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Research article

# Transcutaneous auricular vagus nerve stimulation improves cognitive decline by alleviating intradialytic cerebral hypoxia in hemodialysis patients: A fNIRS pilot study

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ABSTRACT

Cognitive impairment is common in hemodialysis patients, possibly due to inadequate cerebral blood flow during hemodialysis. No effective non-pharmacological interventions are available. This study investigates the impact of hemodialysis-induced cerebral hypoxia on cognitive decline in hemodialysis patients and the potential of transcutaneous auricular vagus nerve stimulation (taVNS) as a non-pharmacological intervention. A randomized controlled trial with 36 participants showed that cognitive performance and cerebral oxygenation in the dorsolateral prefrontal cortex (DLPFC) significantly declined in the sham group. In contrast, taVNS improved cognitive function by increasing cerebral oxygenation, with significant correlations to reaction times and MoCA scores. The study suggests that Hemodialysis-induced cerebral hypoxia may contribute to persistent cognitive decline in MHD patients. However, taVNS could be an effective intervention to prevent cognitive impairment in hemodialysis patients by alleviating cerebral hypoxia.

## 1. Introduction

Chronic kidney disease (CKD) is a global health concern, with an estimated 9.1 % prevalence affecting approximately 690 million individuals worldwide. In China, the number of CKD patients is estimated to be around 130 million, ranking first in the world [1]. Maintenance hemodialysis (MHD) is a primary modality of renal alternative therapy, offering a vital treatment option for individuals with CKD [2]. With the growing interest in the "kidney-brain axis", Kelly [3] has well-summarized the brain injury related to the hemodialysis (HD). Due to additional hemodynamic and osmotic stress produced by HD, it promotes ischemic and neurovascular injury in the brain [4–7]. The most common form of brain injury associated with HD is leukoaraiosis [8], a rarefaction of brain white matter (WM) that correlates with cognitive impairment in HD patients. Furthermore, the brain injuries occurring in hemodialysis-dependent patients have been extensively characterized, encompassing a spectrum of structural brain changes such as silent cerebral infarctions, white matter hyperintensities, and cerebral atrophy [3,9]. These alterations are demonstrated to be

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heightened risk for cerebrovascular events, vascular cognitive impairment, and executive function deficits [2,10–12]. Concurrently, impairments across various cognitive domains, including attention, memory, and executive functions, are highly prevalent in MHD patients and are often accompanied by progressive decline [3,13]. It has been reported that the incidence of cognitive impairment among hemodialysis patients ranges from 50 % to 70 % [12,14–16], making it an independent risk factor for mortality [12,17]. Anazodo et al. [18] has confirmed the association between hemodialysis-related acute brain injury and cognitive dysfunction through intradialytic magnetic resonance imaging and spectroscopy. However, the physiological mechanisms underlying hemodialysis-related cognitive impairment remain elusive. It is hypothesized to be linked to reduced cerebral blood flow (CBF) [6,11,19,20] and diminished cerebral oxygenation capacity [21–23] during hemodialysis sessions. However, there are no effective non-pharmacological interventions available in clinical practice.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive technique for detecting cerebral oxygenation levels, including oxyhemoglobin (HbO2) and deoxyhemoglobin (HbR). Compare to electroencephalography (EEG) and cerebral oximetry devices, fNIRS offers superior spatial resolution, allowing for the monitoring of regional cerebral oxygenation and hemodynamics at the level of the cortical microcirculation [24]. Previous studies have indicated that the cerebral regional oxygen saturation (rSO2) reflects vascular compliance and cerebral autoregulation in cerebral micro-vessels, especially in arterioles [25]. Kim et al. [26] found a correlation between the slope of cerebral oxyhemoglobin oscillations during major arterials stenosis or occlusion and vascular reserve capacity. Moreover, Ito and Ookawara et al. [27,28] validated the feasibility of synchronously detecting CBF using fNIRS during hemodialysis in patients with MHD and revealed an association between cerebral oxygenation capacity and cognitive function in MHD patients during hemodialysis. Therefore, fNIRS emerges as a powerful tool for real-time monitoring of cerebral hemodynamics in hemodialysis circumstance, providing critical insights for identification and intervention of hemodialysis-related cerebral hypoxia in clinical practice.

Vagus nerves stimulation (VNS) [29,30] has emerged as a brain stimulation technique that modulates the autonomic nervous system and targeting brain excitability through electrical stimulation of the vagus nerve network. Evidence from imaging studies indicates that VNS can influence CBF changes in a wide range of brain regions, including the brainstem, thalami, hypothalamus, cingulate gyrus, and prefrontal cortex, which may contribute to the amelioration of clinical symptoms [31–33]. Transcutaneous auricular vagus nerve stimulation (taVNS) offers a non-invasive alternative to VNS, it modulates the excitability of the vagus nerve by delivering transcutaneous low-frequency electrical currents to the auricular branch of the vagus nerve (ABVN), which is distributed along the tragus and the cymba concha [34,35]. Badran et al. [36] found that taVNS activated neural circuits in the brainstem nuclei, subcortical structures, and widespread cortical areas, which include those associated with the executive function and working memory [31,37]. The fMRI studies by Kraus et al. [38] and Dietrich et al. [37] reported activation of the blood-oxygen-level-dependent (BOLD) signal in the bilateral sensorimotor and prefrontal cortices during taVNS. Frangos et al. [32] observed sustained activation of the bilateral PFC for nearly 10 min after taVNS cessation. Actually, the benefits of taVNS on CBF and cognitive function have been demonstrated in patients with ischemic stroke [39,40], Parkinson's disease [41], depression [42], and mild cognitive impairment [43]. However, clinical research into the efficacy of taVNS in patients undergoing maintenance hemodialysis (MHD) remains scarce. This study hypothesizes that the reduction in cerebral oxygenation capacity during hemodialysis may be an important factor in associated hemodialysis-related brain injury and cognitive impairment; and taVNS could impede progression of cognitive decline by enhancing CBF during hemodialysis in MHD patients. Therefore, the objectives of this study are: 1) to investigate the relationship between cerebral blood flow alterations and cognitive functions in MHD patients across various hemodialysis sessions using intradialytic functional near-infrared spectroscopy (fNIRS); 2) to conduct a randomized clinical trial to investigate the effects of taVNS on cerebral blood flow and cognitive function in MHD patients.

## 2. Materials and methods

### 2.1. Subjects

From April 2024, to June 2024, a total of 42 patients were recruited from the hemodialysis center of Sir Run Run Hospital, Nanjing Medical University. Six patients were excluded due to not meeting the inclusion criteria or unwillingness to participate in the study. The minimum sample size for the pilot study was calculated based on the formula provided by Viechtbauer et al. [44], which is $n = \frac{\ln(1-\gamma)}{\ln(1-\pi)}$. Specifically, we assumed a 20 % probability ($\pi$) of encountering issues per group (including inclusion/exclusion criteria, assessments, and interventions) in the maintenance hemodialysis (MHD) population during the study. Consequently, a pilot study with 14 participants per group can identify this issue at a 95 % confidence level. Taking into account a dropout rate of 15 %, a sample size of at least 16 participants per group was deemed necessary for this study. Eligible patients were randomly assigned to the taVNS group (n = 18) or the sham group (n = 18) in a 1:1 ratio, using a customized Matlab script to generate pseudorandom sequence with the control of the gender, age, and disease duration. All patients signed an informed consent form. The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Sir Run Run Hospital, Nanjing Medical University at April 2023(2022-SR-40).

Inclusion criteria were as follows: (1) Age ≥18 years; (2) Patients receiving maintenance hemodialysis for ≥3 months with relatively stable condition; (3) Absence of significant cognitive impairment or severe neurological disorders that may affect study results; (4) Ability to cooperate with the study, and provide informed consent.

Exclusion criteria were as follows (1) Presence of significant psychiatric or emotional abnormalities, or a history of mental illness; (2) Severe dementia or language impairments preventing completion of scale assessments; (3) Presence of any neurological or other system diseases affecting cognitive function; (4) History of angina, myocardial infraction, or cardiac surgery within the past year; (5)

Previous surgery involving the vagus nerve stimulation; (6) Use of cardiac pacemakers or other implanted electronic devices; (7) Resting heart rate ≤60 beats per minute; (8) Patients with asthma or tumors.

Termination criteria: (1) Patients unable to tolerate testing procedure or taVNS; (2) Patients unable to complete cognitive functions assessments before and after hemodialysis; (3) Presence of instances unsuitable for the study, including: worsening of the condition, severe adverse events, poor compliance, etc.

### 2.2. Study design

This pilot study was designed as a randomized, single-blind, sham-controlled clinical trial, following the CONSORT 2010 checklist. The trial has been registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn/index.html, ChiCTR2400082917). The patients were randomly 1:1 assigned to two groups by a random number table: the taVNS group (VG) and the sham group (SG). After group allocation, baseline data were collected, including demographics, biochemical assessments and the Montreal Cognitive Assessment (MoCA). Subsequently, patients underwent resting-state fNIRS (rs-fNIRS), a cognitive function test (1-Back task), and sored their fatigue on a fatigue visual analogue scale (VAS-F) through their first hemodialysis session (HD1) following the study commences. After five successive hemodialysis sessions (including the HD1), patients repeated the assessment procedures during the sixth hemodialysis (HD6). At the end of the study, MoCA was reassessed to evaluate the outcome measures. The patients in the VG receives active taVNS throughout the six hemodialysis sessions, while the SG receives sham taVNS. Details of the study design are depicted in Fig. 1A.

During the first and sixth hemodialysis sessions, patients followed a structured examination procedure. Initially, they underwent rs-fNIRS examination, followed by the 1-Back test and VAS-F assessment, conducted half an hour before the hemodialysis session. Ten minutes after the commencement of hemodialysis, participants received 20 min of active/sham taVNS. Subsequently, rs-fNIRS examinations were then scheduled 1 h and 3 h after the initiation of hemodialysis. Concluding the session, 30 min post-hemodialysis, both groups underwent a repeat round of rs-fNIRS, the 1-Back test, and VAS-F assessment. A detailed study procedures during hemodialysis are illustrated in Fig. 1B.

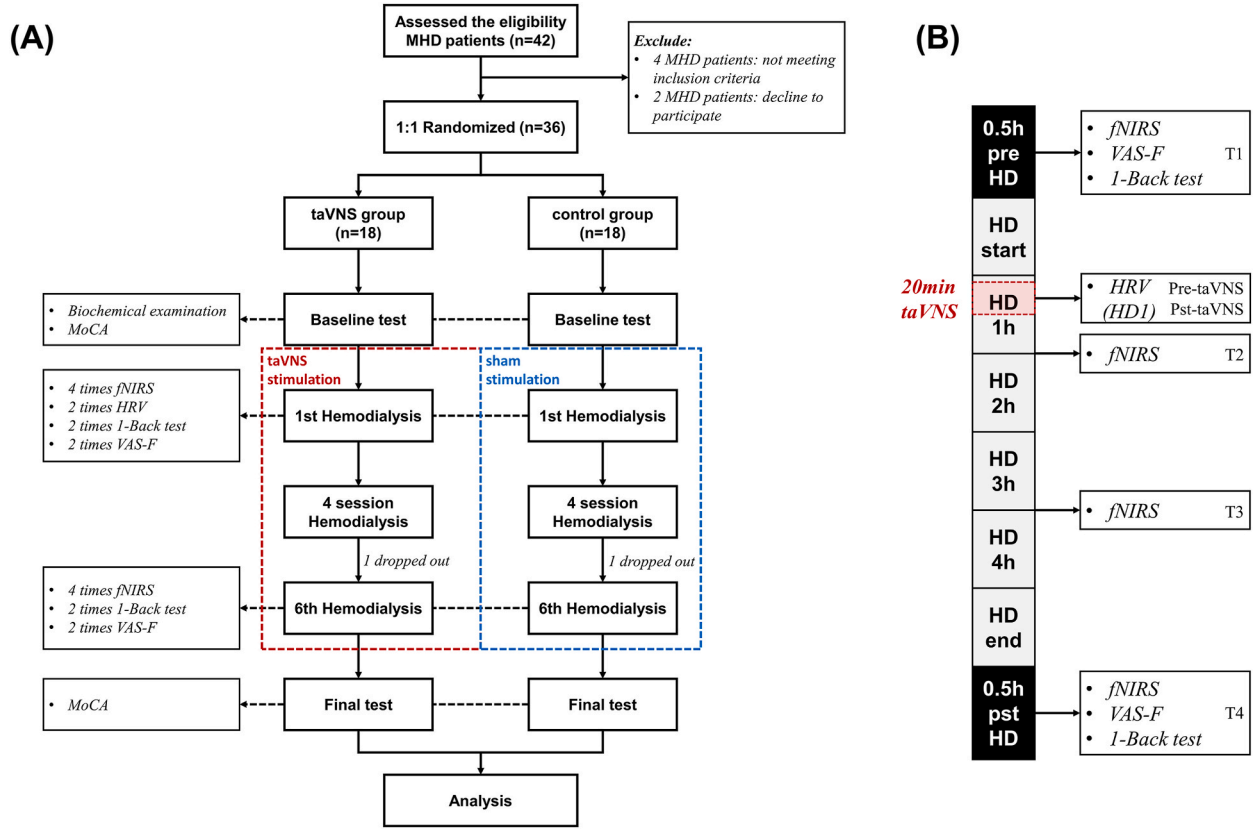


**Fig. 1.** Study flow diagram.
(A) Study design. (B) Examination procedure in HD session. HD: hemodialysis; taVNS: transcutaneous auricular vagus nerve stimulation; fNIRS: functional near-infrared spectroscopy; HRV: heart rate variability; MoCA: Montreal cognitive assessment; VAS-F: visual analogue scale of fatigue.

### 2.3. Transcutaneous auricular vagus nerve stimulation and heart rate variability examination

The taVNS protocol was adapted from previous studies by Li et al. and Wang et al. [45,46], utilizing a transcutaneous vagus nerve stimulator (tVNS501, RISHENA Co., Ltd., Changzhou, China). Before the stimulation, the patient's left auricle cymba conchae and tragus were cleaned with alcohol pads. Patients then wore a specially designed earphone with two dot electrodes, which were positioned over the left ear to deliver a low-frequency electrical current. In accordance with established international consensus [47], the stimulation parameters were reported as follows: a 25 Hz square wave with a pulse width of 200 μs, a stimulation duration of 30s, duty cycle of 1:1, and the current intensity was individually adjusted to the patient's maximum tolerable level without exceeding 10 mA. The taVNS was administered 10 min after the commencement of each hemodialysis session, for a total of 6 sessions. To ensure the single-blindness, patients in the SG wore an earphone of identical shape but without electrodes. Although the stimulation device displayed current readings, no actual current was generated in the sham condition. In addition, participants in the SG were informed that due to individual skin differences and varying sensitivities to stimulation, it is entirely normal not to feel the subtle electrical current applied. During stimulation, all patients' left ear were covered with a black mask.

Additionally, a heart rate variability (HRV) monitor (SA-3000P, Medocore, Korea) was utilized to collect 5-min HRV data from both groups as a biological marker of vagal tone (see Fig. 1B). Average heart rate (HR) and the ratio of low-frequency to high-frequency power (LF/HF) were selected as metrics for HRV in both the time and frequency domains. It is well-established that an increase in parasympathetic nervous system activity correlates with a decrease in HR and a reduction in LF/HF ratio [48].

### 2.4. Neurocognitive assessments

Cognitive function and subjective fatigue levels during hemodialysis sessions were assessed using the MoCA, 1-Back test, and VAS-F. The MoCA is a widely used cognitive screening tool in dialysis units [49], which evaluates patient's overall cognitive performance, encompassing short-term memory, visuospatial skills, executive functions, attention and working memory, language, and orientation, with a maximum score of 30 points, demonstrating superior sensitivity in detecting cognitive impairments [50]. The 1-Back test is a cognitive paradigm that assesses attention and working memory processes under low cognitive load [51]. In this study, the 1-Back test was programmed using E-prime 3.0 software and presented on a portable tablet (292 × 201 mm). The task commenced after the participants confirmed their understanding of the instructions displayed on the screen. Initially, a "+" sign appeared in the center of the screen for 10 s, followed by the presentation of the first two-digit number for 1000 ms. After the number disappeared, the next number appeared 1500 ms later. Patients were instructed to observe the double-digits numbers presented in each trial and to press the left mouse button if the current digit matched the preceding one, or the right mouse button if it mismatched. The test consisted of 50 trials, with 15 matching trials (30 %) and 35 non-matching trials (70 %). The average reaction time (RT) was recorded because of its sensitivity in MHD population [52]. The VAS-F was designed based on the description by Sarah et al. [53], which involves a 10 cm line marked at the ends with "not fatigued at all" and "extremely fatigued", allowing participants to rate their current level of fatigue on a continuous scale.

### 2.5. Functional near-infrared spectroscopy measurements

This study applied a continuous-wave near-infrared imaging device (NIRSmart II-3000A, Huichuang Medical Co., Ltd., China) to capture resting-state cerebral blood flow dynamics. The device consists of seven light source emitters with wavelengths of 730 and 850 nm and an average power of $<1$ mW, as well as seven avalanche diode detectors with a sampling rate of 11 Hz, comprising a total of 19 channels distributed over the subject's forehead. The channels were divided into three regions of interest (ROIs) based on Brodmann areas: bilateral dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and orbitofrontal cortex (OFC). The arrangement of channels and ROIs is illustrated in Supplementary material (Fig. S1). Rs-fNIRS measurements were conducted at specific intervals relative to the first and sixth hemodialysis sessions: half an hour before the hemodialysis sessions (pre-HD1, pre-HD6), 1 h into the sessions (1h-HD1, 1h-HD6), 3 h into the sessions (3h-HD1, 3h-HD6), and half an hour after the completion of the sessions (post-HD1, post-HD6). According to the Campos et al.'s review [54] that a drop in PaO2 and SaO2 occurs at the beginning of HD, reaching a nadir after 30–60 min, we chose 1 h after the start of hemodialysis as a potential point of minimum crSO2 for measurement. Meanwhile, studies suggest that the circulatory stress is greatest for patients at 3h-HD [55]. Therefore, we selected the 3h-HD to assess the sustained effects of hemodialysis on cerebral oxygenation and to observe whether any initial changes in cerebral blood flow and oxygenation stabilize or continue to evolve. During all the measurements, patients were asked to remain still with their eyes closed in a supine position, and to keep their head in a neutral position. Each rs-fNIRS measurement lasted for 10 min.

The processing of fNIRS signals was conducted using MATLAB R2013b (MathWorks, USA). The procedures are as follows: (1) Signal-to-noise ratio (SNR) calculation: The SNR was calculated to assess the quality of each channel. A 10-s time window was used for SNR computation, with the equation $SNR = 20\log10(\mu/\sigma)$ dB, where μ represents the average intensity of the signal and σ represents the signal variance. Channels with SNR $>20$ dB were selected for further analysis. (2) Motion artifacts correction: motion artifacts were collected using a 0.5-s sliding window to traverse the signal. Any difference greater than 6 times the overall standard deviation between the maximum and minimum optical densities within the sliding window was identified as a motion artifact and corrected using spline interpolation. (3) Low-pass filtering: A third-order Butterworth filter was applied for low-pass filtering of the signal to remove device noise and heartbeat interference, with a cutoff frequency set at 0.5 Hz. (4) Concentration changes calculation: relative changes in oxyhemoglobin (HbO2), deoxyhemoglobin (HbR), and total hemoglobin (HbT) for each channel were calculated using the modified Beer-Lambert law (mBLL), with an inter-probe distance of 3 cm and a differential path factor (DPF) of 6. (5) Cerebral rSO2 calculation:

cerebral rSO2 was calculated based on the ROI using the formula: cerebral rSO2 = (Δ[HbO2]/Δ[HbT]) × 100 %. Cerebral SrSO2 is an absolute measure reflecting the oxygenation capacity of the arterial, capillary, and venous vessels in the cerebral cortex [56]. BrainNet Viewer [57] was used to visualize the cerebral rSO2 levels at different time points.

### 2.6. Statistical analysis

Statistical analyses were performed using SPSS software (version 22, IBM Corp., Armonk, NY, USA). The normality of demographic data was assessed with the Shapiro-Wilk test. Continuous variables were presented as Mean (SD). Based on the normality of the data, paired t-tests or Wilcoxon signed-rank tests were used for within-group comparisons; and independent sample t-tests or Mann-Whitney U tests were used for between-group comparisons. Categorical variables were represented as counts, and were compared using Pearson's chi-square test. Generalized estimating equations (GEEs) with linear regression models were used to analyze repeated measures data, assuming a first-order autoregressive working correlation matrix (AR1). For cognitive assessment data, group (VG, SG) and time (pre-HD1, pst-HD1, pre-HD6, pst-HD6) were considered as predictors to evaluate the main effects of group and time, as well as the interaction effect between them. For cerebral rSO2 in each ROI, group (VG, SG), time (pre-HD, 1h-HD, 3h-HD, pst-HD), and hemodialysis sessions (HD1, HD6) were considered as predictors to evaluate their main effects and interactions. Estimated marginal means (EMM) were calculated for within-group and between-group pairwise comparisons with Bonferroni correction. Additionally, Pearson or Spearman correlation analyses were conducted to examine the relationship between changes in cognitive function and cerebral rSO2 before and after the study. Mediation analysis was constructed with the group as the independent variable, cerebral rSO2 and VAS-F as mediators, and MoCA as the outcome variable, using a regression model. Bias-corrected percentile Bootstrap method with 5000 resamples was used to estimate the 95 % confidence intervals for examining the effects of taVNS on cognitive performance. Statistical significance was set at $P < 0.05$.

## 3. Results

### 3.1. Demographics and characteristics

A total of 36 patients with MHD were included in the study, with 18 patients in each of the VG and SG. The average ages of patients in the VG and SG were 53.22 ± 13.17 and 50.22 ± 13.61 years, respectively. Two patients, one from each group, dropped out before

**Table 1**
Baseline demographics and clinical characteristics.

| | Control group (n = 18) | VNS group (n = 18) | t/Z/χ [2] | *P* |
|---|---|---|---|---|
| *Clinical demographics* | | | | |
| **Gender (n, m/f)** | 10/8 | 9/9 | | >0.99 |
| **Age (years)** | 50.22 (13.61) | 53.22 (13.17) | −0.672 | 0.506 |
| **Body weight (kg)** | 62.11 (10.53) | 61.77 (9.66) | 0.1023 | 0.919 |
| **BMI (kg/m$^2$)** | 22.76 (3.01) | 22.62 (2.20) | 0.1651 | 0.87 |
| **HD Duration (years)** | 4.05 (2.90) | 4.31 (2.77) | −0.2704 | 0.788 |
| **IDWG (kg)** | 2.59 (0.62) | 2.62 (0.77) | −0.1191 | 0.906 |
| *Neurobehavioral performance* | | | | |
| **MoCA** | 26.33 (3.07) | 26.17 (4.84) | 0.1234 | 0.903 |
| **VAS-F (score)** | 4.50 (1.15) | 4.28 (1.53) | 0.4932 | 0.625 |
| *Biochemical criteria* | | | | |
| **Hb** | 120.72 (12.15) | 113.50 (14.96) | 1.5898 | 0.121 |
| **$K^+$** | 5.02 (0.90) | 5.12 (0.75) | −0.3549 | 0.725 |
| **$Ca^{2+}$** | 4.54 (5.76) | 12.04 (22.99) | −1.3431 | 0.188 |
| **$P^{3+}$** | 2.02 (0.79) | 1.98 (0.73) | 0.165 | 0.87 |
| **$HCO_3^-$** | 17.85 (2.39) | 17.02 (4.74) | 0.663 | 0.512 |
| **BUN** | 24.95 (5.13) | 26.17 (6.22) | −0.6418 | 0.525 |
| **UA** | 401.03 (143.39) | 385.66 (133.05) | 0.3334 | 0.741 |
| **Cr** | 967.11 (209.08) | 900.48 (245.94) | 0.8758 | 0.387 |
| **β-MG** | 56.75 (64.36) | 142.46 (253.07) | −1.3924 | 0.173 |
| **ALT** | 14.19 (8.47) | 13.39 (9.72) | 0.2634 | 0.794 |
| **AST** | 14.72 (5.80) | 18.18 (18.81) | −0.7462 | 0.461 |
| **ALB** | 42.05 (3.43) | 41.39 (3.42) | 0.5786 | 0.567 |
| **TC** | 3.68 (1.23) | 3.88 (0.87) | −0.5639 | 0.577 |
| **TG** | 2.69 (4.18) | 2.03 (0.97) | 0.6529 | 0.518 |
| **SF** | 97.14 (94.67) | 94.21 (92.61) | 0.0938 | 0.926 |
| **TIBC** | 46.81 (7.98) | 49.45 (8.07) | −0.9885 | 0.33 |
| **URR** | 0.68 (0.09) | 0.67 (0.08) | 0.2073 | 0.837 |

Hb: Hemoglobin; $K^+$: Kalium; $Ca^{2+}$: Calcium; $P^{3+}$: Phosphorus; $HCO_3^-$: Bicarbonate; BUN: Blood urea nitrogen; UA: Uric acid; Cr: Creatinine; β-MG: Beta-Microglobulin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; TC: Total cholesterol; TG: Triglyceride; SF: Serum ferritin; TIBC: Total iron binding capacity; URR: Urea reduction ratio; BMI: Body mass index; HD: Hemodialysis; IDWG: Interdialytic weight gain; MoCA: Montreal Cognitive Assessment; VAS-F: Visual analogue scale of fatigue. The biochemical criteria were collected before the first investigated hemodialysis, and the URR was calculated using the first investigated hemodialysis.

the sixth hemodialysis session. Table 1 summarized the clinical characteristics of the patients, including age, body weight, body mass index (BMI), duration of hemodialysis, and interdialytic weight gain (IDWG), as well as baseline neurobehavioral performance and biochemical indicators. No significant intergroup differences were observed in any of these indicators. Additionally, the LF/HF in the VG showed a significant decrease compared to pre-stimulation ($P = 0.018$), and the change in LF/HF was statistically different when compared to the changes observed in the SG ($P = 0.015$). In contrast, there was no significant statistical difference in HR between groups (Table S1).

### 3.2. Results of neurocognitive assessments

Among the 36 MHD patients included in the study, 8 individuals, representing 22.22 % of the total patients, had MoCA scores <26 at baseline, indicating cognitive impairment, with 4 patients in VG and 4 in the SG. Upon completion of the intervention, the number of patients with cognitive impairment increased to 13, with all new cases occurring in the SG. Furthermore, the GEE model results showed a significant group × time interaction ($\chi^2 = 23.950$, $P < 0.001$) and a main effect of time ($\chi^2 = 4.227$, $P = 0.04$) for MoCA scores. Pairwise comparisons found a significant decrease in MoCA scores in the SG at the end of the study (Pst-HD6), with a statistically significant difference compared to the VG (Table S2, Fig. 2C). Similarly, a significant group × time interaction effect ($\chi^2 = 51.262$, $P < 0.001$), a group main effect ($\chi^2 = 38.987$, $P < 0.001$), and a time main effect ($\chi^2 = 8.405$, $P = 0.038$) were also observed for RT in 1-Back task. Within-group comparisons showed that RT in the SG was significantly prolonged at Pst-HD1, Pre-HD6, and Pst-HD6 compared to baseline, whereas the VG indicated a significant reduction in RT at Pre-HD6 and Pst-HD6. Between-group comparisons showed that RT in the VG was significantly shorter than that in the SG at Pst-HD1, Pre-HD6, and Pst-HD6 (Table S2, Fig. 2A). VAS-F scores exhibited a significant group × time interaction effect ($\chi^2 = 10.451$, $P = 0.015$), a group main effect ($\chi^2 = 8.503$, $P = 0.004$), and a time main effect ($\chi^2 = 42.449$, $P < 0.001$). Within-group pairwise comparisons indicated a significant increase in VAS-F scores in the SG at Pst-HD1 and Pst-HD6 compared to baseline, while no significant changes were observed in the VG. Between-group pairwise comparisons revealed that the VAS-F scores in the VG were significantly lower than those in the SG at Pst-HD1 and Pst-HD6 (Table S2, Fig. 2B).

### 3.3. Results of cerebral regional oxygen saturation

The GEE model revealed a significant group × time interaction effect for cerebral rSO2 in the DLPFC ($\chi^2 = 40.681$, $P < 0.001$). Additionally, cerebral rSO2 in the DLPFC exhibited a significant main effect of time ($\chi^2 = 11.898$, $P = 0.008$) and session ($\chi^2 = 7.068$, $P = 0.008$). Within-group pairwise comparisons found a significant decrease in cerebral rSO2 in the DLPFC of the SG at 1h-HD1 and pst-HD1 compared to pre-HD1. In contrast, no significant differences were observed in the VG(Fig. 3A). Between-group pairwise comparisons demonstrated that cerebral rSO2 in the VG was significantly higher than in the SG at 1h-HD1, 1h-HD6, and Pst-HD6 (Table S3, Fig. 3A and B). For the VLPFC, a significant group × time interaction effect was observed ($\chi^2 = 11.61$, $P = 0.009$). Between-group

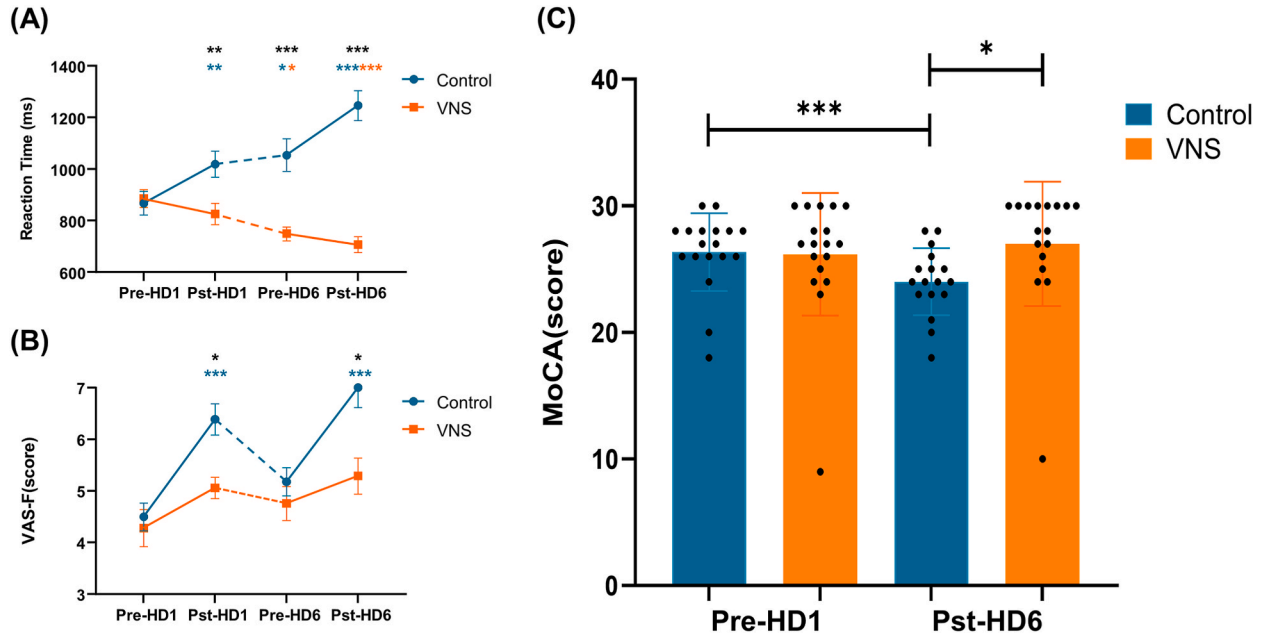


**Fig. 2.** Results of neurocognitive assessments.
(A) Changes of RT in two groups. (B) Changes of VAS-F in two groups. (C) Changes of MoCA in two groups. RT: reaction time; VAS-F: Visual analogue scale of fatigue; MoCA: Montreal Cognitive Assessment.

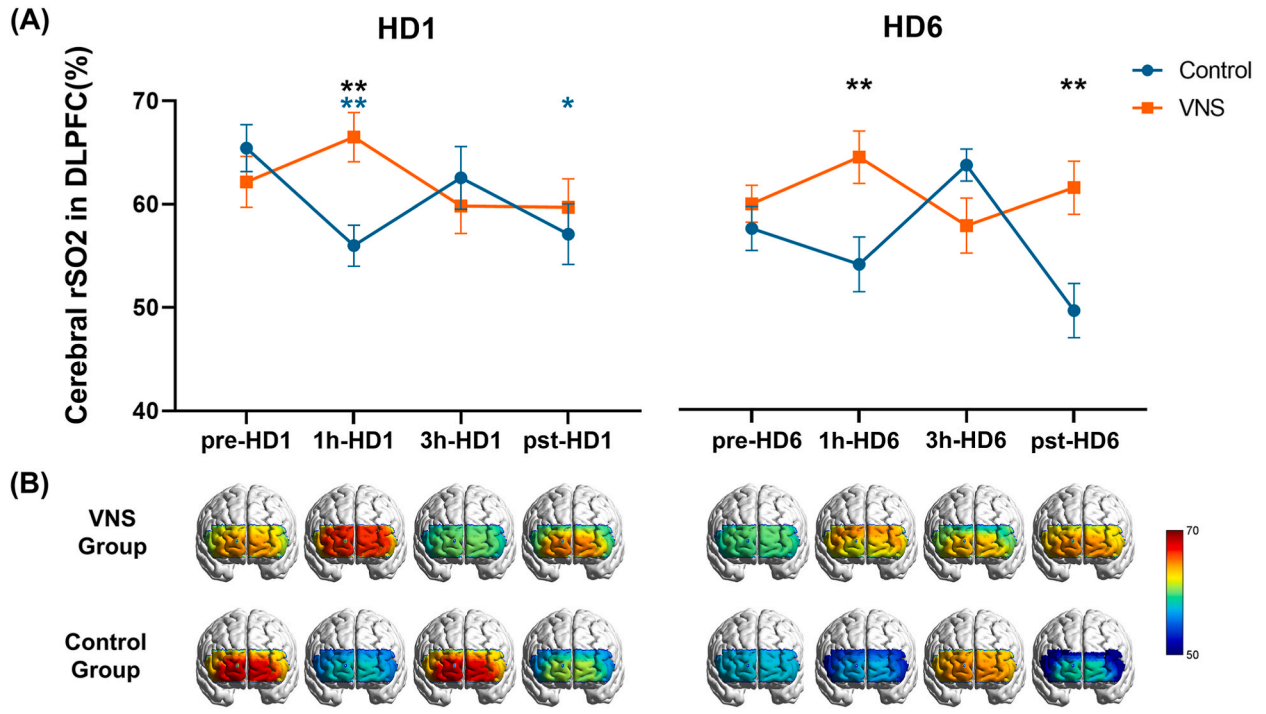


**Fig. 3.** Results of fNIRS examination.
(A) Cerebral rSO2 fluctuation of DLPFC in two groups. (B) Visualization of cerebral rSO2 at different time points. HD1: first hemodialysis; HD6: sixth hemodialysis; rSO2: regional saturation; DLPFC: dorsolateral prefrontal cortex.

pairwise comparisons revealed that cerebral rSO2 in the VLPFC of the SG was significantly lower than in the VG at 1h-HD6, with no significant differences observed for other time or session effects (Table S3, Fig. 3A and B). No significant effects were found for cerebral rSO2 in the OFC.

### *3.4. Correlation between cognitive decline and oxygenation impairment*

Correlation analysis showed significant negative correlations between changes in cerebral rSO2 in DLPFC and the changes in RT in 1-Back task for both in both the SG and the VG ($r = -0.679$, $P < 0.01$; $r = -0.764$, $P < 0.001$, respectively). Moreover, changes in cerebral rSO2 in the DLPFC were significantly positively correlated with changes in MoCA scores for both groups ($r = 0.681$, $P < 0.001$; $r = 0.570$, $P < 0.05$, respectively), suggesting a positive relationship between cerebral rSO2 levels and cognitive performance as measured by MoCA scores. Additionally, in the VG, changes in VAS-F scores were negatively correlated with RT ($r = -0.511$, $P < 0.05$, Fig. S3).

The regression model indicated that taVNS had a significant positive impact on the MoCA scores (estimate = 3.235, 95 % CI [2, 4.646], $P < 0.001$). Mediation analysis disclosed a positive indirect effect of taVNS on MoCA scores through the mediator of cerebral rSO2 (estimate = 1.494, 95 % CI [0.49, 3.30], $P = 0.004$). The component effects analysis indicated that taVNS could predict an improvement in cerebral rSO2 (estimate = 0.146, 95 % CI [0.07, 0.22], $P < 0.001$). Additionally, cerebral rSO2 was found to significantly influences MoCA (estimate = 10.221, 95 % CI [5.8316, 16.548], $P < 0.001$). However, the indirect effect of taVNS on

**Table 2**
Mediation Analysis of the taVNS on cognitive function.

| Type | Effect | Estimate (95 % CI) | SE | β | P |
|---|---|---|---|---|---|
| Indirect | Treatment → crSO2 → MoCA | 1.494 (0.508, 3.389) | 0.521 | 0.297 | 0.004 |
| | Treatment → VAS-F → MoCA | −0.146 (−0.816, 0.146) | 0.212 | −0.029 | 0.49 |
| Component | Treatment → crSO2 | 0.146 (0.068, 0.222) | 0.039 | 0.544 | <0.001 |
| | crSO2 → MoCA | 10.211 (5.832, 16.548) | 2.320 | 0.546 | <0.001 |
| | Treatment → VAS-F | −1.412 (−2.716, −0.174) | 0.630 | −0.359 | 0.025 |
| | VAS-F → MoCA | 0.104 (−0.122, 0.451) | 0.143 | 0.081 | 0.468 |
| Direct | Treatment → MoCA | 1.888 (0.499, 3.118) | 0.664 | 0.375 | 0.004 |
| Total | Treatment → MoCA | 3.235 (2.000, 4.646) | 0.672 | 0.643 | <0.001 |

SE: Standard error; β: Standardized estimate value; crSO2: cerebral regional oxygen saturation; VAS-F: Visual analogue scale of fatigue; MoCA: Montreal Cognitive Assessment.

MoCA through the VAS-F as a mediator was not statistically significant (estimate = −0.146, 95 % CI [−0.8155, 0.146], P = 0.49). Furthermore, taVNS showed a significant direct effect on MoCA (estimate = 1.888, 95 % CI [0.4991, 3.118], P = 0.004), suggesting that cerebral rSO2 plays a partial mediating role in the relationship between taVNS and MoCA (Table 2).

## 4. Discussion

Hemodialysis-related brain injury is characterized by acute brain damage resulting from hemodynamic changes and osmotic disturbances that occur during hemodialysis sessions [5,58,59]. These physiological alterations could lead to insufficient cerebral blood perfusion, which is most commonly manifested as progressive cognitive impairment. Traditional brain imaging devices are limited to monitor changes in CBF in real-time during hemodialysis whereas fNIRS can meet this demand. As a real-time, non-invasive brain imaging tool, fNIRS is used to monitor cerebral oxygenation capacity and has been effectively applied to MHD patients within dialysis units, as validated by numerous studies [27,60–62]. In this study, fNIRS was utilized to collect cerebral rSO2 fluctuations in the prefrontal cortex of patients at multiple time points to reflect the CBF status and oxygenation during hemodialysis. Cerebral rSO2 mainly depends on the cerebral oxygen supply and the metabolic rate of oxygen consumption. In generally healthy individuals, cerebral rSO2 in the prefrontal cortex is approximately 70 %, while in MHD patients, it is roughly between 50 % and 60 % [27,54,62,63]. Studies have shown that the decline in cerebral rSO2 among MHD patients may be related to intradialytic anemia [64–66]. Additionally, cerebral rSO2 has been demonstrated to exhibit a high consistency with the patient's hemoglobin (Hb) and CBF levels [6,67].

The study found that there is a significant decrease in cerebral rSO2 in the DLPFC of the SG during the 1st hour after the initiation of hemodialysis, followed by a slight ascent by the 3rd hour and a subsequent decline after the end of hemodialysis. These findings suggest that patients undergo considerable fluctuations in CBF during hemodialysis, which may ultimately impair cerebral oxygenation. The observed trends in cerebral rSO2 are consistent with previous reports on arterial oxygen partial pressure (PaO2) and arterial oxygen saturation (SaO2) changes during dialysis by Campos et al. and Polinder-Bos et al., [5,54]. However, the underlying mechanisms remain unclear. Under normal physiological conditions, the brain receives approximately 15%–20 % of cardiac output and maintains relative stability through the vascular tone regulation within the cerebral perfusion pressure range of 60–160 mmHg [68]. This ability to constrict and dilate in response to pressure changes is crucial for maintaining CBF. In MHD patients, however, vascular tone of the cerebral vasculature can be compromised due to impaired calcium-phosphate regulation, leading to inflammation and vascular calcification, and other complications such as diabetes, hypertension, atherosclerosis, and aging. This increases the risk of cerebral ischemia during the hemodynamic stress of dialysis. Interdialytic cerebral ischemia can lead to local lactic acidosis and neuronal toxicity, further impacting post-ischemic recovery [69,70]. Wolfgram's review [62] applied the HD-induced circulatory stress model to summary the potential mechanisms of cognitive impairment caused by impaired cerebral autoregulation, leading to insufficient cerebral perfusion and ischemic injury. Anazodo et al. [71] confirmed the existence of dialysis-related acute brain injury by application of MRI anatomical imaging, diffusion tensor imaging, and magnetic resonance spectroscopy. Their findings showed significant changes in brain tissue volume, diffusion indices, and brain metabolite concentrations during a single dialysis session, consistent with ischemic injury. Moreover, the reduced diffusion in the left inferior fronto-occipital fasciculus of patients was associated with decreased performance in the Trail Making Test test, suggesting that acute brain injury during dialysis may contribute to the decline in cognitive function in MHD patients.

Furthermore, this study found progressive declines in 1-Back RT, VAS-F scores, and MoCA scores in the SG following consecutive hemodialysis sessions. Moreover, a significant correlation was found between the decrease in DLPFC cerebral oxygenation and the decline in RT and MoCA scores. A cross-sectional survey by OoKawara et al. [63] indicated that MHD patients with cognitive impairment had significantly lower cerebral rSO2 than those without cognitive impairment. Kovarova et al.'s results [72] support this, showing that decreased left frontal lobe oxygenation was associated with poorer cognitive performance in chronic HD patients. Cai et al. [73] monitored cerebral venous oxygen saturation in HD patients by quantitative susceptibility mapping. They found that decreased oxygen saturation in the left internal cerebral vein was positively correlated with lower MoCA scores. These results provide evidence for the potential long-term chronic brain damage caused by cerebral rSO2 decline. However, in a one-year longitudinal study, Ookawara et al. [28] found a significant improvement in MMSE scores of patients with chronic kidney disease, and the changes in cerebral rSO2 and BMI were positively correlated with the changes in MMSE scores. The contradictory evidence may be due to various confounding factors affecting cognitive function, including whether patients received dialysis treatment, environmental factors, nutrition, and cognitive reserve. The chronic mechanisms of cognitive impairment caused by hemodialysis still require further exploration.

It is noteworthy that after a two-week intervention, the study observed an increase in the number of individuals with MoCA scores $<26$, rising from 8 at baseline to 13. Notably, all 5 new cases were found in the SG, suggesting a potential preventive effect of taVNS on cognitive decline. Additionally, there was a significant decrease in the LF/HF ratio in the VG, with a significant inter-group difference. The LF/HF ratio, an indicator of cardiac autonomic balance, suggests that the decrease indicates a shift towards parasympathetic dominance, reflecting higher HRV and effective activation of the vagus nerve network by taVNS. Mediation analysis further revealed that the improvement in cerebral rSO2 in the DLPFC mediated the relationship between taVNS stimulation and cognitive performance. This indicated that the upregulation of cerebral rSO2 in the DLPFC may be a potential mechanism underlying the cognitive function improvement in MHD patients induced by taVNS. The vagus nerve, the longest and most intricate among the twelve cranial nerves, plays a bidirectional regulatory role in cardiac rhythms and cortical excitability in the human body [74]. Approximately 80 % of vagus nerve fibers are afferent fibers [75]. The nucleus tractus solitarius (NTS) serves as a "primary hub" within the vagus nerve network, with the majority of afferent fibers from the vagus nerve projecting through the NTS to brainstem nuclei such as the locus coeruleus (LC), dorsal raphe nucleus (DRN), and parabrachial nucleus (PBN) [76–78]. To date, studies have demonstrated the positive effects of

taVNS on cognitive functions such as attention [79], executive functions [80–82], emotion recognition [83,84], associative memory [85], and memory recognition [86]. However, its application in MHD patients remains relatively novel. The mechanism may involve the induction of neurotransmitters release by taVNS. Chronic inflammation and autonomic nervous system disorders are common symptoms in patients with chronic kidney disease and during dialysis. It is hypothesized that the level of inflammatory cytokines and the reduction of HRV reflect the decrease in vagal tone during dialysis, and taVNS can activate the cholinergic anti-inflammatory pathway by releasing acetylcholine (ACh), thereby downregulating pro-inflammatory cytokines such as TNF, IL-1β, IL-6, IL-8, etc., achieving an anti-inflammatory effect [87]. Furthermore, research by Kaczmarczyk et al. [88] has shown that VNS can induce a transformation of microglia phenotype from neurotoxic to neuroprotective, inhibiting pro-inflammatory cytokines while increasing the release of BDNF, bFGF, and anti-inflammatory factors, thus contributing to a "neuroprotective" effect. Some studies propose that the locus coeruleus-norepinephrine (LC-NE) release system activated by taVNS may be a crucial factor in improving learning and memory capabilities [76,89]. These effects offered a possible insight into how taVNS may prevent continuous cognitive decline in MHD patients.

Since this clinical trial is a pilot study with a limited sample size, additional large-sample randomized controlled clinical trials are warranted to further substantiate the efficacy of taVNS in MHD patients.

## 5. Conclusion

The study found that the decline in cerebral oxygenation following hemodialysis may contribute to the persistent impairment of the cognitive function in MHD patients. This finding could be one of the reasons for progressive cognitive decline in chronic MHD patients. Encouragingly, taVNS has the potential to improve the decline in cerebral oxygenation during hemodialysis. This non-invasive intervention could help maintain and even enhance the cognitive performance of MHD patients. Continued study will be essential to confirm these preliminary findings and to explore the full therapeutic potential of taVNS in the context of hemodialysis.

## CRediT authorship contribution statement

**Meng-Huan Wang:** Writing – original draft, Visualization, Software, Formal analysis, Data curation, Conceptualization. **Yi-Jie Jin:** Writing – original draft, Software, Data curation. **Meng-Fei He:** Data curation. **An-Nan Zhou:** Validation, Methodology, Investigation. **Mei-Ling Zhu:** Validation, Investigation, Data curation. **Feng Lin:** Supervision, Project administration, Conceptualization. **Wen-Wen Li:** Supervision, Project administration, Conceptualization. **Zhong-Li Jiang:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization.

## Data availability statement

Given the constraints of our data usage protocols, research data is not deposited in a publicly accessible repository. Data will be made available on request.

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## Declaration of competing interest

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.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39841.

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