Longitudinal Optical Imaging Study for Locomotor Recovery After Stroke

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Background and Purpose—We sought to investigate cerebral mechanisms underlying locomotor recovery after stroke.

Methods—We measured cortical activities during hemiparetic gait on the treadmill before and after 2 months of inpatient rehabilitation in 8 patients with initial stroke (5 men, 3 women; 4 with right and 4 with left hemiparesis; aged 57 years; 3 months after stroke on average), using an optical imaging system.

Results—On the initial evaluation, hemiparetic gait was associated with increased oxygenated hemoglobin levels in the medial primary sensorimotor cortex (SMC) that were greater in the unaffected hemisphere than in the affected hemisphere as well as in the premotor cortex (PMC) and supplementary motor area. On the second examination, the asymmetry in SMC activation significantly improved, and there was enhanced PMC activation in the affected hemisphere. Improvement of the asymmetrical SMC activation significantly correlated with improvement of gait parameters.

Conclusions—Locomotor recovery after stroke may be associated with improvement of asymmetry in SMC activation and enhanced PMC activation in the affected hemisphere. (Stroke. 2003;34:2866-2870.)

Key Words: cerebral cortex ▪ gait ▪ optics ▪ rehabilitation ▪ spectroscopy, near-infrared ▪ stroke

As a result of recent advances in functional neuroimaging such as positron emission tomography and functional MRI, there is growing evidence that functional recovery of the hemiparetic hand after stroke depends on cortical reorganization, including the peri-infarct area in the primary sensorimotor cortex (SMC), other motor-related areas such as the premotor cortex (PMC) and supplementary motor area (SMA) in the affected hemisphere, and some combination of these areas in the unaffected hemisphere.1–10 Little is known about the mechanisms underlying locomotor recovery, one of the essential determinants of rehabilitation outcome in stroke, mainly because of technical limitations in assessing cerebral activation during dynamic movements. An optical imaging technique using near-infrared spectroscopy (NIRS)11–14 has enabled visualization of cortical activation during human gait that centered in the medial SMC and SMA.15 In patients with stroke, hemiparetic gait was associated with asymmetrical SMC activation and recruitment of PMC and pre-supplementary motor area (pre-SMA).16,17 In this longitudinal study we sought to clarify how cortical activation changed in the course of locomotor recovery after stroke.

Subjects and Methods
We evaluated cortical activation during hemiparetic gait on the treadmill in 8 patients with initial stroke (Table). All were right handed. All were transferred to our hospital for inpatient multidisciplinary rehabilitation based on neurodevelopmental technique.18,19 The patients did not reach an independent level in ambulation and activities of daily living after medical treatment and less intensive physical therapy for 2 to 3 months in acute hospitals. Each patient underwent NIRS recording before and after 2 months of inpatient rehabilitation. This study was approved by the local ethical committee. Written informed consent was obtained from each patient.

For NIRS recording, patients walked on the treadmill at a speed of 0.2 km/h. Each 30 seconds of task period for walking was alternated by 30 seconds of rest period for 4 times. Experienced therapists, standing by the patients on the paretic side, assisted them mechanically to ensure safe gait performance by holding them on the foot or thigh of the paretic leg if necessary. Four patients (cases 1, 5, 6, and 7) with severe hemiplegia needed 20% of partial body weight support using the overhead harness with a pelvic belt and thigh strips20,21 to perform the walking task. Task conditions were identical in the 2 measurements before and after inpatient rehabilitation in each individual.

Details of the optical imaging system (Shimadzu) were previously described.15,17 In brief, it consisted of 12 light source fibers and 12 detector fibers, resulting in a 36-channel recording of cortical changes in oxygenated hemoglobin (oxyHb), deoxygenated hemoglobin (deoxyHb), and total hemoglobin. The spatial resolution was a few centimeters beyond the interoptode distance set at 3.0 cm, and the temporal resolution was 380 ms. The optodes were placed tightly on the skull with the use of a holder cap fabricated from custom-made thermoplastic resin. Cz was the marker for ensuring replicable placement of the optodes. An anatomic MRI scan22 revealed that the optodes were located over an area of 13×13 cm in the bilateral hemisphere.
We used oxyHb value as the marker for cortical activity because there was a task-related increase of oxyHb levels without apparent changes in deoxyHb levels in the medial SMC, and the cortical maps based on changes in oxyHb levels were similar to those from functional MRI during foot movements and gait imagery.15 Experimental data have also shown that oxyHb is the most sensitive marker of activity-dependent changes in regional cerebral blood flow.24–26 We obtained images depicting average changes in oxyHb during the 4 task cycles after adapting the linear interpolation to the simultaneously acquired 36-channel data. Each topographic map was corrected to match the anatomic location of the optodes on the brain surface and was overlaid on an anatomic MRI surface image.22 For quantification of activation, we calculated DeltaoxyHb, defined as DeltaoxyHb During Task Period-DeltaoxyHb During Rest Period, in each channel. Data from the latter 20 seconds of the 30-second task periods and the middle 20 seconds of the 30-second rest periods were used because there was approximately a 3- to 5-second delay in the response of hemoglobin oxygenation related to the tasks.15 To compare the amount of regional activation between the serial measurements on different occasions before and after inpatient rehabilitation, we defined regional activation as Average DeltaoxyHb in Channels Covering Each Region/Total DeltaoxyHb of All Channels. To evaluate interhemispheric asymmetry of regional activation, we calculated the laterality index6,10,17 (LI), defined as (DeltaoxyHb in Affected Hemisphere-DeltaoxyHb in Unaffected Hemisphere)/(DeltaoxyHb in Affected Hemisphere+DeltaoxyHb in Unaffected Hemisphere), in each region.

To compare regional activation and LI before and after inpatient rehabilitation, we performed a 2-way repeated-measures ANOVA with time (before and after rehabilitation) as a within-subject factor and site of region (SMC, SMA, PMC, and pre-SMA) as a between-subject factor. Gait and physiological parameters were compared with 1-way repeated-measures ANOVA. The Fisher least significant difference test was used as a post hoc test. Correlation between changes of regional activation and gait parameters was analyzed with linear regression. Statistical significance was set at P<0.05.

## Results

### Cortical Mapping of Gait in Patients With Stroke

Cortical activation maps during hemiparetic gait in individual cases are shown in Figure 2. In the first evaluation, activities were observed in the medial SMC that were fewer in the affected hemisphere than in the unaffected hemisphere, SMA, and PMC. Activation in the pre-SMA and prefrontal cortex varied but tended to be seen in patients with large cortical lesions and severe hemiplegia (Figure 2C and 2D), but there was no activation in the damaged cortical areas, as expected in these patients. In the second study, the asymmetry in SMC improved, and there was enhanced PMC activation, particularly in the affected hemisphere. Prominent pre-SMA or prefrontal activation was observed in patients with large areas of cortical damage (Figure 2C and 2D).

### Regional Activation During Hemiparetic Gait

To confirm the findings from individual cortical maps, we performed group analyses. For regional activation, ANOVA
revealed that there was no significant main effect of time or site. There was a significant interaction between time and site (F_{7,56}=2.329, P=0.0370). These findings indicated that time had distinct effects on regional activation. The effect of time on regional activation was significant only in the PMC in the affected hemisphere. After inpatient rehabilitation (118 days after stroke), the patient needed minimal assistance to perform the task. SMC activation was symmetrical, and new activation was seen in SMA and PMC, especially in affected hemisphere. B, Cortical mapping of gait in case 3, with infarction in right frontoparietal lobe. On day 107 after stroke, the patient needed mild assistance with gait. There was less SMC activation in affected hemisphere than in unaffected hemisphere, but PMC and SMA were bilaterally activated. On the second imaging (176 days after stroke), the patient needed little assistance with gait. SMC were symmetrically activated, and there was persistent activation in PMC and SMA. C, Cortical mapping of gait in case 6, with diffuse infarction in right frontoparietal lobe. On day 102 after stroke, the patient needed moderate assistance to take a step. SMC activation was much less in affected hemisphere than in unaffected hemisphere. After inpatient rehabilitation (118 days after stroke), the patient needed minimal assistance to perform the task. SMC activation was symmetrical, and new activation was seen in SMA and PMC, especially in affected hemisphere. D, Cortical mapping of gait in case 8, with a large hemorrhagic lesion centered in right parietal lobe (arrow). On day 32 after stroke, the patient needed moderate assistance with gait. NIRS imaging showed prominent activation in unaffected hemisphere. After inpatient rehabilitation (98 days after stroke), the patient needed minimal assistance with gait, and enhanced activation was observed in the bilateral SMC, PMC, SMA, and prefrontal cortices.

Gait Performance

After inpatient rehabilitation, motor impairment as measured by the Fugl-Meyer scale and gait performance significantly improved (P<0.05; Table). Cadence was significantly greater (P<0.005) on the second evaluation (55.3±18.6 steps per minute; mean±SD) than on the first evaluation (49.5±17.6). Swing-phase LI was significantly greater (P<0.05) after rehabilitation (−0.113±0.095) than before rehabilitation (−0.199±0.108). Importantly, changes of swing-phase LI significantly correlated with changes of LI in SMC (r=0.723, P<0.0427) but not with changes of LI in PMC, SMA, or pre-SMA (Figure 5). Physiological parameters were comparable between the first and second NIRS measurements. There were no significant differences in baseline blood pressure (measurement 1 versus 2: 120±8/85±12 versus 123±9/86±10 mm Hg), heart rate (84±12 versus 80±10 beats per minute), and arterial oxygen saturation (96±1% versus 96±1%). After the tasks were performed, blood pressure (measurement 1 versus 2: 127±10/92±8 versus 128±8/91±8 mm Hg) and heart rate (93±8 versus 89±7 beats per minute) significantly increased from baseline levels (P<0.01), but the changes were comparable. There were no significant changes in arterial oxygen saturation after the task was performed in either the first or second evaluation (97±1% versus 97±1%).

Discussion

There are 2 major differences in cortical activation patterns during gait between healthy subjects and patients with...
stroke. The first is the asymmetry of activation. Importantly, improvement of LI in SMC activation significantly correlated with improvement of gait performance as assessed by swing-phase LI. This suggests that balanced SMC activation may play an important role in locomotor recovery after stroke. Our findings are compatible with serial functional MRI findings that shift of SMC activation from the unaffected hemisphere to the affected hemisphere paralleled functional recovery of the hand. Thus, improved SMC activation in the affected hemisphere may be one of the common mechanisms underlying recovery of paralyzed limbs.

The other difference is recruitment of motor-related areas. Of note, PMC activation in the affected hemisphere significantly increased after locomotor recovery. PMC and SMA are involved in the purposeful modification and initiation of locomotion through connections with the brain stem, basal ganglia, cerebellum, and spinal cord. Enhanced activation in these areas may possibly be related to improved control of gait performance. Second, enhanced PMC activation may reflect the need for stabilizing proximal limbs and trunk during gait since it participates in control of the contralateral proximal and bilateral axial musculature. Finally, altered activation patterns may result from reorganization of cortical motor networks. Similarly, hand recovery after stroke has been associated with bilateral activation in SMC, PMC, SMA, and cerebellum. The emerging importance of the ipsilesional PMC in motor recovery finds additional support in the experimental literature and the clinical finding that PMC damage decreased locomotor recovery.

Notable activities were seen in pre-SMA and prefrontal cortex. Pre-SMA activation is associated with performance of complex sequential motor tasks, selection of response in a simple choice reaction time task, and the initial stages of skill acquisition. Prefrontal lesions diminished attention to novel events. Thus, these activations are possibly associated with learning of gait, especially in severely affected patients, since patients showed enhanced prefrontal activation in the second evaluation; further studies are needed, however.

It is possible that some of our findings may depend on changes in basic cerebral blood flow rather than changes in brain function since cerebral blood flow and diaschisis evolve over time after stroke. Further studies are also needed to investigate how gait speed, cadence, and body weight support affect cortical activation patterns. NIRS imaging is a highly noninvasive technique, and patients with stroke tolerated the repeated measurements well. If we can elucidate cerebral activation patterns associated with improved real-world outcome, we might develop a brain-based as well as evidence-based rehabilitation technique that would induce the preferred cerebral activation.

Acknowledgments
This work was supported by Funds for Comprehensive Research on Aging and Health and by Medical Frontier Strategy Research from the Ministry of Health, Labor, and Welfare in Japan. We thank and acknowledge Mie Arita for excellent technical assistance and Katsumasa Kii, PT, Tomoyuki Ohashi, PT, and Masamichi Furusawa, PT, for their excellent technique in rehabilitating patients with stroke.

References

Figure 3. Changes of regional activation during hemiparetic gait. Solid line (Pre) represents quantified regional activation in SMC, PMC, SMA, and pre-SMA (pSMA) during hemiparetic gait before inpatient rehabilitation. Dotted line (Post) represents regional activation after inpatient rehabilitation. There was a significant difference ($P<0.05$) in PMC activation in the affected hemisphere (AH). Data are mean±SE. UH indicates unaffected hemisphere.

Figure 4. Changes of interhemispheric asymmetry of regional activation during hemiparetic gait as measured by LI. Positive LI indicates more activation in affected hemisphere than in unaffected hemisphere, and negative LI indicates the reverse. Asymmetry in SMC significantly improved after inpatient rehabilitation ($P<0.05$). Lower, middle, and upper horizontal lines of boxes represent 25th, 50th, and 75th percentiles, respectively. Vertical lines extend from 10th to 90th percentiles.

Figure 5. Changes of LI in SMC (post LI–pre LI) versus changes in gait performance as assessed by swing-phase LI (post swing LI–pre swing LI). There was a significant correlation between these 2 parameters ($r=0.723$, $P<0.0427$).


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Stroke. 2003;34:2866-2870; originally published online November 13, 2003;
doi: 10.1161/01.STR.0000100166.81077.8A
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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