Association between imbalance of cortical brain activity and successful motor recovery in sub-acute stroke patients with upper limb hemiparesis: A functional near-infrared spectroscopy study

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ABSTRACT

Objective: This study was designed to determine the association between motor functional recovery and interhemispheric imbalance in cortical brain activity in sub-cortical stroke patients with moderate-to-severe upper limb hemiparesis admitted to the convalescent rehabilitation ward.

Subjects and Methods: The study included first-ever stroke patients with moderate-to-severe upper limb hemiparesis who received multidisciplinary rehabilitation therapy in the rehabilitation ward. Motor function of the affected upper extremity was evaluated by the Fugl-Meyer assessment (FMA) and action research arm test (ARAT) at one (T1) and three months (T2) after stroke onset. We also conducted serial functional near-infrared spectroscopy (fNIRS) at the same time points and calculated the laterality index (LI), which is based on changes in oxy-hemoglobin in primary sensorimotor cortex (Brodmann Area 4, BA4), pre-motor cortex and supplementary motor cortex (PMC+SMA, BA6).

Results: The study included 8 patients (7 females, mean age: 68.8). Both the FMA and ARAT scores improved significantly during the study. LI did not change significantly from T1 to T2. There was a no significant correlation between changes in LI in each region and improvement in FMA score. In contrast, a significant and negative correlation was noted between ΔLI in BA4 and improvement in ARAT score.

Conclusions: Our results suggested that activation of the non-lesional hemisphere in sub-acute stroke associated with motor recovery in moderate-to-severe upper limb hemiparesis. A multidisciplinary rehabilitation of stroke patients with moderate to severe upper limb hemiparesis might enhance the compensatory movements and pre-existing motor network from the non-lesional motor cortex.

KEY WORDS: cerebrovascular disease, neuroimaging, neurorehabilitation, neuromodulation

INTRODUCTION

Stroke is a major global health care problem and rehabilitation is a major component of clinical management. Hand and arm impairment in particular are often persistent, disability; the activities of daily living and quality of life are disrupted in patients with post-stroke upper limb hemiparesis [1].

Early studies reported the close relation between primary motor cortex activity in the affected hemisphere with functional motor recovery [2-3]. However, there is debate at present on the effect of the non-lesional hemisphere on poststroke functional recovery. On one hand, some studies demonstrated that the activation patterns of the non-lesional hemisphere in stroke patients are associated with poor functional recovery [4-6], while other studies concluded that the non-lesional motor areas facilitated motor performance in stroke patients [6-9]. The difference in the above studies suggests that the effect of non-lesional hemisphere on motor recovery may vary according to certain conditions. Understanding the progression of interhemispheric imbalance in brain activation and its contribution to motor functional recovery is important for effective rehabilitation therapy.

Functional near-infrared spectroscopy (fNIRS) has been used increasingly in studies of rehabilitation, including stroke [10-12]. The NIRS system measures noninvasively the hemodynamic changes in tissues, such as cortical microvessels, by detecting the characteristic absorption spectra of hemoglobin through near-infrared light probes, and thus provides measurement of regional hemodynamic responses associated with cortical brain activation. The results of fNIRS for measurement of cortical neural activity are similar to those obtained by functional magnetic resonance imaging (fMRI) [10]. However, fNIRS has certain technical limitations, such as difficulty of measurement of deep brain areas and low spatial resolution. Nevertheless, the measurement device used in fNIRS is smaller and less costly than that of fMRI. Another advantage of fNIRS is that it allows measurements to be conducted while the patient performs various tasks in a variety of postures. Considered together, the flexibility of the fNIRS justifies its use in clinical studies.

To our knowledge, there are no studies that used fNIRS to assess the association between functional recovery of affected upper extremity in sub-acute stroke patients and interhemispheric imbalance. The present study was designed to determine the true correlation between motor recovery in sub-acute stroke patients with severe to moderate hemiparesis in the convalescent rehabilitation ward and cortical brain activity using measurements obtained through serial fNIRS.

SUBJECTS AND METHODS

This study was conducted at Nishi-Hiroshima Rehabilitation hospital (Hiroshima, Hiroshima). For this study, we included consecutive patients diagnosed with first-ever stroke who had been admitted to the Kaifukuki (convalescent) rehabilitation wards between February 2016 and March 2017. The diagnosis of stroke was based on the computed tomography (CT) or magnetic resonance imaging (MRI). The following inclusion criteria were applied: 1) Diagnosis of cerebral infarction or intracranial hemorrhage in unilateral hemisphere. 2) Clinically evident upper limb hemiparesis. 3) Ability to flex and extend the paretic fingers at the time of admission. 4) Fugl-Meyer Assessment (FMA) score less than 48 [13]. 5) Admission to the convalescent rehabilitation wards of less than 42 days (six weeks) after onset. 6) No cortical lesions evident on CT or MRI. 7) No history of head or brain surgery. 8) No apparent cognitive impairment.

The present study was conducted in compliance with the Declaration of Helsinki. The study protocol received the approval of the ethics committee of the Nishi-Hiroshima Rehabilitation Hospital. All patients were informed about the nature of this study.

After admission to the convalescent rehabilitation ward, the patient received rehabilitation therapy. The Japanese public Medicare insurance system covers all costs associated with the admission to the Kaifukuki (convalescent) rehabilitation wards. These facilities provide interdisciplinary post-acute rehabilitation treatment for stroke patients who require assistance in activities of daily living after acute hospitalization [14]. In this study, all patients received physical and occupational therapy, which focused mainly on ability to walk and activity of daily living, almost 3 hours per day. To enhance functional recovery of the affected upper limb, we applied the shaping techniques and repetitive task practice techniques. Unfortunately, the amount of specific modality or technique of rehabilitation therapy was not recorded during the study.

Serial assessments of motor function of the affected upper limb and brain activity using the fNIRS were conducted at admission (one month after stroke onset, T1) and two months after admission (three months after stroke onset, T2). Evaluation was performed at one day after admission and 60 days after the first evaluation.

The Fugl-Meyer Assessment (FMA) and the ARAT were applied to assess motor function of the affected upper limb. FMA is a performance-based quantitative measure designed to assess various impairments in post-stroke patients. Assessment of upper limb motor function comprises 33 items. The maximum possible motor performance score for the upper limbs is 66 points, with each item rated by a 3-point (0-1-2) ordinal scale. The ARAT is a clinical test of arm motor function. Upper limb movements of pinch, grasp, grip and gross movements were performed and graded on a 4-point scale, with a total score ranging from 0 to 57.

fNIRS measurement

A task involving repetitive movements of flexion and extension of the paretic fingers at frequency of 1Hz with verbal cues, using a block paradigm design (three cycles; rest [15 sec] - hand movements [15 sec] - rest [15 sec]) was applied during fNIRS. For recording of cortical activity during task performance, we used the 49-channel fNIRS system (FOIRE-3000; Shimadzu, Kyoto, Japan), with continuous wave laser diodes at three wavelengths of 780, 805, and 830 nm, and sampling rate of 10Hz [11, 12]. The optodes roughly covered the frontal regions, the primary sensory-motor cortex (M1, Brodmann Area 4; BA4), premotor cortex and supplementary motor area (PMC+SMA, BA6). Based on the International 10-20 System, we used Cz as a reference point for positioning the optodes. We positioned the fNIRS sources and detector across from each other at 3-cm intervals. Based on the modified Beer–Lambert law, values of oxyhemoglobin (HbO) was acquired following changes in levels of cortical concentration. HbO level was selected since it is reliable and sensitive to changes in cerebral blood flow [10]. The location of optodes and the anatomical landmarks on the participant nasion, Cz, and left and right pre-auricular points were marked using a 3D digitizer (FASTRACK, Polhemus, USA).

We used the Statistical Parametric Mapping software package (NIRS-SPM; Welcome Trust Centre for Neuroimaging, London, UK) operated in the MATLAB environment (Mathworks, Natick, MA) to perform spatial registration of channel locations on the Montreal Neurological Institute (MNI) brain. To estimate and remove temporal autocorrelation, we applied Gaussian smoothing with full width at half maximum (FWHM) of 2 sec. We used the wavelet-minimum description length (MDL) based detrending algorithm for correction of signal distortion. To calculate the beta value as the individual task-related activity, the general linear model (GLM) analysis was performed with hemodynamic response curve to model the hypothesized HbO response during experimental conditions. Based on the beta value, i.e., the regression coefficient in the GLM, the topography was plotted based on the location of the channels. When SPM t-statistic maps were computed for group analysis, HbO was considered significant at an uncorrected threshold of $p<0.01$. For group analysis, left/right information was flipped in cases with left-sided hemiparesis.

To investigate the cortical changes in HbO during the execution of hand movements, we selected the M1 (BA4) and PMC+SMA (BA6) as regions of interest (ROI). The selection was based on a previous study [15], which indicated that BA6 plays an important role in functional recovery after motor impairment. We defined appropriate four channels corresponding to each ROI using MNI coordinates of the channels. Before the individual analysis, we used a temporal low-pass cut-off filter with 0.1 Hz to reduce physiological noise, such as cardiac signal and respiration. We calculated the concentrations of HbO_2 during task performance and during 5 sec before the task (referred to as the baseline). We subtracted each baseline concentration from the average concentration during task performance to evaluate the relative change in HbO_2 concentration (ΔOxy-Hb) during specific tasks. We averaged all three trials of the four channels (BA4, BA6), yielding the ΔOxy-Hb for each task (left and right ROI). In order to evaluate interhemispheric asymmetry in regional activation, the laterality index (LI), defined as (ΔOxy-Hb in affected hemisphere – ΔOxy-Hb in unaffected hemisphere) / (ΔOxy-Hb in affected hemisphere + ΔOxy-Hb in unaffected hemisphere) was calculated for each region. Laterality indexes of +1 and -1 represented activation in the lesional and non-lesional hemispheres, respectively.

Statistical analysis

Changes in motor function of the affected upper limb (FMA and ARAT) and those of the LI in the BA4 and BA6 from T1 to T2 were computed and compared using the Wilcoxon signed-rank test. In addition, the Spearman's rank correlation coefficient was computed to assess the correlation between improvement in motor function (ΔFMA and ΔARAT) and the LI in each ROI at T1. Correlation between the changes in motor function tests and those of LI in each ROI from T1 to T2 (ΔLI) was also analyzed. A correlation (r) value less than 0.40 was considered to indicate low correlation and value of 0.40-0.69 represented moderate correlation. The level of significance was set at $p<0.05$. To determine the confounding effect of gender, a sub-group analysis of female patients was performed. All statistical analyses were performed using SPSS 24.0 (IMB SPSS Inc., Armonk, NY).

RESULTS

During the study period, 273 stroke patients were admitted to the hospital. Among them, 8 patients (7 females) met the inclusion and exclusion criteria set out for the present study. Table 1 summarizes the patients' characteristics. The mean age of the study patients was 68.8 years, and the average time between stroke onset and admission to our hospital was 27.5 days.

Table 2 shows the changes in motor function on the affected upper limb and LI in each ROI from T1 to T2. Both outcome measures of the affected upper limb (FMA and ARAT) improved significantly during the study period. The LI in the BA4 and 6 did not change significantly from T1 to T2.

Table 3 shows the correlation between ΔLI and improvement of motor function in sub-acute stroke patients. There was no significant correlation between LI in each ROI at T1 and improvement in both motor function tests. There was a no significant correlation between ΔLI in each ROI and ΔFMA. However, there was a significant, strong and negative correlation between ΔLI in BA4 and the ΔARAT.

Fig 1 shows the results of group analysis. High-level activation was evident in the non-lesional hemisphere. The level of activation increased but was localized to BA4 at T2. We found minute activation in the lesional hemisphere at both time points.

The female patients showed significant improvement in FMA and ARAT of the affected upper limb during the study period. The result of correlation analysis was similar in these patients relative to the entire group, however; there was a no significant correlation between ΔLI in BA4 and the ΔARAT (Table 4).

DISCUSSION

In this study, we analyzed the data of sub-acute stroke patients with sub-cortical lesions, including serial assessments of upper limb hemiparesis and cortical brain activity by using fNIRS. Although the LI in the BA4 and BA6 did not change significantly during the study period, LI in each ROI tended to be lower at three months after stroke onset than at one month after onset. In addition, the results showed a significant and negative correlation between ΔARAT score and ΔLI in BA4, but not between ΔFMA score and ΔLI in each ROI. The sub-group analyses of female patients were similar to those of the entire group.

To date, the contribution of the non-lesional hemisphere to functional recovery after stroke is controversial. Previous studies described bilateral enhanced activation patterns in stroke patients with poor recovery, whereas low recruitment of non-lesional motor structures was observed in patients with good motor function recovery during follow-up [4-6]. These findings point to a negative association between functional recovery and the extent of activity within the non-lesional hemisphere. On the other hand, other studies showed that the non-lesional motor areas were significantly associated with motor performance in stroke patients with subcortical lesions [7-9]. These findings support the notion that activation of the non-lesional hemisphere contributes to motor performance and functional recovery in stroke patients. It is assumed that the contribution of the non-lesional hemisphere to motor recovery may vary according to the severity of brain damage. Therefore, there is a need to determine the specific factors that influence the contribution of the non-lesional hemisphere on functional recovery in stroke patients. However, to our knowledge, there are no studies that examined the association between improvement of motor function of the affected upper limb and changes in cortical imbalance, as assessed by fNIRS in sub-acute stroke patients with severe to moderate upper limb hemiparesis admitted to convalescent rehabilitation ward. This study is the first to show that a shift in brain activation to the non-lesional hemisphere is associated with motor recovery in sub-cortical stroke patients with moderate-to-severe hemiparesis who underwent interdisciplinary post-acute rehabilitation therapy.

One possible explanation for the association between the shift in brain activation to the unaffected hemisphere and functional motor recovery could be the compensatory contribution of non-lesional M1 to motor recovery. In contrast to corticospinal connection, corticoreticulospinal projections are bilateral and thought to be involved in the expression of the flexion synergy [16]. In addition, up-regulation of ipsilateral projections from non-lesional M1 is reported to be associated with functional adaptation in severely affected stroke patients [17]. Based on the above findings, it is possible that enhancement of pre-existing motor network from non-lesional M1 can contribute to the functional motor recovery observed in our stroke patients with moderate-to-severe upper limb hemiparesis.

Although there was a significant correlation between improvement in ARAT score and shift in brain activity, we did not find a significant correlation between improvement in FMA score and shift in brain activation. One possible mechanism for this finding is the difference in the characteristics of FMA and ARAT. In a recent systematic literature review [18], almost all items of the FMA were found to be related to the International Classification of Functioning, Disability and Health framework (ICF) body function and structure domain. In contrast, ARAT contains mainly items related to ICF Activity. In addition, divergent projections from non-lesional hemisphere might account for the multijoint “associated” movements, such as the synergistic flexion (together with weak extension) seen when patients with only poor and moderate recovery attempt isolated hand movements [19]. Therefore, any shift in brain activity to the non-lesional hemisphere correlates with improvement in ARAT, which could reflect compensatory movements, whereas such shift did not correlate with improvement in the FMA, which focuses on fractionized movement in isolated joints.

Our results showed that LI at three months after stroke onset tended to be lower than at one month after onset. A previous study of sub-acute stroke patients with sub-cortical lesions examined by serial fMRI measurements found enhanced cortical activation in the non-lesional hemisphere after rehabilitative training [20]. Our results are consistent with the findings of the aforementioned study where a shift in activation was found after rehabilitation therapy. In addition, the study patients received interdisciplinary rehabilitation therapy that focused mainly on improvement of walking and activity of daily living. This therapy includes compensatory use of the trunk and non-affected upper and lower extremities. Early compensatory use of the non-affected upper limb impairs recovery of the affected limb and possibly results in aberrant synaptogenesis in the peri-lesional cortex [21]. Based on these facts, the compensatory use of non-affected extremity would facilitate the up-regulation of the non-lesional hemisphere in this study.

Limitation

First, we did not evaluate damage of the corticospinal tract using objective measures, such as TMS or structural MRI. It is important to evaluate these modalities in a future study in order to assess the structural integrity of the corticospinal tract and stratify the stroke patients based on baseline severity. Second, the potential effect of the lesion side (right or left side lesion) was not investigated due to the limited number of study patients. Third, the study sample was small and gender imbalanced. Although the results obtained from female patients were similar to those of the entire group, future studies of larger number of patients are necessary to confound the gender factor.

CONCLUSIONS

In this study, we analyzed sub-acute stroke patients with moderate-to-severe upper limb hemiparesis and sub-cortical lesions by serial assessments of upper limb hemiparesis and cortical brain activity using fNIRS. We found a significant and negative correlation between improvement in ARAT score, but not FMA score, and a shift in brain activity to the non-lesional hemisphere. The results indicate that a shift in cortical brain activity to the non-lesional hemisphere is associated with functional motor recovery in sub-acute stroke patients with moderate-to-severe hemiparesis admitted to the convalescent rehabilitation wards. A multidisciplinary rehabilitation for stroke patients with moderate to severe upper limb hemiparesis might facilitate the compensatory movements and pre-existing motor network from non-lesional motor cortex. Therefore, from the viewpoint of functional brain reorganization, it would be necessary to reconsider a suitable rehabilitative program that can improve upper-limb motor function and facilitate brain motoneuron reorganization.

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FIGURE LEGENDS

Fig 1. Group-average activation map of HbO during motor tasks generated using the NIRS-SPM (corrected, p<0.01). Left/right information was flipped in cases with left-sided hemiparesis for group analysis. (A) At one month after stroke onset. We found brain activation in the lesional and non-lesional hemispheres. Activation in the lesional hemisphere seemed weak. (B) A high level of activation was observed in the non-lesional BA4. There was minute activation in the lesional hemisphere.

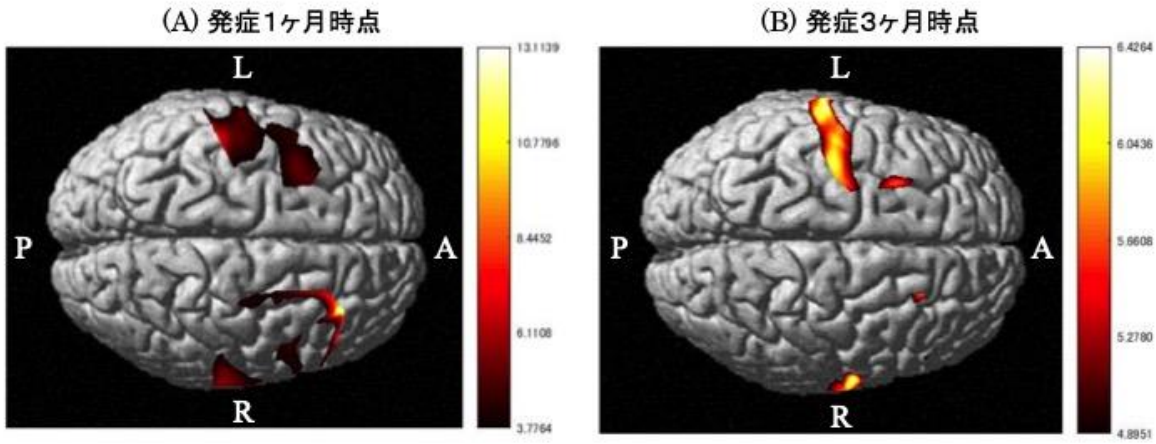

Table 1. Clinical characteristics of the patients

No	Age (yrs)	Sex	Diagnosis	Lesion	Stroke side	Handedness	Time to admission after onset (days)	MMSE at admission
1	66	Male	ICH	Putamen	Right	Right	38	30
2	56	Female	ICH	Putamen	Right	Right	18	28
3	73	Female	CI	Internal capsule	Right	Right	30	24
4	59	Female	ICH	Putamen	Left	Right	33	27
5	75	Female	ICH	Thalamus	Left	Right	40	24
6	75	Female	CI	Putamen	Right	Right	27	30
7	75	Female	CI	Internal capsule	Left	Right	17	27
8	71	Female	CI	Internal capsule	Right	Right	17	30

ICH: Intracranial Hemorrhage, CI: Cerebral Infarction, MMSE: Mini-Mental State Examination.

Table 2. Changes in affected upper limb function and brain activation.

	FMA		ARAT		LI in BA4 area		LI in BA6 area	
No	T1	T3	T1	T3	T1	T3	T1	T3
1	43	59	38	45	0.16	0.32	-0.06	-0.37
2	36	46	11	32	0.23	-1.00	0.48	-1.00
3	23	36	2	24	0.71	0.34	0.73	0.39
4	14	55	6	33	0.50	-0.26	0.21	-0.12
5	47	52	10	24	-0.03	0.42	-0.02	0.08
6	23	49	3	4	-0.46	0.08	0.07	0.10
7	44	59	36	55	-0.73	-0.45	0.13	-0.65
8	30	47	6	34	-0.09	0.02	-0.75	0.11
Mean	32.5	50.4	14.0	31.4	0.36	-0.07	0.09	-0.18
Median	33	50.5	8	34	0.07	0.05	0.10	-0.02
P value		0.012		0.012		0.889		0.263

FMA: Fugl-Meyer Assessment, ARAT: Action Research Arm Test, LI: Laterality Index.

Table 3. Correlations between brain activation and improvement in upper limb function (T2-T1) in sub-acute stroke patients.

	ΔFMA		ΔARAT	
	Spearman's r	P value	Spearman's r	P value
Brain activation at T1				
BA4	-0.119	0.779	0.405	0.320
BA6	-0.214	0.610	0.190	0.651
Changes in brain activation from T1 to T2 (ΔLI)				
BA4	0.024	0.955	-0.714*	0.047
BA6	0.262	0.531	-0.048	0.911

FMA: Fugl-Meyer Assessment, ARAT: Action Research Arm Test, LI: Laterality Index. *<0.05.

Table 4. Correlations between brain activation and improvement in upper limb function (T2-T1) in sub-acute stroke patients (female only).

	ΔFMA		ΔARAT	
	Spearman's r	P value	Spearman's r	P value
Brain activation at T1				
BA4	-0.143	0.760	0.464	0.294
BA6	-0.107	0.819	0.107	0.819
Changes in brain activation from T1 to T2 (ΔLI)				
BA4	0.036	0.969	-0.679	0.094
BA6	0.214	0.645	0.107	0.819

FMA: Fugl-Meyer Assessment, ARAT: Action Research Arm Test, LI: Laterality Index.