Neurovascular coupling dysfunction in end-stage renal disease patients related to cognitive impairment

Supplementary material

Between-group comparison of ALFF, fALFF, ReHo, DC, and CBF

Whole brain GM level

From our results, ESRD patients showed increased averaged CBF and decreased BOLD signals (averaged ALFF, fALFF, ReHo, and DC) values on the whole GM level compared with HCs. (ALFF_HCs = 1.0275, ALFF_ESRD = 0.9968, t = -4.0299, $p < 0.001$; DC_HCs = 1.0508, DC_ ESRD = 1.0168, t = -4.278, $p < 0.001$; fALFF_HCs = 1.0164, fALFF_ ESRD = 1.0085, t = -3.065, $p = 0.0037$; ReHo_HCs = 0.4960, ReHo_ ESRD = 0.44, t = -4.009, $p < 0.001$; CBF_HCs =82, CBF_ ESRD =95, t = 3.935, $p < 0.001$).

The Human Brainnetome Atlas level

In CBF maps, significant between-group differences were found in 27 brain regions of the Human Brainnetome Atlas, as shown in Supplementary Fig. 3. Compared with HCs, ESRD patients showed increased CBF values located in bilateral superior frontal gyrus (SFG), bilateral middle frontal gyrus (MFG), right inferior frontal gyrus (IFG), bilateral orbital gyrus (OrG), bilateral superior temporal gyrus (STG), bilateral insular gyrus (INS), bilateral cingulate gyrus (CG), and right basal ganglia (BG) ($p < 0.05$ after FDR correction).

In ALFF maps, significant between-group differences were found in 12 brain regions of the Human Brainnetome Atlas, as shown in Supplementary Fig. 3. Compared with HCs, ESRD patients showed decreased ALFF values located in left inferior temporal gyrus (ITG), bilateral inferior parietal lobule (IPL), bilateral precuneus (Pcun), right BG and bilateral

thalamus (Tha) ($p < 0.05$ after FDR correction).

In fALFF maps, significant between-group differences were found in 19 brain regions of the Human Brainnetome Atlas, as shown in Supplementary Fig. 3. Compared with HCs, ESRD patients showed decreased fALFF values located in bilateral ITG, bilateral fusiform gyrus (FuG), bilateral parahippocampal gyrus (PhG), right superior parietal lobule (SPL), bilateral IPL, right Pcun, right amygdala (Amyg), bilateral BG and left Tha ($p < 0.05$ after FDR correction).

In ReHo maps, significant between-group differences were found in 16 brain regions of the Human Brainnetome Atlas, as shown in Supplementary Fig. 3. Compared with HCs, ESRD patients showed decreased ReHo values located in bilateral SFG, left MFG, left IFG, bilateral orbital gyrus (OrG), bilateral STG, left MGT, left IPL, bilateral CG, left Amyg and left Tha ($p < 0.05$ after FDR correction).

In DC maps, significant between-group differences were found in 10 brain regions of the Human Brainnetome Atlas, as shown in Supplementary Fig. 3. Compared with HCs, ESRD patients showed decreased DC values located in left IFG, bilateral IPL, bilateral INS and bilateral BG ($p < 0.05$ after FDR correction).

Figure Captions

Fig. 1. Spatial distribution maps between-group differences of the four types of NVC patterns. In comparison with HCs, ESRD patients showed significantly lower ALFF-CBF, fALFF-CBF, ReHo-CBF, and DC-CBF coefficients in 34 brain regions at the Human Brainnetome Atlas ($p < 0.01$, FDR correction). NVC = neurovascular coupling, ALFF = amplitude of low-frequency fluctuation, fALFF = fractional ALFF, ReHo = regional homogeneity, DC =

degree centrality, HCs = healthy control subjects, ESRD = end-stage renal disease, FDR = false discovery rate).

Fig. 2. Multivariate PLSC analysis between the NVC pattern alteration and clinical blood biochemistry tests in ESRD patients. Multivariate PLSC analysis correlating the NVC pattern alteration to clinical blood biochemistry tests revealed one significant LV ($p < 0.05$) which accounted for 38.16% of the cross-block covariance. The pattern identified by the LV showed that the lower fALFF-CBF coefficients in the CG (section A) were positively associated with lower Kt/V values, and were negatively associated with higher serum urea (section B). PLSC = partial least-squares correlation, NVC = neurovascular coupling, fALFF = fractional amplitude of low-frequency fluctuation, CBF = cerebral blood flow, LV = latent variable, CG = cingulate gyrus, Kt/V= kinetic transfer/volume urea, ESRD = end-stage renal disease.

Fig. 3. Multivariate PLSC analysis between the NVC pattern's alteration and cognitive variables in ESRD patients. Multivariate PLSC analysis correlating the NVC pattern's alteration to cognitive variables revealed one significant LV ($p < 0.05$), which accounted for 46.70% of the cross-block covariance. The pattern identified by the LV showed that lower fALFF-CBF coefficients in the CG (section A) were positively associated with lower SR-S values (section B). PLSC = partial least-squares correlation, NVC = neurovascular coupling, fALFF = fractional amplitude of low-frequency fluctuation, CBF = cerebral blood flow, CG = cingulate gyrus, LV = latent variable, SR-S = short-term delayed recall score, ESRD = end-stage renal disease.

Fig. 4. Multivariate PLSC analysis between the clinical blood biochemistry tests and cognitive variables**.** Multivariate PLSC analysis correlating the clinical blood biochemistry tests to cognitive variables revealed one significant LV ($p < 0.05$), which accounted for 73.50% of the cross-block covariance. The pattern identified by the LV showed that lower Kt/V and hemoglobin were positively associated with lower IR-S and SR-S values in ESRD patients. PLSC = partial least-squares correlation, LV = latent variable, Kt/V= kinetic transfer/volume urea, IR-S = immediate recall total score, SR-S = short-term delayed recall score, ESRD = end-stage renal disease.

Fig. 5 Mediation analysis. In the mediation analysis, the independent factor was Kt/V and the dependent variable was a short-term memory function indicator. These were reflected by the SR-S, while the fALFF-CBF coefficient in the CG served as the proposed mediator. The mediation analysis result indicated that NVC dysfunction (lower fALFF-CBF coefficient) in the CG partially mediated the effect of Kt/V on the short-term memory function deficits (c' = 0.698, $p = .003$) in ESRD patients. Kt/V= kinetic transfer/volume urea, NVC = neurovascular coupling, fALFF = fractional amplitude of low-frequency fluctuation, CBF = cerebral blood flow, CG = cingulate gyrus, SR-S = short-term delayed recall score, ESRD = end-stage renal disease.

Supplementary Fig. 1. Flowchart of imaging analysis. BOLD = blood oxygen level dependent, ALFF = amplitude of low-frequency fluctuation, fALFF = fractional ALFF, ReHo = regional

homogeneity, DC = degree centrality, CBF = cerebral blood flow, NVC= neurovascular coupling, GM= grey matter.

Supplementary Fig. 2. Spatial distribution of averaged CBF, ALFF, fALFF, ReHo, and DC maps. These maps were averaged across subjects within each group. ALFF = amplitude of low-frequency fluctuation, fALFF = fractional ALFF, ReHo = regional homogeneity, DC = degree centrality, CBF = cerebral blood flow.

Supplementary Fig. 3. Between-group comparisons of ALFF, fALFF, ReHo, DC, and CBF maps. Compared with HCs, ESRD patients showed increased CBF and decreased BOLD signals (ALFF, fALFF, ReHo, and DC) values in multiple brain regions. BOLD= blood oxygen level dependent, ALFF = amplitude of low-frequency fluctuation, fALFF = fractional ALFF, ReHo = regional homogeneity, DC = degree centrality, CBF = cerebral blood flow, ESRD= end-stage renal disease, HCs = healthy control subjects.

Supplementary Fig. 4. Four types of brain region-based NVC patterns. (A) ALFF-CBF, (B) fALFF-CBF, (C) ReHo-CBF, and (D) DC-CBF patterns. The numbers associated with different brain regions were consistent with the numbers in the Human Brainnetome Atlas. The green line in each map referred to the NVC pattern's average correlation coefficients of brain regions in healthy controls, and the corresponding red dots are referred to the NVC pattern's average correlation coefficients of brain regions in ESRD patients. NVC = neurovascular coupling, ALFF = amplitude of low-frequency fluctuation, fALFF = fractional

amplitude of low-frequency fluctuation, ReHo = regional homogeneity, DC = degree centrality, CBF = cerebral blood flow, ESRD = end-stage renal disease.