Functional near-infrared spectroscopy combined with unilateral task-oriented training with and without an orthosis in subacute stroke: A pilot study

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Abstract

Background

The recovery of upper extremity motor deficits represents a functional challenge for persons with stroke. The aim of this study was to evaluate the mechanisms of Unilateral task-oriented training combined with dynamic hand orthosis for the recovery in subacute stroke by using functional near-infrared spectroscopy (fNIRS).

Methods

This was a pilot randomized, controlled, assessor-blinded trial. A total sample of 30 subacute persons with stroke were randomized into two groups: the orthosis group and the usual exercise group. All participants received four weeks (60 min/day, 5 days/week) of unilateral upper limb training. The orthosis group wore a dynamic hand orthosis during half the training (30 min/day). O₂Hb concentrations and a laterality index for bilateral premotor cortex, sensorimotor cortex by fNIRS were calculated as outcome indicators that were measured at baseline and 4 weeks after the interventions. Clinical outcomes were collected for correlation analysis.

Results

No significant difference in O₂Hb concentrations change between two groups. Cortical activation shifted from the ipsilateral to the contralateral premotor cortex and from the contralateral to the ipsilateral sensorimotor cortex in both groups. In the Orthosis group, the change of Fugl-Meyer Assessment of arm score was positively correlated to the shift to contralateral premotor cortex activation and the change of Action Research Arm Test score was positively correlated to the shift to ipsilateral sensorimotor cortex activation. In the UL group, a negative correlation was observed between the shift to ipsilateral sensorimotor cortex and changes of Fugl-Meyer Assessment of arm score.

Conclusion

This is the first fNIRS study to explore the mechanism of recovery in subacute stroke after utilizing unilateral task-oriented training and a dynamic orthosis. The current results suggest that fNIRS combined with clinical tests may be useful to evaluate the mechanism of stroke recovery after different rehabilitation interventions. *Trial registration:* Registered on January 11, 2018 at ClinicalTrials.gov (NCT03396939). <https://clinicaltrials.gov/ct2/home>.

Background

Persons with stroke may experience a high rate of disability (1, 2). In the acute stage of stroke, two-thirds may experience upper limb and hand dysfunction and three months after stroke onset, 50% still experience disability in regard to arm-hand performance, such as loss of fine motor control and deficits in motor planning and sensorimotor integration(3). Many persons with stroke, 30%–66%, experience reduced motor function in the upper extremity 6 months after debut(4). The upper extremity functions are important for independence in activities of daily living and for perceived quality of life(5). Spontaneous recovery, defined by Bernhardt as the amount of improvement in body function and activity when the recovery of behavior is improved in the absence of a specific, targeted treatment and occurs during a time-sensitive window(6). The subacute stroke phase which may be defined as an early subacute phase(7 days-3 months) and a late subacute phase(3-6 months) since stroke onset (6). The recovery in combination with targeted treatment tends to occur within the first 3 months after stroke onset (7, 8). Interpretations in stroke rehabilitation depend on the elucidation of both spontaneous and therapeutic-driven mechanisms of recovery (8). Through either repairment of impairment (regaining movement patterns before stroke) ,or through compensation (using alternative movements, methods to accomplish the same goal), functional recovery can occur. Rapid establishment of independence in activities of daily living through compensatory strategies is emphasized in current neurorehabilitation practice(9). Thus, rehabilitation training is suggested initiating early to enhance and direct spontaneous recovery. Furthermore, high-quality evidence related to the effectiveness and mechanism of interventions to improve upper limb function is urgently needed(10).

The application of a dynamic hand orthosis combined with task-oriented training has been reported during subacute stage in case studies (11) (12) (13). These moderate-to-severe stroke persons may display small or modest improvements and appear to benefit from training with a dynamic arm orthosis(13). However, studies on the possible neuroplastic mechanism based on task-oriented training methods combined with assistive devices for subacute persons with stroke and particularly randomized controlled trials (RCT) remain scarce (14) (15). Functional near-infrared spectroscopy (fNIRS) can be used to monitor the change of direct and indirect brain regions-regions of interest (ROI)(16) involved in complex motor learning(17) to reflect cerebral cortical reorganization during the process of stroke recovery(18) (19) (20) (21). fNIRS has many advantages, including non-invasiveness, low-cost, portability, and ease of operation(22) (23) ,that make it suitable for studying the cortical response to simple or complex motor stimulation.

Premotor cortex (PMC) is defined as the anterior half of the precentral gyrus and the anterior bank of the precentral sulcus and the sensorimotor cortex (SMC) is defined as the combination of primary motor and primary sensory. We selected these two area as ROI which plays an important role in functional recovery after motor impairment. Therefore, the aim of this study was to determine the clinical effectiveness of the dynamic hand orthosis in the early subacute stroke period and explore the recovery mechanism with lateralization and oxygenated hemoglobin changes based on motor-task related regions of interest by use of fNIRS in subacute persons with stroke in this paper.

Methods

Design

A Randomized, controlled trial.

Subjects

A total of 30 persons with stroke were recruited from the neurorehabilitation ward in the China Rehabilitation Research Center (CRRC) from August 2019 to February 2020. The participants were divided into two groups: one unilateral task-oriented training combined with a dynamic hand orthosis group (Orthosis Group) and a usual exercise group (UL group), with 15 persons with strokes in each group.

Inclusion criteria First Stroke Age > 18 years 14-90 days since stroke (± 3 days) Partly finger movement (defined as ≥ 10 degree of active finger flexion) **Exclusion criteria** Full finger extension Language and/or cognitive impairments that preclude the person from following instructions (defined as Mini-Mental State Examination, MMSE ≤ 20 score) Other health conditions that preclude the person from undergoing rehabilitation, such as severe depression, anxiety, mental symptoms, internal disease (Fig. 1).

Randomization and blinding

A computer-generated randomization number table was generated in Excel and maintained off-site. Group allocations were distributed in opaque envelopes. To ensure data reliability, the clinical scale and fNIRS measurements were blinded to the testers.

Interventions: unilateral task-oriented training (UL practice) with And without an orthosis

All the persons with stroke performed task-oriented therapy for the affected upper extremity, for 5 times/week, for 4 consecutive weeks. Individual therapist-supervised upper limb practice could be divided into smaller sessions throughout the training but was set to be 60 minutes in total for arm and hand. The 60 minute session was divided into 10 minutes gross motor training, 10 minutes fine motor training, 10 minutes intensive training, and 30 minutes of activities of daily living training. The Orthosis group wore a hand orthosis device on the affected hand during the supervised UL practice for 30 minutes. The Usual Care group performed supervised UL practice without orthosis for 60 minutes. All the persons with stroke were under the supervision of a licensed OT therapist in both groups. The position of training was individually adapted and performed either in sitting or standing.

The dynamic hand orthosis (Saeboglove®, Saebo Inc, Charlotte, NC) used in the study is a hand device equipped with a proprietary tension system that extends the persons' fingers and thumb when grasping. The orthosis was used during repetitive task training, including constant grip-release actions. Releasing is facilitated through finger extension just after the grasping movement has ended ⁽¹³⁾. The support provided

to hand opening can be adjusted by the therapist or the persons themselves, depending on the amount of assistance required to accomplish tasks.

Clinical outcome measures

Clinical outcome measures included the Grip Strength Evaluation (Jamar Digital Hand Dynamometer, kg), the Action Research Arm Test (ARAT) ⁽¹³⁾ and the Fugl-Meyer Assessment of the arm (FMA-arm) ⁽²⁴⁾, were evaluated at the time of recruitment and 4 weeks of unilateral task-oriented training with and without an orthosis.

fNIRS experimental procedure

fNIRS measurements were performed at the same day of recruitment and the day after 4 weeks of intervention with the subjects in an upright, sitting position, with the eyes closed. Both upper limbs were placed on the knees, with proximal and trunk relaxed. The subject was instructed to grip-release a 9.06-kilogram grip ring with the hemiplegic hand. The experiment used a block design with 5 repeated cycles of 30 s rest and 15 s movement. The experiment started with a 10 s pre-scan and a 30 s rest time, which were not used for statistical analysis. The participant was instructed to repeatedly grip-release with the hemiplegic hand 5 times at a steady speed, guided by an auditory metronome during the 15 second period. The task required the participant to relax the non-grasping hand and to avoid any movements other than those required for the motor tasks during the performance of the one-handed grip-release task. Activation and relaxation were monitored and recorded by the tester.

Data acquisition

The optical signal was measured using a 48-channel near-infrared spectroscopy (NIRS) machine (Hitachi, ETG-4100). Near-infrared lights with wavelengths of 695 nm and 830 nm were guided by optical fiber bundles and transmitted into the brain through the cranium to measure changes in the oxyhemoglobin (O₂Hb) and deoxyhemoglobin (de-O₂Hb) concentration at a sampling frequency of 10 Hz during the motor task. Two plastic probe holders (4 × 4 matrix) with 24 channels positioned on either side of the head were placed on the scalp over the persons' bilateral motor-related areas. The source-detector probe geometry of the fNIRS system is shown in Fig.1B. A total of 8 sources and 8 detector fiber bundles were positioned on each plastic probe holder. The probes were placed 3 cm away from each other, to monitor the cortical activation over two 9 cm × 9 cm rectangular fields of view. The electroencephalography (EEG) International 10-20 system Cz, C3, C4 anatomical measurements were used as reference points to ensure that the optical probe setup was placed over 6 ROIs (25) , including the bilateral SMC, PMC and PFC. A three-dimensional (3D)-digitizer was used to record the exact locations of each fNIRS probe for a

standard brain before converting these coordinates into the locations of the forty-eight channels in an estimated Montreal Neurological Institute (MNI) space using the MATLAB toolbox NIRS-SPM (26). The positioning of the 48 channels on a reconstructed 3D brain is shown in Fig.2A (20). Based on the mean MNI coordinates and Brodmann's area (BA) correspondences, the 6 ROIs were covered by the following channels for the left and the right hemispheres: the left SMC was covered by channels 4, 5, 6, 8, and 9 (both sides of C3); the right SMC was covered by channels 25, 29, 32, 36, and 39 (both sides of C4); the left PMC was covered by channels 11, 12, 13, 15, and 16; the right PMC was covered by channels 26, 30, 33, 37, and 40; the left PFC was covered by channels 18, 19, 20, 22, and 23; and the right PFC was covered by channels 27, 31, 34, 38, and 41 (Fig.2B).

fNIRS data processing and image analysis

All artifact data were autodetected and corrected by the open-source HOMER software, implemented in MATLAB(27). Any data with obvious motion artifacts or damaged channels in any block/rest period were manually excluded from further analysis. Then, a 0.01–0.1 Hz bandpass filter was applied to remove global fluctuation due to heartbeat (0.8–2.0 Hz), respiration (0.1–0.33 Hz), and Mayer waves (0.1 Hz or lower) (28) (29).

fNIRS outcome measures

Oxygenated hemoglobin changes based on SMC and PMC

After preliminary data processing as above, fNIRS was used to classify motor-related brain activity on the sensor-level, and the original light intensity data was converted into a change in the blood oxygen concentration. The average change in O₂Hb concentration during the movement period and the rest period during each of the five blocks were statistically analyzed. Because fNIRS relies on hemodynamic responses, which take some time to occur, O₂Hb and de-O₂Hb signals are typically considered to mark changes in neural activity with a lag of roughly four seconds [10-14s] (30). Thus the data of 10 second to 15 second since each block begun were statistically analyzed finally. We used a task-related increase in O₂Hb concentration value as the marker for cortical activity (31).

Calculating the lateralization index (LI)

Hemispheric dominance during a motor task is usually expressed for an ROI by calculating the lateralization index. The LI was determined from the sum of oxy-hemoglobin concentrations in channels in each ROI as $LI = \frac{(\text{contralateral O}_2\text{Hb concentration} - \text{ipsilateral O}_2\text{Hb concentration})}{(\text{contralateral O}_2\text{Hb concentration} + \text{ipsilateral O}_2\text{Hb concentration})}$ (20) (32). LI values range from -1 to 1, with a score of 1 indicating a purely contralateral ROI (contralateral hemisphere of the tested hand)

affected hemisphere) and -1 indicating a purely ipsilateral ROI (ipsilateral hemisphere of the tested hand-unaffected hemisphere) activation. The change of LI values for PMC and SMC= (LI values post-intervention) - (LI values pre-intervention).

Statistical analysis

All statistical analyses were performed using SPSS 19.0. The clinical characteristics (age, gender, time since stroke onset, stroke type, amount of therapy, side of hemiplegia) were compared between the two groups. Measurement data conforming to normal distributions are presented as the mean $\pm$ standard deviation (mean $\pm$ SD), and within-group comparisons were performed using paired t-tests. Measurement data with non-normal distribution were compared with the rank-sum test. Measurements between the two groups for continuous variables were compared with a two-sample t-test or Mann-Whitney U test. Between group continuous data were analyzed with Chi-square test. Pearson's correlation coefficient was used to analyze the correlation between the change of LI and clinical scales. LI data are presented as the mean $\pm$ SD. The change of LI values for PMC and SMC between group was analyzed with two independent samples t-test. Analysis of changes in O₂Hb levels in SMC and PFC: Paired t-test was used to compare before and after the intervention, and an independent-samples t-test was used for comparisons between the two groups. Significance was set at $p < 0.05$. The confidence interval was 95%.

Sample size and statistical power

Based on the prior feasibility study from Yih, ipsilesional ARAT scores increased by 7.3 ± 3.3 from the first clinical scale assessment (0 week) to the second clinical scale assessment (12 week), If a paired sample design is assumed, to achieve 80% power of test, at $\alpha = 0.05$, $1 - \beta = 0.8$, $SD = 1.96 \times 7.3 = 14.308$, a total of 33 sample size in each group will achieve. Considering that the sample size is consistent with recommendations in the design of pilot studies, a sample of 15 cases was recruited in each group.

Results

Characteristics of persons with stroke

There were no dropouts. No significant differences were observed between the two groups for age, gender, time since stroke onset, stroke type, amount of therapy, or hemiplegia side (Table 1, $p > 0.05$).

Table 1 General characteristics of persons with stroke(n=30)			
characteristic	Orthosis group	UL group	p-value
N	15	15	
Age, years, mean±SD	62.67±8.95	55.80 ±12.42	0.093
Gender, n(%)			
Male	10 66.67%	13 86.67%	0.195
Female	5 33.33%	2 13.33%	
Time since onset, days, mean±SD	53.66 ±25.64	51.20 ±24.94	0.818
Stroke type ,n(%)			
Hemorrhage	6 40.00%	5 33.33%	0.705
Infarction	9 60.00%	10 66.67%	
Amount of therapy, hours, mean±SD	3.20 ±0.53	3.25±0.56	0.829
Hemiplegia, n(%)			
Left	5 33.33%	7 46.67%	0.456
Right	10 66.76%	8 53.33%	
Handedness			NS
Left-handed	1 6.67%	0	
Right-handed	13 86.67%	15 100%	
Double-handed	1 6.67%	0	

Values are presented as means ± standard deviations and percentages. Abbreviations: UL group: Usual exercise group, NS: not applicable.

fNIRS results

Analysis of O₂Hb changes based on ROI within-group and between-group comparisons

In the Orthosis group, 1 case of ambidexterity and 1 case of left-handedness were excluded, leaving O₂Hb data from 13 right-handed cases for analysis. In the UL group, 2 cases of incomplete or interfering data were removed, leaving 13 cases of right-handedness to analyze. Changes in the mean O₂Hb

concentrations in the PMC and SMC pre and post-intervention were compared between the two groups (concentration unit: $\times 10^{-6} \mu\text{mmol/l}$).

Within-group comparisons

In the Orthosis group, the mean O₂Hb concentration for the ipsilateral PMC and contralateral PMC increased after intervention but not significantly (p=0.178 and p=0.341). The mean O₂Hb concentration for the ipsilateral SMC and contralateral SMC increased but not significantly (p=0.881 and p=0.419).

Also in the Usual Care group, the mean O₂Hb concentration for the ipsilateral PMC increased after intervention as well as the mean O₂Hb concentration for the contralateral PMC but not significantly (p=0.89 and p=0.98). The mean O₂Hb concentration for the ipsilateral SMC increased after intervention, but the mean O₂Hb concentration of the contralateral SMC decreased, there were no significant differences (p=0.38 and p=0.65). (Table 2)

Table 2 Changes in the mean O₂Hb concentrations in the PMC and SMC within -Group

	Orthosis group		Within-group	UL group		Within-group
Ipsi-PMC	Pre	Post	p=0.178	Pre	Post	p=0.89
	1.9508	4.9154		2.9365	3.0368	
Contra-PMC	Pre	Post	p=0.341	Pre	Post	p=0.98
	1.9280	2.9764		2.4449	2.4641	
Ipsi-SMC	Pre	Post	p=0.881	Pre	Post	p=0.38
	2.5539	2.7165		2.4221	3.4261	
Contra-SMC	Pre	Post	p=0.419	Pre	Post	p=0.65
	2.1985	2.7729		3.1034	2.4224	

Values are presented as means. Abbreviation: Ipsi:Ipsilesional, Contra:Contralesional,O₂Hb: Oxygenated hemoglobin .

Between-group comparisons

The between-group comparison showed no significant differences in mean O₂Hb changes in the PMC and SMC between the two groups: the change in the ipsilateral PMC (F=5.912, p=0.364); the change in the contralateral PMC (F=1.315, p=0.302), the change in the ipsilateral SMC (F=0.008, p=0.556), and the change in the contralateral SMC (F= 0.567, p = 0.400) (Table 3)

Table 3 Changes in the mean O₂Hb concentrations in the PMC and SMC between-Group

		Orthosis group	UL group	Between-group
Ipsi-PMC	Post-Pre	2.9645	0.1002	p=0.364
Contra-PMC	Post-Pre	1.0483	1.0029	p=0.302
Ipsi-SMC	Post-Pre	0.1626	0.0191	p=0.556
Contra-SMC	Post-Pre	0.5744	-0.68105	p=0.400

Values are presented as means. Abbreviation: Ipsi:Ipsilesional, Contra:Contralesional,O₂Hb: Oxygenated hemoglobin .

Analysis of LI

Within-group comparisons

In the Orthosis group, the LI for the PMC decreased from positive to negative, indicating a shift in the cortical activation from the ipsilateral PMC to the contralateral PMC after intervention. The mean LI value of the SMC increased from negative to positive, suggesting a shift in the cortical activation from the contralateral SMC to the ipsilateral SMC after the intervention. In the Usual Care group, the mean LI value for the PMC decreased, suggesting a shift in cortical activation from the ipsilateral to the contralateral PMC. The mean LI value of the SMC increased from negative to positive, suggesting a shift in cortical activation from the contralateral SMC to the ipsilateral SMC after treatment (Table 4).

Table 4 The mean LI value of the PMC and SMC of two groups

		Orthosis group		UL group	
		Pre	Post	Pre	Post
PMC		0.53±1.06	-0.32±0.69	0.08±0.44	0.03±0.67
SMC		-0.84±1.27	0.10±0.88	-0.18±0.54	0.21±0.39

Between-group comparisons

No significant differences in the change of LI values for SMC(p=0.074), and no significant differences in the change of LI values for PMC(p=0.087) between the two groups.

Relationship between change of LI value and clinical test Outcomes

All the persons with stroke (n=30) completed all clinical scale tests. In this study, change scores of ARAT and FMA-Arm will be reported in the correlation analysis.

In the Orthosis group, a significant positive linear correlation was observed between the change of FMA-arm scores and LI changes for PMC ($r=0.588$, $p^*=0.035$) (Fig. 3 A), ARAT scores and LI changes for SMC ($r=0.554$, $p^*=0.0495$) (Fig. 3 D). But no significant linear correlation was observed between the change of FMA-arm scores and LI changes for SMC ($r=-0.010$, $p=0.974$) (Fig. 3 B), the change of ARAT scores and LI changes for PMC ($r=0.177$, $p=0.563$) (Fig. 3 C).

In the Usual Care group, a significant negative linear correlation was observed between the change of FMA-arm scores and LI changes for SMC ($r=-0.705$, $p^*=0.007$) (Fig. 3 B'). But no significant linear correlation was observed between changes of FMA-arm scores and LI changes for PMC ($r=0.327$, $p=0.276$) (Fig. 3 A'), the changes of ARAT scores and LI changes for PMC ($r=-0.503$, $p=0.863$) (Fig. 3 C'), the changes of ARAT scores and LI changes for SMC ($r=0.068$, $p=0.825$) (Fig. 3 D').

Discussion

In this study, we analyzed the change of O_2Hb in bilateral SMC, PMC by fNIRS during grip-release task in subacute persons with stroke following task-oriented training combined with and without a dynamic hand orthosis, no significant difference was between group. Similar shift of activation from the contralateral to the ipsilateral SMC, from the ipsilateral to contralateral PMC were observed in both groups. A significant positive correlation was only observed between the shift to contralateral PMC activation and change of FMA-arm score, between the shift to contralateral SMC and change of ARAT score in the Orthosis group. In the UL group, a negative correlation was only observed between the shift to ipsilateral SMC and changes of FMA score.

Analysis of Oxygenated Hemoglobin Changes

Many studies have shown that O_2Hb was the most sensitive marker for changes in regional cerebral blood flow activity (31). Previous studies have suggested that the recovery of hand function after stroke was related to the activation of some cortical areas, such as the bilateral SMC, PMC, and cerebellum(33). In line with previous studies(34), our results indicate that the increased activation of the bilateral SMC and PMC has a compensatory role for both groups. A decrease in O_2Hb concentration in contralesionally SMC in UL group may represent the reduced demand for task-related synaptic activity, suggesting that fewer neurons are required to complete the same action task as previous study⁽³⁵⁾. However, no significant difference was found in activation between the two groups, most likely due to small sample size.

Based on these O_2Hb result, in the future study, if a paired sample design is assumed to compare the differences of ipsilateral PMC within-group, to achieve 80% power of test, at $\alpha=0.05$, 1-

$\beta=0.8, \delta=1.96 \times 2.96=5.80$, a total of 562 sample size (two-tailed) in Orthosis group will achieve. If a group design is assumed to compare the differences of ipsilateral PMC between-group, to achieve 80% power of test, at $\alpha=0.05, 1-\beta=0.8, q_1=q_2=0.5, \delta=1.96 \times 2.86=5.61$, a total of 193 sample size (two-tailed) in each group will achieve. The sample size of further study could be based on this study.

Analysis of Lateralization Index (LI)

Studies have shown that the LI can be used to evaluate the recovery of motor function in persons with stroke(20) (36) (37). There is a similarity in cortical activation patterns during this grip-release task between two groups. Our results are compatible with some fMRI researches that the shift of SMC and PMC activation paralleled functional recovery of the hand (38).

Based on previous studies, PMC is involved in the purposeful modification and initiation of motion through connections with the brain stem, basal ganglia, cerebellum, and spinal cord(39). PMC activation may reflect the need for stabilizing proximal limbs and related to improved control of upper-limb performance(40). This activation of the contralateral brain area provides recruitment of additional neural resources due to the increased demands of the damaged motor system (41, 42).

SMC is an integral part of basic motor network associated with upper-limb recovery, our study supports this enhanced compensation in ipsilateral SMC(43) (38), this result was consistent with most studies that report a recovery of motor function (21) (40). These results reflect the reorganization of brain areas, however, the role of ipsilateral SMC or contralateral SMC has been controversial, opposite results could be seen in some studies (36, 40).

There are some reasons to explain these results of no difference. Firstly, according to the timeline of stroke recovery, the first week until the first month post-stroke is a critical time for neural plasticity and should be a target for recovery trials(6). However, if the persons were enrolled within 4 weeks since stroke, they may only have arm synergies, without hand grasping movement. More suitable motor task should be considered for fNIRS in the early subacute period. Secondly, only two test points and 4-weeks observation time may be insufficient. Applying repeated measurements at series of time points that start early and continue into the chronic phase in larger sample persons may help to establish understanding of recovery mechanism. Informed by series of time points data, new treatments would have a higher likelihood of being identified a true treatment effect. Third, the complexity of the task and motor intensity may affect the results(44-47). Cortical hemodynamic response to simple or complex motor stimuli differ to duration and intensity(46) (48). Longer duration and higher intensity may lead to feasible results of group-level differences.

Relationship between change of LI value and clinical test outcomes

Some findings pointed that after received multidisciplinary rehabilitation therapy, a negative association between changes of FMA score and the shift to ipsilateral M1 (primary motor area), a positive association between changes of ARAT score and the shift to contralateral M1 could be seen(43). Our study of UL group is consisted with these findings (Fig. 3,B'), but no similar trend could be seen in Orthosis group (Fig. 3,B). One possible explanation could be the compensatory contribution of ipsilateral M1 to motor recovery in UL group(40). Our study of Orthosis group is also consisted with Riecker's findings(43) (D), which means the shift to contralateral SMC activation plays an important role in the increase of ARAT score in Orthosis group. In a consistent functional magnetic imaging (fMRI) study performed by Bütetisch(49), the contralateral cortex was also shown to play an important role in functional recovery.

According to a systematic literature review (50), FMA was related to multi-joint associated movement, ARAT was related to hand movements combined with synergistic movement. Any shift in brain activity to the ipsilateral hemisphere correlates with improvement in ARAT, but not correlates with improvement in FMA. In our study, there was no significant correlation between LI changes for PMC and ARAT score in any of the group. (Fig. 3 C, C'). Due to the great individual difference, the significant difference of correlation analysis in two groups may be affected. This result may indicate that the relationship between the lateralization shift of PMC and ARAT was not a sensitive indicator to show the recovery mechanism in the two group.

In the Orthosis group, a positive correlation was between changes of FMA-arm score and the shift to **contralateral** PMC (Fig. 3 A), this result suggested that the shift to **contralateral** PMC activation which was related to the preparation of movement for control and posture was significant correlative to the upper limb motor function in the Orthosis group, but no significant correlation in the UL group (Fig. 3 A'). However, a negative correlation was in Shoji's small sample study(37), individual differences and small sample should be considered when interpreting these results.

Limitations.

There are several limitations of this study. Because of limited samples, larger variability in motor recovery could affect the interpretation of the results. Besides,

related to inclusion criteria and peculiarity of recruiting center, the time 14-90 days baseline with a mean day approximately 50-day is a bit late to make use of the therapeutic time window of approximately 20 days (4 weeks) for max influence on neuroplasticity by rehabilitative training. Lack of repeated measurements at each week is another limitation. In the further fNIRS analysis and study, other outcome measures, such as peak and time-to-peak should be concerned, O₂Hb and LI values for ROI in different hemispheric dominance (51) subgroups may have more interesting results.

Conclusions

In this pilot study, after unilateral task-oriented training with and without an orthosis in subacute stroke, there was no significant difference in O₂Hb concentrations change—the shift of LI for SMC and PMC. The associations with FMA-arm, ARAT and the activation shift of ROI was different and moderate, possibly indicating the usefulness with fNIRS. Sufficient samples, intervention time, and different rehabilitation intensity should be considered to obtain strong evidence in the future studies.

Declarations

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Authors' contributions

C.J.Z.L. is the first author. T.Z. is the corresponding author. Y.W. and C.J.Z.L. implemented, enrolled participants and collected data. T.Z., B.L., X.X.D. designed the experiment. F.B.H. as the occupational therapy guide and explained fNIRS methodology. H.J.Z. as the clinical scale tester, Y.L.W. performed statistical analysis. All authors discussed and approved the final manuscript. C.J.Z.L. wrote the paper.

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Availability of data and materials

The datasets used in the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Regional Committee for Medical and Health Research Ethics (No. 2017/1915 REK sør-øst D) and the China Rehabilitation Research Center Ethics Committee (No. 2019-112-1). Trial registration: Registered on January 11, 2018 at ClinicalTrials.gov

(NCT03396939). <https://clinicaltrials.gov/ct2/home>. All participants provided written informed consent prior to enrolling in the study.

Consent for publication

No identifiable information is contained in this paper.

Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Abbreviations

SMC Sensorimotor cortex; PMC Premotor cortex; PFC, Prefrontal cortex; UL group Unilateral task-oriented training group; ARAT Action research arm test; FMA-arm Fugl-Meyer assessment of the arm; FNIRS Functional near infrared spectroscopy; O₂Hb Oxygenated hemoglobin; LI, Laterality Index; ROI Region of interest; Ipsi-hemisphere Ipsilesional hemisphere; Contra-hemisphere Contralesional hemisphere.

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Figures

Figure 1

Flowchart of steps

Figure 2

Experimental setting of the optodes A. 3D location of the optodes exposed to the brain surface of a standard brain. A total of 32 optodes. B. The channels covering the SMC, PMC and PFC, comprising 8 light source fibers (red) and 8 detectors (blue), were arranged on the scalp to enable 48 channel measurements. The Cz position of the international 10-20 system was the marker for ensuring the replicable placement of the optodes.

Figure 3

Correlation for the paretic arm between changes for PMC, SMC and clinical tests in two groups A A' Correlation between laterality index changes for PMC-PMC-LI and FMA-arm scores in the Orthosis group (A) and UL group (A'); B B' Correlation between laterality index changes for SMC-SMC-LI and FMA-arm scores in the Orthosis group (B) and UL group(B'); C C' Correlation between laterality index changes for PMC-PMC-LI and ARAT scores in the Orthosis group (C) and UL group (C'); D D' Correlation between laterality index changes for SMC-SMC-LI and ARAT scores in the Orthosis group(D) and UL group (D'); A point (black circle) represents a change for a single patient measurement. The dotted line indicates that there is a significant linear correlation.

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