Chapter 5

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Figure 5-1 (see p. 114)

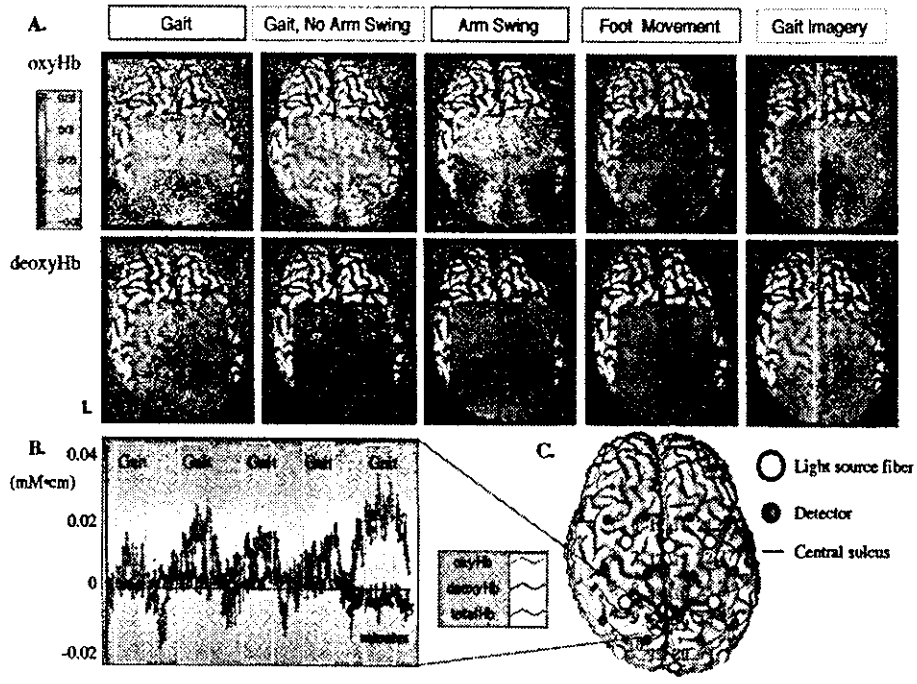

Figure 5-2 (see p. 115)

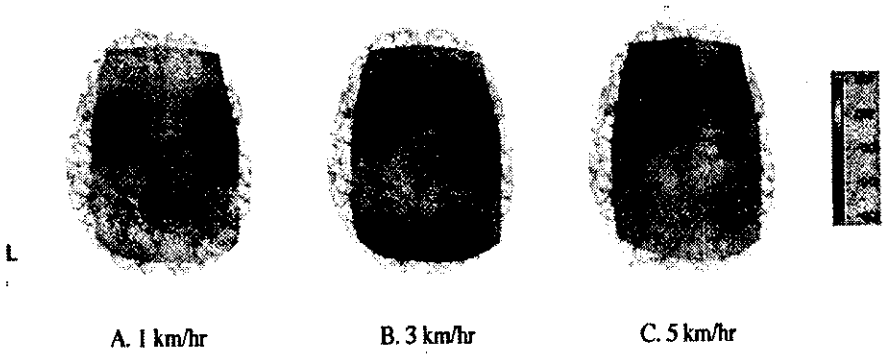

Figure 5-3 (see p. 116)

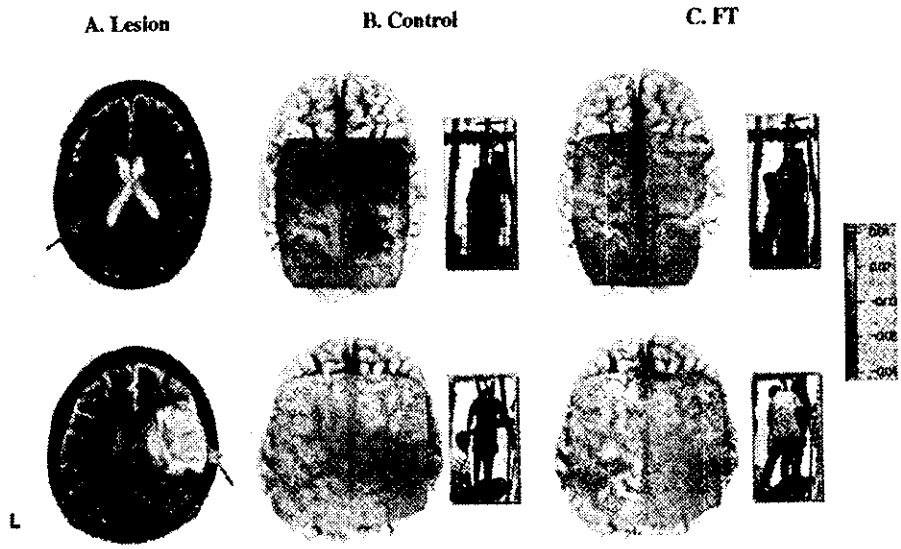

Figure 5-4 (see p. 116)

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Prefrontal and premotor cortices are involved in adapting walking and running speed on the treadmill: an optical imaging study

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We investigated changes of regional activation in the frontal cortices as assessed by changes of hemoglobin oxygenation during walking at 3 and 5 km/h and running at 9 km/h on a treadmill using a near-infrared spectroscopic (NIRS) imaging technique. During the acceleration periods immediately preceded reaching the steady walking or running speed, the levels of oxygenated hemoglobin (oxyHb) increased, but those of deoxygenated hemoglobin (deoxyHb) did not in the frontal cortices. The changes were greater at the higher locomotor speed in the bilateral prefrontal cortex and the premotor cortex, but there were less speed-associated changes in the sensorimotor cortices. The medial prefrontal activation was most prominent during the running task. These results indicate that the prefrontal and premotor cortices are involved in adapting to locomotor speed on the treadmill. These areas might predominantly participate in the control of running rather than walking.

Keywords: Near-infrared spectroscopic imaging technique; Oxygenated hemoglobin; Deoxygenated hemoglobin

Introduction

Experimental studies have indicated that bipedal gait is controlled by the cerebral cortices including motor neurons in the medial portion of the primary motor cortex (Ferrier, 1876; Leyton and Sherrington, 1917; Penfield, 1950) as well as the spinal central pattern generators and multiple motor centers in the brainstem (Armstrong, 1988; Drew, 1988; Mori et al., 2001; Nutt et al., 1993). In human gait, a study using single photon emission computed tomography showed activation in the multiple areas including the supplementary motor area, medial sensorimotor cortex, striatum, and cerebellum (Fukuyama et al., 1997). A near-infrared spectroscopic (NIRS) imaging study revealed that walking at the pace of 1 km/h on a treadmill was associated with a bilateral increase of oxygenated hemoglobin (oxyHb) in the medial sensorimotor cortices and the supplementary motor areas (Miyai et al., 2001). However, it is unclear whether there is also a significant relationship between cerebral activation and physiological parameters of gait such as speed and cadence. It is also not known how the rostral regions in the frontal cortices, such as the prefrontal and the premotor cortex, are involved in locomotor control, In the elderly, walking improved the performance of cognitive tasks involving prefrontal executive functions, such as a switching task, a response compatibility task, and a stopping task to abort a preprogrammed action (Kramer et al., 1999). A study has shown that habitual jogging improves a branching task combining the main visuospatial delayed-response and subroutine go/no-go task associated with the anterior prefrontal function (Harada et al., 2004; Koechlin et al., 1999). In patients with hemiparetic stroke, enhanced premotor activation in the affected hemisphere was associated with locomotor recovery (Miyai et al., 2002, 2003). Thus, we hypothesized that the prefrontal and premotor cortices are involved in the control of human walking and running. To test this hypothesis, we evaluated cortical activation patterns associated with locomotor speed as assessed by relative changes of oxyHb and deoxygenated hemoglobin (deoxyHb) levels using an optical imaging technique. Our results indicated that the prefrontal–premotor regions and sensorimotor cortices are activated differentially during walking and running and that the prefrontal activation is prominent, especially during running.

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Methods

Subjects and tasks

A total of nine, right-handed, healthy subjects (seven males, two females; mean age ± SD, 28.1 ± 7.4 years; range 22–46 years) without known neurological abnormalities participated in the experiments. This study was approved by the Ethical Committee of Bobath Memorial Hospital, and a written informed consent was obtained from each subject. The subjects performed three types of locomotor tasks (walking at 3 and 5 km/h, and running at 9 km/h) on a treadmill (Model 3200; SportsArt Ind., WA). Fig. 1 illustrates the temporal sequence of the task design.

Each locomotor task consisted of a 90-s task period and a 60-s rest period (30-s rest before and after each task period) for three repetitions. Subjects were instructed to stand still on the treadmill belt for 30 s, and then a verbal instruction to 'start' was given. The treadmill reached the target speed at 13 s later from the start at 3 km/h walking (Fig. 1-1), at 17.5 s later at 5 km/h walking (Fig. 1-2), and at 28 s later at 9 km/h running (Fig. 1-3), and the speed was steady until 120 s after the start when the treadmill was stopped. In the running task, each subject began to run 45 s after the starting locomotion when treadmill speed reached 6 km/h. During walking and running, subjects swung their arms without excessive efforts. Each subject was asked to stand still on the treadmill during the rest period. The order of the three treadmill speeds was randomized, except that running at 9 km/h was not chosen as the first task for safety reasons. All tasks were recorded on videotape (SONY; DCR-PC120, Tokyo, Japan) to calculate the cadence (steps/min). Blood pressure (mm Hg) and heart rate (beats/min) were measured immediately before and after each task. Arterial oxygen saturation was also monitored using a pulse oxymetry.

NIRS imaging

The details of the NIRS imaging system (OMM-2001, Shimadzu, Kyoto, Japan) using continuous wave laser diodes with wavelengths of 780, 805, and 830 nm were described previously (Miyai et al., 2001). We used a 42-channel system with 28 optodes, consisting of 12 light-source fibers and 16 detectors. A custom-made holder cap for the optodes was attached to the scalp and a weight balancer for the fibers enabled stable measurement during walking and running. The interoptode distance was set at 3.0 cm. The location of the optodes on the skull covering an area of 13 × 15 cm in the frontoparietal regions is schematically shown in Fig. 2A.

Thus, 42 square grids of the NIRS topographic map consisted of seven rows and six columns and were labeled as Channels (Ch) 1 to 42. The light-source fiber next to the posterior one in the center row was located in the Cz position. An anatomical 3-D T1-weighted MRI scan was performed with marking the optode location on the skull by vitamin D capsules. In two subjects, the anatomical MRI was normalized to a standard stereotaxic space (Ashburner and Friston, 1999; Ashburner et al., 1997; Friston et al., 1995), using a Montreal Neurological Institute (MNI) brain template, which corresponds to the space described by Talairach and Tournoux (1988). The normalization was performed using SPM99 (Wellcome Department of Cognitive Neurology, London, UK). Coordinates of each optode were then converted into MNI coordinates. Thus, the anterior commissure (AC) line (Picard and Strick, 2001) was approximately corresponded to the line between the second and third rows (i.e., Ch 37 and 38, Figs. 2B and C). Accordingly, the left and right PFC were covered by Channels 15, 16 and 22, 23, the left and right PMC by Channels 3, 4, 10, 11 and 31, 32, 38, 39 (Picard and Strick, 2001), the left and right m-SMC by channels 19, 20 and 26,27, and the left and right l-SMC by Channels 5, 6, 7 and 40, 41, 42, respectively (Fig. 2B). The lower limb areas in the PMC [Talairach and Tournoux's coordinates R (40, −4, 60) and L (−32, −8, 64)], as reported by Buccino et al. (2001), were found to be located in Channels 11 and 32.

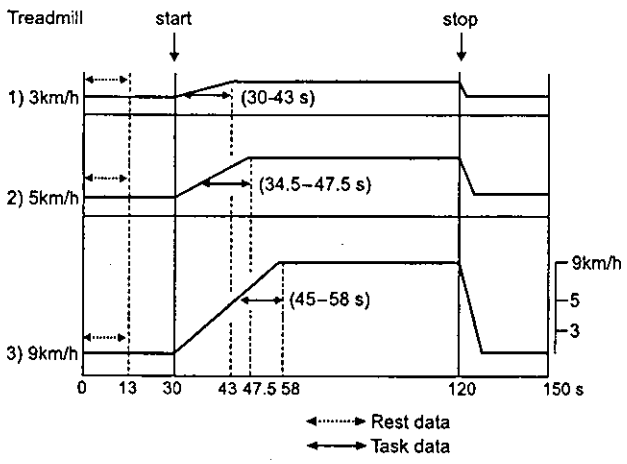

Fig. 1. Design for the sequence of three tasks with (1) 3 km/h walking, (2) 5 km/h walking, and (3) 9 km/h running. Subjects performed 150-s of locomotor tasks consisting of 30-s rest period before the locomotion, 90-s locomotion period, and 30-s rest period after task for three repetitions at each speed. Data were sampled for the 13-s period from 0 to 13-s as Rest data and for 13-s period just before reaching each constant speed as Task data. See text for details.

Data analysis

Changes of hemoglobin concentration were represented as mMol·cm. These data were sampled at the rate of 190 ms. Since previous findings (Hoshi et al., 2001; Strangman et al., 2002; Wolf et al., 2002) and our own findings (Miyai et al., 2001, 2002) have shown that oxyHb was the most sensitive marker for task-related hemodynamic changes, we used oxyHb levels for the assessment of regional cortical activation. We derived data and made calculations from 42 channels from the "ΔoxyHb during task period − ΔoxyHb during rest period." Task data were obtained from the 13-s period that immediately preceded reaching the constant speed because the period corresponded to data from start point of the task (30 s) to the point of plateau speed (43 s) at 3 km/h. To compare data in the comparable period, we analyzed data between 34.5 and 47.5 s at 5 km/h, and 45 and 58 s at 9 km/h, as indicated by solid arrows in Fig. 1. Rest data were obtained from the first 13 s of the rest periods (0–13 s), as indicated by a dotted arrow in Fig. 1. We obtained images depicting averaged changes of oxyHb from three cycles of each task, after adapting the linear interpolation to the 42-channel data recorded simultaneously from each channel. Our previous data suggested that even one cycle was sufficient to get reliable images (Miyai et al., 2001). Each channel was corrected to match the anatomical location on the brain surface, and the corrected maps were finally overlaid on anatomical MR images.

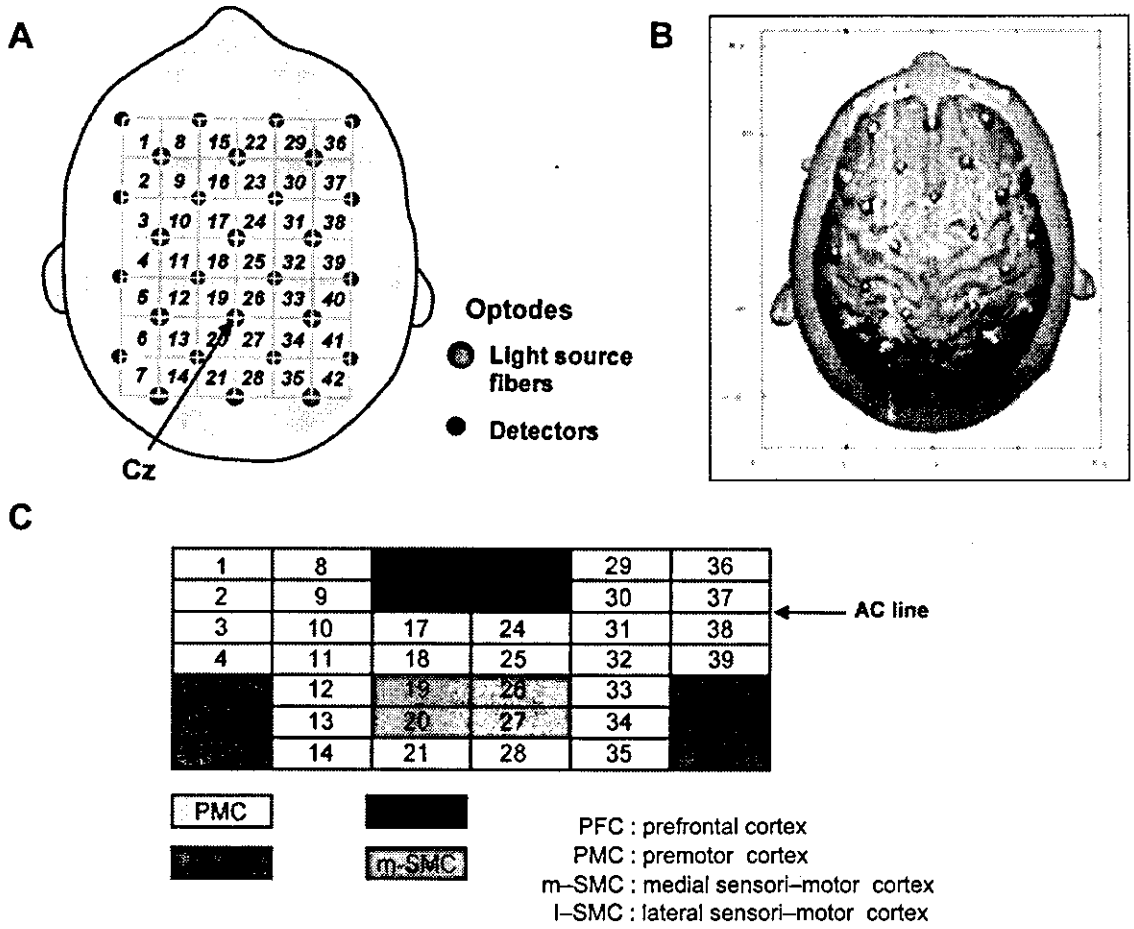

Fig. 2. Schematic for location of the optodes. (A) Twenty-eight optodes, constituting 12 light-source fibers and 16 detectors, were arranged on the scalp that enabled 42-channel measurement. (B) The anatomical location of the optodes exposed onto the normalized brain surface. (C) The channels covering the PFC are shaded in red, those covering the PMC in yellow, those covering the m-SMC in green, and those covering the l-SMC in purple. See text for details. AC indicates anterior commissure.

We calculated the regional activation ratio in each channel as defined by "ΔoxyHb in each channel" / "total ΔoxyHb from all 42 channels × 100%". The maximal value of regional activation ratio from the channels covering each region was used as an index for regional activation and was statistically analyzed. We performed a two-factorial repeated-measures ANOVA with the site of region as a between-subject factor and locomotion speed as a within-subject factor. Fisher protected least significant difference test was used as a post hoc test. Task performance (cadence) and physiological parameters (heart rate, blood pressure, and SaO_2) were analyzed by using an unpaired t test or one-factorial ANOVA. Statistical significance was set at $P < 0.05$.

Results

As locomotor speed increased from 3, 5, and then 9 km/h, cadence significantly increased linearly, and the heart rate and blood pressure increased slightly after 3 and 5 km/h walking, but the increase was greater after 9 km/h running. SaO_2 was affected by none of the tasks (Table 1). Fig. 3 illustrates representative data for temporal changes of oxyHb, deoxyHb, and totalHb during locomotor tasks at different speeds in the PFC, PMC, m-SMC, and l-SMC.

In the PFC, PMC, and m-SMC, oxyHb and totalHb levels began to increase bilaterally before starting the locomotor tasks especially at 9 km/h and reached to the peaks before the treadmill speed got steady. After reaching constant speed, these levels decreased and tended to return to the baseline or below the baseline levels during performing the locomotor tasks. After stopping locomotion, there were temporal drops in oxyHb levels before returning to the baseline levels. In the PFC, PMC, and m-SMC, the increase in oxyHb levels were the greatest at 9 km/h but appeared to be similar between 3 and 5 km/h. In the l-SMC, there were no increases in oxyHb levels at 3 km/h and slight increases at 5 and 9 km/h, probably due to prominent arm swings. Compared with changes of oxyHb levels, few changes were seen in deoxyHb levels as reported previously (Miyai et al., 2001, 2002, 2003). Accordingly, changes in totalHb levels were similar to those in oxyHb levels. To compare regional activation patterns at different speeds, changes of oxyHb levels before reaching the constant speed were chosen for the quantitative analyses and for developing the topographic maps. Fig. 4 shows an example of cortical activation patterns during locomotion at different speeds.

During walking at 3 km/h, activation mostly centered in the bilateral m-SMC. The left PMC appeared to be slightly activated while the other regions were not. During 5 km/h walking, the m-SMC activation appeared to be similar to that at 3 km/h. The left

Table 1
Averaged changes of heart rate, systolic blood pressure, diastolic blood pressure, and SaO_2 before and after performing the tasks, and cadence during the tasks

	Heart rate (beats/min)	Systolic BP (mm/Hg)	Diastolic BP (mm/Hg)	Cadence (steps/min)	SaO_2 %
before task	74.4 ± 9.9	118.7 ± 10.4	77.7 ± 8.2		
3 km/h	83.4 ± 12.3	118.2 ± 11.8	82.3 ± 12.0	77.7 ± 5.2	97.6 ± 0.5
5 km/h	91.9 ± 13.2	117.7 ± 11.5	81.8 ± 7.6	95.6 ± 3.0	97.6 ± 0.5
9 km/h	136.5 ± 12.5	136.6 ± 12.5	91.2 ± 10.1	145.7 ± 10.4	98.0

$n = 9$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

PMC activation was more prominent at 5 km/h than at 3 km/h. During 9 km/h running, the bilateral prefrontal cortices including the left medial and right lateral regions, as well as the PMC and m-SMC, were highly activated. Although the activations shown in Fig. 4 were stronger in the left side than in the right, such laterality of activation was inconsistent between subjects. However within subject, activation patterns were almost identical during three cycles of locomotor tasks at each speed. We also compared differences in regional activation between the left and right hemispheres and found no significant difference at any locomotion speed (Table 2).

Thus, we chose to use the averaged data from the left and right hemispheres for quantification.

Regional activation ratios during locomotion at different speeds are shown in Fig. 5. A two-factorial repeated-measures ANOVA revealed a significant main effect for site of region [$F(3, 64) = 4.383$, $P < 0.05$] and a significant interaction between locomotion speed and site of region [$F(6, 64) = 2.809$, $P < 0.05$] but no significant main effect for speed. This indicated that there were distinct activation patterns during locomotion at different speeds. Post hoc tests showed that activations in the PFC, PMC, and m-SMC were significantly greater than that in the l-SMC ($P < 0.05$). Furthermore, the PFC activation was significantly greater during running at 9 km/h than during walking at 3 and 5 km/h ($P < 0.05$). The PMC activation tended to be greater as the locomotor speed and cadence increased, but there was no statistical significance. There were few changes associated with the speed in the m-SMC.

Discussion

During the 13-s periods that immediately preceded reaching the constant locomotor speed on the treadmill, the PFC and PMC activation tended to increase as locomotor speed and cadence increased. Interestingly, the m-SMC activation appeared to be unchanged or decreased as the locomotor speed increased. In

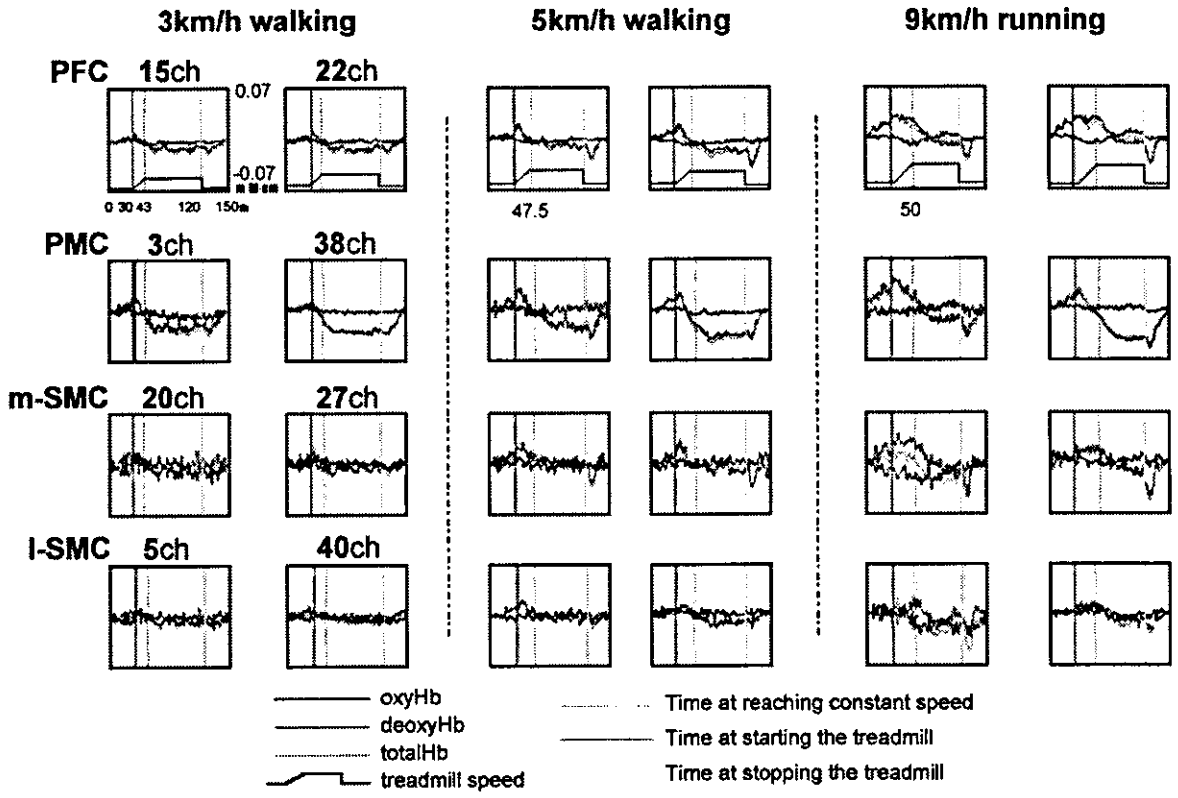

Fig. 3. Changes of regional hemoglobin concentration in the PFC, PMC, m-SMC, and l-SMC during locomotor tasks in a subject. Red lines indicate oxyHb levels (mMol · cm), blue lines indicate deoxyHb, and green lines indicate totalHb. Black lines indicate treadmill speeds. The orange vertical lines indicate the starting points of the locomotor tasks, dotted vertical lines indicate the time when the treadmill speed reached the plateau, and yellow vertical lines indicate the end point of the tasks. Each figure shows the averaged value of the three cycles.

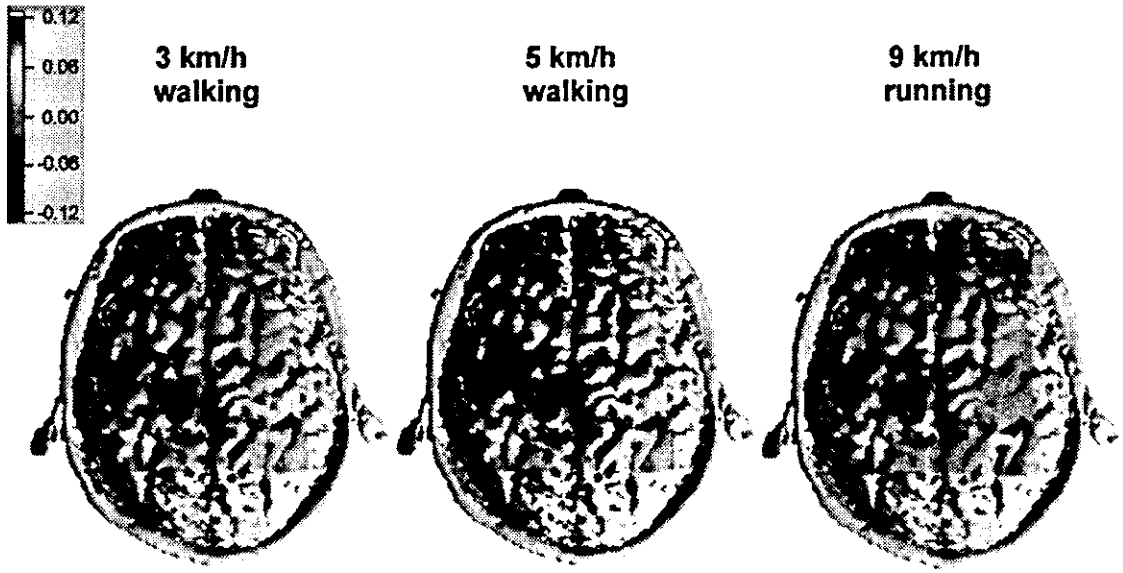

Fig. 4. Cortical mapping of locomotion tasks based on changes in oxyHb levels. The scale indicates the color coordinates of concentration changes (mMol · cm). See text for details.

contrast, several previous studies have demonstrated a linear correlation between regional cerebral blood flow (CBF) in the hand area of the human primary motor cortex and the rate or amplitude of finger tapping (Blinkenberg et al., 1996; Kawashima et al., 1999; Rao et al., 1996; Sadato et al., 1996) and power grip forces (Ehrsson et al., 2000). These areas may be related to repetitive rate or force. This discrepancy might be partially due to the fact that the locomotion is controlled by hierarchical mechanisms including the spinal central pattern generators and supraspinal multiple motor centers such as the cerebellum, subthalamic, and brainstem locomotor regions. The frontal lobes and basal ganglia loops are involved in higher motor control when one is faced with complex environmental conditions (Armstrong, 1988; Drew, 1988; Nutt et al., 1993). Therefore, it is possible that our failure to demonstrate a positive relationship between locomotor speed and the m-SMC activation might reflects a shift of the motor control center to the hierarchically lower or higher levels. Thus, control mechanism of locomotion might be different from that of hand movements or simple leg movements (Sahyoun et al., 2004).

The increases of oxyHb and totalHb levels in the PFC, PMC, and m-SMC were seen before starting the locomotor tasks especially at 9 km/h. We also reported similar findings in the previous study for cortical mapping of gait at 1 km/h (Miyai et al., 2001). It is possible that such phenomenon might be related to anticipatory or preparatory activities for locomotion (Kubota and Hamada, 1978; Tanji and Evarts, 1976) and that anticipatory or preparatory load might increase with the increment of locomotor speed to be executed. The increases in oxyHb levels after starting locomotor tasks were not sustained while subjects performed the tasks at the steady speed. Instead, the oxyHb concentration decreased to below baseline levels, especially in the PMC. This phenomenon might be at least partially explained by changes of neurovascular coupling (Hoshi et al., 2001; Wolf et al., 2002). Specifically, there might be a mismatch between CBF and the cerebral metabolic rate of oxygen ($CMRO_2$) when CBF decreased secondarily under the steady or decreased neural activities during the locomotion at the constant speed. In the PFC and the m-SMC, the oxyHb levels returned to the baseline while subjects kept performing the tasks, suggesting that these areas were most active during the acceleration phase of locomotion. Additionally, immediately after stopping the locomotor tasks at 5 and 9 km/h, there were drops (dips) in the oxyHb levels. These dips, although they occurred after completion of locomotion, appear to be similar to initial or early dips (Buxton, 2001; Mayhew et al., 2000; Thompson et al., 2003). Although the decrease in oxyHb levels can be explained either by decreased CBF, increased consumption, or decreased cerebral blood volume, it is also possible that neural activities related to discontinuation of the locomotion could produce a relative increase in $CMRO_2$ and consequent decrease in oxyHb levels. Similarly, within 3 s after the initiation of the hand motor task, the region where the concentration change of both oxyHb and deoxyHb was detected corresponded to the center of gravity of the motor response to transcranial magnetic stimulation,

Table 2
Regional activation ratios in the left and right hemispheres during locomotion at different speeds

	3 km/h		5 km/h		9 km/h	
	LH	RH	LH	RH	LH	RH
PFC	2.62 ± 1.68	2.64 ± 1.20	3.94 ± 1.83	2.67 ± 2.06	4.76 ± 2.59	4.39 ± 1.34
PMC	3.86 ± 2.00	3.29 ± 1.99	2.92 ± 1.53	3.77 ± 1.81	4.19 ± 2.65	3.86 ± 1.51
m-SMC	3.76 ± 1.43	4.34 ± 1.97	3.75 ± 1.95	2.98 ± 1.13	3.93 ± 1.77	3.29 ± 1.22
l-SMC	1.95 ± 1.18	1.86 ± 0.91	1.87 ± 1.30	2.23 ± 1.06	1.68 ± 1.74	1.76 ± 0.53

Data (%); average ± SD, LH indicates left hemisphere, RH; right hemisphere.

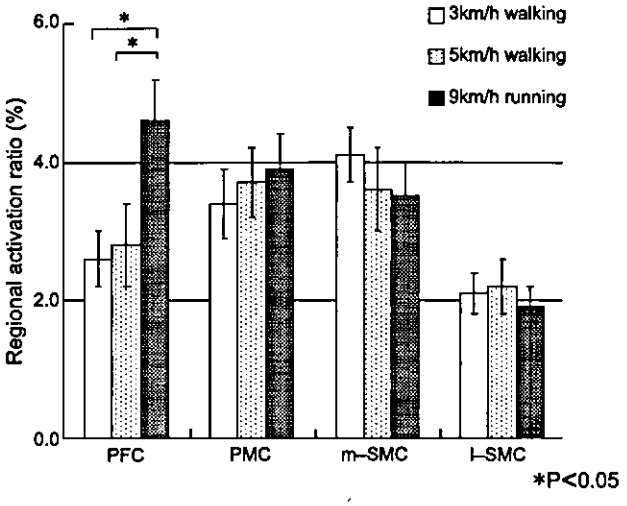

Fig. 5. The relationship between locomotor speed and regional cortical activation as assessed by the regional activation ratio. The data are mean ± SE (%). See text for details.

suggesting that cortical oxygen metabolism precedes the blood flow response (Akiyama et al., 2003). General changes in CBF associated with rises in blood pressure and heart rate are unlikely since there were distinct time courses of hemoglobin oxygenation among different cortical regions. However, these possibilities remain to be established in future studies.

Our data revealed that the PMC as well as the PFC are involved in control of locomotion at different speeds. It has been suggested that the dorsal PMC plays a role in the selection, planning, and execution of voluntary movements (Grafton et al., 1998; Kubota and Hamada, 1978; Weinrich and Wise, 1982), and in motor preparation (Boussaoud, 2001; Simon et al., 2002). Clinical studies have suggested that the PMC plays a crucial role in locomotor recovery after stroke (Miyai et al., 1999, 2002, 2003). Observation of foot movements activated the more dorsal sector in the ventral PMC than did observation of hand movements (Buccino et al., 2001). In the present study, the PMC activation during locomotion appeared to involve both the dorsal and ventral PMC. Thus, the PMC activation might reflect the neural mechanisms underlying the execution of bipedal movements for controlling locomotor speed in the acceleration phases of walking and running. For hand movements, the PMC might be involved in control of complex hand movements since precision grip also induces increased activities in the PMC as well as in the SMC compared with power grip (Ehrsson et al., 2000).

The PFC activation was most prominent during running. Running also induced the greatest changes in physiological parameters such as blood pressure and heart rate as well as cadence. Since electric stimulation of the medial prefrontal cortex induced the increase in blood pressure (Fulton, 1951; Kaada et al., 1949), it might be possible that high blood pressure and the PFC activation were related to each other. More importantly, the PFC has been shown to play a crucial role in attention (Averbeck et al., 2002; Büchel and Friston, 1997; Haxby et al., 1994; Koechlin et al., 2000; Wood and Grafman, 2003). This suggests that the PFC is likely to be involved in sustaining attention to keep up with the increase of the treadmill speed by maintaining the posture on the treadmill and by preparing the appropriate leg movements to adapt to the changes in treadmill speed. It might also be possible that the PFC activation is associated with the motor learning process of performing the running task in an unusual situation on the treadmill. The present study used oxyHb levels as a marker for cortical activation. Although NIRS experiments using rats with exposed cortex revealed evidence of robust changes not only in oxyHb but also in deoxyHb (Lindauer et al., 2001; Martin et al., 2002; Mayhew et al., 2001), oxyHb has been shown to be more sensitive to human cortical activities than deoxyHb, probably due to the higher signal-to-noise ratio associated with scattering of light through the scalp, skull and relatively inactive brain tissue (Strangman et al., 2002; Wolf et al., 2001). Further studies are necessary to investigate the relationships among the changes of oxyHb and deoxyHb, cerebral metabolism, and neural activities using multimodal approaches including NIRS, PET, fMRI, and transcranial magnetic stimulation.

Conclusion

Multiple motor areas including the PFC, PMC, and m-SMC were activated during the periods before reaching a constant speed of walking and running. The prefrontal and premotor cortex might be involved in controlling locomotion to adapt to the increasing speed in the acceleration phases.

Acknowledgments

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特集 神経リハビリテーション

脳卒中のリハビリテーション*

宮井一郎**

Key Words: stroke, functional recovery, neurorehabilitation, neuroimaging, plasticity

はじめに

欧米の複数のrandomized controlled trialから，脳卒中ユニットという脳卒中に特化した病棟におけるリハビリテーション(以下，リハと略)を含めた多角的専門チームアプローチが患者の死亡率を減少させるだけでなく，患者の日常生活動作(ADL)や歩行などの能力障害を改善，在院日数を短縮し，自宅復帰率を高めることが明らかになった[1]．脳卒中ユニットの効果は早期リハ，集中リハ，そして，多角的専門チームアプローチによるところが大きいと考えられる[2][3]．しかし，具体的なリハの方法論の大部分は経験則に依存し，evidence based medicineの立場から推奨される具体的なストラテジーはほとんどない．脳卒中ユニットに関する欧州からの報告は，neurodevelopmental technique(Bobath)を採用したものが多いが，他の理学療法との効果の差は明らかではない[4]．実際にどのようなリハを行うかはセラピストの教育や環境に左右されるのが現状である．リハの方法論の有効性を証明するには，その具体的な内容に関して"open the black box"する作業が必要である[5]．患者の現実的な日常生活動作の改善の背景には，機能障害(たとえば片麻痺)の改善だけでなく健側の機能代償や廃用，関節拘縮などの二次障害の改善，生活環境の最適化や家族・介助者の訓練なども大きく関与するからである．

さて，脳卒中による運動麻痺や感覚障害などの機能障害はいうまでもなく脳損傷から生じたものである．脳損傷部位がつかさどっていた機能が残存する神経ネットワークで代償されれば，機能回復(つまり麻痺の改善)が得られるはずである．実際，近年の機能的脳画像，神経生理学的手法の進歩から，運動麻痺，感覚障害，失語症などの機能障害の回復に伴って損傷された神経ネットワークの再構成が起こることがわかってきた[6]．どのような再構成が機能回復に結びつくか明らかにすることで，ある特異的なリハ介入がもたらす効果の検証を，現実的な機能予後と脳内メカニズムを関連づけながら行うことが可能になってきた．

脳卒中における機能回復の特性

脳卒中後の機能回復は，急性期とそれ以降で臨床的特徴もその神経学的基盤も異なると考えられる．ドラマチックな機能回復は，発症後の数週間以内に起こり[7]，一次運動野とその下降路における浮腫軽減，圧迫減少，血流再開などによって規定されるため，病変部位や大きさ，急性期治療の成否の影響が大きい．発症後1カ月で，患者の1/4で神経症状は消失し，1/3で日常生活は完全自立する．これらはもともと軽症で

* Neurorehabilitation for enhancing poststroke recovery.

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自然回復したか，急性期治療が奏効したためと考えられ，リハの有効性を考える上でのバイアスとなる[8]．急性期以降の回復は徐々に起こり，3カ月から6カ月にかけて回復曲線はなだらかになり，初期の障害が強いとプラトーになるには時間を要する[1)7)]．手の運動麻痺の回復は，発症初期の機能障害に依存する部分が大きく，一次運動野や錐体路の損傷，とくに線維が集束する内包後脚病変の有無は手指の巧緻性回復の鍵になる．ボバース記念病院の成績では(n=1,056)，発症後1～3カ月で入院リハを開始した患者で，開始時廃用手例の29.7%は改善したが，実用手を獲得したのは0.2%のみであった．しかし，開始時に大まかな麻痺手の把握運動が可能な患者では，37.5%の患者が実用手レベルに到達した．一方，歩行機能は発症後数カ月以上経過しても改善する可能性がより高い．もっとも障害の強い入院時歩行不能例に限っても60.3%(入院時発症後3カ月以内の70.9%，6カ月以内の54.8%，12カ月以内の43.9%)が改善し，32.6%が自立歩行を獲得した[9]．

上肢機能回復脳内機構とリハの方法論

上肢麻痺回復に関するpositron emission tomography(PET)やfunctional magnetic resonance imaging(fMRI)を用いた機能的脳画像研究に共通した所見は，①麻痺と同側の一次運動野にも賦活がみられること，②運動前野や補足運動野などの運動関連領野の両側性賦活がみられること，③皮質病変の場合，病変周囲の賦活がみられることである．経時的研究では機能回復あるいは訓練による機能改善に伴って，麻痺手の運動時，運動野や運動前野の賦活が病変半球で優位になることが示されている[6)10)～12)]．非病変半球の機能的役割については議論が多いが，経頭蓋磁気刺激(TMS)で非病変半球を抑制すると，麻痺手の運動時間を遅延させることから，少なくとも非病変半球の賦活がmaladaptiveでないと考えられる[13)]．

完全麻痺でない場合，上肢に関する訓練効果はタスクに特異的に訓練量に関連して現れる傾向がある．上肢機能訓練のストラテジーにconstraint-induced movement(CIM)訓練がある[14)]．健側上肢を三角巾やミットなどで拘束して麻痺側を使用せざるを得ない状態を作る(強制使用)ものである．したがって，この訓練法の適応は，ある程度手指の動きが保たれている症例に限られる．CIMに関する研究で重要な点は，発症後1年以上の慢性期でも麻痺手機能が改善する可能性と麻痺側上肢機能の改善とともに一次運動野の機能的再構成が起こる可能性が示されたことである[15)]．すなわち，TMSにより麻痺手の運動誘発電位が誘発される頭皮上の領域がCIM後に病変半球で増加した(図1)．これはNudoら[16)]が見出した，リスザルの感覚運動野梗塞のモデルで小さなパレットからエサをとるという訓練後，一次運動野内の梗塞周囲の手の領域が広がる現象に対応すると考えられる．これらは病変半球の一次運動野内のマッピングの変化と機能回復の関連を示唆する．一方，大きなパレットからエサをとるという単純な運動の繰り返しは脳マッピングの変化を起こさない[17)]．これらから実際の能力よりやや難易度の高い課題を与えるような訓練が有効で，その効果は病変半球の一次運動野内のマッピングの変化と関連することを示唆する．ラットを用いた実験でも，脳梗塞後に運動が十分にできる「richな」環境のみでは麻痺側前肢機能は不変で，それに加えて麻痺前肢でエサをとる訓練を行ってはじめて前肢機能が改善する．また，このときに非病変半球の一次運動野の前肢領域の錐体細胞の樹状突起の増加がみられることもわかっている[18)]．

歩行機能回復の脳内機構とリハの方法論

安静の必要なPETやfMRIは歩行時の脳賦活を調べることには適さない．われわれは，近赤外線光を用いたスペクトロスコピー(NIRS：near-infrared spectroscopy)による光イメージング(機能的NIRS：fNIRS)を応用し，歩行時の脳活動を測定した[19)]．fNIRSで捉えることができる脳活動は，典型的には大脳皮質の酸素化ヘモグロビン(oxyHb)の増加と脱酸素化ヘモグロビン(deoxyHb)の減少で，その時間的変化は局所の脳血流増加と並行し，脳血流増加によるによるoxyHbの増加が酸素消費の増加を上回ることを反映すると考

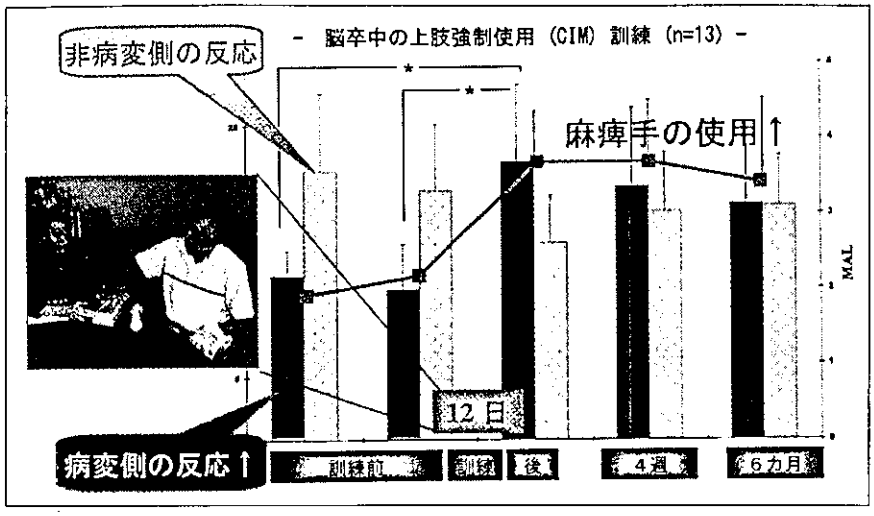

図1　麻痺側上肢の強制使用（CIM）訓練後の運動野の地図の変化
健側手に日中の90％の間ミットをはめて麻痺手を使用せざるを得ないような状況を12日間作り訓練を行うと，麻痺手の使用頻度が増す（MAL：motor activity log，折れ線）だけでなく，頭皮上の磁気刺激に反応する領域が病変半球で拡大した（黒棒）．（文献[15]およびhttp://www.excite.emory.edu/より改変引用）

えられる．一般的にoxyHbの変化の方がdeoxyHbの変化より大きい．したがって，fNIRSで評価される「脳賦活」は神経細胞の興奮の増加や発火の増加といった電気生理学的に定義された脳活動と同義ではない．健常人ではトレッドミル上の歩行に伴い，ほぼ対称的に内側一次感覚運動野中心にoxyHbの増加がみられた（図2）．一方，deoxyHbのタスクに関連した変化はほとんどみられなかった[19]．歩行関連課題中のoxyHb変化の平均を線形補間して得られた機能画像では，歩行時には内側一次感覚運動野と補足運動野，立ったまま腕振りのみ行うと一次感覚運動野の外側部の賦活がみられた．足関節運動では内側一次感覚運動野と補足運動野の賦活がみられるが，その範囲は歩行と比較すると小さかった．歩行の想像時は足運動時より吻側の補足運動野に賦活がみられた．なお，同一被験者の足関節運動と歩行の想像をタスクとしたfMRIの結果はfNIRS機能画像の所見と類似していた[19]．

次に同様の手法を用いて脳卒中患者の歩行時の脳賦活を評価し，さらにそれがリハ介入により変化するか，その即時効果を検証した．片麻痺患者の歩行時に麻痺側下肢の振り出しを補助するためには，足部をもって機械的に助ける方法（図3-A）と骨盤部に促通手技（骨盤部の後傾や回旋を助けることにより麻痺下肢そのものの動きを出すテクニック）を用いる方法が考えられる（図3-B）[20]．後者における骨盤～股関節からの感覚運動刺激は，麻痺足の筋活動を誘発するのに重要であることがわかっている[21]．機械的な麻痺側下肢の補助下での脳卒中患者の片麻痺歩行時の一般的な特徴は，感覚運動野の賦活が病変半球で減少し，病変半球の運動前野賦活が増加していることであった（図4-A, B）[22]．後者の特徴は，とくに皮質・皮質下を含む広汎な病変による重度麻痺患者でより明らかであった（図4-A, B-下段）．リハ介入の即時効果として，機械的補助のかわりに促通手技を用いるとより病変半球の賦活が増加して感覚運動野の賦活が対称的になり，運動前野などの運動関連領野の賦活も増加した（図4-C）[22]．次に，実際にこのような脳賦活が機能回復促進につながるのかを検証するため約3カ月の入院リハの前後で経時的に測定しリハ介入の長期効果を調べた．リハ後の歩行改善時，促通手技を用いない歩行のfNIRS画像（図4-D）は，リハ前に促通手技を用いた歩行の画像（図4-C）に類似しており，この手技によってもたらされた脳賦活は機能回復に有益であることが示

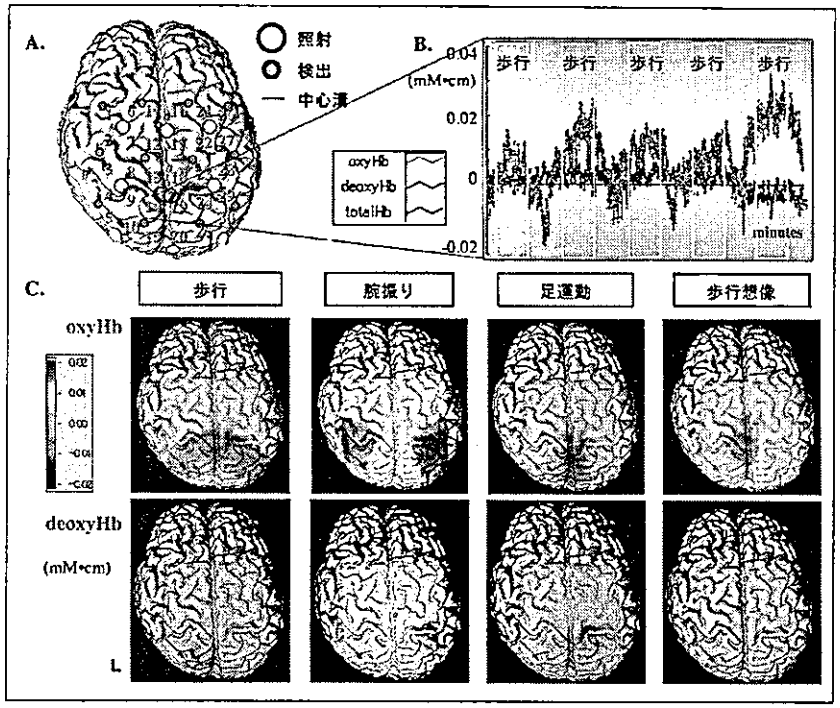

図2 fNIRSによる健常人の歩行時の脳賦活測定

A：照射用光ファイバーと検出用の光ファイバーの配置．頭部の光ファイバー接触位置に脂肪を成分とするマーカを貼りつけてMRI構造画像を撮像し三次元レンダリングした図である．照射と検出の間隔は3 cmで，この例では9本の照射と12本の検出との組み合わせで30チャンネルの計測を行っている．中央の照射ファイバーをCzに配置した．

B：歩行時（1 km/hr）のチャンネル14（左内側一次感覚運動野付近）のHb波形の健常人8例の平均値を示す．歩行によってoxyHbが増加するが，deoxyHbはほとんど変化しなかった．赤がoxyHb，青がdeoxyHb，緑が総Hb．

C：歩行時，内側一次運動感覚野と補足運動野中心に対称的に賦活（oxyHb増加）がみられる．DeoxyHbの変化は少ない．歩行せずに腕振りのみ行うと賦活は外側のみにみられる．足関節運動（座位）では内側一次運動感覚野に歩行に比較して限局して，歩行の想像（座位）では歩行より吻側の補足運動野中心に賦活がみられた．（文献[19]より改変引用）

唆された[23]．定量的評価のために脳卒中8例（男5，女3，右/左麻痺4/4，平均57歳，平均発症後3カ月）で，促通手技を用いない歩行時のoxyHb変化を約3カ月の入院リハ前後で比較すると，病変半球の運動前野でリハ後に有意にoxyHbが増加していた．さらに感覚運動野のoxyHb変化の非対称性を表すlaterality indexの改善と歩行の振り出し時間の非対称性を表すlaterality indexの改善が有意に相関しており，感覚運動野賦活の対称性の改善は歩行の改善が関連することが示された[23]．歩行機能回復における運動前野の役割は，pure motor hemiparesisにおいて，錐体路変性の指標であるMRI上のワーラー変性の有無は最終的な歩行機能予後に影響を与えないこと[24]や，中大脳動脈領域の広汎な脳梗塞で運動前野に病変が及ぶと，移動に関する機能予後が不良であること[25]からも支持される．

歩行に関する強制使用のストラテジーのひとつとしてbody weight supported（BWS）treadmill trainingがある．もともと脊髄損傷による対麻痺の訓練として考案されたもので，パラシュートのジャケットを装着して，体重支持装置で体重の一部を免荷し，トレッドミル上で訓練を行うものである[26]．図4の下段の症例はこの訓練を応用して歩行時の脳賦活を測定した．脳卒中に対してはカナダでRCTが行われ，6週間の免荷下

図3　歩行訓練におけるリハ介入の例

Aは麻痺足をセラピストが持って振り出しを機械的に助ける方法．Bは骨盤から股関節にかけてセラピストが後傾，回旋をハンドリングすることにより麻痺側下肢の振り出しと立脚を助ける促通手技と呼ばれる方法．

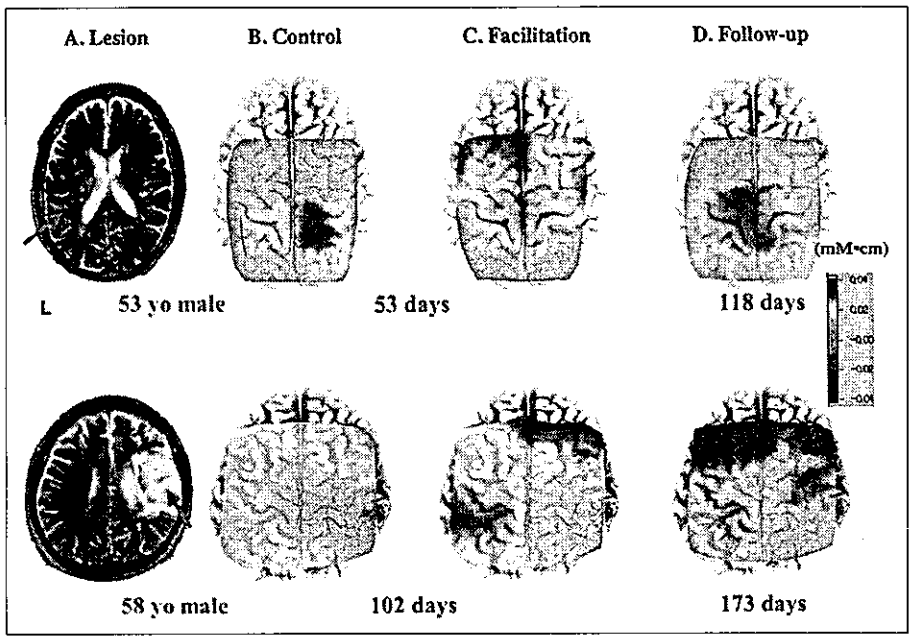

図4　片麻痺歩行時の脳賦活―リハ介入による即時効果と長期効果―

左から，A. 病変部位，B. リハビリテーション開始時の歩行時の脳賦活(control：機械的補助．図3-A参照)，C. リハビリテーション開始時の歩行時の脳賦活(facilitation：促通法．図3-B参照)，D. 約3カ月のリハビリテーション後の歩行時の脳賦活(follow-up)を示す．

上段：53歳，右利き男性．発症後53日の左放線冠の脳梗塞(A)．病変半球運動感覚野の賦活が減少しているが(B)，骨盤への促通手技による介助歩行では賦活がより対称的で運動前野の賦活も見られる(C)．(D)発症後118日の自力歩行では，(C)に近い賦活パターンがみられた．

下段：58歳，右利き男性．発症後102日の右中大脳動脈領域の広汎な脳梗塞(A)．麻痺が重度で20%の体重免荷を要した．麻痺足振り出しの機械的な補助(B)より，促通手技(C)の方が，病変側運動前野と非病変側運動感覚野の賦活が増加している．(D)発症後173日に(B)と同じ条件で測定したところ，上段の例と同様に賦活パターンは(C)と類似していた．(文献[22][23]より改変引用)

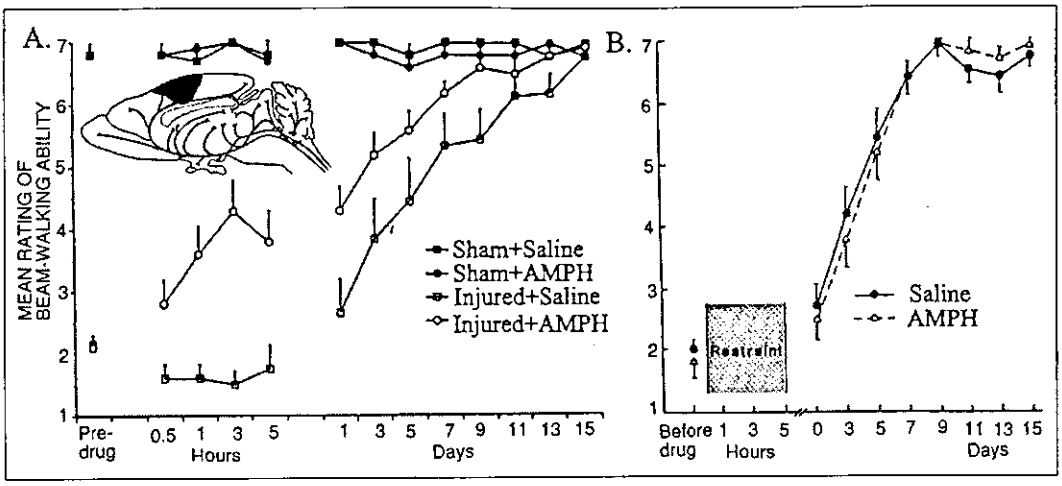

図5 Amphetamineによる機能回復促進効果

ラットの一側感覚運動野損傷モデルにおけるbeam walkingスコア(1：歩行不能 ～ 7：正常)の変化を示す．Amphetamineの機能回復促進効果(A)は，投与後ラットを拘束していると(Restraint)，消失し(B)，薬剤と運動をcoupleすることが機能回復促進に必須であることを示唆する．AMPH：amphetamine(2 mg/kg)．(文献[31]より改変引用)

のトレッドミル訓練は免荷しないトレッドミル訓練に比較して，歩行速度，バランス，下肢麻痺，歩行可能距離を有意に改善することが示された[27]．Parkinson病の歩行障害に対しても有効性が示されている[28][29]．この訓練は免荷度，トレッドミル速度，訓練時間，回数などを定量化できるため，どの施設でも再現可能である．方法論としては，手の訓練と同様に難易度を変化させ，トレッドミル速度をできるだけ上げていくと効果が出やすいとされている．有効性の機序はまだ不明であるが，脊髄のcentral pattern generatorや大脳の運動関連領野の賦活が考えられる[22][26][30]．

薬剤と理学療法の併用による機能回復促進

虚血性脳卒中において急性期の治療の焦点は早期の血管再開通，神経保護にあるが，それ以降は残存した神経ネットワークの再構築をいかに促進するか，という視点が必要である．とくにノルアドレナリン作動性神経伝達と麻痺の回復は密接な関係にある．Feeneyら[31]は，運動感覚野損傷を受けたラットの麻痺の回復がamphetamineによって促進されることを見出した．ノルアドレナリンを損傷された大脳の反対側の小脳に注射しても同様の作用が得られる．リハにとって重要なことは，amphetamineの投与後，ラットを拘束しておくとこの促進作用が失われることで，薬物とリハをcoupleする必要(symptom-relevant experience)を示唆する．臨床的にも，亜急性期のamphetamineとリハの併用が脳卒中の麻痺の改善に有効であることが小規模なRCTで示唆されている[32]．しかし，症例数が少なく研究デザインもまちまちであるため，まだ確定的な結論は出ていない．また，dopamineと理学療法の併用も同様な効果があること示唆されている[33]．

一方，機能回復に悪影響を及ぼす薬剤も存在すると考えられる．脳卒中の診療において神経伝達を修飾するような薬剤として使用される機会が多いのが，向精神薬，抗不安薬，抗てんかん薬などである．このような薬剤や降圧剤であるα_2アゴニストやα_1拮抗薬は，動物の脳損傷モデルにおいて運動機能回復を遅らせる作用が示されている．臨床上もclonidine, prazosin, haloperidol, phenytoin, phenobarbitalやbenzodiazepine系薬物の使用が運動機能の回復を遅らせる可能性が指摘されている[11]．

脳卒中にうつ状態が合併しやすいことは1980年代より注目されており，poststroke depression (PSD)と呼ばれる．PSDの頻度は診断基準，発症後日数，患者群の選択などにより，20%から70%

台とかなり幅があるが，発症後から1年にかけては少なくとも30%から40%は存在すると考えられる．PSDの存在は脳卒中患者のリハ参加に対する障害となり，ときにはセラピーそのものの拒否につながる．事実，PSDを放置すると機能予後は悪化する[35]．神経伝達の観点から作用の異なる抗うつ剤と理学療法の併用効果が検討されている．脳卒中には選択的セロトニン再取り込み阻害薬が安全性，機能回復の面から好ましいとする報告が多い[36][37]

おわりに

脳卒中後の機能回復に伴って損傷を受けた神経ネットワークの再構成が起こり，それがリハビリテーション(リハ)により修飾されることがわかってきた．脳賦活の変化と機能予後の関連づけから考えられるリハの方法論の展開や神経伝達を促進する薬物の併用によるリハ効果の増強など新しいストラテジーが生まれつつある．外部環境としての多彩なチームアプローチに加えて，麻痺肢の使用頻度を増加させる訓練やセラピストから感覚運動刺激から随意性をひき出すための訓練などが考えられる．

ただし，ここで述べたことは脳卒中リハの多彩なプロセスのごく限られた側面である．すなわち機能障害の治療だけでなく，日常生活動作訓練，健側筋力低下や関節可動域制限などの二次的な問題の治療，運動耐性の増強，補装具の適用，高次機能障害や脳卒中後うつ状態に対する介入，介護者の訓練，住宅改造などの環境設定や介護保険で提供される社会的資源の導入など多岐にわたり，どれも欠くことができない役割を担っている．これらすべてを複合して個々の患者に最適なリハ介入を行うことでさらに機能回復が促進されると考える．

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