PTJ: Physical Therapy & Rehabilitation Journal | *Physical Therapy*, 2021;101:1–10
https://doi.org/10.1093/ptj/pzab140
Advance access publication date May 31, 2021
**Original Research**

# Brain Function Changes Induced by Intermittent Sequential Pneumatic Compression in Patients With Stroke as Assessed by Functional Near-Infrared Spectroscopy

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## Abstract

**Objective.** Intermittent sequential pneumatic compression (ISPC) can effectively promote cerebral perfusion and collateral blood supply in patients with stroke. However, the effects of ISPC on cerebral oscillations are still unclear.
**Methods.** The tissue concentration of oxyhemoglobin and deoxyhemoglobin oscillations were measured by functional near-infrared spectroscopy under resting and ISPC conditions in 27 right-handed adult patients with stroke. Five characteristic frequency signals (I, 0.6–2 Hz; II, 0.145–0.6 Hz; III, 0.052–0.145 Hz; IV, 0.021–0.052 Hz; and V, 0.0095–0.021 Hz) were identified using the wavelet method. The wavelet amplitude (WA) and laterality index (LI) were calculated to describe the frequency-specific cortical activities.
**Results.** The ISPC state of patients with ischemic stroke showed significantly increased WA values of the ipsilesional motor cortex (MC) in the frequency intervals III ($F_{37} = 8.017$), IV ($F_{37} = 6.347$), and V ($F_{37} = 5.538$). There was no significant difference in the WA values in the ISPC state compared with the resting state in patients with hemorrhagic stroke. Also, the LI values of the prefrontal cortex and MC in patients decreased more obviously in the ISPC state than in the resting state despite no significant difference.
**Conclusion.** The significantly increased WA values in the frequency intervals III, IV, and V in the MC of patients with ischemic stroke might be related to cortical activity in the MC in addition to increased cerebral perfusion. The decreased LI values in the prefrontal cortex and MC indicated that the ISPC may have had a positive effect on the functional rehabilitation of these regions.
**Impact.** This study provides a method for assessing the effects of ISPC on cerebral oscillations, and the results benefit the optimization of ISPC parameters in personalized treatment for the functional recovery of patients with stroke.

**Keywords:** Cerebral Oscillation, Intermittent Sequential Pneumatic Compression, Laterality Index, Stroke, Wavelet Amplitude



**Received:** May 26, 2020. **Revised:** February 8, 2021. **Accepted:** April 16, 2021

## Introduction

Stroke is one of the most common neurological diseases. This ailment is characterized by high morbidity, mortality, and disability rates and not only reduces the quality of life of patients but also creates heavy social and economic burden.[1] Stroke survivors generally manifest behavioral deficiencies, such as hemiplegia or cognitive dysfunction, and they have extremely high rehabilitation needs. Effective rehabilitation after stroke is of great significance in the related functional recovery of patients.

Intermittent sequential pneumatic compression (ISPC), as an effective physical therapy, has been proven to have important clinical significance for the rehabilitation of motor and sensory functions in stroke patients.[2,3] ISPC can produce a type of circulating pressure that acts on the extremities and tissues of the hemiplegic side through the repeated inflation and deflation of an air bag in an ordered and regular manner. This process can promote the flow of blood and lymph and improve microcirculation.[4] ISPC has been commonly attributed to antithrombotic, fibrinolytic, and vasodilation effects.[5] The increase in the pressure gradient and flow velocity of blood and the subsequent increase in arterial flow induced by ISPC has been suggested as a possible mechanism to improve the condition of patients with stroke.[2,5,6] Changes in the pressure gradient and flow of blood can affect the variations in cerebral oscillations.[7] However, the effect of ISPC on the changes in cerebral oscillations remains unclear. Given the popularity of ISPC and its importance in stroke rehabilitation, understanding its effects on brain function is crucial.

With the development of functional near-infrared spectroscopy (fNIRS), its use in the assessment of brain function and brain behavioral interactions has attracted increasing interest. fNIRS is a well-developed optical imaging method based on hemodynamic responses. Specifically, fNIRS can effectively detect changes in oxygenated hemoglobin ($\Delta O_2Hb$) and changes in deoxygenated hemoglobin ($\Delta HHb$) concentration levels in the microcirculation of brain tissues with good spatial and temporal resolutions.[8,9] Relative to other noninvasive conventional functional imaging tools, such as functional magnetic resonance imaging and positron emission tomography, fNIRS is a safe, convenient, and inexpensive method with few physical or environmental constraints and contraindications.[10,11] Thus, fNIRS is readily applicable to clinical settings for the detection of hemodynamic fluctuations in patients with stroke of different states.

Recent neuroscience research shows that the focal damage after stroke exerts a profound effect on the network connectivity structure of the entire cortical region and causes differences in the cerebral hemispheres. The wavelet amplitude (WA) and the laterality index (LI) are 2 important indicators for evaluating the degree of brain activation and hemispheric differences.[12,13] WA is the magnitude of the fluctuation of the original signal measured by multichannel fNIRS at a certain frequency. This parameter can reflect the activation of the cerebral cortex. The activation of the cerebral hemisphere can be effectively evaluated by the degree of regional damage; that is, less activation means more damage.[14] LI is extensively used to assess the activation balance between hemispheres. The lateralization of ipsilesional and contralesional hemispheres reveals the greatest asymmetry at 1 month in patients with stroke, and lasted until 6 months after onset.[15] During recovery, the balance between the hemispheres may be associated with physiologic recovery.

In the present study, $\Delta O_2Hb$ and $\Delta HHb$ were measured in the prefrontal cortex (PFC), motor cortex (MC), and temporal lobe cortex (TLC). We hypothesized that ISPC could induce cortical activation in patients with stroke. This study aimed to investigate the effects of ISPC on cerebral oscillations. The results may help broaden the understanding of the contribution of ISPC to stroke recovery.

## Methods

### Patients

A total of 30 right-handed adults with stroke, which was confirmed with either computed tomography scan or functional magnetic resonance imaging, were recruited to participate in this study as inpatients of the Department of Rehabilitation Hospital of the National Research Center for Rehabilitation Technical Aids, China. All individuals were stable after a first or recurrent stroke. These individuals had unilateral hemiplegia and moderate to severe motor dysfunction in the upper limbs and hemiplegic lower extremities. Of the selected individuals, 3 were excluded because of loose detectors. Thus, 27 individuals (12 with left hemiplegia and 15 with right hemiplegia) were finally included in the study. The clinical details for the participants are shown in the Table.

In this ISPC study, the exclusion criteria were as follows: left-handed, extremity dermatitis, postoperative vein ligation, gangrene and recent extremity skin graft, severe varicose veins or arteriosclerosis, severe extremity or pulmonary conditions, extreme leg deformity or open wounds, and brain trauma or previous brain surgery.

The basic information (including experimental purposes, procedures, schedules, announcements, and contributions) of the experiment was explained to the participants. All participants were required to have adequate sleep and were not allowed to participate in ISPC therapy within 24 hours before the experiment.

### Procedures

Before the experiment, the participants were required to sit for 5 to 10 minutes in a noiseless environment to eliminate existing hemodynamic reactions induced by their activity. Then, the professional therapist fitted the ISPC equipment to the participants. One day before the experiment, the staff recorded the participants' basic information, including sex, age, height and weight, blood pressure, and disease history.

The ISPC experiment was divided into 2 states, namely, the resting and ISPC states. Each state lasted for 10 minutes. During the resting state, the patients were instructed to stay awake with their eyes closed and remain quiet. Then, all participants received ISPC intervention. At present, the clinical practice guidelines had no specific recommendations for treatment parameters for ISPC.[16–19] Although the time parameters used in the study differed, such as using a cycle of 20 seconds[20] or 30 seconds[21] or an elastic cycle of 20 to 70 seconds,[22] it is considered that a short-duration compression (<20 seconds) could effectively facilitate fluid circulation in the body.[23] Also, there was no uniform standard for pressure parameters, such as 45 mm Hg,[22] 70 mm Hg,[21] or 140 mm Hg.[20] However, it was the consensus of the researchers that the selection of

**Table.** Clinical Details for Patients With Stroke[a]

| Patient | Age (y) | Sex | Type of Stroke | Side of Hemiplegia | Site of Lesion | Time Since Stroke (mo) | Other Diseases | NIHSS Score | Fugl-Meyer Assessment Score | | | BP Before ISPC (mm Hg) | BP After ISPC (mm Hg) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Upper | Lower | Balance | | |
| 1 | 80 | F | Ischemic | R | Basal ganglia | 3 | CAD | 2 | 47 | 27 | 8 | 106/85 | 105/75 |
| 2 | 74 | M | Ischemic | R | Basal ganglia | 3 | EH, HLP | 13 | 24 | 9 | 2 | 137/73 | 142/85 |
| 3 | 76 | M | Ischemic | R | Basal ganglia, thalamus | 2 | DM, CAD, EH | 8 | 31 | 25 | 6 | 120/68 | 134/85 |
| 4 | 61 | M | Ischemic | R | Basal ganglia | 2 | DM, EH | 9 | 16 | 21 | 8 | 131/83 | 142/88 |
| 5 | 74 | M | Ischemic | R | Basal ganglia | 4 | EH, HLP | 2 | 46 | 26 | 7 | 125/73 | 130/74 |
| 6 | 50 | M | Ischemic | R | Basal ganglia | 5 | EH | 4 | 39 | 16 | 10 | 125/75 | 135/78 |
| 7 | 67 | M | Hemorrhagic | R | Basal ganglia | 5 | EH, HLP | 5 | 43 | 32 | 12 | 119/75 | 130/90 |
| 8 | 61 | M | Ischemic | R | Basal ganglia | 5 | EH, HLP | 3 | 45 | 26 | 11 | 142/86 | 145/89 |
| 9 | 74 | M | Ischemic | R | Basal ganglia | 5 | EH, HLP | 2 | 41 | 22 | 8 | 138/76 | 148/86 |
| 10 | 61 | M | Ischemic | R | Basal ganglia | 6 | EH, HLP | 2 | 45 | 25 | 12 | 100/65 | 105/69 |
| 11 | 45 | M | Hemorrhagic | R | Basal ganglia | 2 | EH, HLP | 11 | 6 | 28 | 8 | 128/77 | 128/83 |
| 12 | 69 | M | Hemorrhagic | R | Thalamus | 4 | CAD, EH | 2 | 28 | 18 | 8 | 118/73 | 133/78 |
| 13 | 53 | M | Ischemic | R | Basal ganglia, thalamus | 3 | EH | 7 | 47 | 25 | 12 | 121/84 | 125/82 |
| 14 | 69 | M | Hemorrhagic | R | Thalamus | 6 | CAD, EH | 2 | 28 | 12 | 10 | 107/68 | 112/71 |
| 15 | 61 | M | Ischemic | R | Basal ganglia | 5 | EH, HLP | 3 | 28 | 10 | 11 | 116/66 | 117/63 |
| 16 | 71 | M | Ischemic | L | Thalamus | 2 | EH | 7 | 44 | 25 | 12 | 147/71 | 162/82 |
| 17 | 66 | F | Ischemic | L | Basal ganglia | 2 | HLP | 3 | 47 | 31 | 8 | 143/92 | 144/94 |
| 18 | 75 | M | Hemorrhagic | L | Thalamus | 5 | DM, EH | 4 | 61 | 33 | 12 | 131/72 | 155/79 |
| 19 | 66 | F | Ischemic | L | Basal ganglia | 3 | HLP | 6 | 53 | 33 | 10 | 139/89 | 143/92 |
| 20 | 61 | M | Ischemic | L | Basal ganglia, corona radiata | 5 | EH, HLP | 21 | 5 | 2 | 0 | 168/107 | 179/113 |
| 21 | 57 | M | Ischemic | L | Basal ganglia | 1 | CAD, EH | 7 | 61 | 33 | 12 | 118/70 | 130/88 |
| 22 | 45 | M | Ischemic | L | Basal ganglia, corona radiata | 1 | None | 8 | 29 | 10 | 3 | 119/70 | 113/65 |
| 23 | 54 | M | Hemorrhagic | L | Basal ganglia | 3 | EH, HLP | 16 | 24 | 12 | 4 | 120/80 | 133/84 |
| 24 | 45 | M | Ischemic | L | Basal ganglia | 2 | None | 8 | 29 | 10 | 6 | 130/77 | 144/77 |
| 25 | 75 | M | Hemorrhagic | L | Thalamus | 3 | DM, EH | 15 | 6 | 1 | 4 | 121/78 | 130/80 |
| 26 | 54 | M | Hemorrhagic | L | Basal ganglia | 3 | EH, HLP | 16 | 21 | 8 | 2 | 138/96 | 140/98 |
| 27 | 81 | M | Hemorrhagic | L | Thalamus | 6 | DM | 23 | 5 | 0 | 0 | 160/80 | 165/88 |

[a] BP = blood pressure; CAD = coronary artery disease; DM = diabetes mellitus; EH = essential hypertension; F = female; HLP = hyperlipidemia; L = left; M = male; NIHSS = National Institutes of Health Stroke Scale; R = right.

pressure must be a compromise between venous vacuity and patient comfort.[23] In addition, studies had shown that 80 to 110 mm Hg may be the appropriate range for pressure selection.[24] On the basis of these guidelines, an inflation time of 15 seconds, a deflation time of 15 seconds (cycle of 30 seconds, 0.03 Hz), and a peak value of 100 mm Hg for the patient's hemiplegic limb were selected as the intervention parameters for ISPC. All measurements were performed with the patients resting in the supine position. In any symptomatic or suspicious event (such as pain and tenderness, swelling, warmth, hypoxia, respiratory events, chest pain, redness or discoloration, or distention of surface veins of the lower limbs), the study was terminated immediately. The fNIRS was implemented continuously throughout the experiment.

## Functional Near–Infrared Spectroscopy

The fNIRS measurement used NirSmart (Danyang Huichuang Medical Equipment Co, Ltd, China), a 24-channel tissue oxygenation monitor with a continuous wave. Each sensor of the instrument consisted of a 2-wavelength light-emitting diode, which served as the source optode and emitted light at wavelengths of 760 and 850 nm, and a detector optode. The interoptode distance was 30 mm. The differential path-length factor value was set to 7.0. The extinction coefficients of the 760-nm wavelength were $1.4866 \times 10^3$ ($O_2Hb$) and $3.8437 \times 10^3$ (HHb), and those of the 850-nm wavelength were $2.5264 \times 10^3$ ($O_2Hb$) and $1.7986 \times 10^3$ (HHb). The instrument measured the raw light intensity signals. On the basis of different absorption spectra, the concentrations of $\Delta O_2Hb$ and $\Delta$HHb were calculated from the changes in detected light intensity using the modified Lambert–Beer law, assuming constant scattering. The calibration function of the instrument and the corresponding template were used to ascertain the channels to fill exactly in correspondence of the 10/10 electrode positions according to different head sizes. The elastic band was completely fixed between the template and the head. The hair of the participant must be fully poked to ensure that the probe was in direct contact with the scalp of the participant when the near-infrared light source and detector probes were placed in the template. The templates and probes were symmetrically positioned over the regions of the left and right PFCs, left and right MCs, and left and right TLCs, as shown in Figure 1. Signals with a low signal-to-noise ratio were removed, and the sampling rate was 10 Hz.

## Data Preprocessing

The preprocessing method for fNIRS data was elaborated in our previous studies.[25–30] In brief, each participant's signals were visually inspected to detect whether the noise has changed the signal characteristics. Three participants were excluded from subsequent analysis due to excessive head artifact interference in their signals. Then, a moving average filter with a time window of 3 seconds was used to eliminate the obvious abnormal points in the signal. The artifact portion was determined by identifying the sliding window SD above a certain threshold and was removed by cubic spline interpolation. Independent component analysis was then performed on the $\Delta O_2Hb$ and $\Delta$HHb signals of each channel. All of the independent component analysis–derived components were visually inspected to determine which components might be related to noise and artifacts, including cardiac pulsations and respiratory signals, thereby reducing interference in fNIRS measurements. Finally, we improved the signal-to-noise ratio

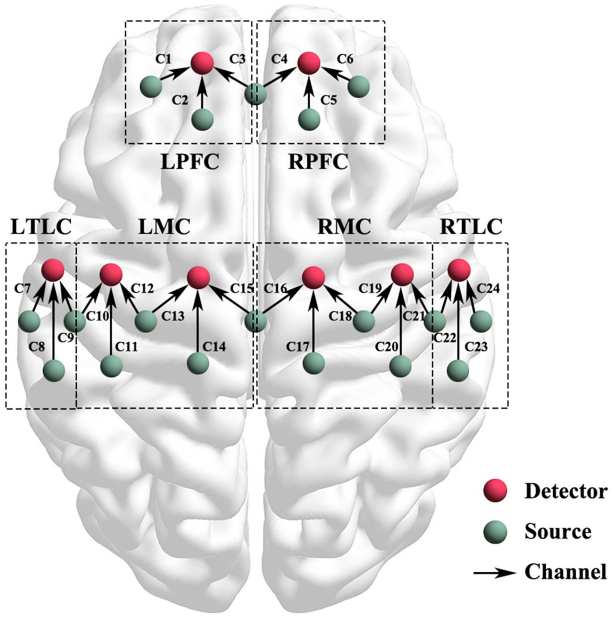


**Figure 1.** Schematic diagram of the experimental setup. Configuration of 18 source optodes, 8 detector optodes, and 24 measurement channels.

and retained the 0.0095- to 2-Hz portion of the filtering signal obtained using the 6-order Butterworth band-pass filter.

The spontaneous cerebral oxygenation signals have different physiological sources, and each physiological source corresponds to a specific frequency interval. In our previous studies, 5 frequency intervals corresponding to different physiological sources were identified.[13,31,32] The frequency intervals of 0.6 to 2 Hz and 0.145 to 0.6 Hz reflected the synchronization of cardiac (I) and respiratory (II) activities in the cerebral regions; 0.052 to 0.145 Hz, 0.021 to 0.052 Hz, and 0.0095 to 0.021 Hz were regarded as myogenic (III), neurogenic (IV), and endothelial cell metabolic (V) activities, respectively. These provide new ideas and methods for understanding the reorganization of the brain. In addition, to facilitate the presentation of the results, the data for the left and right sides of the brains of patients with left hemiplegia were replaced at the channel level. Thus, the left hemisphere of the brain represents the ipsilesional region in subsequent sections of this article.

## Wavelet Amplitude

Continuous wavelet transform, as a transformation method of time series from time domain to frequency domain, was used in this study to obtain the main component of time series in frequency domain. Tunable filter band lengths were used to provide the appropriate time and frequency resolution,[33] which projected the time series onto the time-frequency plane, thereby obtaining the time-frequency-amplitude 3-dimensional map. The results of wavelet transform were averaged over the time domain to obtain the WA of each $\Delta O_2Hb$ and $\Delta$HHb signal at each time and frequency, which reflects the magnitude of the fluctuation of the original signal at a certain frequency. The WA of each $\Delta O_2Hb$ and $\Delta$HHb signal represents the changes in regional cerebral blood flow with the activity of the cerebral cortex during different conditions. Functional hyperemia or neurovascular coupling could increase regional cerebral blood flow by activating

local neurons to match the needs of local brain cells and the supply of blood and nutrients in the task state.[34] Thus, WA is characterized by the intensity or activation of the cerebral cortex.

### Laterality Index

One extensively used method for assessing hemispheric activation balance in brain function studies is the LI.[12] In this study, LI is calculated according to the classical formula,[35] and LI for a given contralesional (C) and ipsilesional (I) hemispheric activation is calculated by the sum of the WA values. Thus, the LI is defined as follows:

$$LI = \left(\sum WA_C - \sum WA_I\right) / \left(\sum WA_C + \sum WA_I\right)$$

In this case, the value of LI ranges from 1 (contralesional activation only) to −1 (ipsilesional activation only).

### Statistical Analysis

Data were analyzed using the normal test (Kolmogorov–Smirnov test) and the variance uniformity test (Levene test) to ensure that the assumptions required to analyze the parameters were satisfied. The Pearson correlation was used for correlation analysis. A 1-way analysis of variance was performed according to the region used to determine the interregional WA and LI. The Bonferroni correction was applied to the $P$ values for the multiple comparisons. In total, there were $1 \times 5 = 5$ intergroup pairwise comparisons (resting state vs ISPC state; 5 frequency intervals); thereby, the corrected $P$ value threshold was set at $P < .01$.

## Role of the Funding Source

The funders played no role in the design, conduct, or reporting of this study.

## Results

### Cerebral Activation

As shown in Figures 2A and 2B, the application of ISPC had an obvious effect on the original signals in the cerebral cortex. After the wavelet transform of the original signals in the 2 states, it was found that the WA value of the ISPC state was higher than that of the resting state at 0.0095 to 0.145 Hz. Therefore, the main influence of ISPC on cerebral oscillation occurred in the intervals III to V, as shown in Figure 2C. Figure 2D shows the activation of different brain regions, and the activation of the MC and TLC under the ISPC state was higher than that under the resting state.

Specifically, the ISPC state of patients with ischemic stroke showed significantly higher WA values in the ipsilesional MC in the frequency intervals III ($F_{37} = 8.017$, $P = .0016$), IV ($F_{37} = 6.347$, $P = .0088$), and V ($F_{37} = 5.538$, $P = .0048$), the contralesional MC in the frequency intervals III ($F_{37} = 8.559$, $P = .0012$), IV ($F_{37} = 7.081$, $P = .0024$), and V ($F_{37} = 7.413$, $P = .002$), and the ipsilesional TLC ($F_{37} = 4.965$, $P = .0064$) and contralesional TLC ($F_{37} = 3.23$, $P = .0048$) in the frequency interval III than in the resting state, as shown in Figure 3. There was no significant difference in the WA values of the ISPC state and the resting state in patients with hemorrhagic stroke.

The results of the Pearson correlation analysis for WA and the Fugl-Meyer Assessment showed that the ipsilesional MC of patients with ischemic stroke was significantly correlated with the upper extremity in the frequency intervals III ($r = 0.594$, $P = .002$), IV ($r = 0.551$, $P = .004$), and V ($r = 0.489$, $P = .006$) and with the lower extremity in the frequency intervals III ($r = 0.594$, $P = .007$), IV ($r = 0.591$, $P = .008$), and V ($r = 0.57$, $P = .011$). Specifically, WA was significantly correlated with flexor synergy in the intervals III ($r = 0.511$, $P = .025$) and IV ($r = 0.454$, $P = .045$); movement combining synergies in the intervals III ($r = 0.502$, $P = .029$), IV ($r = 0.518$, $P = .023$), and V ($r = 0.523$, $P = .022$); movement out of synergy in the interval III ($r = 0.511$, $P = .026$); and normal reflex activity in the interval V ($r = 0.461$, $P = .047$) in the upper extremity. In the lower extremity, WA was significantly correlated with reflex activity in the intervals III ($r = 0.549$, $P = .015$), IV ($r = 0.578$, $P = .01$), and V ($r = 0.611$, $P = .005$); extensor synergy in the intervals III ($r = 0.562$, $P = .012$), IV ($r = 0.573$, $P = .01$), and V ($r = 0.548$, $P = .015$); movement combining synergies in the intervals III ($r = 0.558$, $P = .013$), IV ($r = 0.569$, $P = .011$), and V ($r = 0.566$, $P = .012$); and movement out of synergy in the intervals IV ($r = 0.524$, $P = .021$) and V ($r = 0.476$, $P = .039$). In addition, the contralesional MC of patients with hemorrhagic stroke was significantly correlated with flexor synergy ($r = -0.838$, $P = .009$) and extensor synergy ($r = -0.74$, $P = .036$) in the interval III.

### Lateralization

The LI values of patients with ischemic and hemorrhagic stroke in the resting and ISPC states are shown in Figure 4. During the resting state, the LI values of the MC and TLC were negative. Compared with the resting state, the LI values of the PFC and MC decreased in the ISPC state in the frequency intervals II to V, whereas that of the TLC showed minimal change. No significant difference in the LI values was found between the 2 states. Figure 5 shows the changes in the individual LI values of each patient with ischemic stroke (Fig. 5A) or hemorrhage stroke (Fig. 5B) from the resting state to the ISPC state. After ISPC administration, LI values decreased in 17 patients. However, the LI values of 10 patients (5 patients with ischemic stroke, 5 patients with hemorrhagic stroke) showed an increase or no change.

The correlation between the change in the LI value of each patient from the resting state to the ISPC state and the National Institutes of Health Stroke Scale (NIHSS) was analyzed with Pearson correlation. The results showed that the LI value was significantly correlated with the NIHSS in intervals III ($r = -0.479$, $P = .012$), IV ($r = -0.406$, $P = .035$), and V ($r = -0.416$, $P = .031$) in the PFC.

## Discussion

This study mainly investigated the effects of ISPC on the cerebral oscillations in patients with stroke as measured by fNIRS. The fNIRS signals are mainly composed of systemic activity components, evoked neurovascular couplings, and nonevoked neurovascular couplings.[36] Five characteristic frequency intervals possibly reflect systemic regulation activities and neurovascular couplings. Frequency intervals I and II reflect systemic regulation activities, whereas frequency intervals III to V indicate neurovascular coupling. The patients with ischemic and hemorrhagic strokes were analyzed

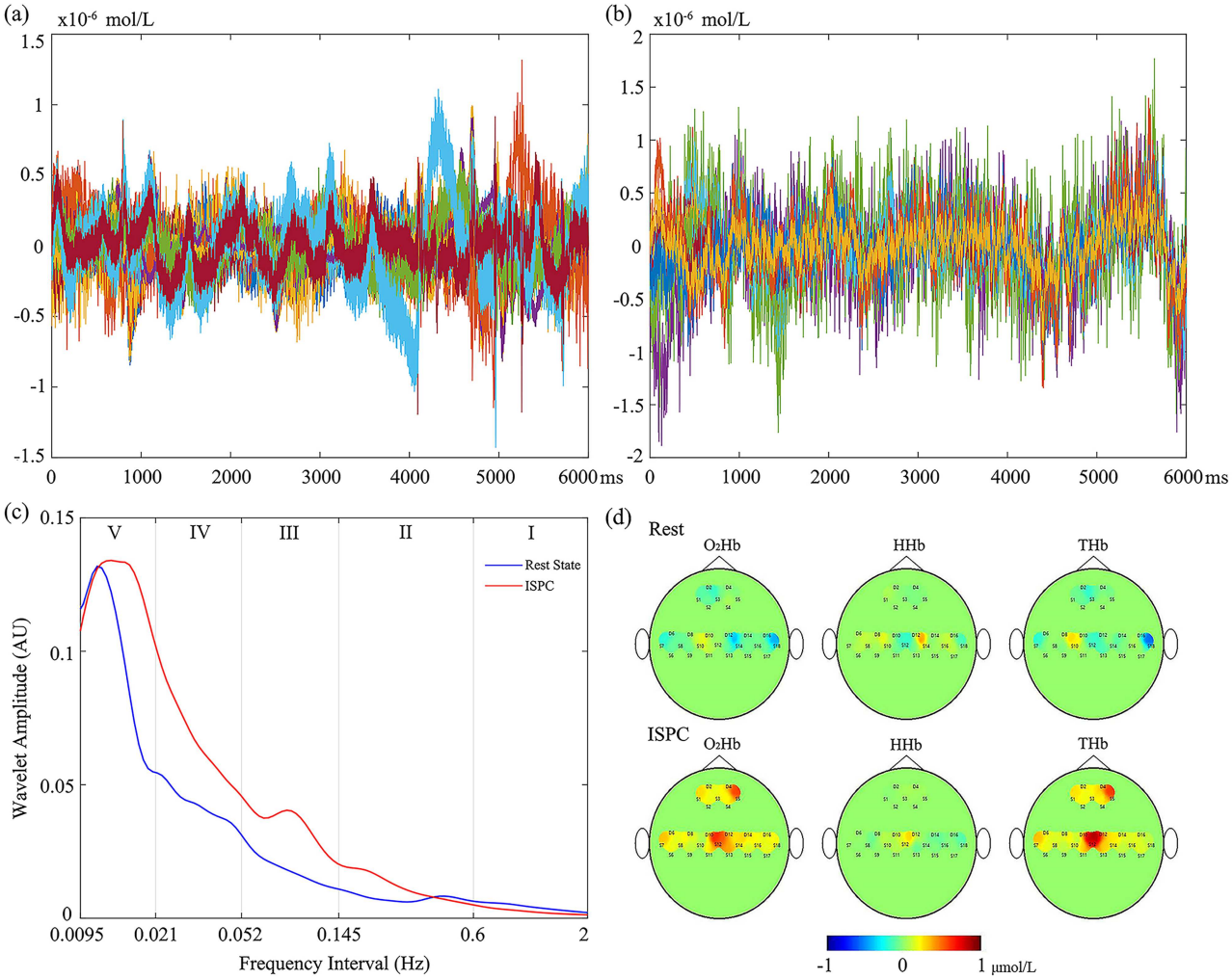


**Figure 2.** Cerebral oscillation changes in different states. (A and B) Original signals during resting state and intermittent sequential pneumatic compression (ISPC) state, respectively. Different colors represent blood oxygen signals collected from different channels. There are 24 channels in total. (C) Mean value of wavelet amplitude (WA) corresponding to 0.0095- to 2-Hz signals of all channels in both states after the wavelet transform. (D) Concentrations of the 3 parameters during the 2 states, representing cortical activation. The letters indicate the positions of the light source and detector. On the basis of the baseline set by the system, red represents higher activation than the blue.

separately. The WA values of patients with ischemic stroke were significantly increased in the bilateral MCs in the frequency intervals III to V and in the TLCs in frequency interval III in the ISPC state than in the resting state. In addition, the LI values showed a downward trend in the PFC and MC with the application of ISPC. Personalized studies showed that the LI values of a number of patients with ischemic and hemorrhagic strokes did not change or increased only after the application of 0.03 Hz of ISPC.

In patients with ischemic stroke, the WA values of the bilateral MCs in intervals III to V and those of the bilateral TLCs in interval III increased more obviously in the ISPC state than in the resting state. This result indicated that ISPC could facilitate the activation of bilateral MCs and TLCs in various spontaneous oscillations. The results of Pearson correlation analysis for spontaneous oscillations and behavioral data showed that WA and physical performance, including reflex activity, flexor synergy, movement combining synergies, movement out of synergy, and normal reflex, were significantly positively correlated. However, the significance of WA was not found in patients with hemorrhagic stroke, suggesting that ISPC may be more suitable for patients with ischemic stroke, and the cerebral activation induced by ISPC plays an important role in the recovery of limbs in patients with ischemic stroke.

A seminal observation was that the changes in WA in bilateral MCs and TLCs by ISPC occurred mainly in interval III. This interval is associated with myogenic activity, which might originate locally from the intrinsic myogenic activity of the smooth muscle cells of the vessels[37,38] that are partly under autonomic control.[39] Within the 0.1-Hz frequency, arterial pressure oscillations occurred spontaneously with Mayer waves in the conscious patients.[40,41] Because the Mayer wave is closely related to the arterial baroreceptor reflex and is usually enhanced during states of sympathetic activation, the mechanical pressure and stimulation of the sympathetic nerve caused by ISPC exert an effect on the amplitude of the Mayer wave. This factor may explain the markedly higher ISPC state than the resting state in interval III.

The WA values of the bilateral MCs were higher in the ISPC state than in the resting state in interval IV, which

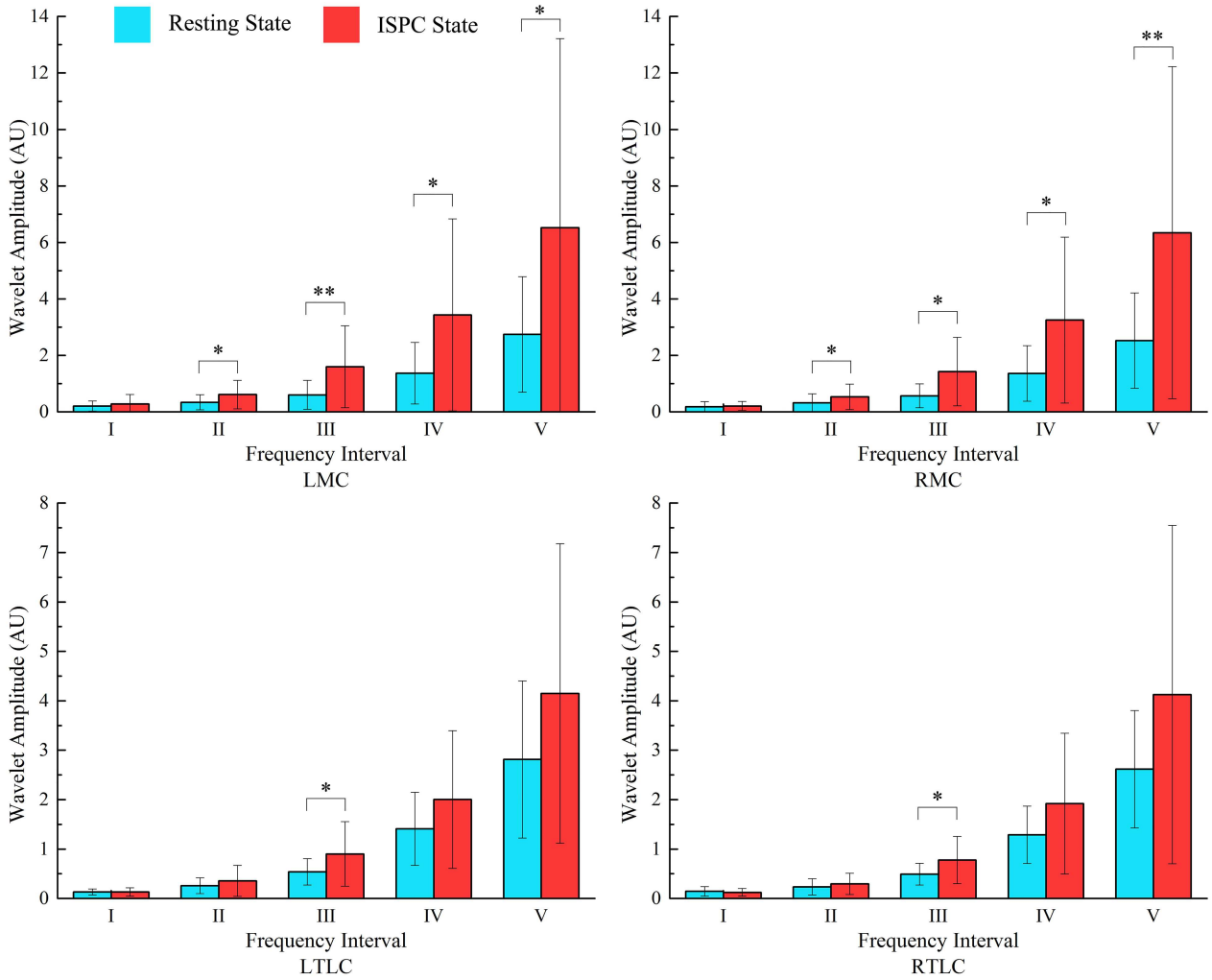


**Figure 3.** Comparative results for wavelet amplitude (WA) values between resting state and intermittent sequential pneumatic compression (ISPC) state in the motor cortex (MC) and the temporal lobe cortex (TLC). $*P < .01$, $**P < .002$.

showed that the ISPC had a positive effect on the neurogenic activity in the bilateral MCs of the patients with ischemic stroke. The cerebral oscillations in frequency interval IV are vascular reactions of neurogenic origin.[42] The autonomous nervous system participates in vasoconstriction by regulating the release of substances that affect the activities of smooth muscles. This process can regulate the overall blood flow in response to local conditions. Because an ISPC of 0.03 Hz was used in this study and the frequency of 0.03 Hz is within the range of the frequency interval IV (0.052–0.145 Hz), the remarkable activation in the frequency interval IV may be related to the parameter setting of ISPC.

Frequency interval V is associated with endothelial cell metabolic activities, which can produce and release potent vasodilatory and vasoconstrictive factors, such as nitric oxide and endothelin.[42] Given that neuronal cells, glial cells, vascular endothelial cells, and other cells jointly comprise the basic unit of the neurovascular coupling effect, the endothelial cell activities are closely related to nervous activities.[34] The substance that affects smooth muscle activity released by the sustained activity of the autonomic nervous system and endothelial cells maintains the basal level of vasoconstriction, thus causing the vascular smooth muscle to contract or relax as the intravascular pressure changes. In summary, ISPC may not be limited to the intervention of limbs but also affects cerebral oscillations.

A lateralized activation pattern in motor cortical regions is a known factor determining the degree of recovery of motor function in individuals with stroke.[7] The different activation intensity of each brain region determines the distribution of brain resources.[14] Previous studies have shown that the movement of the hemiplegic limbs of individuals with stroke can activate the bilateral motor areas and contribute to sensorimotor integration.[43] It is consistent with the findings of this study. The increased WA values in this work indicated that ISPC may enhance the myogenic and endothelial cell metabolic activities of bilateral MCs in individuals with ischemic stroke, which may be conducive to strengthening the MC control of movement type, 3-dimensional movement trajectories, and velocity.[44,45]

One of the primary interests in this study was to assess the hemispheric activation balance. Previous studies have shown that enhanced contralesional activation after stroke translates into a reduced or even negative LI; accordingly, the LI of patients with stroke is lower than normal values on average.[35] This result is consistent with our findings, in

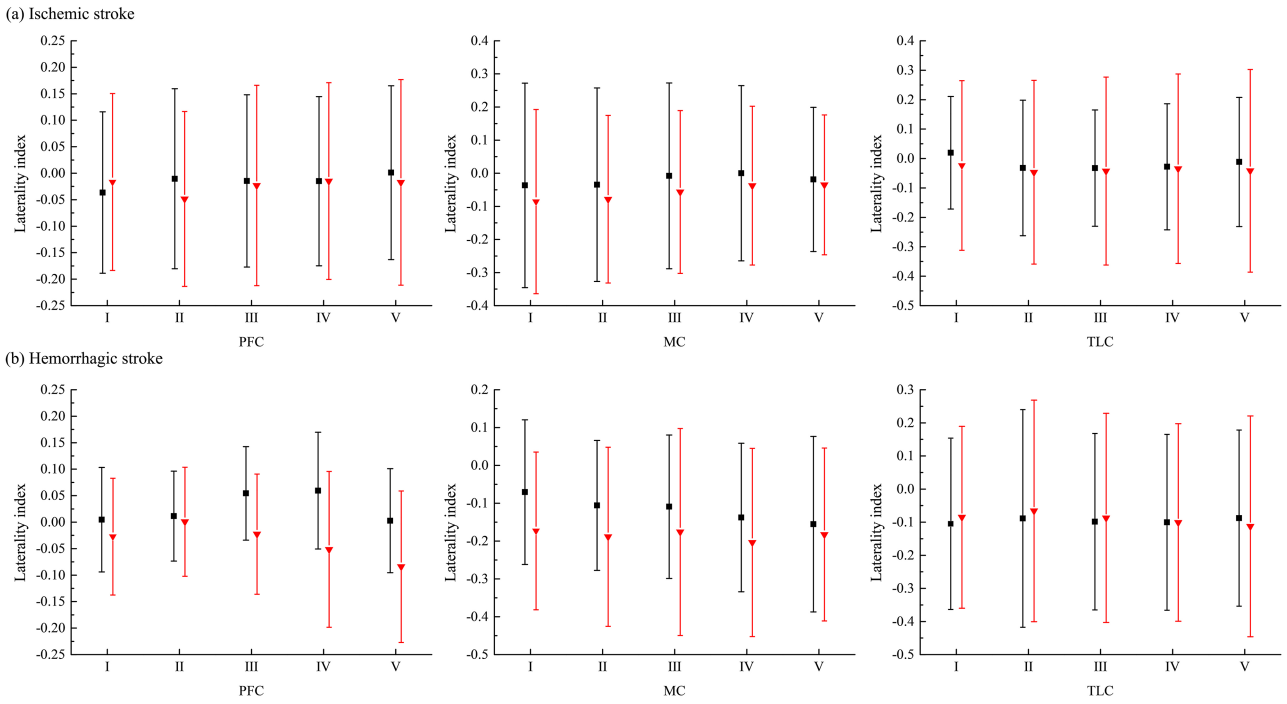


**Figure 4.** Changes in laterality index (LI) in each brain region under resting state and intermittent sequential pneumatic compression (ISPC) state in patients with ischemic stroke (A) and hemorrhagic stroke (B).

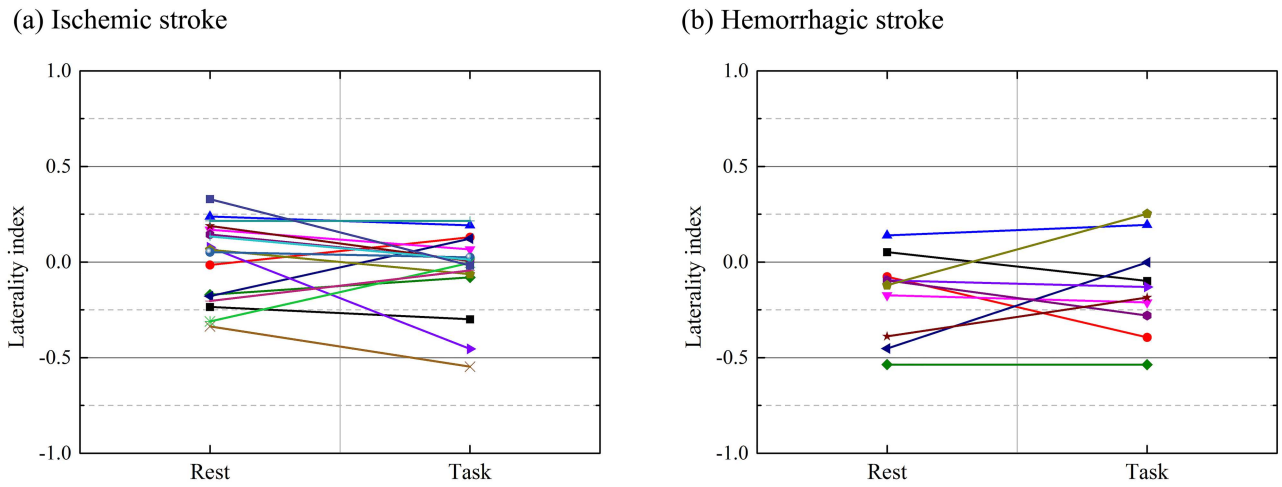


**Figure 5.** Changes in individual laterality index (LI) values in each patient with stroke from resting state to intermittent sequential pneumatic compression (ISPC) state.

which the patients' LI of the MC and TLC was lateralized to the ipsilesional hemispheric region. It is worth noting that when ISPC was applied, ipsilesional MC and PFC exhibited an increasing trend of laterality, but there was no significant difference compared with the resting state. The increasing trend of laterality reflected an increased WA in the ipsilesional hemispheric region or a decreased WA in the contralateral hemispheric region, which is beneficial for regional functional rehabilitation of stroke patients. On the one hand, the correlation between the activation of ipsilesional MC and the recovery of motor function has been demonstrated in early stroke rehabilitation.[15,46,47] Although PFC is not considered as a primary motion region, the activation of the ipsilesional PFC may benefit the reinforcement of the management of the cognitive load required for motor performance.[48–50] On the other hand, the decreased contralesional cortical activation after stroke is common regardless of the lesion location, and this phenomenon may be related to physiologic recovery.[43,44] Studies have demonstrated that the noninjured MC may aid ipsilesional MC via ipsilateral projections or by acting on the ipsilateral MC by the connection.[51] Although the existing evidence in this study did not show that ISPC had a significant effect on the change in LI, this trend was still worthy of attention.

According to a personalized analysis of patients, the LI values of patients did not change or only increased after the application of ISPC, reflecting the relative insensitivity of ipsilesional regions of these patients to an ISPC of 0.03 Hz.

The Pearson correlation analysis showed that the change in LI value from the resting state to the ISPC state was negatively correlated with the NIHSS, indicating that the relatively insensitive group had better NIHSS scores. This result suggested that 0.03-Hz ISPC therapy may be inappropriate for certain patients with better preservation of neurological, cognitive, and motor functions. Cerebral autoregulation, which is a blood flow–regulating mechanism, protects the brain tissue from hyperperfusion or hypoperfusion within a wide range of blood pressure fluctuations.[52] This mechanism is closely related to spontaneous oscillation and is controlled and affected by myogenic, neurogenic, and metabolic mechanisms.[53] After the onset of stroke, the effectiveness of cerebral autoregulation has been demonstrated to decrease and change with the progression of the disease's time course.[54–57] Therefore, the cerebral autoregulation in different degrees of damage and rehabilitation node is affected distinctly by neurogenic activity. This phenomenon may explain the nonsensitivity of several patients to 0.03 Hz of ISPC. Our study shows that an ISPC of 0.03 Hz is not suitable for all patients with stroke and that more personalized treatment options should be considered in subsequent ISPC interventions.

### Limitations

Our study has several limitations. The first limitation is that the sample comprised mostly men (89%), probably because of geographical variations. In the future, female participants need to be recruited to improve the understanding of cortical activation in individuals with stroke. Second, the severity of stroke was not classified. Different effects of ISPC on individuals with mild stroke and severe stroke were not analyzed in detail. Third, given the preliminary nature of this work, clinical trials on other key parameters of ISPC were not conducted. According to the existing research results, the ISPC parameters adopted by individuals with stroke with different degrees of disease and different stages of rehabilitation should be different. Therefore, a personalized ISPC intervention plan should be the focus of future research.

## Author Contributions

Concept/idea/research design: H. Xie, Z. Li
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## Funding

This project was supported by the National Key Research and Development Project (2020YFC2004200), the National Natural Science Foundation of China (Grant No. 31771071, 11732015, 61675013), the Fundamental Research Funds for Central Public Welfare Research Institutes (118009001000160001), and the Key Research and Development Project of Jiangxi Province (20202BBGL73057).

## Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

## Ethics Approval

The experimental procedures were approved by the Human Ethics Committee of the National Research Center for Rehabilitation Technical Aids and were in accordance with the ethical standards specified by the Helsinki Declaration of 1975 (revised in 2008). All patients provided written informed consent prior to participation.

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