	0.053
	Deep network	-2.489	0.014
	Frontoparietal network	-1.719	0.088
Deep network	Deep network	-4.031	<0.001
	Frontoparietal network	-5.016	<0.001
Deep network	Frontoparietal network	-2.865	0.005

Abbreviations: FC, functional connectivity; ESRD, end-stage renal disease; HCs, healthy controls; WM, white matter; FDR, false discovery rate.

Supplementary Table 3. Between-group differences of the FCC in WM network between ESRD patients and HCs (FDR corrected)

WM functional network	WM functional network	*t*-value	*p*-value
Corona radiate network	Frontal network	-3.670	<0.001
	Pre/post-central network	1.343	0.182
	Deep network	-4.775	<0.001
	Middle temporal network	-5.680	<0.001
	Cerebellar network	-5.209	<0.001
	Occipital network	-0.552	0.582
	Orbitofrontal network	-3.345	0.001
	Deep network	-3.748	<0.001
Frontal network	Deep network	-3.158	0.002
	Frontoparietal network	-1.040	0.300
	Pre/post-central network	1.134	0.259
	Deep network	-4.100	<0.001
	Middle temporal network	-5.162	<0.001
	Cerebellar network	-5.999	<0.001
	Occipital network	0.010	0.992
	Orbitofrontal network	-3.491	0.001
	Deep network	-4.144	<0.001
Pre/post-central network	Deep network	-4.748	<0.001
	Frontoparietal network	-2.953	0.004
	Deep network	-0.002	0.999
	Middle temporal network	-3.215	0.002
	Cerebellar network	-2.970	0.004
	Occipital network	-2.749	0.007
	Orbitofrontal network	0.239	0.811
	Deep network	-2.013	0.046
Deep network	Deep network	-0.809	0.420
	Frontoparietal network	-0.754	0.453
	Middle temporal network	-4.089	<0.001
	Cerebellar network	-4.413	<0.001
	Occipital network	0.305	0.761

	Orbitofrontal network	-3.153	0.002
	Deep network	-3.208	0.002
	Deep network	-1.393	0.166
	Frontoparietal network	1.200	0.233
	Cerebellar network	-0.870	0.386
	Occipital network	2.998	0.003
Middle temporal network	Orbitofrontal network	-3.089	0.002
	Deep network	-4.767	<0.001
	Deep network	-3.672	<0.001
	Frontoparietal network	-4.370	<0.001
	Occipital network	2.888	0.005
Cerebellar network	Orbitofrontal network	-4.096	<0.001
	Deep network	-3.038	0.003
	Deep network	-4.133	<0.001
	Frontoparietal network	-4.724	<0.001
Occipital network	Orbitofrontal network	1.291	0.199
	Deep network	0.411	0.682
	Deep network	1.806	0.073
	Frontoparietal network	-1.151	0.252
Orbitofrontal network	Deep network	-1.071	0.286
	Deep network	-2.727	0.007
	Frontoparietal network	-1.048	0.297
Deep network	Deep network	-1.640	0.104
	Frontoparietal network	-4.080	<0.001
Deep network	Frontoparietal network	-1.421	0.158

Abbreviations: FCC, functional covariance connectivity; ESRD, end-stage renal disease; HCs, healthy controls; WM, white matter; FDR, false discovery rate.

Supplementary Table 4. Between-group differences in WM functional network interactions between ESRD patients and HCs (FDR corrected)

GC pattern	Layer	WM functional network	*t*-value	*p*-value
Excitatory	Middle → Superficial	Corona radiate network → Frontal network	-2.389	0.018
		Corona radiate network → Pre/post-central network	-3.404	0.001
		Corona radiate network → Cerebellar network	-3.469	0.001
	Superficial → Deep	Middle temporal network → Deep network	-3.076	0.003
	Superficial → Middle	Middle temporal network → Corona radiate network	-2.030	0.044
		Middle temporal network → Cerebellar network	-3.196	0.002
		Middle temporal network → Occipital network	-2.835	0.005
	Superficial → Superficial	Middle temporal network → Orbitofrontal network	-1.985	0.049
		Middle temporal network → Pre/post-central network	-3.716	<0.001
		Frontoparietal network → Occipital network	-2.140	0.034
	Deep → Superficial	Deep network → Occipital network	-2.119	0.036
Inhibitory	Superficial → Superficial	Pre/post-central network → Middle temporal network	2.283	0.024
		Orbitofrontal network → Frontal network	2.136	0.035
		Orbitofrontal network → Pre/post-central network	2.171	0.032
		Cerebellar network → Middle temporal network	2.017	0.046
	Superficial → Deep	Orbitofrontal network → Deep network	3.302	0.001
	Superficial → Middle	Pre/post-central network → Corona radiate network	2.127	0.035

Abbreviations: GC, Granger causality; ESRD, end-stage renal disease; HCs, healthy controls; WM, white matter; FDR, false discovery rate.

Supplementary Table 5. The In/Out strength in tri-layer WM functional networks between ESRD patients and HCs (FDR corrected)

In/Out strength	HCs	ESRD	*t*-value	*p*-value
Superficial				
In strength	2.71(2.01)	1.97(1.45)	-2.490	0.014*
Out strength	2.73(2.00)	1.97(1.48)	-2.557	0.012*
Middle				
In strength	2.89(1.72)	1.35(1.10)	-2.385	0.028*
Out strength	4.09(2.16)	2.66(1.44)	-1.743	0.098
Deep				
In strength	2.62(1.88)	2.15(1.70)	-1.985	0.049*
Out strength	2.27(1.48)	1.84(1.58)	-1.014	0.315

Note.—data are mean (standard deviation). Abbreviations: ESRD, end-stage renal disease; HCs, healthy controls; WM, white matter; FDR, false discovery rate. * Indicates a statistically significant difference after FDR corrected.

Supplementary Table 6. The classification results based on WM functional network metrics (LOOCV cross-validation)

Classifier	Accuracy	Specificity	Sensitivity	AUC
K-Nearest Neighbor	89.06%	90.00%	88.46%	0.940
Logistic Regression	79.69%	74.00%	83.33%	0.858
Support Vector Machine	89.06%	80.00%	94.87%	0.919
Adaptive Boost	90.62%	82.00%	96.15%	0.916
Random Forest	95.31%	88.00%	99.00%	**0.982**
Categorical Naive Bayes	78.91%	74.00%	82.05%	0.832

Abbreviations: LOOCV = leave-one-out; CI = confidence interval; AUC = Area under curve

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