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Age-related alterations in phase synchronization of oxyhemoglobin concentration changes in prefrontal tissues as measured by near-infrared spectroscopy signals

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ABSTRACT

The prefrontal cortex plays an important role in planning complex cognitive behavior, personality expression, and decision making. This study aims to assess the phase synchronization of signals of the oxyhemoglobin concentration changes ($\Delta[HbO_2]$) in the left and right prefrontal tissues through near-infrared spectroscopy (NIRS) with wavelet phase coherence (WPCO) method. The NIRS signals were continuously recorded from the left and right prefrontal lobes in 43 healthy elderly subjects (age: 69.6 $\pm$ 8.4 years) and 40 young healthy subjects (age: 24.5 $\pm$ 1.7 years) during the resting state. Phase synchronization between the left and right prefrontal oscillations in six frequency intervals (I, 0.6–2 Hz; II, 0.145–0.6 Hz; III, 0.052–0.145 Hz; IV, 0.021–0.052 Hz; V, 0.0095–0.021 Hz; and VI, 0.005–0.0095 Hz) was analyzed using the WPCO method. The WPCO values of elderly subjects were significantly lower in frequency intervals I ($F = 7.376$, $p = 0.010$) and III ($F = 6.418$, $p = 0.016$) than those of the young subjects. Low phase coherence in intervals I and III indicates reduced synchronization of cardiac activity in the prefrontal area and weakened prefrontal functional connectivity, respectively.

Introduction

Several studies investigated strong correlations among spontaneous fluctuations in distinct regions of the brain, termed as "resting-state functional connectivity" (RSFC), through functional magnetic resonance imaging (fMRI) (Damoiseaux et al., 2006; De Luca et al., 2006; Fox and Raichle, 2007) and near-infrared spectroscopy (NIRS) (Lu et al., 2010; White et al., 2009; Zhang et al., 2010). RSFC, an important feature of healthy brain functions, is mainly intrinsic and involves information processing used to interpret, respond, and predict environmental demands (Raichle, 2010).

Normal aging is associated with marked structural and functional alterations in cardiovascular and cerebrovascular systems (Safonova et al., 2004). Wang et al. (2010) investigated age-related changes in large-scale brain functional networks during memory encoding and recognition; they found age-related changes mainly in long-range connections with widespread reductions in the fronto-temporal and temporo-parietal regions, as well as few age-related increases in the posterior parietal regions. Li et al. (2015) demonstrated that older individuals exhibited weakened RSFC between the supplementary motor area and the left anterior insular cortex. Geerligs et al. (2014) reported that aging considerably affects connectivity not only within functional networks but also between different functional networks in the brain. Brain networks in the elderly show reduced modularity (less distinct functional networks) and local efficiency.

Decline in cognitive function in terms of age, postural instability, and falls is common in old people (Moro et al., 2014). Although the causes of cognitive function impairments are multifactorial, the prefrontal cortex (PFC) in an elderly population can be used as an important predictor of cognitive function. Functional NIRS studies indicated that the PFC is involved in the maintenance of attention-demanding balance tasks (Mihara et al., 2008; Moro et al., 2014). Hagen et al. (2014) demonstrated the presence of age-related differences upon PFC activation. Our previous study showed reduced spontaneous activity in the PFC of aged individuals (Li et al., 2013). Alterations in resting-state coherence may be utilized as a sensitive and early indicator of aging diseases (Zhang and Raichle, 2010). Aging affects functional connectivity among brain areas; however, minimal information is known about the effects of aging on the phase synchronization of the left and right prefrontal neural activation in elderly subjects in various frequency bands.

Phase synchronization is the relationship between the phases of two oscillatory components at a specific frequency (Bernjak et al., 2012).

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Phase synchronization is high if a phase difference is maintained between two signals. Wavelet phase coherence (WPCO) can be used to evaluate this match between the instantaneous phases of the two signals (Bernjak et al., 2012). WPCO analysis is used to analyze the relationship among oscillations in skin blood flow, temperature and oxygen saturation, intracranial pressure, and arterial blood pressure (ABP) signals within specific frequency ranges (Bandrivskyy et al., 2004; Bernjak et al., 2012; Gao et al., 2015; Han et al., 2014; Kvandal et al., 2013).

NIRS is an increasingly popular technology for studying brain function. This technique can be used to determine changes in local oxygenated and deoxygenated hemoglobin concentrations as an indirect measure of neuronal activity similar to the blood oxygen level-dependent fMRI signals (Ferrari and Quaresima, 2012; Medvedev 2014; Obrig et al., 2000). In addition to low cost and portability, NIRS has reasonable spatial and excellent temporal resolution (Medvedev, 2014). The temporal correlation of oxyhemoglobin concentration ($\Delta[HbO_2]$) oscillations exhibits robust spatial interactions over the prefrontal, temporal, and occipital lobes (Mesquita et al., 2010), as well as frequency-specific functional connectivity within the frequency range of 0.009–0.1 Hz (Wu et al., 2008; Sasai et al., 2011).

This study aims to assess changes in the phase synchronization of prefrontal tissue $\Delta[HbO_2]$ signals measured through NIRS with wavelet-based coherence method in healthy elderly and young subjects during the resting state. The wavelet-based approach may provide an easy and non-invasive method for assessing the degenerative processes of brain function.

Methods and materials

Subjects

Eighty-three subjects, including 43 healthy elderly individuals (age: 69.6 ± 8.4 years; Group elderly) and 40 healthy young individuals (age: 24.5 ± 1.7 years; Group young), were recruited from Shandong University. Elderly healthy subjects (age > 60) consisted of retired staff, whereas young subjects (30 > age > 20) comprised postgraduate students from the university. Exclusion criteria included the following: presence of diabetes mellitus, hypertension, and subarachnoid hemorrhage; insufficient heart, lung, kidney, and liver functions; smoking or drinking habits; and additional medications (angiotensin-converting enzyme, inhibitors/angiotensin II receptor blockers, and calcium channel blockers). A diagnosis of hypertension was performed when systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg (Jones et al., 2003). 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 blood pressure, was recorded (Table 1). Informed consent was obtained from all participants. The experimental procedures were approved by the Human Ethics Committee of Shandong University and in accordance with the ethical standards specified by the Helsinki Declaration of 1975 (revised in 1983).

Table 1
Characteristics of the participants.

Parameter	Old	Young	p for difference
Age (years)	69.6 (8.4)	24.5 (1.7)	0.000***
BMI	24.1 (3.5)	22.5 (1.2)	0.055
Female sex	47.4%	32.6%	0.319
Systolic blood pressure (mm Hg)	119.7 (27.6)	117.4 (11.9)	0.750
Diastolic blood pressure (mm Hg)	71.6 (7.1)	71.2 (8.0)	0.799

Values are presented as means and standard deviations and percentages.
p values for differences are calculated using t-test for means and standard deviations, and Chi-square test for percentages, ***<0.001.

Measurement

The left and right prefrontal $\Delta[O_2Hb]$ signals were obtained from simultaneous measurements during the resting state for 20 min. After recording the basic information of the subjects, measurements were performed on the subjects in their comfortable sitting posture to minimize head and wrist movements. The $\Delta[O_2Hb]$ signals in the left and right PFC regions of the subjects were recorded with the tissue saturation An Heng monitor (TSAH-200, developed by Tsinghua University, China). This method was previously described by Li et al. (2014). The forehead of each subject was cleaned with medical alcohol. Sensors were fixed with a flexible adhesive fixation pad, and an elastic band was carefully placed symmetrically on each side of the forehead (15 mm lateral to the cerebral midline) to avoid the sagittal sinus and at least 20 mm above the eyebrow to avoid the frontal sinus (Li et al., 2010). Before the measurements, the sensors were secured with a black elastic plaster wrapped around the forehead to ensure the absence of background light (Li et al., 2010). The sampling rate of the NIRS-measured $\Delta[O_2Hb]$ signals of the PFC regions was set at 10 Hz.

Data preprocessing

After removing the abnormal points via the moving average method, the $\Delta[O_2Hb]$ signals were bandpass-filtered with a fifth-order Butterworth filter at a low cutoff frequency of 0.005 Hz to remove slow variations and at a high cutoff frequency of 2 Hz to remove uncorrelated noise components. The upper limit of 2 Hz was also established to include heart rate frequency, whereas the lower limit was selected to include the possible regulatory mechanisms of the tissue oxygenation signal (Li et al., 2010, 2013; Shiogai et al., 2010).

Wavelet-based phase coherence analysis

Wavelet transform and wavelet-based coherence analyses were described in our previous studies (Cui et al., 2014; Li et al., 2014). Briefly, the continuous wavelet transform plots the function onto the time–frequency plane. Wavelet amplitude (WA) was averaged to indicate frequency specificity over time domain. Coherence was obtained from two complex oscillatory time series with internal correlations. The instantaneous phases, i.e., $\varphi_{1k,n}$, and $\varphi_{2k,n}$, were calculated at each time t_n and frequency f_k for both signals (Bandrivskyy et al., 2004). The indices k and n refer to discrete frequency and time, respectively.

The phase difference between the components at a given frequency is φ_t and varies as a function of time t (between 1 and T). The mean phasor P is given by the following equation (Han et al., 2014; Kvandal et al., 2013):

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

where T is the whole length of the time series, and the amplitude of P is the phase coherence, which defines synchronization. The value of phase coherence, which is between 0 and 1, quantifies the tendency of the phase difference between the two signals to remain constant at a particular frequency (Bernjak et al., 2012). High-phase coherence indicates a typical phase difference between the wavelet transforms at this frequency.

The term phase agreement indicates the similarity between the values of phase differences for different subjects (Kvandal et al., 2013). The subject n exhibits the typical phase difference φ_n. The sample-averaged phasor M over all subjects is given by:

$$M = \frac{1}{N}\sum_{n=1}^{N} e^{i\varphi_n}. \quad (2)$$