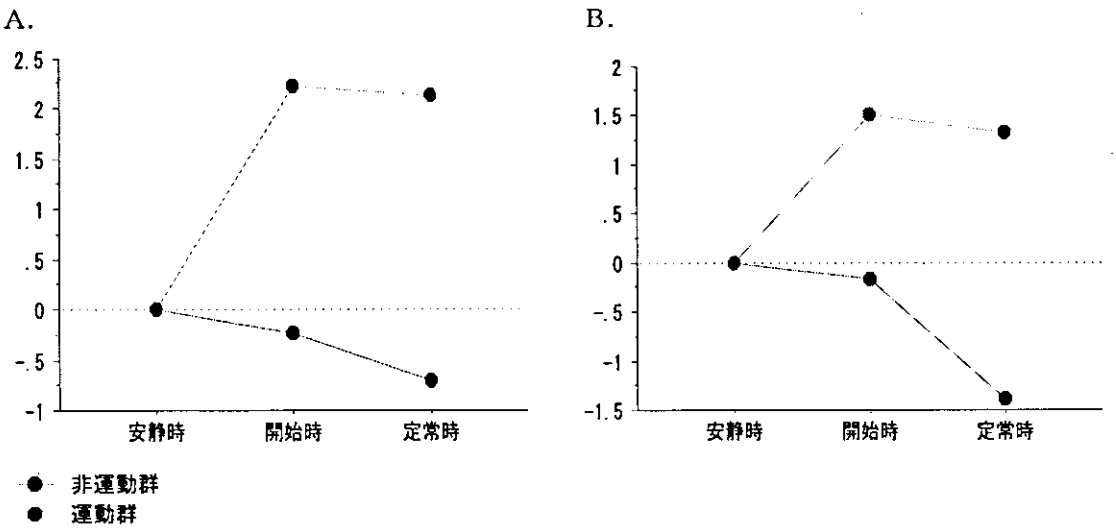
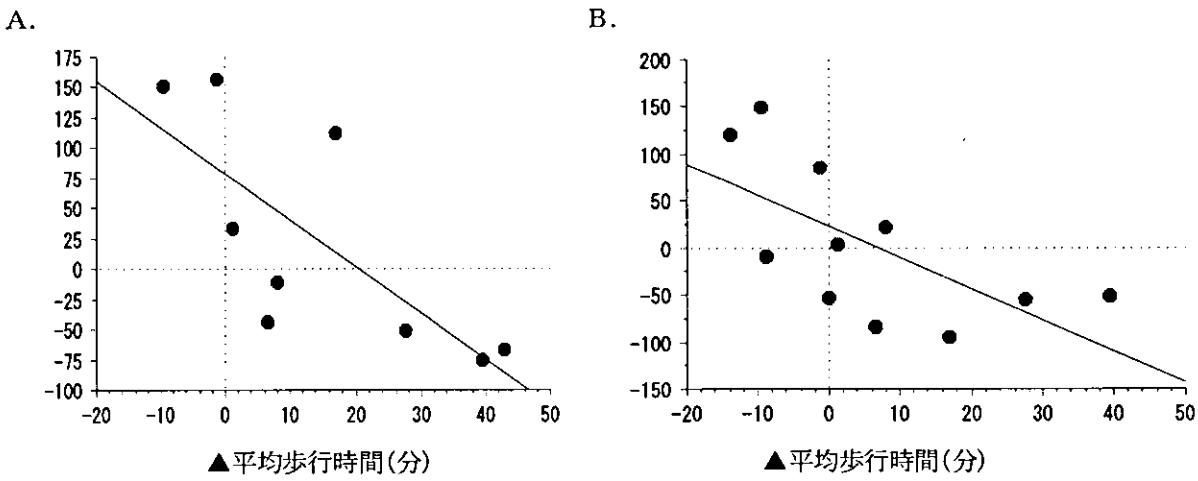
図5.　運動群、非運動群における測定前後での脳賦活の変化



A．70%強度歩行中の左側前頭前野の経時的脳賦活の変化。B．70%強度歩行中の左側運動前野の経時的脳賦活の変化。図は Effect Size((18 週間後のデータ平均－初回データ平均)/ 初回データ SD)で示した。

図6．測定前後での歩行変化率と脳賦活変化率との関係



A. 50%歩行定常時、前補足運動野の賦活変化率と平均歩行時間の変化率との関係。B．50%歩行開始時、内側一次感覚運動野の賦活変化率と平均歩行時間の変化率との関係。

研究成果の刊行に関する一覧表

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NEURO-BEHAVIORAL DETERMINANTS OF INTERLIMB COORDINATION
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Stephan P. Swinnen
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Chapter 5

CORTICAL NETWORKS ASSOCIATED WITH LOCOMOTION IN MAN AND PATIENTS WITH HEMIPARETIC STROKE

Ichiro Miyai
Neurorehabilitation Research Institute, Bobath Memorial Hospital, Osaka, 536-0023, Japan

Abstract: A recently developed optical imaging system using near-infrared spectroscopy enabled real-time monitoring of cortical activation during various locomotor tasks. Cortical activation was assessed as increased levels of regional oxygenated hemoglobin. In healthy subjects, walking at 1km/hr was associated by cortical activation that centered in the medial sensorimotor cortices and supplementary motor areas. Walking at higher speed (3 km/hr or 5 km/hr) tended to induce decreased rather than increased activation in the sensorimotor cortices. In patients with hemiparetic stroke, cortical activation patterns during hemiparetic gait were characterized by asymmetrical activation in the sensorimotor cortices and recruitment of other motor-related areas such as the premotor cortices and the prefrontal regions. Importantly activation patterns could be modified by rehabilitative intervention. A facilitation technique, by which therapists assisted patients to walk by pressing the hip forward and backward to ensure the stability of the stance and swing phase of the paretic leg, induced enhanced activation in the motor related areas, particularly that in the premotor area. Partial body weight support during gait training on the treadmill tended to decrease overall activation. It remains undetermined whether these changes in cortical activation patterns are associated with good locomotor recovery in patients with stroke.

Key words: locomotion, near-infrared spectroscopy (NIRS), optical imaging, cerebral cortex, stroke, hemiparesis, gait, functional recovery, neurorehabilitation

1. INTRODUCTION

Experimental studies have indicated that bipedal movements such as walking, are controlled by cerebral cortices including motor neurons in the

medial portion of the primary motor cortex (Ferrier, 1876; Penfield, 1950; Leyton and Sherrington, 1917) as well as spinal central pattern generators and multiple motor centers in the brainstem (Armstrong 1988; Drew 1988; Nutt et al., 1993). However there have been few studies concerning the cerebral mechanisms for human gait, mainly due to the limitations of functional neuroimaging techniques for studying dynamic movements. A neuroimaging study using single photon emission computed tomography revealed that the supplementary motor area, medial primary sensorimotor area, the striatum, the cerebellar vermis and the visual cortex were involved in human gait (Fukuyama et al., 1997). The noninvasive and flexible features of the optical imaging technique using near-infrared spectroscopy (NIRS), provide stable real-time monitoring of cortical activation during dynamic as well as static tasks. Although most NIRS studies have replicated previous findings from functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies for motor (Hirth et al., 1996, Orbig et al., 1997; Colier et al., 1999), visual (Kato et al., 1993; Meek et al., 1995; Hock et al., 1996; Takahashi et al., 2000) and cognitive tasks (Villringer et al., 1993; Hock et al., 1995; Sakatani et al., 1998; Watanabe et al., 1998; Sato et al., 1999, Hoshi et al., 2000) in humans, NIRS imaging might be most useful in mapping the human brain during locomotor tasks, such as gait (Miyai et al., 2001b) and even running (Suzuki et al., 2002), and in mapping the brain of neonates and children (Bartocci et al., 2000; Taga et al., 200; Isobe, et al., 2001; Hintz, et al., 2001) for which fMRI and PET are ill-suited.

2. THE NIRS IMAGING TECHNIQUE AND ITS APPLICATION TO STUDIES OF HUMAN LOCOMOTION

We are using a 30 to 42-channel NIRS imaging system (OMM-2001, Shimadzu, Kyoto, Japan, Fig. 5-1) depending on the number of detector fibers and light source fibers using continuous wave laser diodes with wavelengths of 780, 805, and 830 nm (Eda et al., 1999). This system detects the absorption spectrum of hemoglobin that depends on its oxygenation state and cortical changes in oxygenated hemoglobin (oxyHb), deoxygenated hemoglobin (deoxyHb) and total hemoglobin (totalHb). Another approach of data acquisition is time-resolved spectroscopy that also assesses the distribution of photon arrival times (Boas et al., 2002; Villringer and Orbig, 2002). In our continuous wave system, each optode with an interoptode distance set to 3.0 cm was placed tightly on the skull using a custom-made

holder cap and the optical fibers were suspended from a weight-balancer system to avoid motion-related artifacts during locomotor tasks on the treadmill (Fig. 5-1). An anatomical 3-D MRI scan, performed with marking the optode position on the skull by vitamin D capsules, revealed that the optodes covered an area over fronto-parietal cortices including the primary sensorimotor cortices (SMC), supplementary motor areas (SMA), and premotor cortices (PMC) with 30-channel measurement (Fig. 5-2C), but also including the prefrontal cortices and pre-supplementary motor areas with 36 or 42-channel measurement. Cortical "activation" during locomotor tasks on the treadmill was assessed as increased levels of oxyHb since changes of deoxyHb levels were much less sensitive (Miyai et al., 2001b; Hoshi et al., 2001; Wolf et al., 2002; Strangman et al., 2002). Strangman and colleagues found strong correlations between blood-oxygenation level-dependent (BOLD) fMRI changes and all optical measures including oxyHb, deoxyHb, and totalHb concentrations, with oxyHb providing the strongest correlation, probably due to the superior contrast-to-noise ratio for oxyHb relative to deoxyHb from optical measurements, rather than physiology related to BOLD signal interpretation (Strangman et al., 2002).

3. CORTICAL MAPPING OF HUMAN GAIT

Figure 5.2B shows the time course of changes in hemoglobin oxygenation during walking at 1 km/hr in channel 14 covering the left medial SMC. Levels of oxyHb and totalHb in channels covering the medial SMC started to increase 3 to 5 s after the task onset of walking at 1 km/hr, reached a plateau at 5 to 10 s, and returned to the baseline 3 to 5 s after the end of the task (Fig. 5-2B). Increase of oxyHb and totalHb levels tended to begin earlier as subjects repeated the tasks, probably due to anticipation of starting the tasks. We obtained images depicting increase in cortical oxyHb levels after adapting the linear interpolation to the simultaneously acquired data from neighboring source-detector pairs. Each NIRS map was corrected to match the anatomical location of the source-detector pairs on the brain surface and was overlaid on anatomical MRI surface images (Fig. 5-2A).

Different types of locomotor task activated distinct cortical networks (Fig. 5-2A). Walking on the treadmill at 1 km/hr induced bilateral cortical activation in the medial SMC as well as the SMA. Cortical activation during walking with and without arm swing holding side-rails did not differ although there was apparently less activation in the SMA without arm swing than with arm swing. Simple alternating foot movements were associated with localized activation in the medial SMC. Alternating arm swing without walking activated the lateral SMC. Gait imagery induced more rostral

activation centered in the SMA although execution of gait performance and gait imagery appeared to share the similar neuronal networks as supported by PET findings for the changes of regional cerebral blood flow during motor execution and imagery of foot movements in the learning process of the sequence (Lafleur et al., 2002). FMRI findings in the same subjects during foot movements and gait imagery revealed similar activation patterns to those seen in NIRS imaging based on the oxyHb mapping, (Miyai et al., 2001b). Thus it is suggested that coordinated movements such as gait with arm swing and imagery for locomotion might induce enhanced activation in the SMA than less coordinated movements such as gait without arm swing and alternating foot movements do. These findings are in accordance with findings that coordination of wrist and hand movements in different directions was associated with extra activation of the SMA as compared to movements in the same direction (Debaere et al., 2001).

How does locomotor speed affect cortical activation? Unexpectedly, walking at high speed (3 km/hr or 5 km/hr) induced smaller activation in the SMC than walking at low speed (1 km/hr) did (Fig. 5-3) since previous studies showed a positive relationship between force or frequency of finger movements and the amount of SMC activation (Dettmers et al., 1995; Kawashima et al., 1999; Waldvogel et al, 1999). Experimental studies in mammalian quadrupeds have demonstrated that locomotor control is not simply explained by cortical mechanisms and that brain mechanism for gait have a hierarchical structure, including spinal central pattern generators and supraspinal multiple motor centers such as the cerebellum, subthalamic locomotor region, mesencephalic locomotor region, ventral tegmental field, and dorsal tegmental fields (Armstrong 1988; Drew 1988; Nutt et al., 1993). The frontal lobes and basal ganglia loops are involved in higher motor control under complex environmental conditions. Experimental lesions of the motor cortex do not prevent animals from walking on a smooth floor although they impair tasks requiring a high degree of visuomotor coordination such as stepping over an obstacle (Pearson and Gordon, 2000). Our data using an extended 42-channel optical imaging system covering the prefrontal regions, revealed that these areas were more active at 1km/hr than at 3 or 5 km/hr (Fig. 5-3). Furthermore a preliminary result on optical imaging of human running, showed an enhanced prefrontal activation during the acceleration phase of running at 9 km/hr that might require more complex control than walking at the ordinary pace at 3 or 5 km/hr (Suzuki et al., 2002). Each subject was more comfortable and felt making less effort when walking at 3 or 5 km/hr that was the ordinary pace of human walking than at 1 km/hr or running at 9km/hr on the treadmill. Thus these findings might be in accordance with the idea that the main controller of locomotion

might shift from the cortical to the subcortical levels (especially to the spinal cord) during automatic locomotion at ordinary pace.

4. CORTICAL MAPPING OF PATHOLOGICAL GAIT IN HEMIPARETIC STROKE AND ITS CLINICAL RELEVANCE IN NEURO-REHABILITATION

Another way to investigate the neural mechanisms controlling human locomotion is studying patients with gait disorders due to neurological diseases, such as stroke and Parkinson's disease. Hemiparetic gait in patients with stroke is characterized by decreased speed and cadence, asymmetry of swing and stance phase, and abnormal synergic patterns of the affected upper and lower limbs during the whole gait cycles (Roth et al., 1997; Davis, 2000). The latter is primarily due to damage in the primary motor cortex in the unilateral cerebral hemisphere and/or its descending motor pathway, including the corona radiata, internal capsule, cerebral peduncle, and ventral brainstem. We evaluated cortical activation patterns during hemiparetic gait in patients with stroke using the same optical imaging system as described above (Miyai et al., 2001c, 2002b, 2002c). Basic differences of cortical activation patterns between normal gait and hemiparetic gait are 1) asymmetry of activation in the SMC and 2) recruitment of other motor-related areas such as the PMC and the prefrontal regions in patients with stroke (Fig. 5-4). Activation patterns appear to depend on the severity of hemiparesis as well as on the location and size of cerebral lesion. In patients with ambulatory stroke due to capsular lesion, hemiparetic gait was associated with asymmetrical activation in the SMC, with less activation in the affected hemisphere than in the unaffected hemisphere. In patients with severe impairment due to combined damage in the cerebral cortex and subcortical regions including the whole internal capsule and the basal ganglia, recruitment of the PMC - especially in the affected hemisphere - was another characteristic finding during assisted hemiplegic gait (Miyai et al., 2002b).

Figure 5-1. Measurement of cortical activation during walking using an optical imaging system.
A. A subject performing a walking task on the treadmill. B. A custom-made head holder cap fixing light source fibers (blue) and detector fibers (red) on the skull. See text for details.
(See color plate section.)

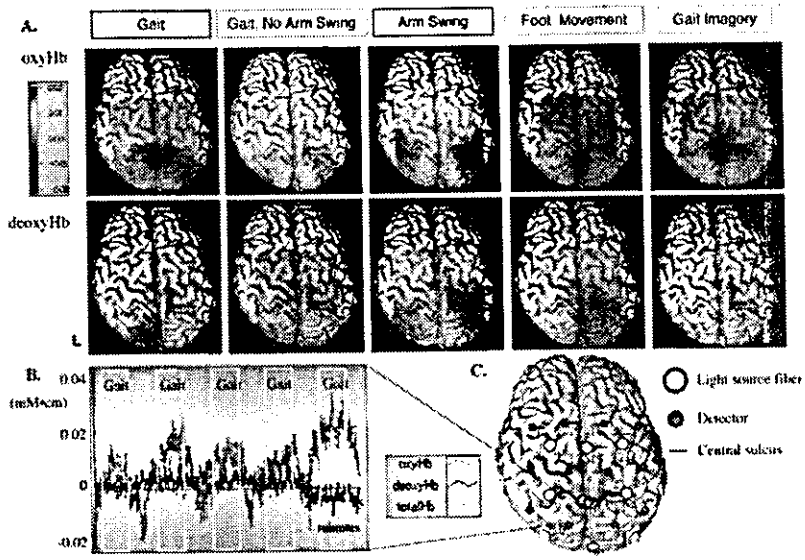

Figure 5-2. Cortical activation during various locomotor tasks (30 channel recording). A. Different locomotor tasks were associated with distinct cortical activation patterns, as assessed by changes in oxyHb levels in a healthy subject (41 year old, right handed male). There was bilateral activation in the medial SMC and SMA during walking on the treadmill at 1 km/hr, similarly but less in the rostral regions during walking without arm swing, in the lateral SMC during arm swing without walking, in the medial SMC and the SMA during foot movements. Gait imagery activated more rostral regions than foot movements did. L: Left. B. Whole time series of oxyHb (red), deoxyHb (blue), and totalHb (green) levels (mM□cm) during gait at 1 km/hr (n=8) obtained from channel 14 covering the left medial SMC. The time series is composed of 5 task periods (30 s) alternating with 5 rest periods (30 s). This figure shows the average time series for 8 healthy subjects in channel 14, which covers the left medial SMC. There were few changes in deoxyHb levels. C. Location of each optode exposed to the brain surface image and assigned channel numbers.
(See color plate section.)

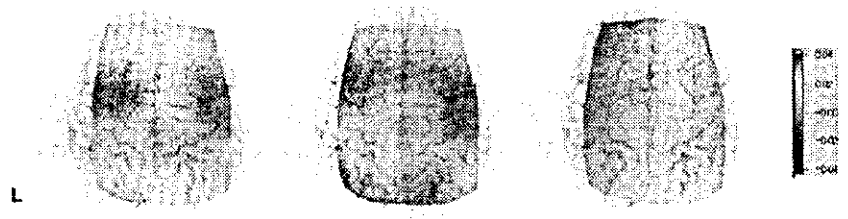

Figure 5-3. Cortical mapping of gait (42 channel recording) at different speeds in a healthy subject (25 years old, right-handed female).
Each mapping is based on changes in oxyHb levels (mM□cm) during walking on the treadmill. Note that activations in the medial SMC and SMA as well as in the prefrontal areas decrease as locomotor speed increases. *(See color plate section.)*

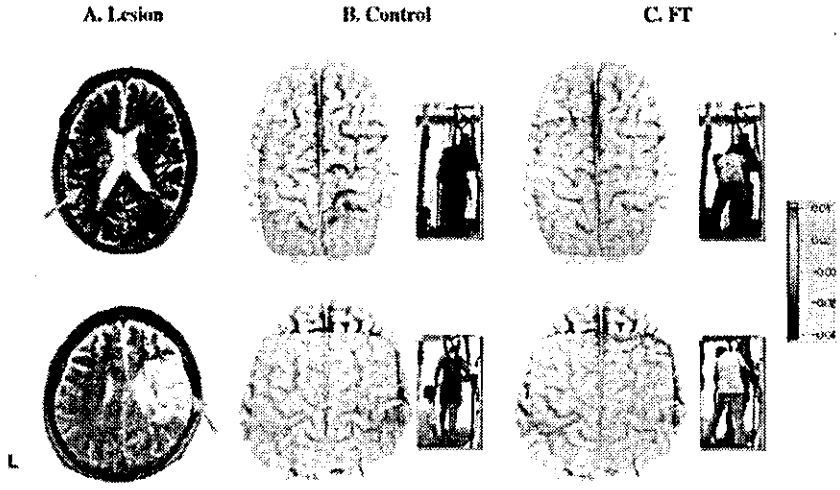

Figure 5-4. Cortical mapping of hemiparetic gait (36 channel recording) in patients with stroke.
Upper row: Cerebral activation during right hemiparetic gait on the treadmill in a patient with subcortical stroke (53 year old right handed male, 53 days poststroke) in the left corona radiata (A: arrow). During unassisted gait (B. 0.2 km/hr), SMC activation was asymmetrical with less activation in the affected hemisphere than in the unaffected hemisphere. During assisted gait by a therapist who facilitated swing and stance of the paretic leg by providing sensorimotor stimulation to the pelvis (C. FT: facilitation technique), SMC activation appears to be symmetrical with enhanced activation in the premotor and prefrontal areas. Lower row:

Cerebral activation during left hemiplegic gait in a patient (58 year old right handed male, 102 days poststroke) with diffuse infarction in the territory of the right middle cerebral artery (A: arrow). The patient needed partial body weight support (20% of body weight) to perform the locomotor tasks (0.2 km/hr). During assisted gait by a therapist that mechanically supported the swing of the paretic leg (B), mild activations are observed in the premotor and prefrontal regions of the affected hemisphere and in the parietal regions of the unaffected hemisphere. Enhanced activation in these regions and the unaffected SMC are observed during FT (C). Note that there is no activation in the damaged cortical regions. (Miyai et al., 2001b, Copyright© 2001, Elsevier Science, Reprinted by Permission Elsevier Science). *(See color plate section.)*

Importantly, activation patterns could be modified by rehabilitative interventions including therapeutic handling, such as a facilitation technique and partial body weight support (BWS) during locomotor training. During the facilitation technique, therapists (a) pressed the hip forward and backward to prevent hyperextension of the knee in the stance phase, (b) assisted flexion of the knee for the initiation of the swing phase with the weight well over the sound leg, and (c) prevented the pelvis from being hitched up as the hemiparetic leg moved forward (Bobath, 1978; Davis, 2000). A neurophysiological study demonstrated that this technique induced a more balanced walking pattern with a prolonged single stance period of the affected leg, an unobstructed hip movement, enhanced weight acceptance and a faster gait as immediate effects (Hesse et al., 1998). A crucial role of proprioceptive afferent inputs from the hip joints in the generation of locomotor activity, has been also shown in patients with complete spinal cord injury, trained with partial BWS on the treadmill (Dietz et al., 2002).

Real-time NIRS measurements during treadmill training in patients with hemiparetic stroke revealed that the facilitation technique (a) induced enhanced overall activation in motor-related cortical areas, particularly in the PMC of the affected hemisphere (Fig. 5-4) and (b) that it improved asymmetry of cortical activation (Fig. 5.5) along with improvement of gait asymmetry and increased cadence (Miyai et al., 2002b). These observations suggest that this technique immediately modifies cerebral activation patterns during pathological walking. Dietz et al. also demonstrated that interlimb coordination during walking depended on a supraspinal input since unilateral locomotion on the treadmill with partial BWS (70 %) in patients with spinal cord injury was associated with a normal pattern of leg muscle EMG activity only restricted to the moving leg, while in the healthy subjects a bilateral EMG activation occurred during unilateral locomotion. Thus improved gait performance might be associated with sensory inputs from the hip joints during assisted walking using a facilitation technique that modifies motor execution at the cortical levels. It is likely that some of these activation patterns in multiple motor related areas might lead to restoration of hemiparetic gait in patients with stroke.

There is growing evidence that the PMC and SMA play crucial roles in controlling human locomotion. In healthy subjects, right parieto-premotor activation has been shown to be involved in execution of limb-independent antiphase movements of hands or feet (de Jong et al., 2002). Moreover, the early phase of learning of an explicitly known sequence of foot movements, was associated with increases in regional cerebral blood flow in the bilateral dorsal premotor cortex and cerebellum as well as in the left inferior parietal lobule (Lafleur et al., 2002). The PMC and SMA are involved in the purposeful modification and initiation of locomotion through connections with the brainstem, basal ganglia, cerebellum, and spinal cord (Armstrong et al., 1988; Drew et al., 1988; Nutt et al., 1993). These areas participate in control of the contralateral proximal musculature and bilateral axial musculature (Freund et al., 1985; Halsband et al., 1993). Parallel motor pathways among the primary motor cortex, PMC, SMA and the final effectors in the spinal cord are known to exist (Fries et al., 1993; Fink et al., 1997). Neuroimaging studies, using single photon emission computed tomography in patients with Parkinson's disease, showed reduced activity in SMA during hypokinetic gait (Hanakawa et al., 1999b) as compared with healthy subjects, suggesting that these areas are associated with generating steady gait cycles in human. They also observed an enhanced activity of the PMC when hypokinetic gait was improved by visual cues (Hanakawa et al., 1999a).

An important role of the PMC in locomotor recovery is supported by a clinical observation that damage in the PMC might predict poor mobility outcome in patients with diffuse stroke in the territory of the middle cerebral artery (Seitz et al, 1998; Miyai et al., 1999). Patients with capsular stroke with MRI evidence for Wallerian degeneration of the pyramidal tract below the level of lesion, exhibited comparable final locomotor outcome to those without evidence for Wallerian degeneration although the former showed delayed improvement (Miyai et al., 1998b). Furthermore, the location of lesion rather than the volume of lesion could be related to mobility outcome after stroke. Multiple damage in the basal ganglia-thalomocortical motor circuits including the SMC, PMC, and SMA (Alexander and Crutcher, 1990), might result in better outcome than single-locus damage in these structures after stroke (Miyai et al., 1997, 2000b). More specifically, the greater volume of damage in the networks might possibly act to stimulate more effective reorganization of the intact structures. Thus, both functional neuroimaging studies and lesion studies indicate that the SMC and PMC as well as the primary motor cortex and its descending pathway might control, either in a parallel or hierarchical manner, human gait over subcortical and spinal centers.

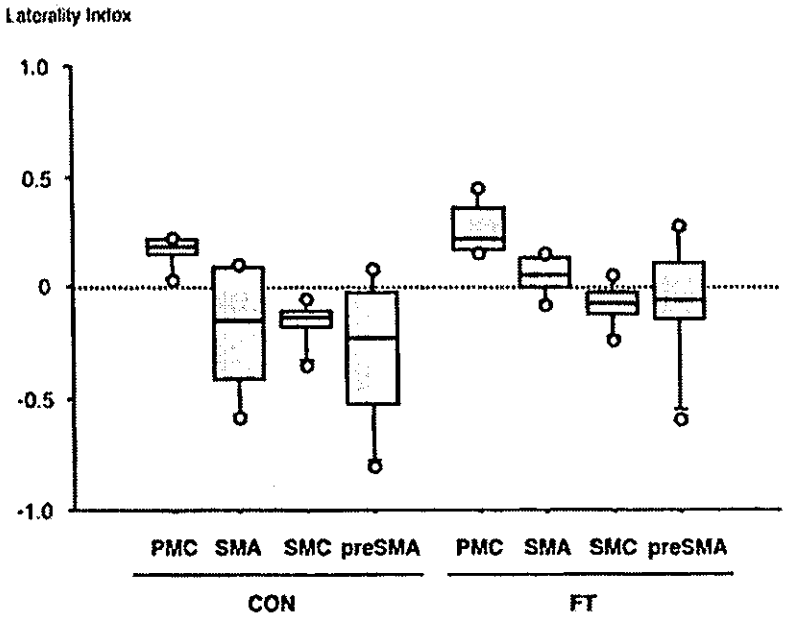

Figure 5-5. Changes of Laterality Index (LI) in the motor-related areas during hemiplegic gait with different types of rehabilitative intervention (n=6).
Asymmetry in cortical activation during hemiplegic gait was assessed in six patients with severe stroke (4 males, 2 females; 4 with right and 2 with left hemiplegia; 57 years old and 3 months poststroke on average). LI was defined as (ΔoxyHb in the affected hemisphere - ΔoxyHb in the unaffected hemisphere) / (ΔoxyHb in the affected hemisphere + ΔoxyHb in the unaffected hemisphere). Positive LI indicates more activation in the affected hemisphere than in the unaffected hemisphere and negative LI indicates the reverse. An ANOVA revealed that there were significant main effects, both for type of rehabilitation ($F[1, 20] = 12.810$, $p = 0.0019$) and site of region ($F[3, 20] = 6.102$, $p = 0.0040$). There was no significant interaction between these factors. Namely, the facilitation technique (FT) improved asymmetry of cortical activation during hemiparetic gait. LI was significantly greater in the PMC than in the SMA ($p < 0.05$), SMC ($p < 0.005$), and preSMA ($p < 0.001$). The lower, middle, and upper horizontal lines of the boxes represent 25th, 50th, and 75th percentiles, respectively. The vertical lines extend from the 10th to the 90th percentiles (Miyai et al., 2002b, Copyright© 2002, Wiley-Liss, Inc., Reprinted by Permission John Wiley & Sons, Inc.).

Locomotor training on a treadmill with partial BWS by means of an overhead harness with a pelvic belt and thigh has the advantage that it is easy to describe and therefore replicable in any rehabilitation facility. Recent studies have shown that treadmill training with partial BWS is effective in improving mobility outcome in patients with spinal cord injury (Visintin et

al., 1989; Wernig et al., 1992; Dobkin 1999), stroke (Hesse et al., 1994, 1995; Visintin et al., 1998), cerebral palsy (Schindl et al., 2000), and Parkinson's disease (Miyai, et al., 2000a, 2002a). The favorable outcome in treadmill training with partial BWS might be attributed to BWS rather than to treadmill walking since all patients initially tolerated a higher treadmill speed when walking on the treadmill with BWS than without BWS. A controlled trial, comparing the effect of treadmill training with BWS and without BWS in stroke, also showed greater efficacy of the former therapy than the latter (Visintin et al., 1989). However the mechanisms for the functional improvement remain unclear. Enhancement of the central pattern generator has been postulated as a mechanism for the efficacy of treadmill training with partial BWS. Our preliminary observation revealed that BWS tended to decrease overall activation (Fig. 5-6). Thus it is also possible that improvement of hemiparetic gait during treadmill training with partial BWS might be associated with improved efficacy of SMC activation.

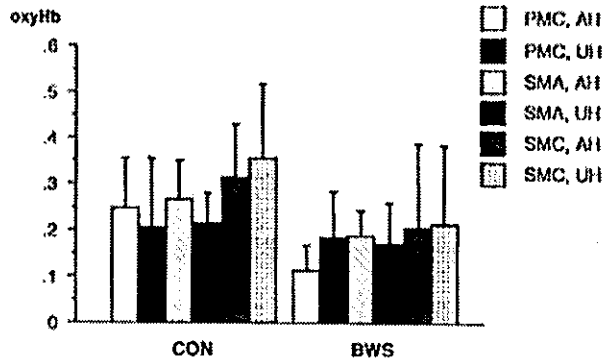

Figure 5-6. Effect of body weight support (BWS) on cortical activation during hemiparetic gait.
Cortical activation was measured during treadmill training with and without BWS (10 %) in 5 hemiparetic patients due to initial subcortical stroke (4 males, 1 female; 2 with right and 4 with left hemiparesis; 57 years old on average, and 2 months poststroke). For purposes of quantification of the activation, changes of oxyHb during the task period were integrated and then subtracted from integrated values of the changes during the rest period (n=5). Two-factorial repeated measures ANOVA demonstrated a significant main effect for BWS [$F(1,24) = 32.739$, $p < 0.0001$]. Post-hoc test revealed that BWS induced significantly smaller

activation ($p<0.0001$) than control (CON). There was no main effect for site of region or no significant interaction between BWS and site of region, suggesting that BWS generally reduced cortical activation (Miyai et al., 2001b). Error bars are mean ± SD. AH: affected hemisphere, UH: unaffected hemisphere.

5. CEREBRAL MECHANISMS FOR LOCOMOTOR RECOVERY VERSUS HAND RECOVERY FOLLOWING STROKE

In stroke, restoration of gait is the major goal of neurorehabilitation. More than 70 % of patients with stroke are expected to be able to walk after inpatient rehabilitation (Miyai et al., 1998a; Yagura et al., 2003) whereas functional prognosis of the paretic hand is mostly determined by the initial impairment (Nakayama et al., 1994; Duncan et al., 2002; Yagura et al., 2003). Thus locomotor function appears to be less vulnerable to the brain damage than hand function. This might be partly due to the hieratical control of human locomotion as described above and the properties of the functional anatomy, controlling the distal and proximal muscles of the extremities. More specifically, axial and proximal muscles are controlled by bilateral corticospinal pathways whereas distal muscles are principally controlled by contralateral corticospinal pathways (Davidoff, 1990). This implies that the limbs might receive discordant efferent commands from both hemispheres and neural-crosstalk (Swinnen, 2002) might play an important role in locomotor recovery.

Changes of cortical activation involving multiple motor-related areas during hemiparetic gait as discussed above, are similar to those reported in functional neuroimaging studies regarding cerebral mechanisms for recovery of hand function in patients with stroke. Although patients generally made remarkable recoveries at the time of the studies in most neuroimaging studies using finger movement tasks, reorganization after stroke involved several candidate regions, including the peri-infarct area in the primary motor cortex of the injured hemisphere, the PMC and SMA in the damaged hemisphere, and some combination of these areas in the undamaged hemisphere (Chollet et al., 1991; Weiller et al., 1992, 1993; Cramer et al., 1997; Cao et al., 1998)

Several functional neuroimaging studies have shown that the ratio of contralateral to ipsilateral SMC and/or PMC activity during paretic hand movement increased as the paretic hand regained function (Marshall et al., 2000; Calautti et al., 2001; Miyai et al., 2001a, Feydy et al., 2002). This finding was confirmed by observation from Carey et al. (2002) that was designed to clarify the specific effect of rehabilitative training on brain

activation. They showed that improved motor performance after intensive finger tracking training was accompanied by brain reorganization in patients with chronic stroke. The reorganization was characterized by a shift of cortical activation from predominantly ipsilateral to the affected hand to contralateral in SMC, and PMC. An increase in the hand area of the primary motor cortex in the damaged hemisphere after rehabilitative training was also shown in neurophysiological studies of primates with experimental cortical lesions (Nudo et al., 1996) and patients with chronic stroke (Liepert et al., 2000). Furthermore, a preliminary attempt to expand the hand area by combining rehabilitative training and deafferentation of proximal muscle by regional anesthesia in the upper brachial plexus, revealed some improvement of hand function in patients with chronic stroke (Muellbacher et al., 2002). Thus the capacity for reorganization in the primary motor cortex might be essential for good recovery of hand function after stroke.

Involvement of the PMC in the cerebral mechanisms of motor recovery of the affected hand is supported by the observation that improved finger movements in patients with middle cerebral artery infarction was associated with bilateral activation of the PMC (Seitz et al., 1988). Patients with capsular infarct and Wallerian degeneration on MRI appeared to require greater cortical reorganization than those without Wallerian degeneration to reach the similar functional level, since the former group showed persistent ipsi-lesional fMRI activation during grasping tasks of the paretic hand (Miyai, et al., 2001a). The emerging importance of the ipsi-lesional PMC in motor recovery finds additional support in the in vivo experimental literature (Liu et al., 1999).

In contrast, the ipsilateral corticospinal tract appears to play an important role in functional recovery of the paretic hand in cases who suffered from brain damage during the perinatal period and in some exceptional cases with adult stroke. Eyre and colleagues showed that ipsilateral responses to transcranial magnetic stimulation showed significantly shorter onsets than contralateral responses but similar thresholds and amplitudes in neonates. From 3 to 18 months, ipsilateral responses were significantly smaller and had significantly higher thresholds and longer onset latencies than contralateral responses. Accordingly, subjects with hemiplegic cerebral palsy exhibited ipsilateral responses with onsets, thresholds and amplitudes similar to those of contralateral responses, whereas small and late ipsilateral responses were observed after transcranial magnetic stimulation of the intact cortex in subjects with adult stroke (Eyre et al., 2001). Only few adult cases with stroke represent ipsi-lesional hemiparesis because of the predominant uncrossed corticospinal pathways (Hosokawa et al., 1996, Terakawa et al., 2000). However, the clinical relevance of the ipsilateral pathways in functional recovery in adult stroke is still suggested by the observation of

two patients with stroke whose recovered limbs became re-paralyzed when they developed a new stroke in the other hemisphere (Fisher, 1992). Furthermore, bilateral hand movements have shown to enhance activation of the primary motor cortex in the affected hemisphere, as compared with unilateral movements of the affected hand after stroke (Staines, et al., 2001). Since gait performance is bipedal by nature, multiple structures including the PMC and SMA as well as bilateral SMC appear to be involved in locomotor recovery as discussed above. Thus impairment of locomotion due to damage in some of these structures, is more likely compensated for than impairment of hand function for a longer period after the insult.

6. SUMMARY

A comparison of the findings from neuroimaging studies regarding hand recovery after stroke and the current optical imaging studies, indicates that improved asymmetry in the SMC activation and recruitment of other motor related areas, especially the ipsi-lesional PMC, might be closely related to restoration of gait in hemiparetic stroke. However it remains to be determined what type of activation is associated with favorable locomotor recovery unless further longitudinal studies correlate real-world functional outcome with changes in cortical activation patterns. A preliminary serial optical imaging study showed that improvement of the asymmetry in the sensorimotor activation significantly correlated with improvement of asymmetry in gait parameters (Miyai et al., 2002c). These approaches might contribute to the establishment of brain-based as well as evidence-based strategies for neurorehabilitation.

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