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Original Article

Relationship between phase lag index measured by electroencephalography and cognitive dysfunction in patients with cerebral small vessel disease

Dan Liu, Xiuqing Tong, Zhi Cao, Shujun Shi, Lin Ma

Department of Neurology, The Affiliated Hospital of Inner Mongolia Medical University, Hohhot 010050, Inner Mongolia, China

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Abstract: Objectives: Cerebral small vessel disease (CSVD) is a primary cause of cognitive impairment (CI) in the elderly. This study aims to explore the relationship between the phase lag index (PLI), derived from electroencephalography (EEG), and cognitive dysfunction in patients with CSVD. Methods: This retrospective study included patients diagnosed with CSVD from May 2020 to December 2023. EEG data were recorded using 64 electrodes and analyzed for PLI across four frequency bands. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Blood pressure variability was monitored using a 24-hour portable device. Results: The study included 264 patients, categorized into two groups: CI group (n = 102) and no CI group (n = 162). The CI group exhibited significantly lower global alpha-band PLI (0.28 vs. 0.31, P = 0.006) and reduced alpha-PLI across multiple electrode pairs (0.27 vs. 0.30, P = 0.004). Cognitive scores were also lower in the CI group (MMSE: 26.25 vs. 27.76, P = 0.004; MoCA: 25.38 vs. 26.63, P = 0.007). Additionally, the CI group had higher 24-hour mean systolic blood pressure (SBP, 140.68 vs. 136.36 mmHg, P = 0.038) and lower daytime SBP coefficient of variation (9.46% vs. 10.63%, P = 0.002). Receiver operating characteristic analysis revealed that F8-P8 PLI had an area under the curve of 0.608, indicating moderate discriminatory ability for identifying cognitive dysfunction. Conclusion: Decreased phase synchronization in the EEG alpha-band correlated with cognitive dysfunction in CSVD patients, indicating that impaired neural connectivity may serve as a potential electrophysiological biomarker.

Keywords: Relationship, phase lag index, electroencephalography, cognitive dysfunction, cerebral small vessel disease

Introduction

Cerebral small vessel disease (CSVD) is increasingly recognized as a major contributor to cognitive impairment (CI) and other neurological disorders in the aging population [1]. While traditionally overshadowed by larger vessel pathologies in neurology, the implications of CSVD on cognitive health have gained increasing attention, especially given the global aging population [2]. This condition involves various pathological changes in the small blood vessels of the brain, leading to white matter lesions, lacunes, and microbleeds, which, in turn, impair neural connectivity and brain function. The cognitive consequences of these vascular changes can range from mild CI to more severe forms of dementia [3].

The exploration of neurophysiological biomarkers has become pivotal in understanding the underlying mechanisms of cognitive dysfunction associated with CSVD [4]. Electroencephalography (EEG), a non-invasive technique for evaluating cerebral activity, provides valuable insights into brain network dynamics essential for cognitive processes [5]. The phase lag index (PLI), derived from EEG data, has emerged as a promising metric for assessing synchrony within brain networks [6]. PLI quantifies the phase coupling between EEG signals, reflecting the degree of neural connectivity and coherence across brain regions [7]. Alterations in PLI have been associated with cognitive decline in various neurodegenerative and vascular conditions, positioning it as a key marker for investigating cognitive dysfunction in CSVD [8].

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Previous studies have established that neural synchrony, particularly within specific EEG frequency bands like the alpha band, was crucial for cognitive functions such as memory, attention, and executive function [9]. Alpha-band activity is particularly relevant, given its association with higher-order cognitive processes and its sensitivity to disruptions in cerebral connectivity, as evidenced by reductions in phase synchronization [10, 11]. Disrupted alpha synchronization may reflect impaired connectivity across cortical networks resulting from microvascular damage, a hallmark of CSVD [11]. However, the specific relationship between alterations in alpha-band PLI and cognitive function in CSVD patients remains underexplored [12].

The relationship between vascular health and cognitive function is complex and multifaceted [13]. Hypertension, particularly systolic hypertension, along with other vascular risk factors, has been implicated in the etiology of CSVD, and, by extension, in cognitive decline [14]. However, routine clinical measures often fail to capture these subtle yet significant changes in cerebral microcirculation that affect cognition [15].

In summary, this study aims to investigate the relationship between PLI, assessed by EEG, and cognitive dysfunction in patients with CSVD. It systematically examined alpha-band PLI as a novel electrophysiological biomarker for cognitive dysfunction associated with CSVD. By combining EEG-based neural synchrony with a comprehensive vascular risk analysis, we presented an innovative approach. Our goal is to provide new insights into the mechanisms of cognitive impairment and offer practical tools for clinical evaluation.

Materials and methods

Ethics statement

This research was approved by the Institutional Review Board and Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University. As the study was retrospective and utilized only de-identified patient data, informed consent was waived. This waiver was granted by the Institutional Review Board and Ethics Committee in accordance with regulatory and ethical standards for retrospective research.

Study design, inclusion and exclusion criteria

A total of 264 patients diagnosed with CSVD at the Affiliated Hospital of Inner Mongolia Medical University between May 2020 and December 2023 were included in this study. Participants were categorized into two groups based on the presence or absence of CI: the CI group, comprising 102 individuals with CI, and the no CI (NCI) group, consisting of 162 individuals without CI. The diagnostic criteria for CI in CSVD cases were based on the Clinical Practice Guideline for CI in CSVD [16].

Inclusion Criteria: Diagnostic criteria for CSVD [17]; Age ≥ 60 years; EEG assessment completion; Absence of cognition-affecting medications; Availability of complete medical records.

Exclusion Criteria: Neuropsychiatric disorders or other medical or neuropsychological conditions (e.g., alcohol and/or drug abuse) that could lead to brain dysfunction; Severe autoimmune diseases, malignant tumors, or serious infections; Conditions, current or historical, affecting cognitive function (e.g., Parkinson's disease, epilepsy); Family history of dementia; History of cranial surgery, major organ damage (e.g., liver, kidneys), or impairments in vision or hearing.

Evaluation approach

The PLI was assessed using EEG with the MOBEE 24 EEG system (Xltek Inc., Canada) [18]. A total of 64 scalp electrodes were arranged according to the international 10-20 system, with 60 channels utilized for recording. Two reference electrodes were positioned on the participants' mastoids. Data were recorded for 10 minutes at a sampling frequency of 1,000 Hz, with participants keeping their eyes closed and remaining awake to avoid interference from visual attention. EEG data were subsequently analyzed using the EEGLAB toolbox in MATLAB.

Preprocessing of EEG Signals: Artifacts arising from eye movements, including horizontal eye movement and vertical eye movement, were removed during preprocessing. Additionally, re-referencing was performed using the average signals from the left and right mastoid sensors [19].

Bandpass Filtering: The EEG data underwent bandpass filtering within the frequency range of 0.1-30.0 Hz. Notch filtering at 49-51 Hz was applied to remove power line interference, and the data were subsequently resampled to 500 Hz. To facilitate analysis, the EEG data were divided into 3-second epochs, with artifacts from eye movements, muscle activity, and cardiac signals being systematically removed.

The PLI quantifies the strength of inter-channel phase coupling by evaluating the asymmetry in instantaneous phase differences ($\Delta\varphi$ (t)) distributions between signal pairs. Phase differences were estimated using the Hilbert transform, revealing consistent phase lead-lag relationships between signals. For two time series with phase differences $\Delta\varphi$ (tk) (k = 1 ...N), PLI is computed as: PLI = |<sign[$\Delta\varphi$ (tk)]>|, where "sign" denotes the signum function, <·> the mean, and |·| the absolute value. The PLI ranges from 0 to 1, where 0 indicates complete synchronization and 1 represents perfect phase locking with a consistent non-zero phase difference. PLI values were calculated between all node pairs across four frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz). Each EEG channel signal was processed as a real-valued time series, generating a 62 × 62 connectivity matrix.

Data collection

Patient data were extracted from medical records, including demographics, baseline disease characteristics, blood lipid and hematological parameters, cognitive scores, EEG findings, PLI values for all frequency bands, full-electrode alpha-band PLI, blood pressure variability, and blood pressure coefficient of variation. The Berg Balance Scale (BBS) was utilized to evaluate balance function [20]. This scale comprises 14 items, each scored from 0 to 4, where 4 indicates normal performance and 0 signifies an inability to perform the task or a need for substantial assistance. Higher total scores (ranging from 0 to 56) indicate superior balance capability. The Cronbach's alpha coefficient of the BBS has been reported as 0.81 [21], suggesting good internal consistency.

Assessment of cognitive function

Cognitive status and the severity of CI were evaluated using the Mini-Mental State Examination (MMSE) [22]. This instrument assesses cognitive function across seven domains: temporal orientation, spatial orientation, immediate memory, attention and calculation, delayed memory, language, and visuospatial abilities. Scores range from 0 to 30, with lower scores reflecting poorer cognitive performance. Specifically, scores between 27 and 30 indicate normal cognition, whereas scores below 27 signify CI. The Cronbach's alpha coefficient for the MMSE was reported as 0.71 [23], indicating acceptable internal consistency. The Montreal Cognitive Assessment (MoCA) was employed to assess the cognitive function of all participants. This scale assesses eight cognitive domains, including visuospatial and executive functions, naming, memory, attention, language, abstraction, delayed recall, and orientation. It comprises 30 items, with a maximum attainable score of 30; scores of 26 or above are considered indicative of normal cognitive function. Higher MoCA scores correspond to better cognitive performance. The Cronbach's alpha coefficient for the MoCA was determined to be 0.75 [24], reflecting acceptable internal reliability.

Monitoring of blood pressure variability

Twenty-four hour ambulatory blood pressure monitoring was conducted using a portable device (Wanzhong Yixin Health Management Group Co., Ltd., Suzhou; Medical Device Registration No. 20172212432). Blood pressure readings were recorded every 30 minutes during the daytime (6:00 AM to 10:00 PM) and every 60 minutes during the nighttime (10:00 PM to 6:00 AM) [25]. For data to be considered valid, at least 80% of the measurements over the 24-hour period were required to be successfully recorded [26]. The following parameters were included in the analysis: 24-hour mean systolic blood pressure (SBP), 24-hour mean diastolic blood pressure (DBP), 24-hour MAP, daytime mean SBP, daytime mean DBP, nighttime mean SBP, nighttime mean DBP, 24-hour systolic blood pressure coefficient of variation (SBPCV), 24-hour diastolic blood pressure coefficient of variation (DBPCV), daytime SBPCV, daytime DBPCV, nighttime SBPCV, and nighttime DBPCV [27].

Statistical analysis

Statistical analyses were performed using SPSS 29.0 (IBM Corp., Armonk, NY, USA). Cate-

Table 1. Demographic characteristics

Parameter	NCI group (n = 162)	CI group (n = 102)	t/χ^2	P
Age (years)	67.45 ± 5.91	67.82 ± 5.33	0.518	0.605
Gender (Male/ Female)	91 (56.17%)	52 (50.98%)	0.680	0.410
Education (years)	10.49 ± 1.74	10.18 ± 1.56	1.502	0.134
BMI (kg/m^2)	23.66 ± 1.68	23.81 ± 1.57	0.739	0.460
History of hypertension	5.67 ± 3.21	6.23 ± 3.45	1.342	0.181
History of diabetes	153 (94.44%)	93 (91.18%)	1.052	0.305
Smoking history	62 (38.27%)	45 (44.12%)	0.887	0.346
Alcohol consumption (weeks)	58 (35.80%)	38 (37.25%)	0.057	0.811
Physical activity (hours/week)	4.37 ± 2.13	3.65 ± 1.89	2.784	0.006
Social engagement (activities/month)	7.56 ± 3.34	6.47 ± 2.98	2.688	0.008

NCI: no cognitive impairment; CI: cognitive impairment; BMI: body mass index.

gorical variables were summarized as frequencies and percentages ([n (%)]), and comparisons between groups were performed using the chi-square test. Continuous variables were first assessed for normality using the Shapiro-Wilk test. Variables with a normal distribution were expressed as means ± standard deviations (M ± SD), whereas those with a non-normal distribution were presented as medians and interquartile ranges. Depending on the distribution, between-group comparisons of continuous variables were conducted using either independent samples t-tests or Mann-Whitney U tests. A two-tailed *P*-value of < 0.05 was considered indicative of statistical significance.

Results

Demographic characteristics

In this study exploring the association between the PLI measured by EEG and cognitive dysfunction in patients with CSVD, demographic characteristics were compared between the NCI group and the CI group (**Table 1**). There were no statistically significant differences between the two groups in terms of age, sex distribution, years of education, body mass index, history of hypertension, history of diabetes, smoking status, or alcohol consumption (all P > 0.05). However, significant between-group differences were observed in levels of physical activity and social engagement. Patients in the NCI group reported higher levels of physical activity, with an average of 4.37 hours per week, compared to 3.65 hours per week in the CI group (t = 2.784, P = 0.006). Additionally, the NCI group engaged in more social activities per month, with a mean of 7.56 activities, versus 6.47 activities in the CI group (t = 2.688, P = 0.008). These results suggest that lower levels of physical activity and reduced social participation may be associated with CI in patients with CSVD.

Baseline disease characteristics

Patients in the CI group had a significantly longer duration of CSVD diagnosis, with a mean of 5.37 years compared to 4.95 years in the NCI group (t = 2.568, P = 0.011) (**Table 2**). A higher proportion of patients in the CI group had a history of stroke (23.53% vs. 13.58%, $\chi^2 = 4.306$, P = 0.038) and transient ischemic attacks (16.67% vs. 5.56%, $\chi^2 = 8.703$, P = 0.003). Gait speed was significantly reduced in the CI group, with an average of 1.04 m/s compared to 1.12 m/s in the NCI group (t = 3.019, P = 0.003). Similarly, balance function, as assessed by the Berg Balance Scale, was poorer in the CI group, with a mean score of 48.75 versus 50.34 in the NCI group (t = 2.975, P = 0.003). In addition, urinary incontinence was more common in the CI group (26.47% vs. 15.43%, $\chi^2 = 4.822$, P = 0.028), as was the presence of cerebral microbleeds (34.31% vs. 17.28%, $\chi^2 = 9.991$, P = 0.002).

Blood lipid and hematological parameters

There were no significant differences between the NCI and CI groups in triglyceride, total cholesterol, high-density lipoprotein or low-density lipoprotein (all P > 0.05). Similarly, hemoglobin, albumin, white blood cells, neutrophils, and lymphocytes were comparable between groups, showing no significant variation (all P > 0.05) (**Table 3**).

Table 2. Baseline disease characteristics

Parameter	NCI group (n = 162)	CI group (n = 102)	t/χ^2	P
Duration of CSVD diagnosis (years)	4.95 ± 1.03	5.37 ± 1.45	2.568	0.011
History of stroke	22 (13.58%)	24 (23.53%)	4.306	0.038
History of TIA	9 (5.56%)	17 (16.67%)	8.703	0.003
Gait speed (m/s)	1.12 ± 0.18	1.04 ± 0.22	3.019	0.003
Balance (Berg Balance Scale score)	50.34 ± 3.67	48.75 ± 4.56	2.975	0.003
Urinary incontinence	25 (15.43%)	27 (26.47%)	4.822	0.028
Presence of cerebral microbleeds	28 (17.28%)	35 (34.31%)	9.991	0.002

CSVD: cerebral small vessel disease; TIA: transient ischemic attack; NCI: no cognitive impairment; CI: cognitive impairment.

Table 3. Blood lipid and hematological parameters

Parameter	NCI group (n = 162)	CI group (n = 102)	t	P
TG (mmol/L)	1.2 ± 0.34	1.23 ± 0.37	0.642	0.522
TC (mmol/L)	4.35 ± 0.42	4.29 ± 0.47	1.062	0.289
HDL (mmol/L)	1.17 ± 0.13	1.14 ± 0.17	1.768	0.079
LDL (mmol/L)	2.53 ± 0.36	2.58 ± 0.56	0.867	0.388
Hemoglobin (g/L)	113.75 ± 14.74	111.45 ± 14.83	1.234	0.218
Albumin (g/L)	42.74 ± 5.23	41.87 ± 6.01	1.232	0.219
White blood cell count ($\times 10^9$/L)	11.34 ± 2.88	11.64 ± 2.47	0.882	0.379
Neutrophil count ($\times 10^9$/L)	9.65 ± 1.86	9.45 ± 1.87	0.830	0.407
Lymphocyte count ($\times 10^9$/L)	1.41 ± 0.57	1.44 ± 0.45	0.413	0.680

NCI: no cognitive impairment; CI: cognitive impairment; TG: triglycerides; TC: total cholesterol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

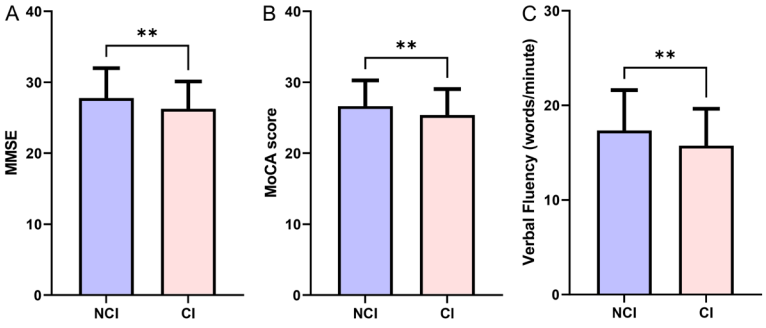

Figure 1. Comparison of cognitive assessment scores. A: MMSE score; B: MoCA score; C: Verbal Fluency. NCI: no cognitive impairment; CI: cognitive impairment; MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment. **P < 0.01.

Cognitive assessment scores

Cognitive performance was significantly better in the NCI group across all measures (**Figure 1**). The NCI group demonstrated higher MMSE scores (27.76 vs. 26.25; t = 2.912, P = 0.004) and MoCA scores (26.63 vs. 25.38; t = 2.700, P = 0.007) compared to the CI group. Verbal fluency was also superior in the NCI group, with a greater number of words generated per minute (17.34 vs. 15.75; t = 3.057, P = 0.002).

EEG monitoring results

A significantly greater proportion of patients in the NCI group exhibited normal clinical parameters compared to the CI group (64.20% vs. 41.18%; χ^2 = 13.419, P < 0.001). Moderate abnormalities were more frequent in the CI group (19.61% vs. 7.41%; χ^2 = 8.746, P = 0.003), and severe abnormalities were observed exclusively in the CI group (6.86% vs. 0%; χ^2 = 8.916, P = 0.003). No significant differences were observed in the edge state or mild abnormality categories (both P > 0.05) (**Table 4**).

PLI across frequency bands

The NCI group demonstrated a significantly higher PLI in the alpha band compared to the CI group (0.31 vs. 0.28; t = 2.788, P = 0.006). No

Table 4. EEG monitoring results

Parameter	NCI group (n = 162)	CI group (n = 102)	χ^2	P
Normal	104 (64.20%)	42 (41.18%)	13.419	< 0.001
Edge state	26 (16.05%)	15 (14.71%)	0.086	0.769
Mild abnormality	20 (12.35%)	18 (17.65%)	1.428	0.232
Moderate abnormality	12 (7.41%)	20 (19.61%)	8.746	0.003
Severe abnormality	0 (0%)	7 (6.86%)	8.916	0.003

EEG: electroencephalogram; NCI: no cognitive impairment; CI: cognitive impairment.

Table 5. PLI across frequency bands

Parameter	NCI group (n = 162)	CI group (n = 102)	t	P
δ	0.31 ± 0.08	0.32 ± 0.07	1.029	0.305
θ	0.28 ± 0.07	0.29 ± 0.08	1.061	0.289
α	0.31 ± 0.08	0.28 ± 0.07	2.788	0.006
β	0.16 ± 0.07	0.15 ± 0.07	1.101	0.272

NCI: no cognitive impairment; CI: cognitive impairment; PLI: phase lag index; δ: delta; θ: theta; α: alpha; β: beta.

significant group differences were observed in the delta, theta, or beta bands, with corresponding PLI values of 0.31 vs. 0.32 (t = 1.029, P = 0.305), 0.28 vs. 0.29 (t = 1.061, P = 0.289), and 0.16 vs. 0.15 (t = 1.101, P = 0.272), respectively (**Table 5**).

PLI of alpha frequency band across electrode pairs

Figure 2 presents EEG recordings from two groups of patients with CSVD, stratified by cognitive status. In panel A, representing patients without CI (NCI group), the EEG waveforms appear relatively smooth and regular, suggesting stable and synchronized neural activity consistent with preserved cognitive function. Correspondingly, the PLI values in this group indicate minimal phase synchronization disruption, supporting the presence of well-coordinated cortical connectivity. In contrast, panel B illustrates EEG waveforms from patients with CI (CI group), characterized by increased amplitude fluctuations and frequency variability. These features reflect greater desynchronization and disrupted neural communication, aligning with the clinical presentation of cognitive dysfunction. The elevated irregularity in PLI values further highlights abnormal neural synchronization patterns in the CI group.

Quantitative analysis revealed that PLI values in the alpha frequency band were consistently higher in the NCI group across multiple electrode pairings (**Table 6**). Significant between-group differences were observed in the following electrode pairs: central left-parietal left (0.33 vs. 0.31; t = 2.438, P = 0.015), central right-temporal parietal right (0.32 vs. 0.30; t = 2.313, P = 0.021), frontal left-central left inferior (0.30 vs. 0.28; t = 2.479, P = 0.014), frontal right-parietal left (0.31 vs. 0.29; t = 2.774, P = 0.006), anterior temporal right-temporal parietal right (0.30 vs. 0.27; t = 2.889, P = 0.004), parietal right-central parietal left (0.29 vs. 0.27; t = 2.384, P = 0.018), central parietal left-occipital left (0.31 vs. 0.29; t = 2.273, P = 0.024), and central parietal left inferior-occipital right (0.30 vs. 0.28; t = 2.150, P = 0.032).

Blood pressure variability

Patients in the CI group exhibited significantly higher SBP across all time periods compared to the NCI group (**Table 7**). The 24-hour mean SBP was 140.68 mmHg in the CI group versus 136.36 mmHg in the NCI group (t = 2.092, P = 0.038). Similarly, daytime and nighttime mean SBP values were elevated in the CI group (143.37 mmHg vs. 137.95 mmHg, t = 2.248, P = 0.025; and 138.86 mmHg vs. 133.36 mmHg, t = 2.173, P = 0.031, respectively). Additionally, the 24-hour MAP was significantly higher in the CI group (63.42 mmHg vs. 60.48 mmHg; t = 2.079, P = 0.039). In contrast, no significant differences were observed between the groups in 24-hour, daytime, or nighttime DBP or in daytime/nighttime MAP values (all P > 0.05).

Blood pressure coefficient of variation

The NCI group demonstrated a higher daytime SBPCV compared to the CI group (10.63% vs. 9.46%; t = 3.128, P = 0.002). However, no significant differences were observed between

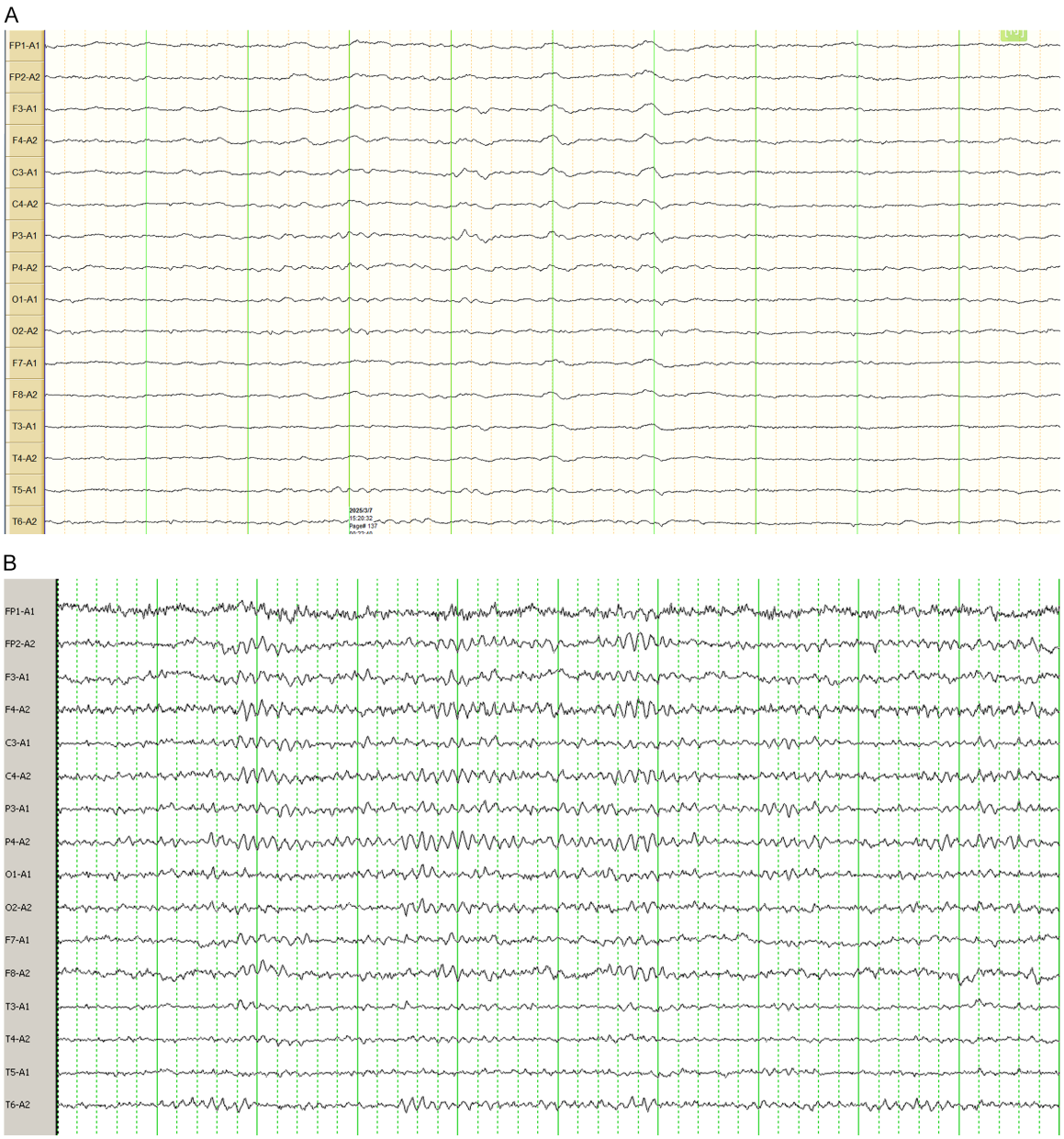

Figure 2. Electroencephalogram. A: NCI group; (CI); B: CI group. NCI: no cognitive impairment; CI: cognitive impairment.

the groups in 24-hour SBPCV (10.42% vs. 10.48%; t = 0.138, P = 0.891), or in 24-hour DBPCV (12.83% vs. 12.69%; t = 0.357, P = 0.722). Similarly, there were no statistically significant differences in nighttime SBPCV (P = 0.082), nighttime DBPCV (P = 0.737), or daytime DBPCV (P = 0.245) (**Figure 3**).

Receiver Operating Characteristic (ROC) analysis results

ROC analysis was performed to assess the diagnostic performance of various parameters for identifying cognitive dysfunction in patients with CSVD (**Table 8**). Among EEG-derived PLI, the anterior temporal right-temporal parietal right electrode pair exhibited the highest area under the curve (AUC) of 0.608 (sensitivity = 0.676, specificity = 0.525; Youden index = 0.201), indicating moderate discriminatory ability. Clinical variables such as physical activity and social engagement showed AUC values of 0.594 and 0.593, respectively, indicating limited diagnostic utility. Duration of CSVD diagnosis (AUC = 0.612; Youden index = 0.224) and

Table 6. PLI of alpha frequency band across electrode pairs

Parameter	NCI group (n = 162)	CI group (n = 102)	t	P
C3-P3	0.33 ± 0.07	0.31 ± 0.06	2.438	0.015
C4-P8	0.32 ± 0.08	0.30 ± 0.07	2.313	0.021
F3-C5	0.30 ± 0.07	0.28 ± 0.07	2.479	0.014
F4-P3	0.31 ± 0.08	0.29 ± 0.06	2.774	0.006
F8-P8	0.30 ± 0.08	0.27 ± 0.07	2.889	0.004
P4-CP3	0.29 ± 0.08	0.27 ± 0.05	2.384	0.018
CP3-O1	0.31 ± 0.06	0.29 ± 0.07	2.273	0.024
CP5-O2	0.30 ± 0.06	0.28 ± 0.07	2.150	0.032

NCI: no cognitive impairment; CI: cognitive impairment; PLI: phase lag index; C3: central left; P3: parietal left; C4: central right; P8: temporal parietal right; F3: frontal left; C5: central left inferior; F4: frontal right; F8: anterior temporal right; P4: parietal right; CP3: central-parietal left; O1: occipital left; CP5: central-parietal left inferior; O2: occipital right.

Table 7. Blood pressure variability

Parameter	NCI group (n = 162)	CI group (n = 102)	t	P
24h mSBP	136.36 ± 13.67	140.68 ± 17.79	2.092	0.038
24h mDBP	75.58 ± 12.65	76.48 ± 13.84	0.542	0.589
dmSBP	137.95 ± 18.72	143.37 ± 19.63	2.248	0.025
dmDBP	76.06 ± 11.67	78.42 ± 11.67	1.596	0.112
nmSBP	133.36 ± 19.85	138.86 ± 20.23	2.173	0.031
nmDBP	73.65 ± 12.34	76.28 ± 14.32	1.583	0.115
24h MMP	60.48 ± 7.58	63.42 ± 12.95	2.079	0.039
MAP	95.30 ± 17.56	97.78 ± 16.37	1.148	0.252

NCI: no cognitive impairment; CI: cognitive impairment; 24h mSBP: 24-hour mean systolic blood pressure; 24h mDBP: 24-hour mean diastolic blood pressure; dmSBP: Daytime mean systolic blood pressure; dmDBP: Daytime mean diastolic blood pressure; nmSBP: Nighttime mean systolic blood pressure; nmDBP: Nighttime mean diastolic blood pressure; 24h MMP: 24-hour mean arterial pressure; MAP: mean arterial pressure.

gait speed (AUC = 0.614; Youden index = 0.189) demonstrated relatively better performance and may serve as potential markers for cognitive dysfunction. In contrast, parameters, including history of stroke, history of transient ischemic attacks, urinary incontinence, presence of cerebral microbleeds, MMSE score, MoCA score, and various blood pressure measurements, yielded lower AUC values (0.534-0.585), implying weaker discriminatory power. Notably, 24-hour MAP achieved an AUC of 0.593 with a relatively high Youden index of 0.262 (sensitivity = 0.422, specificity = 0.840). Furthermore, ROC curve analysis of the PLI metric revealed a strong ability to distinguish CI from NCI patients with CSVD, with an AUC of 0.867 (**Figure 4**), indicating high diagnostic accuracy.

Discussion

With global aging population on the rise, the relationship between CSVD and CI has garnered increasing research attention. In this study, we investigated the association between PLI, as assessed by EEG, and CI in patients with CSVD. Our findings provide novel insights into the underlying neural connectivity alterations associated with CI and highlight the potential clinical utility of EEG-based functional connectivity measures in the early detection and monitoring of cognitive decline in this population.

The observed differences in alpha-band PLI between the CI and NCI groups reflect alterations in neural connectivity that may underlie divergent cognitive outcomes in patients with CSVD. Prior research has indicated that alpha-band activity is critical for cognitive processes, including attention, memory, and sensory processing [28, 29]. The observed reduction in alpha-band PLI in the CI group likely reflects disrupted phase synchronization across cortical networks, potentially impairing the efficient transmission of information [30]. Such disruption may result from microvascular pathology characteristic of CSVD, which compromises neuronal integrity and alters functional connectivity and network dynamics [31]. Accordingly, decreased PLI may signify a breakdown in the brain's capacity to coordinate activity across distributed neural ensembles, thereby contributing to CI - a finding consistent with previous studies [32].

Moreover, alterations in phase synchronization, as evidenced by changes in PLI, are consistent with findings in other neurodegenerative disorders, such as Alzheimer's disease, where reduced network efficiency has been shown to correlate with greater degrees of CI [33]. The

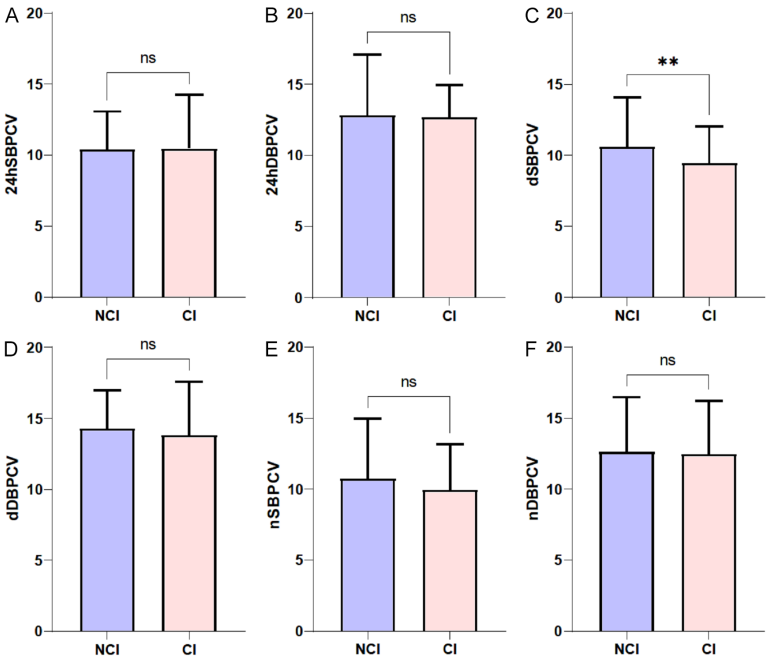

Figure 3. Blood pressure coefficient of variation. A: 24h SBPCV; B: 24h DBPCV; C: dSBPCV; D: dDBPCV; E: nSBPCV; F: nDBPCV. NCI: no cognitive impairment; CI: cognitive impairment; 24h SBPCV: 24-hour systolic blood pressure coefficient of variation; 24h DBPCV: 24-hour diastolic blood pressure coefficient of variation; dSBPCV: Daytime systolic blood pressure coefficient of variation; dDBPCV: Daytime diastolic blood pressure coefficient of variation; nSBPCV: Nighttime systolic blood pressure coefficient of variation; nDBPCV: Nighttime diastolic blood pressure coefficient of variation. ns: no significant; **P < 0.01.

physiological basis for these findings may lie in the microangiopathic changes characteristic of CSVD, which trigger a cascade of neuroanatomical alterations, including cerebral atrophy, white matter lesions, and cortical thinning [34]. These structural changes compromise the integrity and function of brain networks, leading to widespread disruptions in network connectivity, as reflected by abnormal PLI patterns observed in EEG recordings.

In addition to impaired neural synchrony, this study identified several demographic and clinical characteristics associated with CI. Patients in the CI group exhibited not only reduced PLI but also a range of risk factors indicative of diminished cognitive resilience. Notably, lower levels of physical activity and reduced social engagement significantly distinguished the CI group from the NCI group. These lifestyle factors may contribute to cognitive decline by limiting cognitive stimulation and negatively affecting overall physical health. Consistent with previous studies, physical inactivity and social isolation have been recognized as significant risk factors for cognitive deterioration, associated with both vascular pathology and neurodegenerative processes [35, 36].

Interestingly, our study found no significant differences in routine blood parameters between the two groups, suggesting that conventional markers of vascular health, such as blood lipids, may not adequately reflect the risk of CI in CSVD. In contrast, elevated blood pressure, particularly SBP, was more pronounced in the CI group and has been consistently associated with cognitive decline [37, 38]. Consistent with previous studies identifying hypertension as a key contributor to vascular injury and small vessel pathology, our findings support the link between elevated SBP and ischemic changes in CSVD [39]. Persistent hypertension may aggravate cerebral vascular damage, thereby exacerbating the underlying pathology and impairing cognitive function [40]. Moreover, the observed reduction in daytime SBPCV in the CI group may reflect impaired vascular elasticity or autonomic dysfunction, both of which can compromise cerebral perfusion and further contribute to cognitive deterioration.

Furthermore, cognitive assessments such as the MMSE and MoCA further support the presence of cognitive dysfunction in patients with altered PLI, exhibiting significant correlations with impaired neural synchronization. While these neuropsychological tests are widely validated and clinically useful, prior studies have suggested that they may not fully capture the complexity of CI, especially in CSVD, where subtle disruptions in neural connectivity can play a critical role [41]. The incorporation of EEG-based metrics, such as PLI, provides an objective and quantifiable approach that reflects underlying neurophysiological dysfunc-

Table 8. ROC analysis results

Parameter	Best threshold	Sensitivities	Specificities	AUC	Youden index	F1 score
Physical activity (hours/week)	4.615	0.735	0.457	0.594	0.192	0.266
Social engagement (activities/month)	8.845	0.814	0.377	0.593	0.191	0.209
Duration of CSVD diagnosis (years)	5.240	0.588	0.636	0.612	0.224	0.543
History of stroke	0.500	0.235	0.864	0.550	0.099	0.324
History of TIA	0.500	0.167	0.944	0.556	0.111	0.266
Gait speed (m/s)	1.085	0.627	0.562	0.614	0.189	0.329
Balance (Berg Balance Scale score)	47.735	0.461	0.772	0.609	0.233	0.390
Urinary incontinence	0.500	0.265	0.846	0.555	0.111	0.351
Presence of cerebral microbleeds	0.500	0.343	0.827	0.585	0.170	0.424
MMSE	24.925	0.402	0.778	0.601	0.180	0.422
MoCA score	25.645	0.569	0.636	0.590	0.205	0.353
Verbal Fluency (words/minute)	18.860	0.824	0.395	0.607	0.219	0.196
normal	0.500	0.588	0.642	0.615	0.230	0.339
Moderate abnormality	0.500	0.196	0.926	0.561	0.122	0.299
Severe abnormality	0.500	0.069	1.000	0.534	0.069	0.128
α	0.335	0.833	0.333	0.584	0.166	0.197
C3-P3	0.355	0.804	0.377	0.591	0.181	0.219
C4-P8	0.295	0.529	0.660	0.594	0.189	0.374
F3-C5	0.325	0.765	0.370	0.583	0.135	0.258
F4-P3	0.335	0.784	0.414	0.581	0.198	0.230
F8-P8	0.295	0.676	0.525	0.608	0.201	0.300
P4-CP3	0.305	0.765	0.432	0.577	0.197	0.245
CP3-O1	0.265	0.363	0.790	0.570	0.153	0.441
CP5-O2	0.235	0.265	0.864	0.570	0.129	0.473
24hm SBP	153.275	0.245	0.920	0.573	0.165	0.357
dmSBP	147.500	0.451	0.710	0.583	0.161	0.472
nmSBP	142.915	0.441	0.722	0.577	0.163	0.469
24h MMP	67.830	0.422	0.840	0.593	0.262	0.503
dSBPCV	12.135	0.882	0.352	0.599	0.234	0.140

ROC: operating characteristic; AUC: area under the curve; CSVD: cerebral small vessel disease; TIA: transient ischemic attack; MMSE: mini-mental state examination; MoCA: Montreal cognitive assessment; α: alpha; C3: central left; P3: parietal left; C4: central right; P8: temporal parietal right; F3: frontal left; C5: central left inferior; F4: frontal right; F8: anterior temporal right; P4: parietal right; CP3: central-parietal left; O1: occipital left; CP5: central-parietal left inferior; O2: occipital right; 24h mSBP: 24-hour mean systolic blood pressure; dmSBP: Daytime mean systolic blood pressure; nmSBP: Nighttime mean systolic blood pressure; 24h MMP: 24-hour mean arterial pressure; dSBPCV: Daytime systolic blood pressure coefficient of variation.

tion, thereby complementing traditional cognitive assessments and enhancing the sensitivity of early detection.

Overall, our findings highlight the potential of PLI as a valuable electrophysiological biomarker for detecting cognitive dysfunction in patients with CSVD. By enabling the identification of specific patterns of neural dysconnectivity, PLI offers insights that extend beyond those obtainable through conventional clinical or neuropsychological assessments. This approach aligns with a growing body of evidence supporting the use of EEG-derived metrics to assess brain function across various pathological conditions, underscoring the importance of network connectivity and neural synchronization as crucial determinants of cognitive health.

These findings carry several important implications for clinical practice and potential therapeutic strategies. First, routine assessment of PLI, particularly within the alpha frequency band, may assist clinicians in identifying patients at higher risk for cognitive decline, enabling earlier monitoring and timely interven-

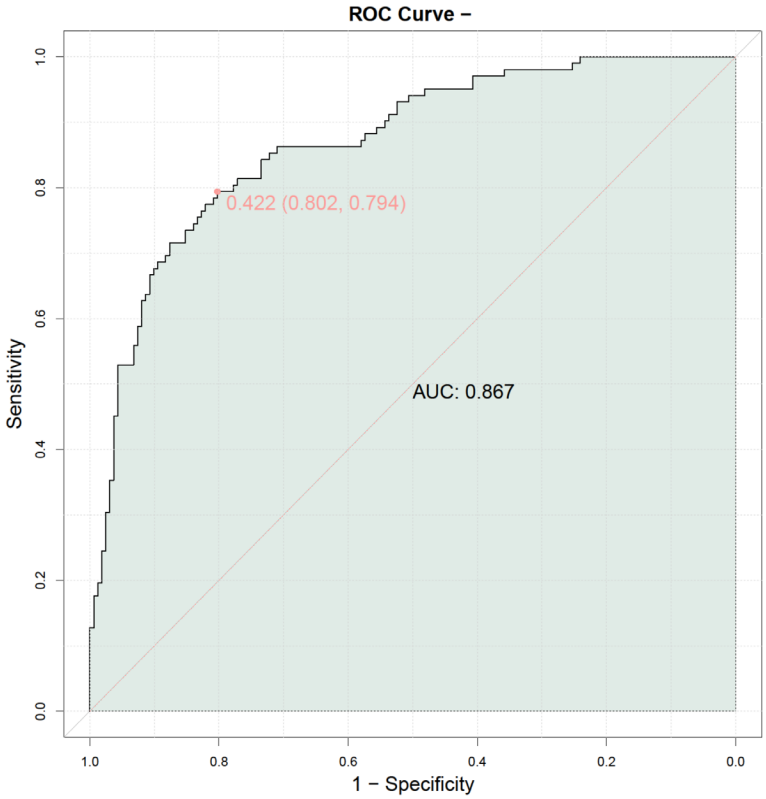

Figure 4. ROC curve analysis of PLI. ROC: operating characteristic; AUC: area under the curve.

tion to preserve cognitive function. Second, interventions aimed at enhancing cerebral perfusion and neural connectivity - such as physical activity, cognitive engagement, and optimal blood pressure control - should be prioritized in individuals with or at risk for CSVD-related CI. Furthermore, the development of neuroprotective therapies specifically targeting the restoration of neural synchrony may complement existing treatment approaches and further improve patient outcomes.

While this study provides valuable insights into the relationship between PLI and cognitive dysfunction in patients with CSVD, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference, making it unclear whether changes in neural synchrony are a cause or consequence of CI. Second, the study sample may not fully represent the broader CSVD population, potentially limiting the generalizability of the findings. Additionally, although PLI served as an informative measure of neural connectivity, reliance on a single electrophysiological index may not fully capture the complexity of brain network dynamics. Individual variability in cognitive reserve and compensatory mechanisms was also not accounted for, which may have influenced the robustness of the results. Finally, potential confounding factors, such as comorbid neurodegenerative diseases or systemic health conditions, were not comprehensively evaluated, possibly impacting the observed associations. To address these limitations, future longitudinal studies with larger, more diverse populations are warranted. Incorporating multimodal assessments, such as functional magnetic resonance imaging alongside EEG, may offer a more comprehensive understanding of neural connectivity and its relationship with cognitive function in CSVD. Such approaches could help clarify the causal pathways linking vascular pathology, disrupted network synchronization, and cognitive decline.

In conclusion, this study demonstrates that reduced neural synchronization, as indicated by decreased PLI in the alpha band, is closely associated with CI in patients with CSVD. These findings highlight the potential of EEG-based measures as objective tools for early detection and monitoring of cognitive decline. Incorporating network-level assessments into clinical practice may enhance diagnostic accuracy and guide future interventions aimed at preserving brain connectivity and cognitive function.

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Disclosure of conflict of interest

None.

Address correspondence to: Lin Ma, Department of Neurology, The Affiliated Hospital of Inner Mongolia Medical University, No. 1 Tongdao North Street, Huimin District, Hohhot 010050, Inner Mongolia, China. E-mail: malinfy@163.com

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