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Reversal of neurovascular decoupling and cognitive impairment in patients with end-stage renal disease during a hemodialysis session: Evidence from a comprehensive fMRI analysis

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Abstract

Neurovascular (NV) decoupling is a potential neuropathologic mechanism of cognitive impairment in patients with end-stage renal disease (ESRD). Hemodialysis improves cognitive impairment at 24 h post-dialysis, which suggests a potential neuroprotective effect of hemodialysis treatment on the brain. We investigated the effects of hemodialysis treatment on the reversal of NV decoupling associated with cognitive improvement. A total of 39 patients with ESRD and 39 healthy controls were enrolled. All patients were imaged twice during a dialysis session: before hemodialysis ($T1_{pre\text{-}dialysis}$) and at 24 h after dialysis ($T2_{post\text{-}dialysis}$). The healthy controls were imaged once. NV coupling was characterized based on correlation coefficients between four types of blood oxygen level-dependent signals and cerebral blood flow (CBF). A battery of neuropsychological and blood tests was performed before the imaging. Patients with ESRD showed improvements in memory and executive function at $T2_{post\text{-}dialysis}$ compared with that at $T1_{pre\text{-}dialysis}$. At both $T1_{pre\text{-}dialysis}$ and $T2_{post\text{-}dialysis}$, patients with ESRD had lower amplitude of low-frequency fluctuation (ALFF)–CBF coupling than healthy controls. Additionally, patients with ESRD had higher ALFF–CBF coupling at $T2_{post\text{-}dialysis}$ than at $T1_{pre\text{-}dialysis}$. Higher memory scores, higher hemoglobin level, lower total plasma homocysteine level, lower systolic blood pressure variance, and lower ultrafiltration volume were associated with higher ALFF–CBF coupling in patients with ESRD after a hemodialysis session. These findings indicate that partial correction of anemia and hyperhomocysteinemia, stable systolic blood pressure, and fluid restriction may be closely linked to the reversal of NV decoupling and improvement in cognition in patients with ESRD.

KEYWORDS
arterial spin labeling, end-stage renal disease, hemodialysis, neurovascular coupling, resting-state functional magnetic resonance imaging

1 | INTRODUCTION

Cognitive impairment is prevalent in the population with end-stage renal disease (ESRD) undergoing hemodialysis (HD) (Koren et al., 2021). Cognitive impairment is increasingly being recognized as an important cause of chronic disability (Kurella Tamura & Yaffe, 2011; McAdams-DeMarco et al., 2015; O'Lone et al., 2016), which can complicate treatment and lead to poor clinical outcomes, including dialysis withdrawal, hospitalization, and death (Kuo et al., 2019; Kurella Tamura et al., 2009). As one of the important therapeutic means to sustain the life of patients with ESRD, HD can exert a protective effect on the brain and cognition by removing uremia toxins (Scribner et al., 1998), controlling extracellular volume excess (Schneider et al., 2015; Williams et al., 2004), and partially correcting anemia (Pickett et al., 1999). Understanding the effects of HD treatment on cognitive function and exploring its potential neuropathologic mechanisms could be crucial for early intervention and prognosis improvement in patients with ESRD (Jha et al., 2013).

Several studies have revealed cognition fluctuations in patients with ESRD because of alterations in the levels of uremic toxins and the substantial fluid shifts that occur during HD (Griva et al., 2003; Murray et al., 2007; Williams et al., 2004). Significant improvements in cognitive performance (verbal and visual memory, attention, execution, and psychomotor speed) have been observed in patients at 24 h post-dialysis compared with that at pre-dialysis (Griva et al., 2003; Murray et al., 2007; Schneider et al., 2015; Williams et al., 2004). The cognitive function of patients undergoing HD is optimal at approximately 24 h after HD session, indicating that HD itself might have a protective effect on cognition (Costa et al., 2014; Griva et al., 2003; Murray et al., 2007; Williams et al., 2004). Reversibility of cognitive impairment is important because it helps patients with ESRD to adhere to the complex treatment instructions communicated by physicians (Elias et al., 2015). In a previous study using a neuroimaging technique (Li et al., 2018), we found that increased intrinsic neural activity was significantly associated with memory improvement at 24 h after HD treatment, potentially providing neuropathologic evidence of the protective effect of HD on cognitive function. Most prior neuroimaging studies were focused on the relationships of abnormalities in intrinsic neural activity (Ni et al., 2014) or cerebral blood flow (CBF) (Jiang et al., 2016) with cognitive impairment, which cannot reflect the neurovascular (NV) interactions associated with cognitive impairment reversibility in patients with ESRD after an HD session.

The tight temporal and regional linkage between neural activity and CBF response, which can reflect coordination between the requirements for oxygen and blood supply in the brain, has been termed the NV coupling mechanism (Liang et al., 2013). The NV coupling mechanism is consistent with the interaction between the two main hypotheses concerning the kidney–brain axis: the vascular injury hypothesis and the neurodegeneration hypothesis (Bugnicourt et al., 2013). Our recent neuroimaging findings (Li et al., 2021) revealed that NV decoupling could potentially represent the neuropathologic mechanism of cognitive impairment in patients with ESRD undergoing maintenance HD. However, our study showed only the cumulative effect of long-term HD treatment on NV coupling and cognitive impairment in patients with ESRD. An evaluation of the alterations in NV coupling that accompany cognition impairment reversibility during HD treatment might enhance our understanding of the neuropathologic mechanisms potentially underlying the protective effect of HD on the brain.

In the present study, multimodal neuroimaging analyses and cognition assessments were performed at two time points in a single HD session: before dialysis ($T1_{pre\text{-}dialysis}$) and after 24 h ($T2_{post\text{-}dialysis}$). We also evaluated four blood oxygen level-dependent (BOLD)–CBF patterns, which reflect NV coupling in patients with ESRD, as we previously demonstrated (Li et al., 2021). We further investigated the relationships among alterations in NV coupling, improvement in cognitive performance, and clinical indicators during the HD session. We hypothesized that HD treatment has a positive effect on NV coupling, which may be associated with cognitive impairment reversibility in patients with ESRD.

2 | MATERIALS AND METHODS

2.1 | Participants

This prospective study received local ethics committee approval and was registered at ClinicalTrials.gov (NCT03191409, https://clinicaltrials.gov/ct2/show/NCT03191409). All experiments were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Between July 2020 and June 2021, 39 right-handed patients with ESRD (26 men, 13 women; mean age: 37 ± 1.78 years) undergoing maintenance HD were enrolled (Table 1 and Figure 1). All patients had a dialysis duration more than 3 months. The exclusion criteria were as follows: (1) any evidence of brain lesions (tumor, head trauma, stroke, hemorrhage, or encephalomalacia) based on conventional magnetic resonance (MR) imaging or medical history findings, (2) a history of drug or alcohol abuse, (3) age less than 18 years, (4) any evidence of neurodegenerative or psychiatric disorders, (5) a history of diabetic nephropathy, (6) any evidence of auditory or visual disturbances (blurred vision, hearing loss, and other clinically relevant symptoms incompatible with a neuropsychological assessment), and (7) a history of claustrophobia.

A total of 39 age-, education-, and sex-matched, right-handed, healthy controls (HC) (22 men, 17 women; mean age: 35 ± 1.66 years) were recruited from the local community. The exclusion criteria used for the patients were also used for the HC. The inclusion criteria for HC were age ≥ 18 years, with no relevant medical history of systemic, neurologic, or psychiatric disease.

2.2 | Clinical characteristics

Demographic characteristics, clinical data, and data on indication for dialysis were collected from the medical records of the patients. Blood tests were performed for all patients at $T1_{pre\text{-}dialysis}$ and $T2_{post\text{-}dialysis}$. All patients had been receiving dialysis thrice weekly, with a short mid-week dialysis interval. The HD sessions lasted approximately 4 h,

TABLE 1 Demographic information and clinical characteristics in patients with ESRD and HC

Variable	HC ($n = 39$)	$T1_{pre\text{-}dialysis}$ ($n = 39$)	$T2_{post\text{-}dialysis}$ ($n = 39$)	*t* value	*p* value
Age (years)	34.54 (1.66)	36.65 (1.78)	/	0.10	.323[a]
Gender (M/F)	22/17	26/13	/	0.87[b]	.352[b]
Education (years)	12.25 (0.38)	11.73 (0.29)	/	−1.10	.274[a]
Dialysis vintage (months)	/	44.77 (5.34)	/	/	/
Creatinine (μmol/L)	/	946.89 (33.54)	372.13 (21.24)	19.03	<.001[c,d]
Urea (mmol/L)	/	23.74 (0.95)	7.39 (0.42)	19.61	<.001[c,d]
Cystatin C (μg/L)	/	7.13 (0.60)	8.87 (0.64)	−1.96	.058[c]
Hemoglobin (g/L)	/	112.92 (2.89)	129.33 (3.14)	−8.92	.001[c,d]
Hematocrit (%)	/	34.03 (0.83)	38.15 (0.90)	−7.57	<.001[c,d]
RBC (10^9)	/	3.66 (0.09)	4.16 (0.10)	−8.34	<.001[c,d]
Potassium (mmol/L)	/	4.70 (0.11)	3.60 (0.09)	8.74	<.001[c,d]
Sodium (mmol/L)	/	141.49 (0.44)	139.67 (0.32)	3.72	.001[c,d]
Phosphorus (mmol/L)	/	1.75 (0.10)	1.04 (0.05)	7.19	<.001[c,d]
Calcium (mmol/L)	/	7.22 (5.13)	2.53 (0.04)	0.92	.366[c]
Chlorine (mmol/L)	/	99.36 (0.50)	95.28 (0.42)	8.74	<.001[c,d]
Magnesium (mmol/L)	/	1.12 (0.02)	0.94 (0.01)	8.67	<.001[c,d]
Parathormone (ng/ml)	/	546.53 (71.89)	361.70 (56.34)	4.47	<.001[c,d]
C-reactive protein (mg/L)	/	6.28 (1.46)	5.70 (1.33)	0.29	.767[c]
RDW (fL)	/	47.68 (0.67)	56.67 (10.19)	−0.88	.383[c]
tHcy (μmol/L)	/	47.20 (6.18)	28.79 (3.42)	5.89	<.001[c,d]
Vitamin D (ng/ml)	/	27.59 (2.62)	31.26 (2.71)	−2.58	.014[c,d]
Interleukin-6 (pg/ml)	/	5.67 (1.21)	16.88 (3.80)	−2.97	.005[c,d]
Medication		***N***			**%**
AT1-blocker		9			23
Beta-blocker		37			95
Calcium antagonists		30			77
EPO		39			100
Antidepressants		0			0
Antihistamines		0			0
Analgesics		0			0
Vitamin D		16			41

Note: Unless otherwise indicated, data are mean (SE).
Abbreviations: EPO, erythropoietin; ESRD, end-stage renal disease; HC, healthy controls; RBC, red blood cell count; RWD, red blood cell distribution width; tHcy, total plasma homocysteine.
[a]Analyzed with the independent two-sample *t* test; data in parentheses have a 95% confidence interval.
[b]Analyzed with the chi-square test.
[c]Analyzed with the paired-sample *t* test; data in parentheses represents a 95% confidence interval.
[d]Indicates a statistically significant difference.

and the dialysis dose was titrated to reach at least 1.2 by urea kinetic modeling (Schneider et al., 2015). All treatments were delivered using a German-made dialysis machine (Fresenius 4008: Fresenius, Bad Homburg, Germany) equipped with a polysulfone dialysis membrane (membrane area: 1.6 m^2; dialysate flow rate: 500 ml/min; ultrafiltration volume: 2.64 ± 0.16 L; dialysis duration: 4.43 ± 0.03 h; and blood flow volume: 262.74 ± 3.77 ml/min). A mercury sphygmomanometer was used to measure blood pressure (BP) once every hour during the dialysis session. Simultaneously, blood flow volume, pulse rate, transmembrane pressure, and dialysis venous pressure were recorded from the dialysis machine's parameter monitor. In this patient cohort, the underlying causes of ESRD were glomerulonephritis ($n = 37$), immunoglobulin A nephropathy ($n = 1$), and membranous nephropathy ($n = 1$). Blood tests were not performed in the HC group (Table 1).

2.3 | Neuropsychological assessment

All patients completed a battery of tests twice within 24 h, that is, at $T1_{pre\text{-}dialysis}$ and $T2_{post\text{-}dialysis}$. To control for potential learning effects

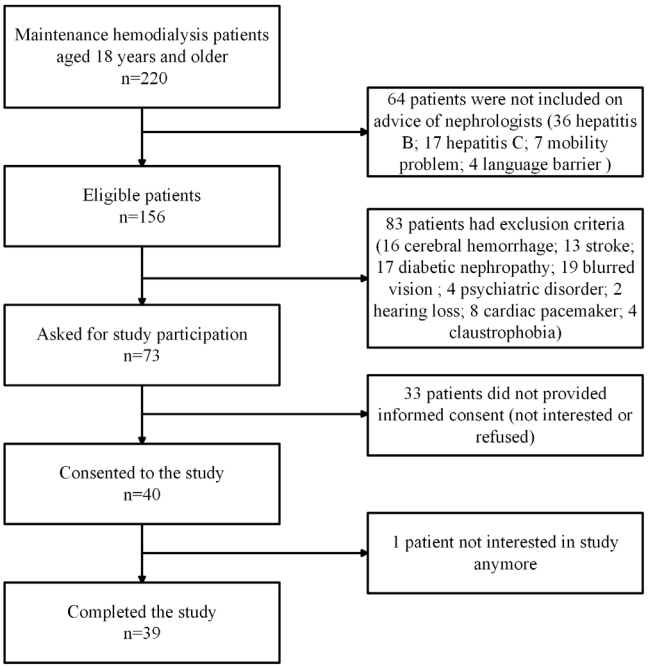

FIGURE 1 Flowchart depicting the progression of patients with end-stage renal disease through the study, from screening to inclusion and finally to study completion

(Falleti et al., 2006), the patients were randomized into two groups using a method similar to that described by Schneider et al. (2015) and Li et al. (2018). In Group 1, the $T1_{pre\text{-}dialysis}$ tests were administered at 1:00 p.m. on a Wednesday before that day's dialysis session; the $T2_{post\text{-}dialysis}$ tests were administered at 1:00 p.m. the next day (Thursday). In Group 2, the $T2_{post\text{-}dialysis}$ tests were administered at 1:00 p.m. on a Thursday after a Wednesday dialysis session; the $T1_{pre\text{-}dialysis}$ tests were administered at 1:00 p.m. the next day, i.e., before the Friday dialysis session (Figure S2). The neuropsychological scales obtained in Group 1 and Group 2 at $T1_{pre\text{-}dialysis}$ were analyzed together. Similarly, the scales obtained in Group 1 and Group 2 at $T2_{post\text{-}dialysis}$ were analyzed together. The HC completed the same battery of tests once, at a time equivalent to $T1_{pre\text{-}dialysis}$. Subsequently, the neuropsychological scales were compared between the patients and HC and between $T1_{pre\text{-}dialysis}$ and $T2_{post\text{-}dialysis}$ in the patients.

All neuropsychological tests were conducted in a quiet room by two clinical psychologists with 10 years of experience in the field. The tests included the Montreal Cognitive Assessment (MoCA), the Auditory Verbal Learning Test–Huashan version (AVLT-H), the Color Trails Test (CTT), the Digital Symbol Test (DST), and the Digit Span (DS) test. These tests are used to evaluate attention, visuospatial skill, language, orientation, executive function, psychomotor speed, and memory (Davis et al., 2021; Mura et al., 2014; Zhao et al., 2015). The Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) were also administered to evaluate the emotional status of the participants (Lovibond & Lovibond, 1995) (Table 2).

2.4 | MR data acquisition

All MR data were obtained using a 3.0T MR scanner (Discovery MR750: GE Healthcare, Chicago, IL, USA) equipped with an eight-channel phased-array head coil. Participants were all instructed to lie quietly with eyes closed, to relax their minds, and to remain awake during imaging. Suitable earplugs and foam padding were used to reduce noise and head motion. To ensure that all participants remained awake, their awareness was checked from time to time during imaging. If any participant was uncomfortable or unable to complete the imaging, the procedure was discontinued. After imaging completion, questions were posed to all participants to verify their cooperation.

The T1-weighted fluid-attenuated inversion recovery images (echo time [TE]: 24 ms; repetition time [TR]: 1750 ms; flip angle [FA]: 111°; inversion time: 780 ms; slice thickness: 6 mm; acquisition matrix: 256 × 256; and slice gap: 0.6 mm) and T2-weighted PROPELLER images (TE/TR: 84/9638 ms; refocus angle: 142 °; slice thickness: 6 mm; gap: 0.6 mm; and matrix: 256 × 256) obtained were used to exclude the presence of intracranial lesions. Individual high spatial resolution T1-weighted anatomic images were acquired using a three-dimensional (3D) brain volume imaging sequence (TE/TR: 3.2/8.2 ms; FA: 15°; thickness: 1 mm; acquisition matrix: 256 × 256; and slice number: 140).

Resting-state functional MR imaging data were acquired using an echo-planar technique sensitive to BOLD signals (TE/TR: 50/2000 ms; FA: 90 °; voxel size: 3 × 3 × 3 mm^3; field of view: 240 × 240 mm^2; thickness: 4 mm; slices: 45; slice gap: 0 mm; and acquisition matrix: 64 × 64). Each scan lasted for 6 min 10 s, and a total of 185 functional volume sequences were collected.

The noninvasive arterial spin labeling MR imaging technique is increasingly being used to measure CBF alterations in patients with ESRD (Jiang et al., 2016). In accordance with the consensus statement published by the Perfusion Study Group of the International Society for Magnetic Resonance in Medicine (Alsop et al., 2015; van Osch et al., 2018), whole-brain CBF measurements were obtained using the 3D pseudo-continuous arterial spin labeling technique (TE/TR: 11/5046 ms; slices: 50; post-label delay: 2025 ms; slice thickness: 3 mm; FA: 111°; field of view: 256 × 256 mm^2; and acquisition matrix: 128 × 128).

2.5 | MR data processing and analysis

The T1-weighted MR data were analyzed using the SPM8 (statistical parametric mapping) software (University College London, The Wellcome Centre for Human Neuroimaging, London, UK [http://www.fil.ion.ucl.ac.uk/spm/]). The resting-state functional MR data were analyzed in the SPM8 software application after preprocessing with DPARSF (Data Processing Assistant for Resting-State fMRI [http://www.restfmri.net/forum/DPARSF]) (Chao-Gan & Yu-Feng, 2010). To create the CBF map, 3D pseudo-continuous arterial spin labeling data were processed using FSL version 6.0.3 (Functional Magnetic Resonance Imaging of the Brain [FMRIB] Software Library; FMRIB, Analysis Group, Oxford, UK; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and the SPM8 software. Four BOLD signals—amplitude of low-frequency

TABLE 2 Neuropsychological assessment in patients with ESRD and HC at $T1_{pre\text{-}dialysis}$ and $T2_{post\text{-}dialysis}$

Variable	HC ($n = 39$)	$T1_{pre\text{-}dialysis}$ ($n = 39$)	$T2_{post\text{-}dialysis}$ ($n = 39$)	*t1* value	*p1* value	*t2* value	*p2* value	*t3* value	*p3* value
AVLT-H									
IR-S	29.67 (0.43)	26.18 (0.60)	28.38 (0.42)	−4.74	<.001[a,c]	−1.90	.061[a]	4.71	<.001[b,c]
SR-S	10.28 (0.18)	9.89 (0.23)	10.13 (0.19)	−1.33	.191[a]	−0.47	.639[a]	0.93	.361[b]
LR-S	10.07 (0.20)	9.59 (0.23)	10.18 (0.19)	−1.60	.115[a]	0.36	.718[a]	2.17	.037[b,c]
REC-S	11.82 (0.51)	11.41 (0.17)	11.67 (0.12)	−2.21	.030[a,c]	−1.04	.301[a]	2.26	.030[b,c]
MoCA									
Total score	27.23 (0.37)	23.64 (0.49)	25.41 (0.41)	−5.83	<.001[a,c]	−3.33	.001[a,c]	5.06	<.001[b,c]
Visuospatial	3.87 (0.12)	3.18 (0.19)	3.36 (0.19)	−3.10	.003[a,c]	−2.34	.022[a,c]	0.70	.487[b]
Name	2.90 (0.06)	2.72 (0.09)	2.92 (0.06)	−1.65	.103[a]	0.31	.760[a]	2.24	.032[b,c]
Attention	5.77 (0.78)	5.36 (0.14)	5.41 (0.13)	−2.57	.012[a,c]	−2.43	.017[a,c]	0.26	.800[b]
Language	2.58 (0.11)	1.82 (0.11)	2.1 (0.07)	−4.99	<.001[a,c]	−3.75	<.001[a,c]	2.95	.006[b,c]
Abstraction	1.82 (0.07)	1.21 (0.08)	1.79 (0.07)	−5.57	<.001[a,c]	−0.26	.793[a]	5.56	<.001[b,c]
Orientation	5.92 (0.04)	5.77 (0.07)	5.74 (0.11)	−1.90	.061[a]	−1.47	.147[a]	−0.57	.571[b]
Delayed memory	4.41 (0.10)	3.49 (0.15)	4.03 (0.11)	−5.29	<.001[a,c]	−2.60	.011[a,c]	2.67	.011[b,c]
CTT part A	41.18 (1.87)	64.54 (4.81)	52.26 (3.47)	4.53	<.001[a,c]	2.81	.006[a,c]	−4.75	<.001[b,c]
CTT part B	82.28 (2.07)	117.21 (6.66)	101.67 (5.39)	5.01	<.001[a,c]	3.35	.001[a,c]	−5.30	<.001[b,c]
DST	8.40 (0.14)	7.13 (0.29)	7.49 (0.21)	−3.91	<.001[a,c]	−3.62	.001[a,c]	1.98	.056[b]
DS-forward	8.64 (0.14)	7 (0.17)	7.31 (0.17)	−7.29	<.001[a,c]	−5.92	<.001[a,c]	2.45	.019[b,c]
DS-backward	6.92 (0.19)	5.1 (0.2)	5.56 (0.18)	−6.55	<.001[a,c]	−5.12	<.001[a,c]	3.26	.003[b,c]
BDI	4.87 (0.67)	14.03 (1.13)	11.31 (1.01)	6.99	<.001[a,c]	5.33	<.001[a,c]	−3.35	.002[b,c]
BAI	24.12 (0.40)	25.95 (0.56)	24.23 (0.37)	2.65	.010[a,c]	0.19	.852[a]	−3.16	.003[b,c]

Note: *t*1-value = *t* ($T1_{pre\text{-}dialysis}$ vs. HC); *p*1-value = *p* ($T1_{pre\text{-}dialysis}$ vs. HC); *t*2-value = *t* ($T2_{post\text{-}dialysis}$ vs. HC); *p*2-value = *p* ($T2_{post\text{-}dialysis}$ vs. HC); *t*3-value = *t* ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$); *p*3-value = *p* ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$). Unless otherwise indicated, data are mean (SE).

Abbreviations: AVLT-H, auditory verbal learning test–Huashan version; BAI, Beck anxiety inventory; BDI, Beck depression inventory; CTT, color trail test; DST, digital symbol test; DS, digital span; ESRD, end-stage renal disease; HC, healthy control; IR-S, immediate recall score; LR-S, long-term recall score; MoCA, Montreal cognitive assessment; REC-S, recognition score; SR-S, short-term recall score.

[a]Analyzed with the two-sample *t*-test; data in parentheses have a 95% confidence interval after controlling age, sex, and education level.

[b]Analyzed with the paired-sample *t*-test; data in parentheses represents a 95% confidence interval after controlling age, sex, and education level.

[c]Indicates a statistically significant difference.

fluctuation (ALFF), fractional ALFF (fALFF), regional homogeneity (ReHo), and degree centrality (DC)—were analyzed to reflect intrinsic brain activity and connectivity. All processing procedures are described in the supplementary material.

2.6 | Statistical analysis

2.6.1 | Between-group differences: Demographic and clinical characteristics and cognitive variables

Demographic differences (age and education level) at baseline between patients and HC (at $T1_{pre\text{-}dialysis}$) were compared using the independent samples *t*-test. Differences in the sex ratio between the two groups were analyzed using the chi-squared test. Differences in clinical blood biochemistry parameters and cognitive variables between patients and HC ($T1_{pre\text{-}dialysis}$ vs. HC and $T2_{post\text{-}dialysis}$ vs. HC) were compared using the independent samples *t*-test. Differences in clinical blood biochemistry parameters and cognitive variables between patients before and after dialysis ($T1_{pre\text{-}dialysis}$ vs. $T2_{post\text{-}dialysis}$) were compared using the paired-samples *t*-test. To detect any order effect in the patient subgroups, the independent samples *t*-test was used to determine whether the two subgroups were equal before their neuropsychological test results were grouped. Multiple linear regression was used to remove any effect of education level (Tsapanou et al., 2019), age, sex (Good et al., 2001), and mood disorder score (Mu et al., 2018) between the groups for each cognitive variable. All statistical tests were two-sided, with a cutoff value of 0.05 for statistical significance, and performed using the IBM SPSS Statistics software (version 20.0: IBM, Armonk, NY, USA).

2.6.2 | Between-group differences: BOLD and CBF maps

Differences in ALFF, fALFF, ReHo, DC, and CBF maps between patients and HC were compared using the independent samples *t*-test

($T1_{pre\text{-}dialysis}$ vs. HC and $T2_{post\text{-}dialysis}$ vs. HC). Differences in ALFF, fALFF, ReHo, DC, and CBF maps between patients before and after dialysis ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$) were compared using the paired-samples *t*-test. Age, sex, education level, and whole gray matter volume were controlled as covariates. A between-group 5000-repetitions permutation test was conducted ($T1_{pre\text{-}dialysis}$ vs. HC, $T2_{post\text{-}dialysis}$ vs. HC, and $T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$), with significant clusters being corrected using the threshold-free cluster enhancement (TFCE) method ($p < .05$, TFCE corrected).

2.6.3 | Between-group differences: NV coupling patterns

To evaluate changes in NV coupling during a dialysis session, brain regions whose BOLD maps were significantly different at $T2_{post\text{-}dialysis}$ and $T1_{pre\text{-}dialysis}$ were extracted. A group-level mask was then constructed to extract the CBF values at the corresponding brain regions, and voxel-wise correlation coefficients between the BOLD signals and CBF values (ALFF–CBF, fALFF–CBF, ReHo–CBF, and DC–CBF) in the significantly different brain regions were calculated to characterize the NV coupling patterns (Hu et al., 2019) (Figure 2). Subsequently, the independent samples *t*-test ($T1_{pre\text{-}dialysis}$ vs. HC and $T2_{post\text{-}dialysis}$ vs. HC) and the paired-samples *t*-test ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$) were used to assess differences in NV coupling patterns between the groups (controlled for age, sex, education level, and whole gray matter volume).

2.6.4 | Correlation analysis

Canonical correlation analysis was used to assess the relationships between altered blood biochemistry parameters and cognitive variables ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$). Stepwise regression analysis was used to assess the relationships between changed NV coupling patterns and cognitive variables, changed NV coupling patterns and blood biochemistry parameters, and changed NV coupling patterns and dialysis treatment indicators ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$).

3 | RESULTS

3.1 | Between-group differences: Demographic characteristics, blood biochemistry parameters, and neuropsychological test results

Table 1 presents the demographic and clinical data for each group ($T1_{pre\text{-}dialysis}$, $T2_{post\text{-}dialysis}$, and HC). Table S1 presents dialysis treatment indicators for patients with ESRD. No significant differences in age, sex, or education level were observed between the groups ($p > .05$). With respect to blood biochemistry parameters, red blood cell count and hemoglobin, hematocrit, vitamin D, and interleukin 6 levels were significantly elevated in the patients at $T2_{post\text{-}dialysis}$ compared with those at $T1_{pre\text{-}dialysis}$ ($p < .05$). In contrast, levels of creatinine, urea, potassium, sodium, phosphorus, chlorine, magnesium, total plasma homocysteine, and parathormone were significantly decreased ($p < .05$).

Compared with HC, patients with ESRD scored significantly more poorly (Table 2) on the AVLT-H (immediate recall and recognition scores), MoCA (total score and visuospatial, attention, language, abstraction, and delayed memory subscores), CTT (parts A and B), DST, DS (forward and backward), BAI, and BDI ($p < .05$) scales at $T1_{pre\text{-}dialysis}$. Similarly, patients with ESRD scored significantly more poorly than HC on the MoCA (total score and visuospatial, attention, language, and delayed memory subscores), CTT (parts A and B), DST, DS (forward and backward), and BDI ($p < .05$) scales at $T2_{post\text{-}dialysis}$. However, at $T2_{post\text{-}dialysis}$ compared with $T1_{pre\text{-}dialysis}$, patients with ESRD scored significantly better on the subitems of the AVLT-H (immediate recall, long-term recall, and recognition scores), subitems of the MoCA (total score and visuospatial, language, abstraction, and delayed memory subscores), CTT (parts A and B), DST, DS (forward and backward), BAI, and BDI scales ($p < .05$).

3.2 | Between-group differences: CBF and BOLD maps

At $T1_{pre\text{-}dialysis}$ and $T2_{post\text{-}dialysis}$, CBF was significantly increased and ALFF, fALFF, and ReHo in multiple brain regions were lower in

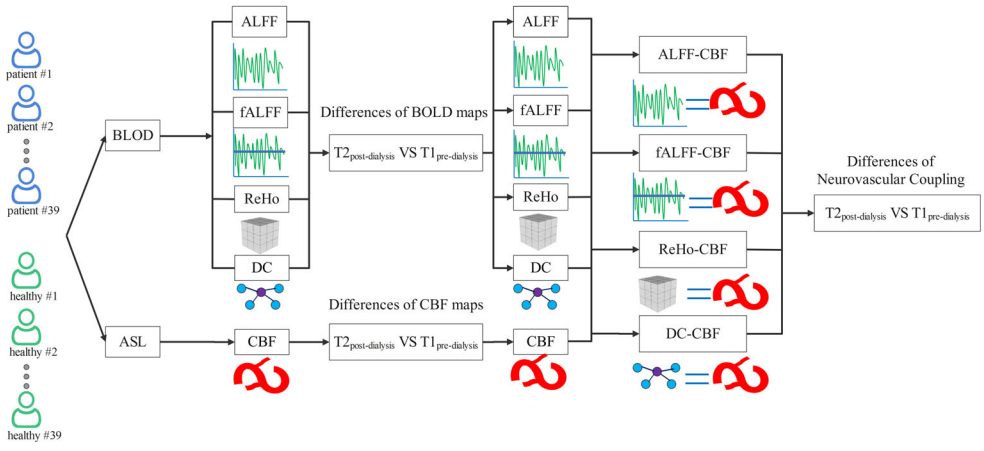

FIGURE 2 The post-processing and analysis procedure of neurovascular coupling during a hemodialysis session

patients with ESRD than in HC ($p < .05$, TFCE corrected; Figure S2 and Tables S2–S5). In patients with ESRD, ALFF and ReHo in multiple brain regions were higher at $T2_{post\text{-}dialysis}$ than at $T1_{pre\text{-}dialysis}$ ($p < .05$, TFCE corrected; Figure 3 and Tables S3 and S4). CBF and fALFF did not differ significantly between $T2_{post\text{-}dialysis}$ and $T1_{pre\text{-}dialysis}$ ($p < .05$, TFCE corrected; Tables S2 and S5). DC was not significantly different in patients at $T1_{pre\text{-}dialysis}$ or at $T2_{post\text{-}dialysis}$ compared with HC or in patients at $T2_{post\text{-}dialysis}$ compared with $T1_{pre\text{-}dialysis}$ ($p < .05$, TFCE corrected). Details of between-group differences in brain regions on BOLD and CBF maps are presented in the supplementary material.

3.3 | Between-group differences: NV coupling patterns

Differences in the BOLD maps for patients at $T2_{post\text{-}dialysis}$ compared with those at $T1_{pre\text{-}dialysis}$ (ALFF and ReHo) were used to calculate their NV coupling patterns (ALFF–CBF and ReHo–CBF correlation coefficients). The brain regions used to calculate ALFF–CBF coupling included the bilateral superior frontal, middle temporal, inferior temporal, and right middle frontal gyri. The brain regions used to calculate ReHo–CBF coupling included the left precentral, left postcentral, left medial frontal, and left superior frontal gyri; the left inferior parietal, right paracentral, and left superior parietal lobules; and the left precuneus.

Compared with HC, patients with ESRD had significantly lower ALFF–CBF coupling at $T1_{pre\text{-}dialysis}$ and $T2_{post\text{-}dialysis}$ ($ALFF\text{–}CBF_{HC}$: 0.640; $ALFF\text{–}CBF_{T1pre\text{-}dialysis}$: 0.301; $ALFF\text{–}CBF_{T2post\text{-}dialysis}$: 0.405; $T1_{pre\text{-}dialysis}$ vs. HC $p < .001$; $T2_{post\text{-}dialysis}$ vs. HC $p < .001$). In patients with ESRD, ALFF–CBF coupling was significantly higher at $T2_{post\text{-}dialysis}$ than at $T1_{pre\text{-}dialysis}$ ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$ $p = .018$, Figure 4a). ReHo–CBF coupling was not significantly different for patients at $T1_{pre\text{-}dialysis}$ or $T2_{post\text{-}dialysis}$ compared with HC or at $T2_{post\text{-}dialysis}$ compared with $T1_{pre\text{-}dialysis}$ ($ReHo\text{–}CBF_{HC}$: 0.380; $ReHo\text{–}CBF_{T1pre\text{-}dialysis}$: 0.374; $ReHo\text{–}CBF_{T2post\text{-}dialysis}$: 0.375; $T1_{pre\text{-}dialysis}$ vs. HC $p = .926$; $T2_{post\text{-}dialysis}$ vs. HC $p = .913$; $T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$ $p = .964$; Figure 4b).

3.4 | Correlation analysis

3.4.1 | Relationship between blood biochemistry parameters and cognitive variables

Changes in blood biochemistry parameters during a HD session were not found to be significantly correlated with changes in cognitive variables ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$) in patients with ESRD ($p > .05$).

3.4.2 | Relationship between NV coupling patterns and blood biochemistry parameters

Increased ALFF–CBF coupling ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$) was positively correlated with hemoglobin improvement ($r = .349$, $p = .026$) and negatively correlated with decreased total plasma homocysteine ($r = -.504$, $p = .002$) (Table 3).

3.4.3 | Relationship between NV coupling patterns and cognitive variables

Increased ALFF–CBF coupling ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$) was positively correlated with improvement in the immediate recall ($r = .328$, $p = .023$) and long-term recall ($r = .505$, $p = .001$) subitems of the AVLT-H (Table 4).

3.4.4 | Relationships between NV coupling patterns and dialysis treatment indicators

Increased ALFF–CBF coupling ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$) was negatively correlated with systolic blood pressure (SBP) variance ($r = -.635$, $p < .001$) and ultrafiltration volume ($r = -.391$, $p = .006$) (Table S6).

4 | DISCUSSION

Our findings contribute significantly to the understanding of cognitive impairment reversibility and its underlying neuropathologic mechanism

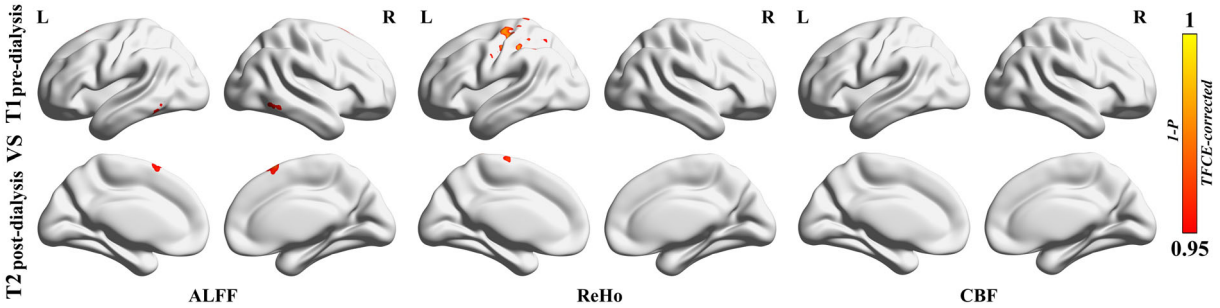

FIGURE 3 Spatial distribution of differences in the maps of the amplitude of low-frequency fluctuation (ALFF), regional homogeneity (ReHo), and cerebral blood flow (CBF) at 24 h after a dialysis session ($T2_{post\text{-}dialysis}$) compared with those before the dialysis session ($T1_{pre\text{-}dialysis}$). Multiple brain regions exhibited higher ALFF and ReHo values at $T2_{post\text{-}dialysis}$ than at $T1_{pre\text{-}dialysis}$ in patients with end-stage renal disease ($p < .05$, TFCE corrected). No significant differences in CBF values were observed between $T2_{post\text{-}dialysis}$ and $T1_{pre\text{-}dialysis}$ ($p < .05$, threshold-free cluster enhancement [TFCE] corrected). The color bar represents the p value

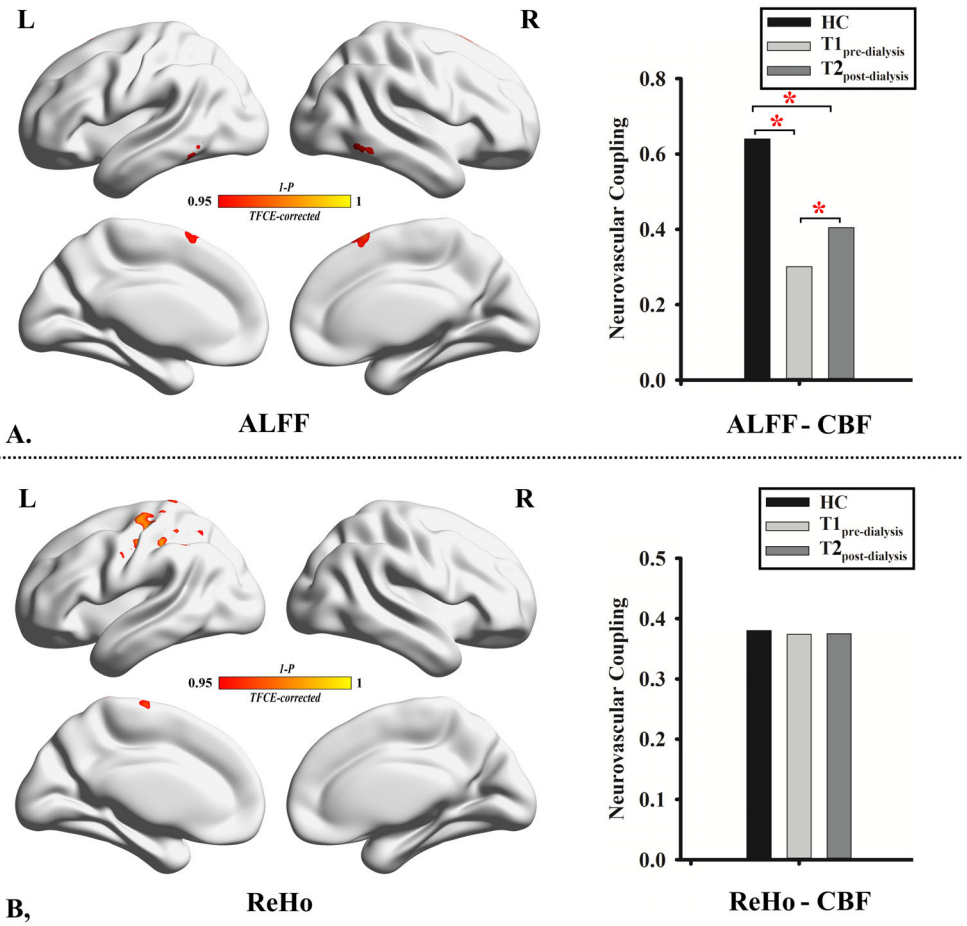

FIGURE 4 Between-group differences in neurovascular (NV) coupling patterns. (a) Amplitude of low-frequency fluctuation (ALFF)–cerebral blood flow (CBF) coupling was significantly lower in patients with end-stage renal disease (ESRD) before a dialysis session ($T1_{pre\text{-}dialysis}$) and at 24 h after that dialysis session ($T2_{post\text{-}dialysis}$) than in healthy controls (HC). In patients with ESRD, ALFF–CBF coupling was significantly higher at $T2_{post\text{-}dialysis}$ than at $T1_{pre\text{-}dialysis}$ ($p < .05$, after controlling for age, sex, education level, and whole gray matter volume). (b) Regional homogeneity (ReHo)–CBF coupling was not significantly different in patients at $T1_{pre\text{-}dialysis}$ or $T2_{post\text{-}dialysis}$ compared with HC or in patients at $T2_{post\text{-}dialysis}$ compared with $T1_{pre\text{-}dialysis}$. The color bar represents the *p* value

in patients with ESRD during a dialysis session. In this study, we confirmed the reversibility of cognitive impairment and NV decoupling after a single HD session, highlighting the potential value of NV coupling as an objective and physiologic biomarker of brain dysfunction in ESRD. Anemia, hyperhomocysteinemia, ultrafiltration volume, and SBP variance could potentially play a critical role in the reversibility of NV decoupling and cognitive impairment during HD sessions.

4.1 | Effect of HD treatment on NV decoupling and cognitive impairment

The tight regional and temporal relationships between neural activity and CBF response are known as NV coupling. Consequently, the patterns of NV coupling (BOLD-CBF coupling) may reflect the coordination of oxygen requirement and blood supply (Liang et al., 2013; Yu et al., 2019). Previous neuroimaging findings revealed that NV decoupling could potentially be a neural mechanism for cognitive impairment in patients with ESRD (Li et al., 2021). Our current findings indicate that in patients with ESRD, NV decoupling occurs mainly in the dorsal medial prefrontal cortex and middle temporal gyrus, which are core regions in the default mode network (DMN). The DMN is believed to be involved in the core processes of cognition, including memory, language processing integration, visual and auditory attention, and mind wandering (Greicius et al., 2003). In patients with ESRD, ALFF and ReHo were higher in DMN regions at $T2_{post\text{-}dialysis}$ than at $T1_{pre\text{-}dialysis}$; however, no significant differences in CBF were observed. This suggests that CBF had returned to the pre-dialysis hyperperfusion state 24 h after patients underwent HD, whereas the DMN regions demonstrated altered spontaneous neural activity, suggesting a mismatch between brain activity and the corresponding perfusion. Several neuroimaging studies (Jiang et al., 2016; Luo et al., 2016; Ni et al., 2014) have found abnormalities in BOLD signals and CBF in the DMN regions, which could explain the cognitive impairment in patients with ESRD. These observations are consistent with our results, suggesting that the DMN is a vulnerable area of neural activity and that patients with ESRD experience cerebral perfusion injury. In this study, patients with ESRD demonstrated better memory and executive function at $T2_{post\text{-}dialysis}$ than at $T1_{pre\text{-}dialysis}$. Moreover, we observed that after a single HD session, NV decoupling in the DMN was reversible and closely related to improvement in memory function. Our findings suggest that the reversibility of NV decoupling reflects the neural correlativity of the observed neurocognitive improvement, which in turn highlights the potential value of NV coupling as an objective and physiologic biomarker of brain dysfunction in ESRD.

We found a significant increase in ReHo mainly in the sensorimotor areas after a single HD session, indicating that in patients with ESRD, abnormal spontaneous neural activity occurred in sensorimotor areas, but the neural activity improved with HD treatment. Our recent neuroimaging study also identified abnormal changes in sensorimotor

TABLE 3 Stepwise regression analysis between increased ALFF-CBF coupling ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$) and blood biochemistry parameters

Variable	Correlation coefficient	*t* value	*p* value	Partial correlation	Collinearity statistics	
					Tolerance	VIF
tHcy[a]	−0.504	−3.383	.002*	−0.519	0.980	1.020
Hemoglobin[a]	0.349	2.348	.026*	0.388	0.980	1.020
Creatinine[b]	0.130	0.824	.417	0.149	0.879	1.138
Urea[b]	0.052	0.295	.770	0.054	0.716	1.398
Cystatin C[b]	0.133	0.897	.377	0.162	0.988	1.012
Potassium[b]	0.145	0.967	.341	0.174	0.975	1.025
Sodium[b]	−0.096	−0.644	.524	−0.117	0.991	1.009
Phosphorus[b]	−0.117	−0.769	.448	−0.139	0.951	1.052
Calcium[b]	0.104	0.672	.507	0.122	0.921	1.085
Chlorine[b]	0.026	0.164	.871	0.030	0.926	1.080
Magnesium[b]	0.039	0.227	.822	0.041	0.774	1.291
Parathormone[b]	−0.036	−0.230	.820	−0.042	0.897	1.115
RBC[b]	−0.273	−0.357	.723	−0.065	0.974	1.026
RWD[b]	0.175	1.189	.244	0.212	0.990	1.010
Hematocrit[b]	−0.207	−0.414	.682	−0.075	0.968	1.033
Vitamin D[b]	−0.060	−0.381	.706	−0.069	0.895	1.118
Interleukin-6[b]	0.126	0.851	.401	0.154	0.999	1.001

Note: *$p < .05$.
Abbreviations: ALFF, amplitude of low-frequency fluctuation; CBF, cerebral blood flow; ESRD, end-stage renal disease; RBC, red blood cell count; RWD, red blood cell distribution width; tHcy, total plasma homocysteine.
[a]Entered variables.
[b]Excluded variables.

functional connectivity in patients with ESRD (Ding et al., 2018); however, in the present study, we found no between-group differences in ReHo–CBF coupling, implying that NV coupling in the sensorimotor areas might not change in patients with ESRD.

4.2 | ESRD-related factors and NV coupling

Partial correction of anemia after HD treatment may play a critical role in NV decoupling and cognitive impairment reversibility in patients with ESRD. In the present study, we found a significant increase in CBF in patients with ESRD who had anemia, which may be related to a reduction in blood viscosity and brain tissue hypoxia (Kuwabara et al., 2002). HD treatment concentrates the blood of patients with ESRD, resulting in a relative increase in hemoglobin level, red blood cell count, and hematocrit level, and eventually increasing blood viscosity and enhancing oxygen transport capability (Idrovo et al., 2021; Kuwabara et al., 2002). Several studies have demonstrated that increased CBF (Jiang et al., 2016) and decreased spontaneous neural activity (H. Lu et al., 2019; Ma et al., 2015) are closely linked to anemia in patients with ESRD, which implies that anemia could be a key factor related to brain dysfunction in ESRD (Marzban et al., 2021). These hypotheses have confirmed that correcting anemia in patients with ESRD can improve cognitive impairment (Temple et al., 1995).

Patients with advanced chronic kidney disease, especially those with ESRD, have high total plasma homocysteine levels (Y. Li et al., 2020). Hyperhomocysteinemia is a risk factor associated with the endothelial vasoregulation of nitric oxide signaling pathways, which can lead to endothelial dysfunction, atherosclerosis, and parenchymal ischemia (Esse et al., 2019; Paganelli et al., 2021). Previous studies have demonstrated that the vascular endothelium and its nitric oxide signaling pathways play a critical role in NV coupling-related vasoregulation (Rosengarten et al., 2003). Increased NV coupling after a single HD treatment is closely related to the reduction in blood homocysteine levels, which may indirectly guide the clinical treatment strategy for hyperhomocysteinemia in patients with ESRD.

4.3 | HD treatment indicators and NV coupling

Our study results suggest that the SBP variance during HD treatment may be involved in the reversibility of NV coupling in patients with ESRD. Hypertension has a profound effect on the neurovascular unit at the cerebrovascular tree, which leads to vascular insufficiency, neuronal injury, cerebral perfusion dysfunction, and cognitive impairment (Iadecola & Gottesman, 2019; Santisteban & Iadecola, 2018). A previous study has suggested that the occurrence of cerebrovascular lesions is related not only to BP severity but also to BP variance (Mancia et al., 2007). BP variance has been confirmed to be an

TABLE 4 Stepwise regression analysis between increased ALFF-CBF coupling ($T2_{post\text{-}dialysis}$ vs. $T1_{pre\text{-}dialysis}$) and cognitive variables

Variable	Correlation coefficient	*t* value	*p* value	Partial correlation	Collinearity statistics	
					Tolerance	VIF
AVLT-H						
IR-S[a]	0.328	2.393	.023*	0.341	0.973	1.027
SR-S[b]	0.150	0.605	.549	0.108	0.305	3.277
LR-S[a]	0.505	3.686	.001*	0.412	0.973	1.027
REC-S[b]	−0.008	−0.059	.953	−0.011	0.941	1.063
MoCA						
Total score[b]	−0.003	−0.022	.982	−0.004	0.970	1.031
Visuospatial[b]	−0.241	−1.810	.080	−0.309	0.964	1.037
Name[b]	0.125	0.859	.399	0.152	0.870	1.150
Attention[b]	−0.050	−0.359	.722	−0.064	0.970	1.031
Language[b]	0.250	1.926	.063	0.327	1.000	1.000
Abstraction[b]	0.212	1.576	.125	0.272	0.965	1.036
Orientation[b]	−0.007	−0.050	.960	−0.009	0.952	1.050
Delayed memory[b]	0.015	0.106	.916	0.019	0.912	1.096
CTT part A[b]	0.142	0.811	.424	0.144	0.602	1.661
CTT part B[b]	−0.117	−0.773	.446	−0.137	0.800	1.251
DST[b]	−0.157	−1.143	.262	−0.201	0.954	1.048
DS-forward[b]	0.038	0.264	.793	0.047	0.927	1.078
DS-backward[b]	0.217	1.599	.120	0.276	0.943	1.061
BAI[b]	0.127	0.928	.361	0.164	0.984	1.016
BDI[b]	−0.066	−0.478	.636	−0.086	0.993	1.007

Note: *$p < .05$.

Abbreviations: ALFF, amplitude of low-frequency fluctuation; AVLT-H, auditory verbal learning test–Huashan version; BAI, Beck anxiety inventory; BDI, Beck depression inventory; CBF, cerebral blood flow; CTT, color trail test; DST, digital symbol test; DS, digital span; ESRD, end-stage renal disease; IR-S, immediate recall score; LR-S, long-term recall score; MoCA, Montreal cognitive assessment; REC-S, recognition score; SR-S, short-term recall score.

[a]Entered variables.

[b]Excluded variables.

independent predictor of subclinical brain damage in patients with hypertension and ESRD regardless of BP level (Mancia et al., 2007; Verdecchia et al., 2007). In our study, BP was recorded using a mercury sphygmomanometer once every hour during an HD session, and thus it did not reflect all BP changes during the entire HD process; however, the observed SBP variance could reflect BP fluctuations in patients with ESRD during HD treatment. Our results therefore suggest that in clinical practice, the effect of BP fluctuations on brain function during a dialysis session is important.

Ultrafiltration volume may also play a role in the reversibility of NV decoupling and cognitive impairment in patients with ESRD. In a preliminary small study (Stefanidis et al., 2005), mean CBF velocity measured in the main cranial arteries was observed to continuously and significantly decrease during HD treatment, in correlation with increased ultrafiltration volume. A subsequent larger study in patients with ESRD undergoing HD confirmed that the decreased mean CBF velocity during HD was associated with higher ultrafiltration volume (Findlay et al., 2019). Interestingly, a more recent study (Polinder-Bos et al., 2018) also indicated that higher ultrafiltration volume was significantly associated with lower CBF during HD treatment in patients with ESRD, potentially indicating a greater hemodynamic stress. Our results also imply that ultrafiltration volume may be involved in the functioning of NV coupling during a dialysis session, which suggests that clinical attention should be paid to the protective effect of fluid restrictions on the brain in patients with ESRD.

4.4 | Limited protective effect of HD treatment on NV decoupling

The maintenance of adequate NV coupling is thought to play a critical role in brain health. Our results suggest that a single HD treatment cannot restore NV coupling to normal levels. Our neuropsychological scales evaluated both reversible and irreversible components of cognitive impairment at 24 h after a single HD treatment in patients with ESRD. The findings suggest that the potentially protective effect of a single HD treatment on the brain is insufficient. Long-term HD treatment can lead to hemodynamic instability, fluctuations in uremic toxin titers, and large fluid shifts, thereby resulting in clinical neurologic injuries such as repetitive cerebral hypoperfusion and hyperperfusion,

cerebral edema, and cerebrovascular disease (Kurella Tamura & Yaffe, 2011; R. Lu et al., 2015; Tryc et al., 2011). The baseline results in our study could reflect the damaging effects of long-term HD treatment with respect to NV decoupling and cognitive impairment in patients with ESRD. Further studies should assess the effects of different HD treatment time points on the brain and cognitive function during long-term follow-up.

4.5 | Limitations and future directions

This study has several limitations. First, the HC did not undergo MR imaging and neuropsychological assessments that corresponded to those in patients with ESRD at $T2_{post\text{-}dialysis}$. Second, although the patients were randomly divided into two groups to control for the potential learning effect (Falleti et al., 2006), using a method similar to those described by Schneider et al. (2015) and Li et al. (2018), the effect of repeated testing could not be completely avoided. Third, previous neuroimaging studies reported a CBF/BOLD ratio to characterize NV coupling (Zhang et al., 2021; Zhu et al., 2017). Future Further studies should consider longitudinal changes in the CBF/BOLD ratio to define an NV coupling pattern in patients with ESRD undergoing HD treatment. Fourth, the BOLD signal after a single HD treatment revealed increased ReHo values mainly in sensorimotor areas, indicating the presence of abnormal sensorimotor function in patients with ESRD. Further studies should explore the relationship between sensorimotor function and HD treatment in those patients. Finally, the ESRD group included 37 patients with glomerulonephritis, 1 patient with immunoglobulin A nephropathy, and 1 patient with membranous nephropathy; therefore, differences in the histopathologic nephropathy types might differentially affect measures of CBF and NV coupling in patients with ESRD (Lau et al., 2017; Prohovnik et al., 2007). However, we did not consider the nephropathy types as covariates.

5 | CONCLUSIONS

Our findings provide valuable insight into the potential neuroprotective effects of HD treatment on cognitive function related to NV coupling in patients with ESRD. Partial correction of anemia and hyperhomocysteinemia, stable SBP, and fluid restriction may be closely involved in the reversal of NV decoupling and cognitive impairment in these patients. Further studies are needed to explore the innovations in HD and ESRD treatment strategies and ways to mitigate NV decoupling and cognitive impairment.

AUTHOR CONTRIBUTIONS

Junya Mu and Ming Zhang provided intellectual content of critical importance to the work described. Peng Li made substantial contributions to the design, concept, analysis, and drafting of the article. Shaohui Ma, Dun Ding, Huawen Zhang, Xinyi Zhu, Xueying Ma, and Jixin Liu revised the article and interpreted the data. All authors approved the version submitted for publication.

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DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the corresponding author, upon reasonable request.

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SUPPORTING INFORMATION

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