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Phase synchronization analysis of prefrontal tissue oxyhemoglobin oscillations in elderly subjects with cerebral infarction

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Purpose: This study aims to assess the phase relationship of prefrontal tissue oxyhemoglobin oscillations using wavelet phase coherence analysis of cerebral Delta [HbO2] signals in cerebral infarction (Cl) patients during the resting state.

Methods: Continuous recordings of near-infrared spectroscopy signals were obtained from the left and right prefrontal lobes in 21 subjects with Cl (Group Cl; age: 76.6 ± 8.5 yr) and 21 healthy elderly subjects (Group Healthy; age: 69.0 ± 7.4 yr) during the resting state. The Group CI was further divide into two groups: Cl with hypertension and Cl without hypertension. The phase synchronization between left and right prefrontal Delta [HbO2] oscillations in four frequency intervals (I, 0.6–2 Hz; II, 0.145–0.6 Hz; III, 0.052–0.145 Hz; and IV, 0.021–0.052 Hz) was analyzed using wavelet phase coherence method.

Results: The phase coherences in intervals III and IV were significantly lower in CI with hypertension than in healthy elderly subjects (F = 12.974, p = 0.001 for III and F = 10.073, p = 0.004 for interval IV). The phase coherence of CI without hypertension in interval III was significantly lower than in healthy elderly subjects (F = 9.909, p = 0.004). Also, the phase coherence in interval IV was significantly lower in CI with hypertension than in CI without hypertension (F = 5.665, p = 0.028). Also, the phase agreement in interval IV showed evident difference between Group CI with hypertension and without hypertension.

Conclusions: The difference in phase characteristics of prefrontal tissue oxyhemoglobin oscillations between the CI patients and healthy elderly indicates altered phase synchronization. Moreover, the CI combined with hypertension would aggravate this process. This study provides new insight into the phase dynamics of cerebral oxygenation and may be useful in assessing the risk for stroke.

Key words: near-infrared spectroscopy, wavelet phase coherence, functional connectivity, cerebral infarction, cerebral oxygenation, spontaneous oscillations

1. INTRODUCTION

Spontaneous oscillations in the low frequency range (<0.1 Hz) have been demonstrated to exhibit strong correlations in distinct regions of the brain in the resting state. This correlation is defined as “resting state functional connectivity,” which has been well reproduced in many studies using functional magnetic resonance imaging (fMRI) (Refs. 2–4) and near-infrared spectroscopy (NIRS). NIRS is an increasingly popular technology for studying brain function. NIRS is based on measuring changes in local oxygenated and deoxygenated hemoglobin concentrations. While brain NIRS shares a common physiological basis to fMRI, it offers several potential advantages in terms of logistics (cost, equipment portability, and patient compatibility) and data quality (temporal sampling density >10 vs <1 Hz). NIRS has become a suitable and easily manageable method to monitor cerebral cortical oxygenation continuously and noninvasively at rest or brain activation.

Functional connectivity has been successfully observed during the resting state in both adult and infant participants using NIRS. NIRS has high temporal resolution and it has revealed a temporal relationship of signals obtained at different brain regions. The correlations in cortical networks concentrate within ultralow frequencies (0.01–0.06 Hz) and it shows distinct frequency-specific features in the functional networks. By decomposing fluctuations of oxygenated hemoglobin and deoxygenated hemoglobin signals into various frequency bands, Sasai et al. investigated the frequency dependency of functional connectivity between diverse regions in the cerebral cortex. The functional connectivity between homologous cortical regions of the contralateral hemisphere showed high coherence in the frequency range of 0.009–0.1 Hz.
Spontaneous activity in prefrontal cerebral oxygenations has been demonstrated to be disturbed in elderly persons,\textsuperscript{17} in persons with cerebral infarction (CI),\textsuperscript{18} and in elderly subjects with hypertension.\textsuperscript{12} Clinical studies demonstrated that resting-state connectivity is altered in disorders such as stroke,\textsuperscript{19} and stroke lesions cause neural dysfunction both at the lesion site and in remote brain regions.\textsuperscript{20} However, it is unclear what patterns of phase relationships in the left and right prefrontal regions are most closely associated with CI, especially in the CI patients with hypertension.

The power spectra of Delta [HbO\textsubscript{2}] signals have been found to exhibit oscillations in various frequency bands.\textsuperscript{18,21–24} Wavelet analysis can detect these oscillations with logarithmic frequency resolution.\textsuperscript{12,18,25} Different characteristic frequencies of Delta [HbO\textsubscript{2}] signals have been identified using wavelet analysis, which indicate possible regulatory mechanisms of the tissue oxygenation signal.\textsuperscript{18,25,26} The oscillations in intervals I (0.6–2 Hz) and II (0.15–0.6 Hz) reflect the effects of cardiac and respiratory activities, respectively.\textsuperscript{18,25,27} The cerebral oscillations in interval III (0.05–0.15 Hz) might originate locally from intrinsic myogenic activity of smooth muscle cells in resistance vessels and this may be partly under autonomic control.\textsuperscript{22,27} The interval IV (0.02–0.05 Hz) is considered to be closely regulated through tight neurovascular coupling and partial autonomic control within the brain.\textsuperscript{28}

The cross spectrum and wavelet coherence are often used in bivariate data analysis to detect phase synchrony between particular frequency components that are common to both of the signals under consideration.\textsuperscript{29,30} In general, the quantification of phase synchrony can be estimated by using the cross spectrum obtained from the Fourier transforms, concept of analytic signal, or complex wavelet transform. The differences between these methods have been demonstrated to be minor, and they are fundamentally mathematical equivalent when typically applied in spectral analyses.\textsuperscript{31,32} However, the cross spectrum obtained from the Fourier transforms of the whole time series is uninformative, and the true cross spectrum must be estimated by use of windowing and averaging.\textsuperscript{30} Also, the coherence approach based on wavelet transform is best suited for treatment of nonstationary data of time series, while the cross spectrum analysis obtained from the Fourier transforms implies stationarity of time series.\textsuperscript{22}

The wavelet phase coherence (WPCO) can identify possible phase relationships by evaluating the match between the instantaneous phases of two signals in various frequency bands.\textsuperscript{33,34} WPCO has been successfully used to analyze the relationships between oscillations in skin blood flow, temperature and oxygen saturation, and intracranial pressure and arterial blood pressure (ABP) signals within certain frequency ranges.\textsuperscript{34–37} In this study, we used the wavelet transform, rather than the Fourier transform or Hilbert transform, approach to the phase coherence as this offers a more intuitive visualization of time–frequency behavior. We hypothesize that the phase synchronization in the left and right prefrontal regions would be altered due to CI. The aim of this study was to assess the phase relationships of left and right prefrontal oxygenations in CI patients during resting state using WPCO analysis.

### 2. METHODS AND MATERIALS

#### 2.A. Subjects

A total of 42 subjects were recruited from Shandong University and local rehabilitation center to participate in this study. Of the 42 subjects, 21 were elderly with cerebral infarction (CI) (age: 76.6 ± 8.5 yr; Group CI). Among them, 8 were subjects with hypertension and 13 subjects without hypertension. Twenty-one were healthy subjects [age: 69.09 ± 7.4 yr; Group Health (G1)]. The CI group was further divide into two groups: CI without hypertension (G2) and CI with hypertension (G3). The affected area of cerebral infarction was different in each subject. Twelve of the affected areas were localized in the left side of the head and nine was in the right side.

Healthy subjects had no history of neurological or vascular disease. Patients included in the study were subjects having infarcts on computed tomography (CT) scan and CI occurred more than 12 months ago. Excluded from the study were subjects with diabetes mellitus; subarachnoid hemorrhage; insufficiency of the heart, lungs, kidneys, and liver; smoking or drinking habits; and additional medications (angiotensin-converting enzyme, inhibitors/angiotensin II-receptor blockers, and calcium-channel blockers). A diagnosis of hypertension was made when systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg.\textsuperscript{38} This was performed in the course of study. A diagnosis of diabetes mellitus was based on clinical assessment or fasting serum glucose level.

Prior to the experiment, basic subject information, including age, weight, height, and BP was recorded (Table 1). Informed consent was obtained from all subjects. The experimental procedures were approved by the Human Ethics Committee of Shandong University and were in accordance with the ethical standards specified by the Helsinki Declaration of 1975 (revised in 1983).

#### 2.B. Measurement

Data for the NIRS signals in left and right prefrontal lobes were obtained from simultaneous measurements. After the age, height, and body mass of the participants were recorded, NIRS measurements were performed on the subjects using the cerebral tissue saturation monitor (TH-200, developed by Tsinghua University, China). As spontaneous oscillations are posture-dependent,\textsuperscript{39} NIRS measurements were collected in their supine position. The TH-200 sensor consisted of a two-wavelength light-emitting diode (LED) and two PIN diodes. The LED component served as the source of emitted light at 760 and 850 nm, whereas the PIN diodes served as the detectors. Photons can penetrate the overlying tissues into the cerebral cortex (gray matter) when the distance between the detector and the source is ≥30 mm. Moreover, the penetration depth can reach the maximum value when the distance is 40 mm.\textsuperscript{40} Therefore, the distances between the light source and the two detectors were set to 30 mm (S1) and 40 mm (S2), respectively. The differential signal (S1–S2) in the optical density (OD) was recorded by the two
detectors and used to obtain the cortical signals including changes in oxyhemoglobin (HbO₂) and deoxyhemoglobin (HHb) using differential spectroscopy based on the modified Beer–Lambert law. This configuration was validated by Ding et al.\textsuperscript{41} The forehead of each subject was cleaned using isopropyl alcohol. Afterward, the sensors were carefully fixed using a flexible adhesive fixation pad and an elastic band. The sensors were placed on the left and right forehead 1.5 cm lateral to the cerebral midline to avoid the sagittal sinus and at least 2 cm above the eyebrow to avoid the frontal sinus. The sensors were carefully secured with a tensor bandage wrapped around the forehead while ensuring no admission of background light. The sampling rate of the NIRS-derived signals was set to 20 Hz. The Delta [HbO₂] signals were monitored at the prefrontal lobes for 15 min using NIRS. To help reduce movement artifact, the volunteers were asked to avoid sudden movements during the measurement.

2.C. Data preprocessing

Wavelet transform was applied to the NIRS time series to decompose the results into signal and uncorrelated noise components in distinct scales. The wavelet transform was calculated in the 0.021–2 Hz frequency intervals. Slow variations defined as below 0.021 Hz and uncorrelated noise components above 2 Hz were removed. The whole signal of 15 min was used to obtain wavelet amplitude and phase coherences. In addition, the average Delta [HbO₂] of all recorded segments was used for signal normalization to avoid systematic differences between subjects and groups.

2.D. Wavelet transform

Wavelet transform is a method that allows the complex transformation of a time series from the time domain to the time–frequency domain. It involves convolving the time series \( g(u) \) with a family of generally nonorthogonal basis functions that are generated from the mother wavelet\textsuperscript{41,42}

\[
W(s,t) = \frac{1}{\sqrt{s}} \int_{-\infty}^{+\infty} \Psi\left(\frac{u-t}{s}\right) g(u) du,
\]

where \( W(s,t) \) is a wavelet coefficient and \( \Psi \) is the Morlet mother wavelet, scaled by the factor \( s \) and translated in time by \( t \). The Morlet mother wavelet is a complex sinusoid modulated by the Gaussian function with basic frequency \( \omega_0 \)

\[
\Psi(u) = \frac{1}{\sqrt{\pi}} e^{-i\omega_0u} e^{-\frac{u^2}{2}},
\]

where \( i = \sqrt{-1} \). The continuous wavelet transform is a mapping of the function \( g(u) \) onto the time–frequency plane. Wavelet scaling enables the detection of oscillations with different frequencies, whereas wavelet translation in time allows the monitoring of spectra evolution over time. The translation from scale to frequency depends upon the particular choice of wavelet. An approximate relationship between wavelet scale and translated frequency, pseudofrequency, \( f_s \), was computed as\textsuperscript{43}

\[
f_s = \frac{f_c}{s \cdot \delta t},
\]

where \( f_c \) is the center frequency and \( \delta t \) is the sampling period. The choice of \( \omega_0 \) is a compromise between localization in time and in frequency. For smaller \( \omega_0 \), the shape of the wavelet favors localization of singular time events, whilst for larger \( \omega_0 \) more periods of the sine wave in the window improve the frequency localization.\textsuperscript{42,44} To detect a frequency, the signal must be observed over at least one period of this frequency. In this study, we choose \( \omega_0 = 5 \), in time, approximately six to seven periods. The wavelet transform was calculated in the frequency interval of 0.021–2 Hz. The upper limit of 2 Hz was set to include the heart rate frequency, whereas the lower limit was selected to include possible regulatory mechanisms of the tissue oxygenation signal.\textsuperscript{18,25,27}

2.E. Wavelet phase coherence

The wavelet coefficients are complex numbers with the complex Morlet wavelet. These values define the absolute amplitude and instantaneous relative phase for each frequency and time. Phase information can be used to investigate the relationships between oscillations from different signals.\textsuperscript{35} The relationship between the phases of two oscillatory processes at a specific frequency is defined as the phase coherence. If a characteristic phase difference is maintained between two signals, they have high phase coherence.\textsuperscript{45}

---

**Table I. Characteristics of the participants.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Healthy (G1)</th>
<th>CI (G2)</th>
<th>CI (G3)</th>
<th>P for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69.0(7.4)</td>
<td>76.6(8.9)</td>
<td>76.6(8.3)</td>
<td>0.052 0.121 0.998</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>24.2(2.8)</td>
<td>21.3(1.9)</td>
<td>22.7(2.9)</td>
<td>0.007** 0.495 0.669</td>
</tr>
<tr>
<td>Female sex</td>
<td>57.1%</td>
<td>30.8%</td>
<td>62.5%</td>
<td>0.363 0.993 0.454</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>124.5(11.6)</td>
<td>131.3(7.8)</td>
<td>160.6(27.0)</td>
<td>0.603 0.000** 0.000**</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>73.7(8.2)</td>
<td>72.5(8.0)</td>
<td>81.0(11.1)</td>
<td>0.997 0.193 0.132</td>
</tr>
</tbody>
</table>

Note: G1, healthy; G2, CI without hypertension; and G3, CI with hypertension. Values are presented as means and standard deviations and percentages. The \( t \)-test was used for means and standard deviations, and chi-square test for percentages. Significant differences are marked with \(^* p < 0.01\) between the G1 and G2. \(^{**} p < 0.01\) between the G1 and G3. \(^{***} p < 0.01\) between the G2 and G3.
WPCO identifies possible relationships by evaluating the match between the instantaneous phases of two signals.\textsuperscript{35}

The instantaneous phases, named $\phi_{1k,n}$ and $\phi_{2k,n}$, were calculated at each time $t_n$ and frequency $f_k$ for both signals.\textsuperscript{34} The indices $k$ and $n$ refer to discrete frequency and time, respectively. The basic frequency is scaled according to $\omega_k = 1.05\omega_{k-1}$ and the time is discretized by $t_n = n\tau$; $\tau = 1s$.\textsuperscript{34}

The phase difference between the components at a given frequency is $\phi_n$ and varies as a function of time $t$ (between 1 and T). The mean phasor $P$ is given by\textsuperscript{36}

$$ P = \frac{1}{T} \sum_{t=1}^{T} e^{i\phi_t}. \quad (4) $$

$T$ is the whole length of the time series. The phase coherence is equal to the amplitude of $P$. The synchronization is defined as the magnitude of $P$, i.e., the phase coherence. The value of the phase coherence is between 0 and 1. It quantifies the tendency of the phase difference between the two signals to remain constant at a particular frequency.\textsuperscript{35} If the phase coherence is high, the subject preserves a particular typical phase difference between the wavelet transforms at this frequency.

The phase difference for each subject can be represented as a unit phasor and the phasors combined in the complex plane. The term phase agreement was introduced to indicate the similarity between values of phase difference determined for different subjects.\textsuperscript{36} Subject $n$ has a typical phase difference $\phi_n$. The sample averaged phasor $M$ over all subjects is given by\textsuperscript{36}

$$ M = \frac{1}{N} \sum_{n=1}^{N} e^{i\phi_n}. \quad (5) $$

The phase agreement is defined as the amplitude of $M$. The phase shift is given by the phase of $M$.

### 2.F. Amplitude-adjusted Fourier transform (AAFT) surrogate signals

When two oscillations are unrelated, their phase difference continuously changes with time; thus, their phase coherence approaches zero. Significant coherence was determined during the evaluation of the coherence of two oscillatory time series that may have variable amplitude and frequency. The method of AAFT surrogates produces surrogates of a signal, in which any temporal relationship with another signal is destroyed but the spectrum of the original data is preserved. The AAFT method is used to estimate the parameters of the null distribution produced by unrelated or uncoupled time series with the same spectral characteristics as the original time series.\textsuperscript{30} With this method, a distribution of coherence values can be generated by subjecting the surrogate signals to exactly the same procedures as the real data. The actual coherence value can be characterized in terms of its rank relative to this distribution (i.e., how many of the surrogate coherence values it exceeds). If the rank is high (close or equal to 100% of the surrogate values) then the actual coherence value is unlikely to have arisen by chance from unrelated signals.\textsuperscript{30} AAFT surrogate signals were generated by shuffling the phases of the original time series to create a new time series with the same means, variances, and autocorrelation functions as the original sequences but without any phase relations.\textsuperscript{35} We then averaged 100 WPCOs from surrogate signals. A WPCO from the original recording was considered statistically significant when it was two standard deviations above the mean surrogate coherence.

### 2.G. Statistical analysis

The phase coherence, age, BMI and BP were expressed as the means (standard deviations) and sex as percentages. The data of each subject were tested for normality (Kolmogorov–Smirnov test) at the group level and for homogeneity of variance (Levene test) to ensure that the values fulfilled the assumption required by the parameter analysis. Significant differences between the characteristics of healthy elderly subjects and of the CI patients with or without hypertension were determined using a t-test (for means and standard deviations), and the chi-square test (for percentages). Two-way ANOVA with factors CI and hypertension were used to determine the main effects on the phase coherence. Post-hoc analyses of the two groups were performed using Bonferroni comparison tests. A difference with $p < 0.05$ was considered statistically significant.

### 3. RESULTS

In this study, periodic oscillations of the Delta [HbO$_2$] signals in the left and the right prefrontal lobes were identified at four frequencies intervals: (I, 0.6–2 Hz; II, 0.145–0.6 Hz; III, 0.052–0.145 Hz; and IV, 0.021–0.052 Hz) (Fig. 1).

Figure 2 shows an example of the phase coherence the left and right prefrontal Delta [HbO$_2$] oscillations and the mean and two standard deviations of AAFT surrogate signals. The phase coherence between the left and right prefrontal Delta [HbO$_2$] oscillations was significant in the four intervals from I to IV.

Figure 3 shows a comparison of the phase coherences of the left and right prefrontal Delta [HbO$_2$] signals among the three groups. The phase coherences in intervals III and IV were significantly lower in CI with hypertension than in healthy elderly subjects ($F = 12.974, p = 0.001$ for III; $F = 10.073, p = 0.004$ for interval IV). Also, the phase coherence in interval III was significantly lower in CI without hypertension than in healthy elderly subjects ($F = 9.909, p = 0.004$). In addition, the phase coherence in interval IV showed significant difference between CI with hypertension and without hypertension ($F = 5.665, p = 0.028$).

As shown in Fig. 4, the phase agreement in interval III showed evident difference between Group Healthy and Group CI with hypertension. Also, the phase agreement in interval IV showed evident difference between Group CI with hypertension and without hypertension. However, the phase shift did not show evident difference in these intervals (Fig. 5).
Typical time series of the simultaneous recordings of Delta [HbO$_2$] signals from a healthy elderly person (a) in the left prefrontal lobe; (b) in the right prefrontal lobe; and (c) the average wavelet amplitude. The vertical lines indicate the outer limits of the frequency intervals: I (0.6–2 Hz), II (0.145–0.6 Hz), III (0.052–0.145 Hz), and IV (0.021–0.052 Hz).

**Fig. 1.** Typical time series of the simultaneous recordings of Delta [HbO$_2$] signals from a healthy elderly person (a) in the left prefrontal lobe; (b) in the right prefrontal lobe; and (c) the average wavelet amplitude. The vertical lines indicate the outer limits of the frequency intervals: I (0.6–2 Hz), II (0.145–0.6 Hz), III (0.052–0.145 Hz), and IV (0.021–0.052 Hz).

### 4. DISCUSSION

In this study, the phase relationship between simultaneously measured left and right prefrontal Delta [HbO$_2$] signals of healthy elderly and CI patients with hypertension was assessed using wavelet-based phase coherence analysis. Our results show that the phase coherence in intervals III and IV exhibited significantly lower level in the CI patients with hypertension than in the healthy elderly subjects. Most strikingly, the hypertension combined with CI did show significant effects on the phase coherence in the CI patients.

The WPCO indicates the consistency of the phase delay between two signals and can quantify the stability of phase difference. It allows the identification of significant coherence even at low common power; this capability is particularly important when low-frequency components significantly contribute to cardiovascular signals. The phase agreement indicates the similarity between values of phase difference determined for different subjects. If it is high, the subjects agree about the typical phase difference between the wavelet transforms of left and right prefrontal Delta [HbO$_2$] signals at this frequency. The high agreement in these components indicates the synchronization of neural activation in the left and right prefrontal regions in healthy elderly subjects during resting state.

The cerebral oscillations in interval III originated locally from intrinsic myogenic activity of smooth muscle cells and these components reflect neural control of the cerebral circulation. It has been demonstrated that there is strong functional connectivity among spontaneous fluctuations of distinct regions of the brain in the low frequency range (interval III) in the resting state. Functional connectivity is characterized by wavelet phase coherence.

**Fig. 2.** Phase coherence (solid line) of the left and right prefrontal Delta [HbO$_2$] signals, mean (dashed line) and two standard deviations (dotted dashed line) of AAFT surrogate signals.

**Fig. 3.** Comparison of the phase coherence among the Group Health, Group CI with hypertension and Group CI without hypertension. Frequency intervals: I (0.6–2 Hz), II (0.145–0.6 Hz), III (0.052–0.145 Hz), and IV (0.021–0.052 Hz). Significant differences are marked with **$p < 0.01$** between the Group CI without hypertension and Group Healthy, *$p < 0.01$* between the Group CI with hypertension and Group Healthy, †$p < 0.05$ between the Group CI with hypertension and without hypertension.

**Fig. 4.** Phase agreement of the healthy elderly and the subjects with cerebral infarction (CI) in the four frequency intervals. Frequency intervals: I (0.6–2 Hz), II (0.145–0.6 Hz), III (0.052–0.145 Hz), and IV (0.021–0.052 Hz).
by a temporal correlation between two raw time series in the low frequency interval (0–0.1 Hz). \[\text{Sasai et al.}^{16}\] reported that functional connectivity between homologous cortical regions of the contralateral hemisphere showed high coherence over a wide frequency range (0.009–0.1 Hz) based on Delta [HbO$_2$] signals. In the present study, the phase coherence in interval III exhibited significantly lower level in the CI patients with or without hypertension than in the healthy elderly subjects.

Clinical studies have demonstrated that resting-state connectivity is altered in disorders such as stroke, suggesting a disruption of neuronal and/or vascular factors that contribute to high correlation in resting-state connectivity networks. \[\text{Stroke lesions cause neural dysfunction both at the lesion site and in remote brain regions.}^{20}\]

Our results show that the lesion resulted in an altered phase synchronization of the left and right prefrontal oscillations. This further conforms a disruption of resting-state connectivity of left and right prefrontal networks in the CI patients.

The oscillations in interval IV are closely regulated through tight neurovascular coupling and partial autonomic control. \[\text{The recordings lasted 900 s and oscillations with}^{28}\]

In the present study, the high phase agreement in interval IV indicated the consistency of the phase delay between left and right prefrontal Delta [HbO$_2$] oscillations under the control neurogenic origins in healthy elderly subjects. However, the phase coherence in interval IV was significantly lower in Group CI without hypertension than in the Group Healthy. This suggests a disruption of resting-state connectivity of left and right prefrontal networks.

It has been demonstrated that hypertension has significant influence on the phase coherence of the left and right prefrontal regions in elderly subjects. \[\text{As there may be some differences in the vessel stiffness of ECA and MCA, the phase of cardiac pulsation in the left and hemisphere may be not in full synchrony.}^{47}\]

4.A. Methodological considerations

NIR light must first pass through the superficial tissue layers (scalp and skull) before reaching the cortex. Therefore, these superficial layers may provide noise as well as nonspecific hemodynamic variations and this would contaminate the measured signal. \[\text{Clinical studies have demonstrated that resting-state connectivity networks may have variable amplitude and frequency. The test was performed by generating AAFT surrogate signals via shuffling of the phases of the original time series to create a new time series with the same means, variances, and autocorrelation functions (and therefore the same power spectra) as the original sequences but without any phase relations. When the coherence value is equal to the standard deviations above the mean surrogate coherence, a temporally constant interference possibly exists between the signals regardless of their spectral similarities or differences.}^{35}\]

The left and right prefrontal tissue oxyhemoglobin oscillations have been demonstrated to exhibit significant WPCOs in intervals from I to IV in the healthy elderly subjects using AAFT. \[\text{The recordings lasted 900 s and oscillations with frequency below 0.01 Hz would be represented with fewer than ten cycles. This may result in an unreliable detection of the amplitude within the interval. Due to the limited recordings period, we did not analyze the oscillations in frequency intervals V (0.095–0.02 Hz) and VI (0.005–0.0095 Hz), which were identified and investigated by Stefanovska et al.}^{42}\]

4.B. Summary

The phase relationship between simultaneously measured left and right prefrontal Delta [HbO$_2$] signals of healthy elderly and CI patients was assessed using wavelet-based phase coherence analysis. Our results show that the phase coherence in intervals III and IV exhibited significantly lower level in the CI patients with hypertension than in the healthy elderly subjects. Moreover, the hypertension did show significant effects on the phase coherence in the CI patients. This study provides new insight into the phase dynamics of cerebral oxygenation and may be useful in assessing the risk for stroke.
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