Premotor Cortex Is Involved in Restoration of Gait in Stroke

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Cortical activation during hemiplegic gait was assessed in six nonambulatory patients with severe stroke (four men, two women; four with right and two with left hemiplegia; 57 years old and 3 months after stroke on average), using a near-infrared spectroscopic imaging system. Each patient performed tasks of treadmill walking (0.2km/hr), alternated with rest every 30 seconds for four repetitions, under partial body weight support, either with mechanical assistance in swinging the paretic leg control (CON) or with a facilitation technique that enhanced swinging of the paretic leg (FT), provided by physical therapists. Gait performance was associated with increased oxygenated hemoglobin levels in the medial primary sensorimotor cortex in the unaffected hemisphere greater than in the affected hemisphere. Both cortical mappings and quantitative data showed that the premotor activation in the affected hemisphere was enhanced during hemiplegic gait. There was also a prominent activation in the presupplementary motor area. Overall cortical activations and gait performance were greater in walking with FT than with CON. These indicate that multiple motor areas including the premotor cortex and presupplementary motor area might play important roles in restoration of gait in patients with severe stroke.

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Although there is evidence that cerebral reorganization underlies functional recovery after stroke based on results from neuroimaging techniques such as positron emission tomography and functional magnetic resonance imaging (MRI), most studies have focused on recovery of paretic hand. Conversely, little is known about the cerebral mechanism of locomotor recovery after stroke because positron emission tomography and functional MRI are ill-suited for assessing cerebral activation during dynamic movements. Recently developed near-infrared spectroscopic (NIRS) imaging technique allows visualization of cortical activities during motor, visual, and cognitive tasks in humans. Using a NIRS topography system, we have shown that cortical activation during human gait centered in the medial sensorimotor cortices (SMCs) and the supplementary motor areas (SMAs) in healthy subjects. In a pilot study in ambulatory patients with stroke, we observed asymmetrical activation in the SMCs during hemiparetic gait. In this study, we focused on nonambulatory patients and hypothesized that multiple motor areas other than SMCs might be involved during assisted hemiplegic gait in patients with severe stroke.

Patients and Methods
Patients
We evaluated cortical activation patterns using NIRS imaging technique during hemiplegic gait on treadmill in six patients with severe hemiplegia due to initial stroke (four men, two women; four with right and two with left hemiplegia, two with cerebral infarction, four with cerebral hemorrhage; 57 ± 13 years old on average, and 81 ± 31 days after stroke). All were right-handed. Sites of lesion in each patient are summarized in the Table. All had severe hemiplegia and needed maximal assistance in walking. Fugl-Meyer scale for the lower extremity (mean ± standard deviation [SD]) was 8 ± 3 (full score = 34). This study was approved by the ethical committee of the hospital. Written informed consent was obtained from each patient.

Tasks for Near-infrared Spectroscopic Imaging
All patients had severe leg paralysis and needed partial body weight support of 20 to 30% using the overhead harness with a pelvic belt and thigh strips to perform walking tasks on treadmill assisted by experienced therapists. Treadmill speed was set at 0.2km/hr. Of note, three patients with the most severe hemiplegia had never experienced walking after the ictus. In addition to body weight support, each patient walked with two different rehabilitative interventions:

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Table. Demographic Data of Patients with Stroke

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Type</th>
<th>Day</th>
<th>Lesion Type</th>
<th>Site</th>
<th>Side</th>
<th>FM/UE</th>
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<td>M</td>
<td>H</td>
<td>66</td>
<td>Sub</td>
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<td>R</td>
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<td>L</td>
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<td>L</td>
<td>66</td>
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</table>

Mean ± SD 57 ± 13 81 ± 31 17 ± 24 8 ± 3

aDays after stroke.
bFull score = 66.
cFull score = 34.

FM = Fugl-Meyer Motor Scale; UE = upper extremity; LE = lower extremity; H = hemorrhage; Sub = subcortex; Pt = putamen; CR = corona radiata; IC = internal capsule; R = right; Ctx = cortex; P = parietal lobe; L = left; I = infarction; F = frontal lobe; T = temporal lobe; SD = standard deviation.

(1) walking with mechanical assistance of the paralyzed leg control (CON), and (2) walking with a facilitation technique to the pelvic regions (FT). For NIRS recording, each 30-second gait period was alternated with a 30-second rest period four times. In CON, therapists held patients in the foot or thigh of the paretic leg to help swing in the swing phase and to ensure stable stand phase. In FT, therapists pressed the hip forward and backward to prevent hyperextension of the knee in the stand phase, assisted flexion of the knee for the initiation of the swing phase with weight well over the sound leg, and prevented the pelvis from being hunched up as the hemiparetic leg moves forward. The order of the two interventions was randomized. For objective measurements of gait performance, we videotaped each walking task and evaluated cadence (steps/minute) and swing phase ratio calculated from time for swing of the paretic divided by time for swing of the sound leg. We also monitored blood pressure, heart rate, and arterial oxygen saturation measured using a pulse oxymetry at the baseline and after each intervention.

Near-infrared Spectroscopic Imaging

Details of the NIRS imaging system were described previously. In brief, the system consisted of 24 optodes including 12 light source fibers and 12 detector fibers resulting in 36-channel simultaneous recording. The system can detect cortical changes in oxygenated hemoglobin (oxyHb), deoxygenated hemoglobin (deoxyHb), and total hemoglobin. Interoptode distance was set to 3.0cm. The light source fiber next to the posterior one in the center row was located in the Cz portion (Fig 1A). The optodes were placed tightly on the skull using a holder cap fabricated from custom-made thermoplastic resin. An anatomical MRI scan showed that the optodes were located over the bilateral frontoparietal cortices covering an area of \(13 \times 13cm\) including the primary SMCs, premotor cortices (PMCs), SMAs, pre-SMAs, part of prefrontal cortices, and the superior parietal lobes.

Near-infrared Spectroscopic Imaging

Time courses of oxyHb levels were clearly associated with the walking tasks, but there were no apparent changes in deoxyHb levels as reported previously. (see Fig 1B). OxyHb levels increased 3 to 5 seconds after the onset of each task, reached a plateau at 10 seconds, and decreased 3 to 5 seconds after the end of each task. We obtained images depicting average \(\Delta\text{oxyHb}\) changes obtained from four cycles of each task after adapting the linear interpolation to the 36 data simultaneously acquired from neighboring source-detector pairs. Each NIRS topographic map was subdivided into 36 square grids, and the form of each grid was corrected to match the anatomical location of the 36 source-detector pairs on the brain surface. The corrected maps were finally overlaid on anatomical MRI surface images. For quantification of activation, we calculated \(\Delta\text{oxyHb}\) during task period - \(\Delta\text{oxyHb}\) during rest period for each channel. Data from the latter 20 seconds of the task periods and the middle 20 seconds of rest periods were used. Based on anatomical MRI and our data in normal subjects, the medial SMCs were covered by the medial parts of the posterior channels (channels 16 and 17 in the left hemisphere, and channels 22 and 23 in the right hemisphere; see Fig 1A). We also defined the SMAs as the medial parts of the middle channels (channels 14 and 15 in the left, and channels 20 and 21 in the right), and the PMCs as the lateral parts of the middle channels (channels 2, 8, 3, 9 in the left, and channels 26, 27, 32, 33 in the right). Furthermore, the pre-SMAs were located in regions rostral to the SMA and above the anterior commissure line (channel 13 in the left and channel 19 in the right). The prefrontal cortices were partially covered by channels 1 and 7 in the left and channels 25 and 31 in the right. To evaluate asymmetry in the amount of activation in each region, we calculated laterality index (LI). LI was defined as \(\frac{\text{\(\Delta\text{oxyHb}\) in the affected hemisphere} - \text{\(\Delta\text{oxyHb}\) in the unaffected hemisphere}}{\text{\(\Delta\text{oxyHb}\) in the affected hemisphere} + \text{\(\Delta\text{oxyHb}\) in the unaffected hemisphere}}\).
Statistical Analysis
To compare the amount of regional activation and LI during gait with various rehabilitative interventions, we performed a two-way repeated measures analysis of variance (ANOVA) with type of interventions (CON and FT) as a within-subject factor and site of cortical regions (SMC, SMA, PMC, and pre-SMA) as a between-subject factor. Gait and physiological parameters were compared using a one-way repeated measures ANOVA. Fisher’s least significant difference test was used as a post hoc test. Statistical significance was set at \( p \) value less than 0.05.

Results
Gait Performance during Assisted Treadmill Walking
After walking tasks, there was significant increase in systolic blood pressure from the baseline (pre/CON/FT = 122 ± 9/133 ± 16/131 ± 17 mm Hg; \( p < 0.05 \)), but there was no significant difference between the two interventions. There were no significant changes in diastolic blood pressure (pre/CON/FT = 89 ± 15/96 ± 9/94 ± 9 mm Hg), heart rate (pre/CON/FT = 87 ± 14/94 ± 8/91 ± 12 beats/min), and arterial oxygen saturation (pre/CON/FT = 97 ± 1/97 ± 0/97 ± 1%). Cadence was significantly greater \( (p < 0.05) \) in FT (44.0 ± 8.7 steps/min) than in CON (41.3 ± 8.5). Similarly swing phase ratio was significantly smaller \( (p < 0.05) \) in FT (1.42 ± 0.34) than in CON (1.60 ± 0.41). These suggested that swinging of the paralyzed leg significantly improved in FT than in CON.

Cortical Mappings of Hemiplegic Gait in Individual Cases
Cortical activation patterns during hemiplegic gait in individual cases are shown in Figure 2. There was less activation in the medial SMC in the affected hemisphere than in the unaffected hemisphere. The most characteristic finding was the PMC activation in the affected hemisphere that was more prominent in FT than in CON. In addition, pre-SMA and prefrontal regions in either the affected or unaffected hemisphere also were activated (see Fig 2A–C). These activations also appear to be more enhanced in FT than in CON. In patients with cortical damages, no apparent activation was observed in the corresponding cortical regions as expected (see Fig 2A and B).

Regional Activation during Hemiplegic Gait
A repeated measures ANOVA for the amount of activation in the motor-related areas showed that there was a significant main effect for type of rehabilitation \( (F[1, 40] = 24.050; p < 0.001) \). This indicated that FT induced generally greater activation than CON. A significant main effect also was seen for site of region \( (F[7, 40] = 2.744; p = 0.0200) \). There was no signif-
significant interaction between the two factors. Post hoc test shown that the PMC activation in the affected hemisphere was significantly greater than PMC in the unaffected hemisphere ($p < 0.05$), SMAs in both hemispheres ($p < 0.005$), SMC in the affected ($p < 0.005$) or unaffected ($p < 0.05$) hemisphere, and pre-SMA in the affected hemisphere ($p < 0.05$). This suggests that the PMC in the affected hemisphere is prominently activated during assisted gait with either rehabilitative intervention (Fig 3). In addition, the pre-SMA in the unaffected hemisphere was activated significantly greater than SMAs in both hemispheres ($p < 0.05$) and SMC in the affected hemisphere ($p < 0.05$).

LI (mean ± SD) was $0.162 ± 0.073$ in the PMC, $-0.185 ± 0.273$ in the SMA, $-0.161 ± 0.101$ in the SMC, and $-0.290 ± 0.343$ in the pre-SMA in CON. In FT, LI was $0.258 ± 0.120$ in the PMC, $-0.050 ± 0.087$ in the SMA, $-0.079 ± 0.102$ in the SMC, and $-0.080 ± 0.297$ in the pre-SMA (Fig 4). ANOVA showed that there was a significant main effect for type of rehabilitation ($F[1, 20] = 12.810; p = 0.0019$). This suggests that FT induced relatively greater activation in the affected hemisphere than CON. There was also a significant main effect for site of region ($F[3, 20] = 6.102; p = 0.0040$). Post hoc test showed that LI was greater in the PMC than in the SMA ($p < 0.05$), SMC ($p < 0.005$), and pre-SMA ($p < 0.001$). Namely, the PMC was dominantly activated in the affected hemisphere, and SMA, SMC, and pre-SMA were dominantly activated in the unaffected hemisphere during walking with either rehabilitative intervention. There was no significant interaction between
type of rehabilitation and site of region, suggesting that there was no basic difference in cortical activation patterns during gait between the two interventions.

Discussion
We have shown that the medial SMCs, SMAs, PMCs, and pre-SMAs are activated during hemiplegic gait in patients with severe stroke. Regional activations in SMCs and SMAs are compatible with the findings in normal subjects16,27 and in a case study.28 However, the SMC and SMA activations were considerably asymmetrical in patients with stroke. Furthermore, we observed enhanced activations in the PMCs, especially in the affected hemisphere as well as in the pre-SMAs.

The PMC activation might reflect adaptive locomotion control, compensation, or reorganization of cortical networks. Because there was little activation in the PMCs and prefrontal cortices during ordinary treadmill gait in healthy subjects,16 the PMC activation might be possibly associated with adaptive motor con-
ntrol to perform the walking task assisted by therapists. Constant external cues from physical therapists during assisted gait also might be related to the activation. Functional neuroimaging and neurophysiological studies have demonstrated that the PMC mediates motor behavior that is dependent on environmental cues in normal subjects and patients with Parkinson’s disease. Compensatory role of the premotor cortex for the paralyzed distal leg should be another possible explanation. PMC participates in control of the contralateral proximal musculature and of the bilateral axial musculature and damage in the PMC resulted in persistent weakness of the contralateral proximal leg. Third, the altered activation patterns seen in our patients might reflect reorganization of cortical motor as reported in functional neuroimaging studies for movements of recovered hand showing bilateral activations in the motor-related areas such as the SMCs, PMCs, SMAs, and cerebellum.

Notable activations also were seen in the pre-SMAs. The pre-SMA is activated in the complex sequential motor tasks. Neurons in the pre-SMAs are activated during the skill acquisition in the monkey. Compensatory role of the premotor cortex for the paralyzed distal leg should be another possible explanation. PMC participates in control of the contralateral proximal musculature and of the bilateral axial musculature and damage in the PMC resulted in persistent weakness of the contralateral proximal leg.

In our study, all patients had severe hemiplegia requiring maximal assistance in gait. Three patients had not experienced walking since the onset of stroke before this experiment. Thus, the pre-SMA activation is possibly associated with a novel motor learning of gait after stroke. Although it is difficult to draw firm conclusion about the cortical process of locomotor recovery from our data, it is likely that the premotor activations including the pre-SMA are associated with restoration of impaired gait in stroke.

Our data also showed that there was a significant difference in the amount of regional activations between the two rehabilitative interventions. Both individual mappings and group analysis showed that overall activations were greater in FT than in CON. It is possible that enhanced sensorimotor stimulations provided by FT might result in both greater cortical activation and better gait performance in FT than in CON, although it needs to be investigated how cortical activation patterns are altered by changes in gait parameters. To determine whether greater cortical activations in multiple motor areas are associated with improved real-world outcome, a long-term follow-up study is also necessary.

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References