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Evaluating interhemispheric synchronization and cortical activity in acute stroke patients using optical hemodynamic oscillations

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Abstract

Objective. An understanding of functional interhemispheric asymmetry in ischemic stroke patients is a crucial factor in the designs of efficient programs for post-stroke rehabilitation. This study evaluates interhemispheric synchronization and cortical activities in acute stroke patients with various degrees of severity and at different post-stroke stages. *Approach.* Twenty-three patients were recruited to participate in the experiments, including resting-state and speed finger-tapping tasks at week-1 and week-3 post-stroke. Multichannel near-infrared spectroscopy (NIRS) was used to measure the changes in hemodynamics in the bilateral prefrontal cortex (PFC), the supplementary motor area (SMA), and the sensorimotor cortex (SMC). The interhemispheric correlation coefficient (IHCC) measuring the synchronized activities in time and the wavelet phase coherence (WPCO) measuring the phasic activity in time-frequency were used to reflect the symmetry between the two hemispheres within a region. The changes in oxyhemoglobin during the finger-tapping tasks were used to present cortical activation. *Main results.* IHCC and WPCO values in the severe-stroke were significantly lower than those in the minor-stroke at low frequency bands during week-3 post-stroke. Cortical activation in all regions in the affected hemisphere was significantly lower than that in the unaffected hemisphere in the moderate-severe stroke measured in week-1, however, the SMC activation on the affected hemisphere was significantly enhanced in week-3 post-stroke. *Significance.* In this study, non-invasive NIRS was used to observe dynamic synchronization in the resting-state based on the IHCC and WPCO results as well as hemodynamic changes in a motor task in acute stroke patients. The findings suggest that NIRS could be used as a tool for early stroke assessment and evaluation of the efficacy of post-stroke rehabilitation.

List of Abbreviations

NIRS	near-infrared spectroscopy	IHCC	interhemispheric correlation coefficient
PFC	prefrontal cortex	WPCO	wavelet phase coherence
SMA	supplementary motor area	WT	wavelet transform
SMC	sensory motor cortex	AAFT	amplitude adjusted Fourier transform
HbO	oxyhemoglobin	NIHSS	national institute of health stroke scale
△HbO	concentration of oxyhemoglobin	NVC	neural vascular coupling
HbR	deoxyhemoglobin	fMRI	functional magnetic resonance imaging
tHb	total hemoglobin		
HRF	hemodynamic response function	SD	standard deviation

1. Introduction

Stroke is an acute neurological disease caused by disruption of the blood supply to the brain, of which approximately 80% are ischemic resulting from an obstruction of blood flow, and 15% are due to a primary intracerebral hemorrhage [1]. Stroke is the second leading cause of death and function impairments worldwide. Especially, in the East Asia region, the incidence of stroke has been found to be the highest among all diseases [2]. Based on the duration from the onset of the disease, the post-stroke can be categorized into the acute, early subacute, subacute, and chronic stages. Previous studies have indicated that the acute and early subacute stages are the most critical time for neural plasticity, which influences further neurologic and motor recovery [3]. A previous functional magnetic resonance imaging (fMRI) study indicated that decreases in interhemispheric functional connectivity associates well with upper extremity impairment after stroke [4]. Therefore, interhemispheric functional connectivity could be used as a potential biomarker to reflect current status and future functional recovery in ischemic stroke patients [5].

Various quantitative indices have been developed for evaluating spontaneous hemodynamic oscillation between two hemispheres in resting as well as for motor tasks assessments [6]. The interhemispheric correlation coefficient (IHCC) was previously used to measure the linear relationship among hemodynamic signals between the two hemispheres in resting-state [7, 8]. In addition to time-domain IHCC analysis, frequency-domain coherence analysis provides magnitude and phase relationships between two signals for extracting characteristics of interactions between two brain areas. Especially, window-based phase coherence function, wavelet phase coherence (WPCO) can be used to determine locally phase-shift behavior between two independent signals in the time-frequency domain [9, 10]. The wavelet transform (WT) offers a window of adjustable length, which is suitable for analyzing low frequency physiological oscillation signals. Moreover, WT also provides simultaneous localization in the time and frequency domain [11], which is reliable for analyzing the instantaneous phase difference between two independent signals. Previous studies have explored the quantitative hemodynamic interhemispheric synchronization in stroke patients [9, 10, 12]. The results of those studies showed significant desynchronized at low-frequency bands (<0.1 Hz) indicating an asymmetry between the two hemispheres in stroke patients.

Moreover, the neural vascular coupling (NVC) is a function that serves as a physiological self-regulation mechanism that allows the brain to work and function normally during a functional task [13]. In a healthy individual, the cortical region related to a given task is supplied more blood than other regions in order to maintain adequate oxygen and glucose necessary for neuron activity [14]. However, this phenomenon is hypothesized to be affected differently by post-stroke severities and stages, which requires further supporting evidence. In contrast to the resting-state synchronization measurement, the change in concentration of oxyhemoglobin (△HbO) was popularly used to assess cortical activation in a specific cerebral cortex through external stimulation such as a motor task due to its sensitive to the change in brain physiological signal [15].

Among various neuroimaging techniques, near-infrared spectroscopy (NIRS) shares similar physiological basics to fMRI in terms of monitoring cerebral cortical activation [16]. In addition to its low cost and portability, NIRS presents various features in clinical studies such as simple setup for various testing positions with adequate temporal resolution (up to 10 Hz) during data recording. The frequency distribution of functional brain signals measured using NIRS reflects a similar origin to that of physiological signals [17, 18]. These features of NIRS make it an appropriate technique for use in brain functional interhemispheric synchronization and cortical activation during resting-state conditions and motor tasks.

Instead of observing resting synchronization between the two hemispheres in a specific type of stroke patient [19], investigating impairments of interhemispheric synchronization and cortical activation in patients with various degrees of stroke severity and measurement times are appealing. We hypothesized that patients with different degrees of stroke severity at various measurement times post-stroke would exhibit different levels of resting-state interhemispheric symmetry presented by IHCC and WPCO as well as cortical activation in the speed finger-tapping tasks observed from concentration of oxyhemoglobin (△HbO) analyses of NIRS data. Furthermore, we also investigated the correlation between the National Institute of Health Stroke Scale (NIHSS) score at admission and the IHCC and WPCO assessed at different stroke stages.

2. Materials and methods

2.1. Participants

Twenty-three stroke patients were recruited from National Cheng Kung University Hospital (NCKUH) in Tainan, Taiwan, to participate in the study. Participants were divided into three groups with different degrees of stroke severity as measured using the NIHSS score at admission [20], including severe-stroke (7 patients, age: 71.6 ± 8.5 years; NIHSS: 21.4 ± 4.8), moderate-stroke (9 patients, age: 70.2 ± 14.3 years; NIHSS: 11.78 ± 2.64), and minor-stroke (7 patients, age: 58.1 ± 10.4 years; NIHSS: 3.57 ± 0.98). The inclusion criterion for the stroke patients was first-time unilateral ischemic

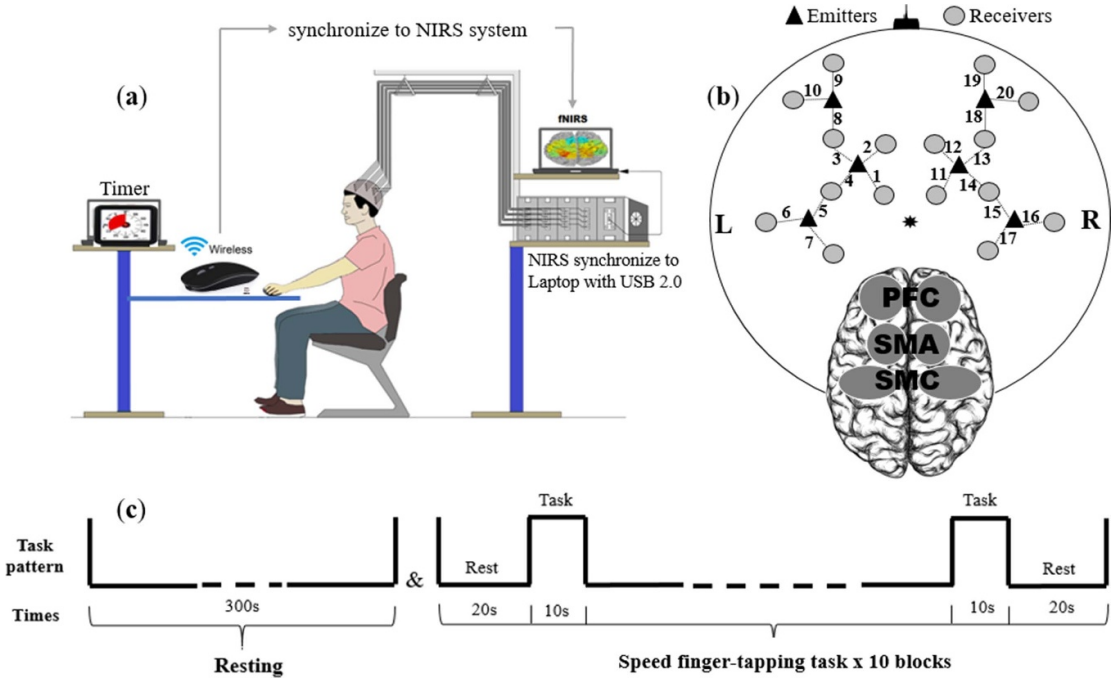

Figure 1. The experimental design. (a) The experimental setup for the NIRS recording. (b) The montage arrangement of the NIRS probe geometry covering bilateral PFC, SMA, and SMC. Gray circles indicate NIRS emitters, Black triangles indicate NIRS receivers, dotted lines with numbers indicate NIRS optical channels. (c) The experimental tasks include resting-state and speed finger-tapping tasks in block design.

stroke within seven days from onset. All of our patients received standard post-stroke care according to the AHA/ASA guideline for the early management of patients with acute ischemic stroke in stroke unit of NCKUH. The standard post-stroke care includes the use of anti-thrombotic agents according to the stroke subtypes, the control of blood pressure, blood sugar, lipid profile and also rehabilitation therapy according to the suggestion of rehabilitation physicians. The rehabilitation would start as early as possible while the stroke symptoms were stabilized. Those with other neurological diseases or upper limb orthopedic conditions were excluded criteria.

2.2. Experiment design

Patients received two sessions of the NIRS recording at week-1 (days 5 to 7) and week-3 (days 14 to 28) after stroke, respectively. The experiment was conducted in a quiet, dimly-lit examination room. Prior to the experiment, all subjects were introduced to the purpose of the study, the experimental procedure and the time expected to complete the study. Participants were also practiced familiarizing themselves with the speed finger-tapping task using their hand contralateral to the lesion (i.e. affected hand) with index finger and middle finger clicking on the right and left of the computer mouse as fast as possible. Following practice task, the participants sat comfortably on a hospital bed with back-head support and were tested in the sitting position. After positioning the cap over the head, NIRS data recording was initiated simultaneously with the experimental tasks. The experiments comprised a 5 min resting-state session followed by a finger-tapping task session with ten repetitions of 10 s of tasks and 20 s of rest. The start, stop, and the number of task blocks were displayed on a LCD monitor placed in front of the participants. A wireless computer-mouse was synchronized to the NIRS system for the purpose of recording the number of tapping in each block of the motor task. Figure 1 shows the details of the experimental setup, the NIRS montage design, and the experimental tasks.

2.3. NIRS recording and preprocessing

The commercial multi-channel continuous-wave NIRScout (NIRX Medizintechnik GmbH, Germany) was used in this study. Each emitter in the NIRScout system consists of two light sources with wavelengths of 760 and 850 nm. The system measures the changes in oxy-hemoglobin (HbO), deoxy-hemoglobin (HbR), and total hemoglobin (tHb) at a sampling frequency of 10 Hz. A montage arrangement of six NIRS light emitters and sixteen receivers was used to compose 20-optical channel arrays at emitter receiver distance of 30 mm based on the EEG 10-20 system, which covers the bilateral prefrontal cortex (PFC), supplementary motor area (SMA), and sensorimotor cortex (SMC), as shown in figure 1(b).

The nirsLAB_v2016 (NIRScout, group) was used to convert optical density (OD) of the NIRS recording to the $\triangle$HbO, which has been proposed to be the most sensitive to changes in physiological signals in the brain [15]. In order to determine the quality of the NIRS signals, we analyzed the power spectrum of

each NIRS data after detrending. A frequency peak at around 1 Hz reflects the cardiac pulsation in the NIRS signal, indicating good contact quality between the optical probes and the scalp [21]. For further analysis, all data was processed offline in MATLAB R2018b (MathWorks, USA).

2.4. Data analyses

2.4.1. IHCCs in resting-state NIRS

The NIRS recordings were first band-pass filtered by a 3rd order Butterworth with a cutoff frequency of 0.02–2 Hz. The filtered signal was further categorized into four frequency bands of interest: I (0.7–2 Hz); II (0.15–0.7 Hz); III (0.06–0.15 Hz), and IV (0.02–0.06 Hz). Previous study has indicated that these four frequency components are mainly related to the responses of cardiac rate, respiratory rate, myogenic, and neuronal activity, respectively [22]. The HbO correlation coefficient of each pair of channels was calculated in four frequency bands of interest and averaged into three cortical regions (the PFC, SMA, and SMC) to present the symmetry of the two hemispheres in the same region. The IHCC value ranges between −1 and 1, where '1' indicates a perfect symmetry and '−1' means total asymmetry between the two hemispheres within a given region [7, 23].

2.4.2. WPCO of resting-state NIRS

WPCO was developed to reflect the resting-state synchronization between HbO signals measured from two different brain regions [9, 10, 18]. WPCO is based on a continuous WT in a time-frequency domain. The spectral properties of signal $x(t)$ in the time-frequency domain presents the complex spectral function $X(\omega_m, t_n) = a_{m,n} + ib_{m,n}$. We obtained the amplitude $|X_{m,n}|$ and the phase $\varphi_{m,n}$ from each time $t_n$and frequency ω_k. From two signals, $x1(t)$ and $x2(t)$, the derived phases $\varphi_{1m,n}$ and $\varphi_{2m,n}$, were used to calculate the relative phase difference $\Delta\varphi_{m,n} = \varphi_{2m,n} - \varphi_{1m,n}$ for the purpose of phase synchronization [24]. The cosine and sine components of the phase difference were computed and then averaged over time for the entire length of the signal. Finally, we used the intensity of the first Fourier mode of the distribution to calculate the phase coherence function by using (1):

$$C_\varphi(\omega_m) = \sqrt{\langle cos\Delta\varphi_{m,n}\rangle^2 + \langle sin\Delta\varphi_{m,n}\rangle^2}. \quad (1)$$

The phase coherence function $C_\varphi(\omega_m)$ value ranged between 0 and 1. A WPCO value equals '1' indicated the signals of two hemispheres were well synchronized, and a WPCO value equals '0' indicated desynchronization between regions in the two hemispheres at a specific frequency ω_m. In addition, the amplitude adjusted Fourier transform (AAFT) was adopted in this study to investigate the significance of the WPCO between two HbO signals [25]. A total of 100 surrogate signals were generated with the key features of the original time series, including the mean, variance, and distribution, but without preserving any phase relationships [26]. The average of WPCO from the 100 surrogate signals was then calculated. The result was considered to be statistically significant when the WPCO of two HbO signals equaled or was higher than the average WPCO of the 100-surrogate data plus two standard deviations [9]. The WPCO was calculated for each pair of NIRS channels at four frequency bands. Finally, the WPCO values of all paired channels within a cortical region were averaged to present the symmetry of resting-state hemodynamic oscillation in acute ischemic stroke patients.

2.4.3. Cortical activation analysis during motor task

The concentration changes in HbO were used in the study as a biomarker to reflect the cortical activation during the motor task [15]. A 3rd order Butterworth band-pass filtered with a cutoff frequency of 0.005–0.2 Hz was applied to eliminate the potential slow drift motion artifact and high-frequency components from the respiratory rate and cardiac pulsation. We defined △HbO as the mean of △HbO at 15 s from the beginning of the task to 5 s after the end of the task in each block due to delayed hemodynamic responses to the task [27]. The △HbO from block 2 to block 10 of all NIRS channels within a cortical region were then averaged to obtain the block averaged response in each cortical region.

2.5. Statistical analyses

All data are presented as mean ± standard deviation (mean ± SD). Fisher's Z-transform was applied for non-Gaussian distribution of IHCC and WPCO before statistical analysis. The transformed IHCCs and WPCO values in each cortical region of PFC, SMA, and SMC at each frequency band were analyzed using a two-way mixed analysis of variance (ANOVA) by group (minor-stroke, moderate-stroke, and severe-stroke) as the between-subject factor and measurement time (week-1 and week-3) as the within-subject factor. Furthermore, the IHCC and WPCO values in four-frequency bands were also applied to investigate the relationship with varied initial NIHSS scores in acute stroke patients using nonparametric Spearman correlation analysis methods. To compare the degree of regional activation during the finger-tapping task, we performed two-way mixed ANOVA by group (minor-stroke and moderate-stroke) as the between-subject factor and three within-subject factors (measurement time: week-1 and week-3; cortical region: PFC, SMA, and SMC; and hemisphere: affected and unaffected). The Bonferroni was used as a post-hoc test for multiple comparison. A p-value $\leqslant 0.05$ was considered statistically significant in all the tests.

3. Results

3.1. Subjects characteristic

Table 1 lists clinical information of the recruited stroke patients including age, gender, brain lesion side, location of stroke, NIHSS, and stroke severity. The average ± SD of age were 71.6 ± 8.5 years, 70.2 ± 14.3 years, and 58.1 ± 10.4 years; gender (M/FM): 6/1, 6/3, 7/0; lesion side (L/R): 4/3, 6/3, 4/3; and NIHSS: 21.4 ± 4.8, 11.78 ± 2.64, and 3.57 ± 0.98 respectively for severe, moderate, and minor stroke groups.

3.2. IHCCs analysis of resting-state NIRS

Figure 2 shows representative IHCC in four frequency bands I–IV measured in week-3 post-stroke at the SMC region of a patient in the severe-stroke group. We can observe that the IHCCs at bands I and II, 0.84 and 0.81, are relatively high compared to 0.49 and 0.11 at the III and IV frequency bands.

The averaged IHCCs for all frequency bands for the three stroke groups measured at week-1 and week-3 are shown in table 2. The ANOVA results revealed a significant interaction effect with 87% of power ($F(2,20) = 4.98$, $p = 0.02$, $\eta^2 = 0.33$) and ($F(2,20) = 6.75$, $p = 0.01$, $\eta^2 = 0.40$) in the PFC; ($F(2,20) = 14.89$, $p = 0.00$, $\eta^2 = 0.60$) and ($F(2,20) = 5.40$, $p = 0.01$, $\eta^2 = 0.35$) for SMA, and ($F(2,20) = 9.37$, $p = 0.00$, $\eta^2 = 0.48$) and ($F(2,20) = 5.28$, $p = 0.14$, $\eta^2 = 0.35$) in the SMC measured at bands III and IV, respectively. The post-hoc tests showed that IHCC for bands III and IV in the severe-stroke patients was significantly lower than the case in the minor-stroke patients ($p = 0.02$, $p = 0.00$) and ($p = 0.02$, $p = 0.00$) for PFC and SMC respectively. In the SMA, the IHCCs for bands III and IV in the moderate-stroke patients and band IV in the severe-stroke patients were significantly lower than those in the minor-stroke patients ($p = 0.02$, $p = 0.01$, $p = 0.02$), respectively. Our results indicated that patients in the moderate-stroke and severe-stroke groups exhibited lower level of symmetry at low frequency bands III and IV between the two hemispheres in week-3 post-stroke.

3.3. WPCO analysis of resting-state NIRS

Figure 3 shows examples of the WPCO values at four frequency bands I-IV, which was measured in the SMC of a patient with a severe-stroke at week-3. The solid line indicates that the WPCO for the two HbO signals showed relatively low in averaged values of 0.50 and 0.59 for bands III (0.06–0.15 Hz) and IV (0.02–0.06 Hz) respectively.

Table 3 lists the averaged WPCO in all frequency bands of three groups measured at week-1 and week-3. The ANOVA results showed a significant interaction effect with 87% of power ($F(2,20) = 10.30$, $p = 0.00$, $\eta^2 = 0.51$) and ($F(2,20) = 6.61$, $p = 0.01$, $\eta^2 = 0.40$); ($F(2,20) = 6.02$, $p = 0.01$, $\eta^2 = 0.38$) and ($F(2,20) = 6.05$, $p = 0.01$, $\eta^2 = 0.38$); and ($F(2,20) = 16.71$, $p = 0.00$, $\eta^2 = 0.63$) and ($F(2,20) = 9.87$, $p = 0.00$, $\eta^2 = 0.50$) for bands III and IV in the PFC, SMA, and SMC, respectively. The post-hoc tests showed that the WPCO in bands III and IV in the severe-stroke patients was significantly lower than those in the minor-stroke patients ($p = 0.03$, $p = 0.01$) and ($p = 0.04$, $p = 0.00$) in the PFC and SMC, respectively. In the SMA, the WPCO at band IV in the severe-stroke patients was significantly lower than that in the minor-stroke patients ($p = 0.02$). The results indicated that the severe-stroke patients had lower symmetry in week-3 post-stroke compared to the minor-stroke group.

3.4. Correlation between NIHSS and resting-state NIRS synchronization

The nonparametric Spearman correlation was used to evaluate monotonic relationships between the NIHSS scores and the quantitative measurements of IHCCs and WPCO at week-1 and week-3. Figure 4 shows an example of the Spearman correlation between the NIHSS scores at admission and the IHCCs and WPCO in the SMC at band IV measured in week-1 and week-3 post-stroke in the 23 ischemic stroke patients. The results in week-3 showed obviously negative correlation coefficient which corresponds to a decreasing monotonic trend between NIHSS scores and the IHCC and WPCO.

Table 4 lists the values of Spearman correlation between NIHSS scores and the IHCC and WPCO of acute stroke patients in the PFC, SMA, and SMC measured in week-1 and week-3. The results showed a significantly decreasing monotonic trend between NIHSS and IHCC band III ($r = -0.75$, $p = 0.00$; $r = -0.60$, $p = 0.01$; $r = -0.68$, $p = 0.00$) and band IV ($r = -0.78$, $p = 0.00$; $r = -0.85$, $p = 0.00$; $r = -0.71$, $p = 0.00$) measured in week-3 for PFC, SMA, and SMC, respectively. In addition, a significant negative monotonic relationship is also found between NIHSS and the WPCO for band III ($r = -0.61$, $p = 0.00$; $r = -0.47$, $p = 0.02$; $r = -0.74$, $p = 0.00$) and band IV ($r = -0.79$, $p = 0.00$; $r = -0.80$, $p = 0.00$; $r = -0.78$, $p = 0.00$) measured in week-3 for the PFC, SMA, and SMC, respectively. Our results indicated that patients with higher degrees of severity would exhibit lower symmetry between the two hemispheres related to both time and phase oscillation.

3.5. Cortical activation during the motor task

There was only one-third of patients in the severe-stroke group could complete the speed finger-tapping tasks in week-1 and week-3 post-stroke. Therefore, data from the severe-stroke patients were pooled together with the moderate-stroke group

Table 1. Characteristics of acute stroke patients.

Subjects	Age	Gender	Lesion side	Lesion region	NIHSS	Stroke severity
1	66	M	R	MCA	24	Severe
2	86	M	L	Insular	10	Moderate
3	70	M	R	Insular	10	Moderate
4	70	M	L	MCA	12	Severe
5	86	M	R	MCA	17	Severe
6	76	M	L	MCA	24	Severe
7	76	M	L	MCA	29	Severe
8	76	M	L	Insular	20	Moderate
9	53	F	R	Insular	19	Moderate
10	67	M	L	IC	3	Minor
11	52	M	L	IC	3	Minor
12	85	F	R	Insular	9	Moderate
13	40	M	R	Thalamus	11	Minor
14	56	M	L	Basal ganglion	3	Minor
15	87	M	R	Insular	24	Moderate
16	71	M	L	Basal ganglion	3	Minor
17	57	M	R	Basal ganglion	3	Minor
18	64	M	R	Pons	5	Minor
19	67	F	L	MCA	22	Severe
20	59	M	L	Insular	8	Moderate
21	60	M	R	MCA	15	Severe
22	50	F	L	MCA	16	Moderate
23	66	M	L	Insular	12	Moderate

Note: F = female; M = male; L = left hemisphere; R = right hemisphere; MCA = middle cerebral artery; IC = inferior colliculus.

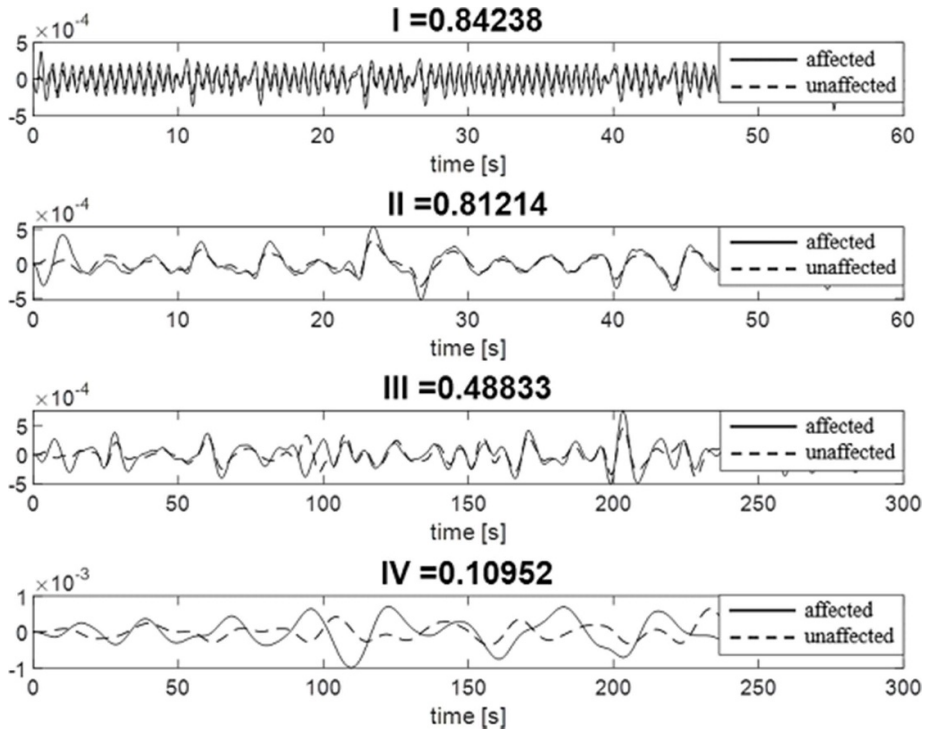

Figure 2. Representative NIRS recordings and the derived IHCC from SMC of a patient with severe-stroke measured in week-3. Relatively low IHCC values can be found at frequency bands of III and IV compared to higher frequencies of I and II. Note that the data are in different time and amplitude scales.

(moderate-severe stroke group) to compare with those of minor stroke group. There were no significant interaction in the finger-tapping rate between group and time ($F(1,12) = 1.98, p = 0.19, \eta^2 = 0.14$). The post hoc tests showed that there was no significant difference in the movement rate for both time ($p = 0.11$) and group ($p = 0.80$). Our results indicated a similar movement rate in all conditions.

Table 2. IHCC values in different cortical regions for patients with various stroke severities.

Regions	Bands	Severe-stroke		Moderate-stroke		Minor-stroke	
		Week-1	Week-3	Week-1	Week-3	Week-1	Week-3
PFC	I	0.87 ± 0.05	0.82 ± 0.15	0.88 ± 0.11	0.91 ± 0.06	0.89 ± 0.05	0.90 ± 0.04
	II	0.73 ± 0.15	0.58 ± 0.22	0.59 ± 0.24	0.70 ± 0.19	0.56 ± 0.27	0.78 ± 0.13
	III	0.58 ± 0.14	**0.42 ± 0.19**	0.61 ± 0.18	0.58 ± 0.20	0.56 ± 0.24	**0.81 ± 0.12**
	IV	0.56 ± 0.19	**0.35 ± 0.19**	0.63 ± 0.20	0.66 ± 0.18	0.74 ± 0.10	**0.84 ± 0.09**
SMA	I	0.91 ± 0.05	0.78 ± 0.20	0.78 ± 0.19	0.83 ± 0.15	0.88 ± 0.09	0.87 ± 0.07
	II	0.81 ± 0.07	0.55 ± 0.21	0.64 ± 0.16	0.71 ± 0.15	0.60 ± 0.20	0.83 ± 0.07
	III	0.76 ± 0.04	0.40 ± 0.18	0.53 ± 0.28	**0.51 ± 0.17**	0.63 ± 0.14	**0.82 ± 0.17**
	IV	0.68 ± 0.14	**0.41 ± 0.07**	0.6 ± 0.26	**0.56 ± 0.23**	0.73 ± 0.21	**0.83 ± 0.14**
SMC	I	0.88 ± 0.05	0.76 ± 0.27	0.80 ± 0.22	0.91 ± 0.06	0.80 ± 0.11	0.87 ± 0.06
	II	0.68 ± 0.21	0.48 ± 0.39	0.53 ± 0.26	0.60 ± 0.27	0.48 ± 0.28	0.74 ± 0.15
	III	0.67 ± 0.16	**0.26 ± 0.15**	0.60 ± 0.25	0.57 ± 0.30	0.50 ± 0.21	**0.82 ± 0.13**
	IV	0.60 ± 0.14	**0.27 ± 0.10**	0.56 ± 0.32	0.58 ± 0.30	0.65 ± 0.27	**0.85 ± 0.06**

Data: untransformed IHCC (mean ± SD) in stroke patients with various severities measured at week-1 and week-3 post-stroke.
$^{*}p \leqslant 0.05$ and $^{**}p \leqslant 0.01$ indicate significant between group differences.

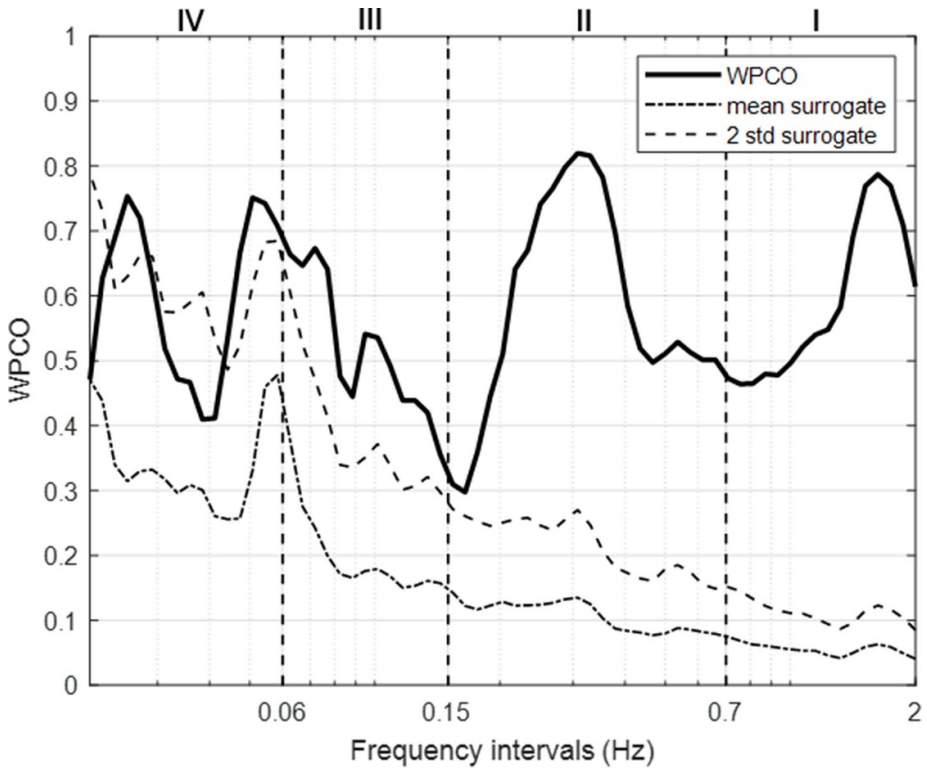

Figure 3. Representative WPCO measurement of a patient with severe-stroke measured at SMC region in week-3. The solid line indicates the WPCO of two HbO signals. The dotted line (…) and dashed line (- - -) show the mean and two standard deviations above the mean for the coherence calculated from 100 amplitude-adjusted Fourier transform (AAFT) surrogate signals, respectively. The vertical lines indicate the outer limits of the four frequency bands I–IV.

Figures 5(a) and (b) show representative hemodynamic response function (HRF) and the block average of △HbO in the affected SMC during the speed finger-tapping tasks from a severe and a minor stroke patient respectively. Result indicated a small fluctuation of HbO response to the tasks in the severe stroke patient. However, a large response is presented in the minor stroke patient.

Table 3. WPCO in different cortical regions for patients with various stroke severities.

Regions	Bands	Severe-stroke		Moderate-stroke		Minor-stroke	
		Week-1	Week-3	Week-1	Week-3	Week-1	Week-3
PFC	I	0.85 ± 0.12	0.86 ± 0.12	0.85 ± 0.16	0.85 ± 0.16	0.87 ± 0.07	0.80 ± 0.12
	II	0.62 ± 0.12	0.58 ± 0.16	0.50 ± 0.20	0.50 ± 0.18	0.51 ± 0.16	0.58 ± 0.16
	III	0.55 ± 0.09	**0.39 ± 0.10**	0.54 ± 0.18	0.50 ± 0.17	0.55 ± 0.11	**0.71 ± 0.16**
	IV	0.61 ± 0.12	**0.45 ± 0.06**	0.64 ± 0.17	0.65 ± 0.16	0.67 ± 0.11	**0.75 ± 0.08**
SMA	I	0.85 ± 0.19	0.83 ± 0.16	0.80 ± 0.23	0.85 ± 0.14	0.83 ± 0.13	0.78 ± 0.13
	II	0.72 ± 0.19	0.62 ± 0.20	0.49 ± 0.18	0.54 ± 0.15	0.47 ± 0.15	0.57 ± 0.20
	III	0.71 ± 0.18	0.56 ± 0.11	0.53 ± 0.22	0.55 ± 0.15	0.56 ± 0.15	0.74 ± 0.17
	IV	0.68 ± 0.18	**0.52 ± 0.05**	0.61 ± 0.19	0.65 ± 0.12	0.72 ± 0.18	**0.82 ± 0.09**
SMC	I	0.84 ± 0.15	0.83 ± 0.16	0.80 ± 0.26	0.81 ± 0.23	0.73 ± 0.16	0.72 ± 0.13
	II	0.65 ± 0.20	0.56 ± 0.18	0.49 ± 0.16	0.49 ± 0.20	0.37 ± 0.17	0.54 ± 0.13
	III	0.59 ± 0.18	**0.39 ± 0.10**	0.55 ± 0.20	0.57 ± 0.19	0.51 ± 0.12	**0.80 ± 0.11**
	IV	0.64 ± 0.14	**0.44 ± 0.07**	0.59 ± 0.16	0.64 ± 0.16	0.68 ± 0.16	**0.81 ± 0.06**

Data: untransformed WPCO (mean ± SD) in stroke patients with various severities measured at week-1 and week-3 post-stroke.
$^{*}p \leqslant 0.05$ and $^{**}p \leqslant 0.01$ indicate significant between group differences.

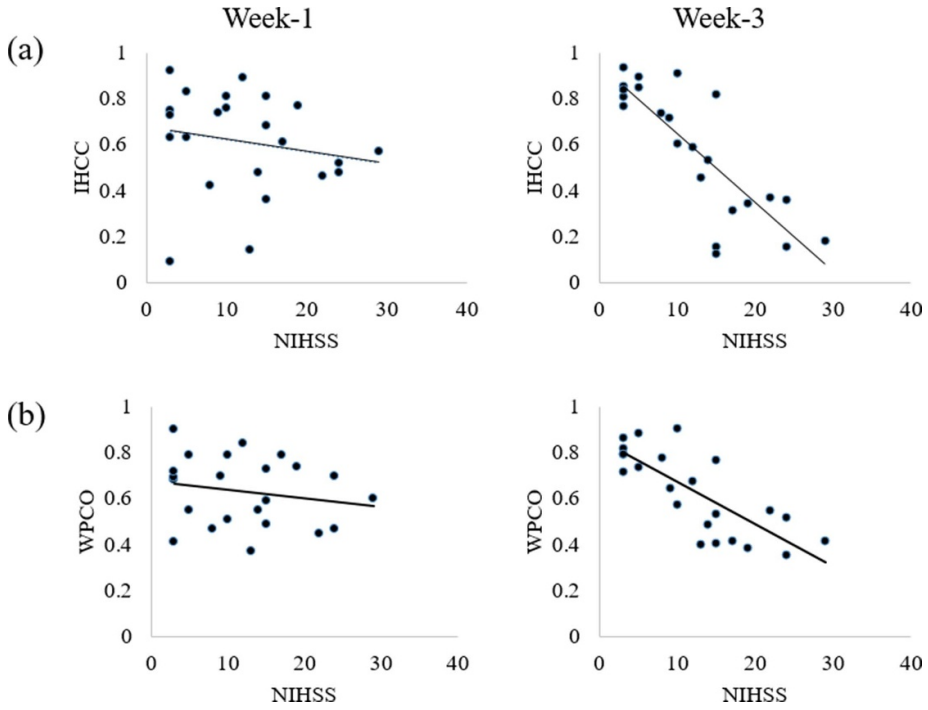

Figure 4. Spearman correlation between the NIHSS score and the resting-state NIRS measurement: (a) the IHCC and (b) the WPCO at band IV in the SMC measured in week-1 and week-3 of 23 stroke patients.

Table 5 lists the averaged △HbO of acute stroke patients in the bilateral PFC, SMA, and SMC measured in week-1 and week-3 during the speed finger-tapping task. The ANOVA results revealed a significant interaction effect with 89% of power ($F(2,12) = 9.35$, $p = 0.00$, $\eta^2 = 0.61$). The post-hoc tests showed that SMC activation in the affected side of minor-stroke patients (0.25 ± 0.18 μM) was significantly higher than that in the PFC (0.12 ± 0.04 μM, $p = 0.04$) measured in week-1. In the moderate-severe stroke cases, the activation of all cortical regions (PFC, SMA, and SMC) on the unaffected side measured in week-1 (0.24 ± 0.21 μM; 0.15 ± 0.06 μM; and 0.22 ± 0.14 μM) were significantly higher than those in the affected hemispheres (0.06 ± 0.06 μM, $p = 0.03$; 0.08 ± 0.07 μM, $p = 0.03$; and 0.05 ± 0.02 μM, $p = 0.00$), respectively. In contrast, SMC activation on the affected

Table 4. Spearman correlation values between initial NIHSS score and IHCC and WPCO in acute stroke patients.

Regions	Bands	NIHSS and IHCC		NIHSS and WPCO	
		Week-1	Week-3	Week-1	Week-3
PFC	I	0.08	−0.29	−0.20	−0.02
	II	0.19	0.08	0.18	−0.07
	III	0.27	**−0.75****	−0.09	**−0.61****
	IV	−0.17	**−0.78****	−0.32	**−0.79****
SMA	I	−0.28	−0.15	−0.10	−0.07
	II	0.22	−0.13	0.34	0.01
	III	0.03	**−0.60****	0.21	**−0.47***
	IV	−0.17	**−0.85****	−0.21	**−0.80****
SMC	I	0.00	−0.11	0.07	0.03
	II	0.35	−0.26	0.14	−0.08
	III	0.23	**−0.68****	0.11	**−0.74****
	IV	−0.20	**−0.71****	−0.19	**−0.78****

$^{*}p \leqslant 0.05$ and $^{**}p \leqslant 0.01$ indicate significant correlation between NIHSS and IHCC and WPCO.

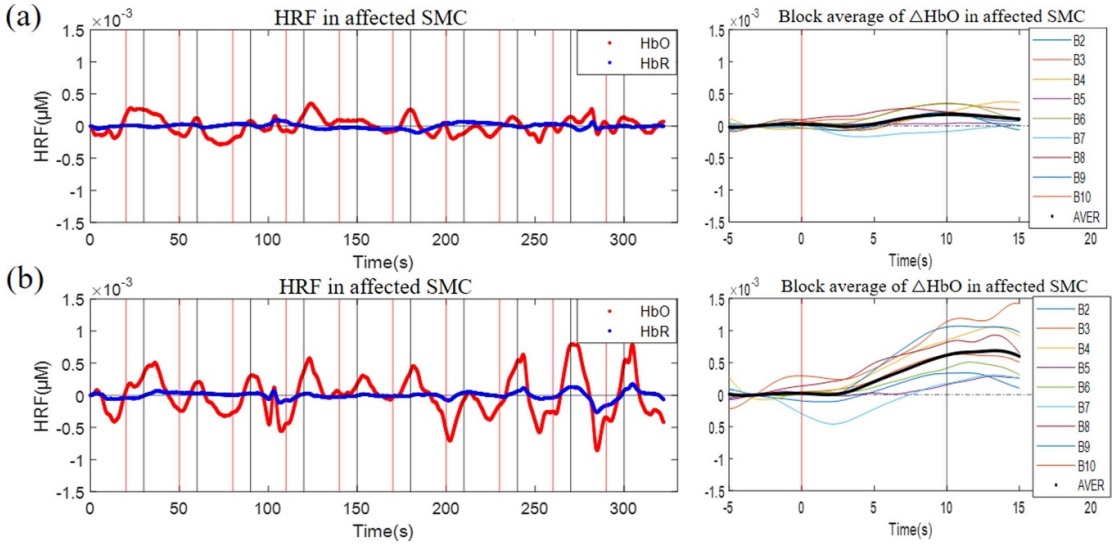

Figure 5. Representative HRF with ten repetitions and its block average of △HbO in the affected SMC during motor tasks in week-1 post-stroke. Red and black vertical lines indicate start and stop of each task block. Red and blue plots indicate the fluctuation of HbO and HbR respectively. (a) Data in a severe stroke patient; (b) Data in a minor stroke patient.

Table 5. HbO concentration of different cortical regions for patients with various stroke severities and post-stroke stages.

Regions	Hemispheres	Minor stroke		Moderate-severe stroke	
		Week-1	Week-3	Week-1	Week-3
PFC	Affected	**0.12 ± 0.04**	0.15 ± 0.07	**0.06 ± 0.06**	**0.06 ± 0.04**
	Unaffected	0.14 ± 0.09	0.12 ± 0.06	**0.24 ± 0.21**	0.09 ± 0.03
SMA	Affected	0.13 ± 0.06	0.12 ± 0.09	**0.08 ± 0.07**	**0.09 ± 0.06**
	Unaffected	0.11 ± 0.04	0.16 ± 0.10	**0.15 ± 0.06**	0.09 ± 0.02
SMC	Affected	**0.25 ± 0.18**	0.15 ± 0.10	**0.05 ± 0.02**	**0.14 ± 0.09**
	Unaffected	0.15 ± 0.15	0.09 ± 0.06	**0.22 ± 0.14**	0.07 ± 0.03

Data (μM): mean ± SD. $^{*}p \leqslant 0.05$ and $^{**}p \leqslant 0.01$ indicate significant differences between regions. $^{\#}p \leqslant 0.01$ indicates significant differences between times. $^{\#\#}p \leqslant 0.01$ indicates significant between-group differences.

side (0.14 ± 0.09 μM) in the moderate-severe stroke group measured in week-3 was significantly greater than that in the PFC (0.06 ± 0.04 μM, $p = 0.00$) and SMA (0.09 ± 0.06 μM, $p = 0.01$), as well as that in week-1 in the same region (0.05 ± 0.02 μM, $p = 0.00$), reflecting enhancement of SMC activation in week-3 in the moderate-severe stroke patients.

4. Discussion

4.1. Resting-state hemodynamic synchronization in acute ischemic stroke patients

The IHCC in the NIRS recordings of the different brain regions was used to represent the similarity in the hemodynamic oscillation in the two hemispheres in the time domain analysis. Our findings showed that the IHCCs in bands III (0.06–0.15 Hz) and IV (0.02–0.06 Hz) in all cortical regions of the minor-stroke group were obviously higher than those in the moderate-stroke and severe-stroke subjects at week-3 post-stroke. The results indicated that stroke patients with higher degree of severity led to less symmetry in low frequency bands III and IV between the two hemispheres. Our findings coincide with previous studies examining symmetry in low-frequency components in stroke victims [7, 8]. WPCO was also used to represent the synchronization between the two hemispheres in terms of phase differences in the frequency domain. Our results show that WPCO at low-frequency bands III and IV was significantly lower in severe-stroke cases than in minor-stroke cases measured in week-3 in all cortical regions. These results coincide with the findings of previous studies showing significant desynchronized in low-frequency bands (<0.1 Hz), which indicates an asymmetry between the two hemispheres in stroke patients [9, 10, 12]. In contrast, we observed no significant changes in the IHCCs and WPCO at high frequency bands I (0.7–2 Hz) and II (0.15–0.7 Hz) representing cardiac and respiratory activities. Our results indicated that the synchronization between the two hemispheres in higher frequency bands were not significantly affected by stroke severities nor post-stroke timing. It is noted that the IHCC of high frequency physiological oscillations in stroke patients was reported to be significantly lower than that in the healthy controls [7]. Therefore, the effect of stroke on high frequency oscillation is interesting for further investigation.

In the current study, we observed a phenomenon of resting-state desynchronization between the two hemispheres in the moderate-stroke and severe-stroke groups at the low frequency ranges. Previous study indicated that the myogenic response and neuronal activity have been considered to be the main contributors of microvascular hemodynamic oscillations in the low frequency bands III (0.06–0.15 Hz) and IV (0.02–0.06 Hz) [22]. The desynchronization between the two hemispheres in the low frequency bands could partially reflect the impairments of the vascular neural network induced by damage to cerebral arterioles and capillary flow patterns after an ischemic stroke [28]. In addition, another previous study demonstrated that a larger infarct volume or higher degrees of severity caused a deeper depth and longer duration of ischemia, which has a significant influence on myogenic response damage [29]. These support the findings of this study on desynchronized oscillation of low-frequency bands. Moreover, a stroke interrupts the blood supply to the surrounding neurons which leads to impaired neurogenic activity in the affected side [30]. Based on these observations, the lower frequency components could be used to differentiate stroke severity instead of higher frequency components.

In the present study, results of both IHCC and WPCO indicated that resting-state desynchronization between the two hemispheres was most evident at week-3 post-stroke, which is considered to be the early subacute stage [3]. A previous study suggested that the acute and subacute stages are critical times for neural plasticity [3], where stroke symptoms are the most clear in the subacute stage [31]. Another finding from a previous study suggested that the asymmetry between the contralesional and ipsilesional M1 is the largest at 1 month post-stroke [32]. The results of the nonparametric Spearman correlation analysis conducted in the present study showing a significant negative monotonic correlation between the initial NIHSS score and IHCCs and WPCO in bands III and IV in week-3, which was similar to the findings of a previous study indicating a positive relationship between stroke severity at admission and the inter-hemispheric phase shifts [12].

4.2. Cortical activation during the motor task in acute ischemic stroke patients

The $\triangle$HbO was used in this study to reflect the cortical activation occurring during the finger-tapping exercise [15] in the ischemic stroke patients. Our results showed that in the moderate-severe stroke, the affected hemisphere activation in all regions (the PFC, SMA, and SMC) was significantly lower than that in the unaffected hemisphere during the finger-tapping tasks in week-1. The results coincide with a previous study which indicates that stroke patients with higher severity exhibit less neuron activity during a motor task [33]. This study confirmed a compensatory response between the two hemispheres during a motor task in the patients with higher degrees of severity. Stroke patients with severe motor deficits exhibited greater activation in intact hemisphere than the affected side, which was not found in patients with mild motor deficits [34]. The finding could be explained by a compensatory recruitment of contralateral motor-related cortices involved in

integrating external information related to the finger-tapping exercise to counter the brain damage from stroke and achieve better movement control [35].

In contrast to the cortical activation in the moderate-severe stroke group, the minor stroke group showed that the PMC and SMA activation had no significant difference between the affected and unaffected hemispheres, nor between week-1 and week-3 measurements. The SMC region showed higher activation than other two regions. These results indicate no significant damage in NVC function in patients with minor stroke. Our results coincide with a previous study which indicates the cortical region related to the task is supplied with more blood than other regions in order to maintain adequate oxygen and the glucose required for neuron activity [14]. However, the SMC activation in the affected hemisphere of the moderate-severe stroke group was significantly enhanced from week-1 to week-3, which implies an improvement of NVC function during the motor task in patients with higher stroke severity in week-3 post-stroke. Previous study supported our finding that the role of activation in the intact hemisphere on promoting the function of affected hemisphere in patients with more severe motor impairments [33]. In addition, the SMC cortical activation in patients with moderate stroke was also significantly greater than that in the PFC and SMA regions in week-3. These results confirm that the SMC region of the contralateral hemisphere is engaged and exhibits changes during a motor task [15].

4.3. Study limitation

The major limitation of the current study is the sample size in each group for both conditions resting-state and motor task was small. In this study, one-third of patients in the severe stroke group could not complete the finger-tapping tasks in both week-1 and week-3 which prohibited the observation of cortical activation in those patients. Further studies could recruit more subjects, including aged matched healthy subjects, to examine the reproducibility of these initial findings. The differences in starting time of rehabilitation for each individual and self-recovery are also limitations of the current study.

5. Conclusions

This study highlights the effects of the degree of severity and related post-stroke period on resting-state interhemispheric synchronization and cortical activation during a motor task in unilateral ischemic stroke patients. In our findings, both IHCC and WPCO indicated generally lower symmetry in patients with moderate and severe stroke compared to those with minor stroke in the early subacute stage (measured in week-3 post-stroke). Furthermore, the negative linear correlation between the initial NIHSS and the IHCC and WPCO for the low-frequency bands in week-3 confirmed the effects of time period post-stroke on cortical symmetry. During the motor task, our findings coincided with previous studies showing that SMC cortical activation is more evident compared to in the PFC and SMA. The activation in the SMC in the minor-stroke subjects in week-1 was generally higher than that in the moderate-severe stroke subject group. In contrast, the SMC cortical activation in the moderate-severe stroke group was significantly increased in week-3 comparing to in week-1. Our results mainly confirm the effects of recovery time on cortical activity post-stroke. Our study suggests that noninvasive NIRS could be used as a tool to rapidly evaluate the symmetry between the two hemispheres in resting-state and cortical activation during a motor task in acute ischemic stroke patients. Future research could apply NIRS as an assessment tool for evaluating neuromodulation schemes such as transcranial electrical stimulation for post-stroke rehabilitation.

Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

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Author contributions

Study design: V T N, Y H L, C W W, P S S, C C L and J J C; data collection: V T N, Y H L, C W W, P S S, and C C L; data analysis: V T N, Y H L, P Y L, S M W, F Y C, and J J C; manuscript writing: V T N, P Y L, S M W, and F Y C; manuscript review and editing: P Y L and J J C; supervision and sponsorship: P S S, C C L, and J J C. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Consent for publication

This study is permitted to be submitted and published in the Journal of Neural Engineering.

Informed consent statement

Informed consent was obtained from all subject involved in the study.

Institutional review board statement

The study protocol was approved by the Institutional Review Board of NCKUH, IBR number: A-ER-108-069 date 21 March 2019.

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