Evidence of Motor Recovery in Chronic Hemiplegic Patients Induced by a Bilateral Symmetric Arm Trainer

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Abstract

Evidence of Motor Recovery in Hemiplegic Stroke Patients Induced by a Bilateral Symmetric Arm Trainer

by

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Doctor of Philosophy in Biomedical Engineering-

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The hemiparesis is the most common deficit after stroke or brain injury, affecting more than 80% of subjects acutely and more than 40% of those patients remained at chronic condition. Within 2 to 5 months after stroke, patients recover variable degrees of function, depending on the initial deficit. An impaired hand function is one of the most serious disability in chronic stroke patients. Therefore, to evaluate the extent of motor dysfunction in the hemiplegic hand is important in stroke rehabilitation.

In this dissertation, motor recoveries in 8 chronic hemiplegic patients with Fugl-Meyer (FM), modified Ashworth scale (MAS), manual muscle test (MMT) scores, electromyography (EMG) responses, cortical activation and white matter changes before and after the training program with a designed bilateral

symmetrical arm trainer (BSAT) system were examined. The training was performed at 1 hr/day, 5 days/week during 6 weeks.

In all patients, FM, MMT and MAS were significantly improved after the 6-week training. EMG responses of the hemiplegic hand were recorded during isometric wrist flexion/extension movements. Delay in onset/offset of muscle contraction and the co-contraction ratio (CCR) of flexor/extensor muscles of hemiplegic hand decreased significantly after the training. We compared cortical activations in different tasks before and after the training program. Functional magnetic resonance imaging (fMRI) studies in unilateral wrist movements showed that cortical activations decreased in ipsilateral SMC but increased in both contralateral SMC and ipsilateral cerebellum. In bilateral wrist movements, bilateral SMC, PMA, SMA and cerebellum showed cortical reorganizations. Laterality index (LI) was significantly increased in affected hand movement after training. Diffusion tensor imaging (DTI) results also showed that fractional anisotropy ratio (FAR) and fiber tracking ratio (FTR) in the posterior internal capsule were significantly increased after the training. It seemed that the cortical reorganization was induced by the 6 week training with the BSAT. In all parameters proposed this study, a significant correlation was found between these parameters (clinical assessments, onest/offset delay, co-contracion ratio, LI, FAR and FTR) and motor recoveries.

This study demonstrated that clinical assessments, EMG, fMRI and DTI can be used to predict motor recovery in chronic hemiparetic patients.

Key Word: Chronic stroke patients, motor recovery, bilateral symmetric arm trainer (BSAT), clinical assessment, electromyogram (EMG), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI)

1. Introduction

Stroke is the second leading cause of death in Korea, followed by the cancer. More than 100,000 new strokes occur in Korea. Approximately 60% to 80% of stroke patients survive [1]. Hemiparesis is the most common deficit after stroke, affecting >80% of subjects acutely and >40% of those patients chronically [2]. Rehabilitation techniques have been more successful in restoring function in the lower limb than in the upper limb [3]. Unfortunately, upper limb function is more important for independent living and self-esteem [4]. Nakayama et al. [5] reported that further recovery of upper extremity function should not be expected unless functional recovery has occurred by the 11^{th} week.

The recovery of voluntary arm movements is one of the main goals in hemiparetic rehabilitation to avoid long-term disabilities in daily living activities. Current upper limb rehabilitation trainings require enormous efforts of physical therapists, resulting in high costs and low efficiency for the treatment. Therefore, upper limb training systems to provide rhythmic movements have been developed for clinical applications [6-8].

Clinical evaluations such as Fugl-Meyer (FM) scores, modified Ashworth scale (MAS) and manual muscle test (MMT) have been used extensively to quantify motor recovery [2]. They are easy to perform, inexpensive, and usually can be conducted in a short time.

In order to expand treatment strategies, the nature of hemiparesis and its relationship to clinical outcome must be further elucidated using quantifiable methods. Hammond et al. [9] and Chae et al. [10] demonstrated significant delays in onset and offset time of muscle contraction in hemiparetic stroke subjects. Hammond et al. [11], Kamper et al. [12], Canning et al. [13] and Pisano et al. [14] reported significant differences in electromyography (EMG)

interference pattern with abnormal co-contractions of agonist and antagonist muscles.

With the recent development in functional neuroimaging modalities such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and transcranial magnetic simulation (TMS), several studies have reported the cortical reorganization induced by physical interventions in hemiplegic patients [15-18]. Functional imaging and electrophysiologic brain mapping techniques have provided substantial insights into the adaptive changes of cerebral networks associated with the recovery from brain damages. These studies demonstrated the recruitment of areas adjacent to brain lesion or ipsilateral motor regions of the unaffected hemisphere after the complete recovery from the upper extremity motor impairment.

Furthermore, the reorganization of both motor and sensory structures occurs in parallel with the improvement of the upper extremity motor function [15,16]. Given the close temporal correlation between these sequential alterations of cerebral activity and the return of voluntary motor control, many of the dynamic changes observed in the cerebral cortex may have a restorative capacity. Accumulated evidences in hemiparetic patients suggest that rehabilitation techniques with repetitive training of functional movements have significant effects on the recovery of motor skills [17,18].

Recovery from focal motor pathway lesions may be associated with a functional reorganization of cortical motor areas. Previous studies of the relationship between motor recovery and the functional consequences have employed fMRI, which provides limitation of the structural information. The recent development of diffusion tensor imaging (DTI) now provides qualitative measures of fiber tract integrity and orientation [19].

The purpose of the present study was to evaluate the upper-limb function recovery in chronic hemiparetic patients after 6 week motor training with the designed bilateral symmetric arm trainer (BSAT) system. For quantitative evidences, we measured clinical assessments such as FMA, MAS, manual muscle test (MMT) scores, EMG characteristics and neuroimaging methods such as fMRI and DTI. Figure 1.1 shows the protocol design for this study.

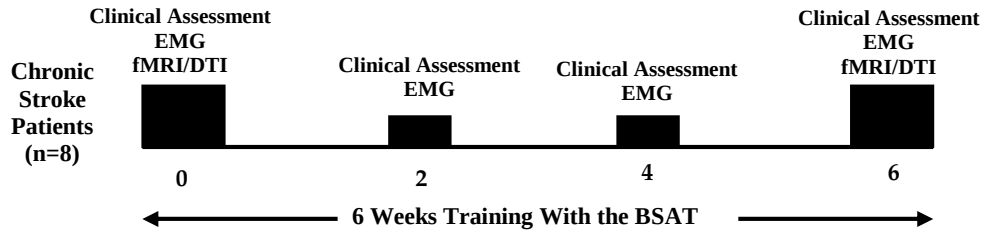

Figure 1.1. Protocol design for this study. Clinical assessments and EMG parameters were measured every two weeks during the 6 week training, fMRI and DTI were measured before and after training.

This dissertation consists of 8 chapters and appendices. In Chapter 2, the basic knowledge to understand this dissertation is explained. Section 2.1 introduces motor recovery procedure in chronic stroke patients. Section 2.2 introduces brief conventional and current stroke rehabilitation techniques including neural mechanisms during bilateral movement and advantages of bilateral movement.

In Chapter 3, experimental setups in this study to understand the following chapters are described. Section 3.1 introduces the compositions, principles and characteristics of the Bilateral Symmetric Arm Trainer (BSAT) designed for motor training. Section 3.2 describes clinical characteristics and inclusion criteria of eight chronic stroke patients for this study. Section 3.3

introduces the protocol of 6-weeks training program suggested for this study. Section 3.4 describes hypotheses of effect on motor function after 6-weeks training.

In Chapter 4, experimental results to evaluate motor recovery using clinical assessments are represented. Section 4.1 introduces the usefulness of clinical assessments for evaluation motor recovery and previous studies in stroke patients. In Section 4.2, the basic knowledge of clinical assessments such as Fugl-Meyer (FM) scores, modified Ashworth scale (MAS) and manual muscle test (MMT), is explained. In Section 4.3~4.6, experimental methods, analytic techniques and results during 6-weeks training with the BSAT, are described.

In Chapter 5, experimental results to evaluate motor recovery using EMG parameters such as onset/offset delay, co-contraction ratio are presented. The correlation between the motor recovery and EMG parameters is analyzed. In Section 5.1 introduces previous studies using EMG in stroke patients. In Section 5.2~5.5, experimental methods, analytic techniques and results compared with before and after 6-weeks training with the BSAT, are described.

In Chapter 6, experimental results to evaluate motor recovery using fMRI are presented. The correlation between motor recovery and cortical reorganization is analyzed. In Section 6.1 introduces previous studies using fMRI in stroke patients. In Section 6.2 the basic knowledge of magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI) and neuroimaging mapping technologies is explained. In Section 6.3~6.6, experimental methods, analytic techniques and results compared with before and after 6-weeks training with the BSAT, are presented.

In Chapter 7, experimental results to evaluate motor recovery using diffusion tensor imaging (DTI) are presented. The correlation between motor recovery and the fractional anisotropy (FA) in DTI and the amount of fiber tracking run through the corticospinal tract in 3D tractography is analyzed. In Section 7.1 introduces previous studies using DTI in stroke patients. In Section 7.2, basic principles of DTI and 3D fiber tracking (tractography) technology are explained. In Section 7.3~5.6, experimental methods, analytic techniques and results during 6-weeks training using with the BSAT, are presented.

Finally, brief conclusions and future works are given in Chapter 8.

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2. Stroke Rehabilitation: Overview

This chapter describes the basic knowledge to understand this dissertation. This chapter consists of three parts: ‘2.1. Motor Function Recovery’ introduces the motor recovery procedure in chronic stroke patients. ‘2.2. Intervention for Rehabilitation’ introduces brief conventional and current stroke rehabilitation techniques. ‘2.3. Bilateral Movement Rehabilitation with Chronic Stroke’ describes neural mechanisms during bilateral movement and advantages of bilateral movement.

2.1. Motor Function Recovery

The hemiparesis is the most common deficit after stroke or brain injury, affecting more than 80% of subjects acutely and more than 40% of those patients remained at chronic condition [1]. Most early-stage hemiparetic patients experience some functional recoveries in weeks to months following brain injury. While many patients recover ambulatory function even after hemiplegia, the restoration of upper extremity motor skills is often less complete. Only 20% of the patients who remain flaccid 2 weeks after stroke or brain injury regain some functions to use their hands [2]. Figure 2.1 shows the general time course of neurological score until approximately 6 months after stroke.

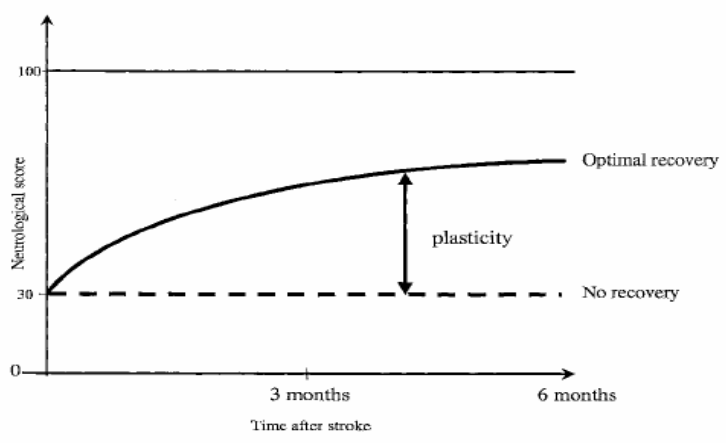

Figure 2.1. Idealization of time course of neurological score (100=normal function) from onset until approximately 6 months after stroke, as a function of plasticity.

In humans, there is abundant evidence that spontaneous recovery of function during the first 3 months after stroke stems from a complex pattern of brain reorganization. Concerning general processes related to spontaneous motor recovery, three major changes have been identified: (a) compensatory changes in the damaged hemisphere in the functional organization of the intact cortical tissue surrounding the infarct[3,4]; (b) the activation of motor areas and ipsilateral corticospinal fibers in the unaffected hemisphere [5]; (c) the increased activation of nonprimary motor areas such as the supplementary motor area, inferior parietal cortex, cingulate, insula, and cerebellum [6-8].

2.1.1. Neural Plasticity of Human Brain

As recent as a decade ago, it seemed inconceivable to neuroscientists that widespread functional and structural plasticity was possible in the cerebral cortex of adult mammals [9, 10]. Even though Hebb [11] championed synaptic plasticity in his 1949 classic book, Organization of Behavior, neural plasticity took time to become accepted [12]. A landmark discovery that stimulated

research and debate concerned nerve growth factor in the adult brain [13]. In a review of neural plasticity and rehabilitation, Cohen and Hallett [14] argued that the discovery of nerve growth factor led to experiments on trophic effects later in life. Currently, neuroscientists accept that neural plasticity, the tendency of synapses and neuronal circuits to change due to the activity, affects the mature brain [15, 16].

Valuable insights into the neurophysiological mechanisms mediating neural plasticity have emerged from the introduction of non-invasive techniques in studies on humans, including positron emission tomography (PET), transcranial magnetic stimulation (TMS), and functional magnetic resonance imagery (fMRI). Fast and slow cortical neuroplasticity have been identified, each distinct in their time-course and underlying mechanisms [17]. Fast neuroplasticity can occur in minutes (within-session plasticity) and reflects changes in the balance of excitation and inhibition within the cortex [18, 19]. This form of neuroplasticity appears to be relatively transient and dependent on down regulation (suppression) of gammaaminobutyric (GABA) inhibition [20, 21]. In contrast, slow neuroplasticity, which occurs over a much longer timecourse (days to weeks: between-session plasticity), is evident through changes in cortical organization and appears to involve long-term potentiation [19]. Between-session plasticity is persistent and stable and can remain even after several months [18]. While between-session plasticity and rehabilitation improvements are dependent on the induction of within-session plasticity, additional long-term benefits depend on modulating the balance of excitation and inhibition [22]. Although there are extensive literatures on neuroplasticity, the present review focuses on cortical plasticity following stroke and, in particular, the growing evidence of therapy-induced neural reorganization.

2.1.2. Functional Reorganization

Reorganization of the brain must occur at some level. It explains the ability to adapt to changes in the environment or recovery from brain injury. Modifications due to the cortical reorganization are thought to occur through at least three different mechanisms. The first of these mechanisms, long-term potentiation (LTP), is a process whereby the synapse effectiveness, or the weight of the connection is altered as a result of a consistent modification of their afferent over time. The effect of this mechanism is typically dissipated over a period of minutes to hours [23] and unless accompanied by the presence of N-methyl-D-aspartate (NMDA) is not permanent. The fundamental argument against LTP is that the extent of reorganization attributable to LTP is within the arborization of one neuron and therefore is unlikely to be the catalyst of the level of reorganization thought to occur following amputation or brain injury. The second and third mechanisms, unmasking and sprouting are the most likely candidates underlying the reported level of reorganization (0.5~2cm) following amputation or brain injury.

2.1.2.1. Unmasking

In case where neuronal connections are lost through such processes as lesions or deafferentation, there is a possibility for unmasking to occur. If the original neuronal connections were acting to inhibit one or more adjacent neurons, that were previously silent because that were inhibited, now may become inhibited, now may become disinhibited or unmasking. When this unmasking occurs at the highest level of processing, for example in the cortex, the effect may be quite small, since the area of inhibition is within a few axon

arborizations. However, many researchers suggest that large-scale reorganization may be affected, when the unmasking occurs at an earlier stage in the processing stream such as in the brainstem or thalamus [24]. Small changes in these areas may then lead to the evidence of larger levels of reorganization at the cortical level.

2.1.2.2. Sprouting

Can the nervous system grow new neurons? These is only very limited concrete evidence to suggest this possibility, but researchers are looking hard to determine if this can happen. The current widely held belief is that no new growth is possible [25]. Can the neurons grow new axons? The current answer is, maybe. Florence et al. [26] have shown that damaged axons from the skin of the hard can grow and innervate new territories in the spine. However, this regeneration was thought to take place only in a special growth mode when the brain was producing a protein, growth-associated protein 43 (GAP-43) that modulates axonal growth and repair. However, Kaas and Florence [25] have suggested that, in the case of amputation or brain injury, this is not the mechanism for new neuronal growth because it involves uninjured nerves, which presumably have no raised levels of growth enhancing compound. This would seem arguable since brain injury is clearly a massive deafferentation process in which many neurons are likely damaged. They suggest, however, another mechanism whereby the deafferentation process of brain injury leads to a decrease in those factors that would inhibit growth and presumably, new growth could consequently occur [25].

2.1.2.3. Unmasking versus Sprouting

Until 1991, there was a general consensus that the limit of cortical reorganization was determined by the extent of thalamocortical axon arborization. Changes within the cortical arborization were likely either induced either by the mechanisms of LTP (on the very small scale) or by unmasking to produce up to 1~2 mm of cortical surface change. Up to two millimeters of change was consequently thought to be the maximum change that could be expected in the adult brain, and up to 1991, there had been no reports of larger scale reorganization. However, the area of the cortex that subserves the hand or a given limb is quite large, on the order of centimeters rather than millimeter. The answer to the question of what happened to this large area if reorganization could affect only 1~2 mm was left at the following explanation. Initially, this large area was thought to be a silent and unresponsive cortical area. As pointed out above, under the mechanisms of LTP and/or unmasking resulting from the disinhibiton of the surrounding neurons, these expansions could only encroach 1~2 mm into the previously denervated area [26]. Calford et al. [27] suggested that this process continually repeated and left only a small core of silent neurons several weeks later.

This evidence supports a model of reorganization limited by 1~2 mm in extent without any additional processes such as sprouting. In 1991, the presumed spatial limits of reorganization was expanded after a work by Pons et al. [28] in which monkeys who had undergone deafferentation 12 to 20 years prior underwent electrophysiological mapping of the somatosensory cortex. They found to have undergone cortical reorganization in the magnitude of 15~20 mm.

There have been a number of theories suggesting possible mechanisms for this larger scale reorganization. Theories propose the awakening of

previously silent projections through unmasking or sprouting [29]. The simplest theory postulates that the reorganization is achieved through the sprouting of new axonal connections. In this theory, neurons outside the newly silenced area would sprout new connections into the silenced zone following normal neuronal arborization code to join functional groups. Similarly, the neuron within the silenced zone would also sprout new connections to areas adjacent to the silenced zone that have not been deprived of their afferents. Interestingly, reorganizations resulting from sprouting are likely to lead to sub-optimal functional results. However, there is little evidence (mentioned above) to indicate even the possibility of sprouting. Even so, sprouting is still considered as a viable mechanism of the reorganization.

Pons et al. [28] have a different approach to the unmasking and amplification (divergence) theory of reorganization. They have suggested that the thalamus is the key to cortical reorganization changes seen cortically. They examined eight monkeys after upper limb deafferentation. The thalamus of each monkey had undergone extensive reorganization and atrophy in the areas normally associated with the upper limb. The normal cortical projection points of these areas of the thalamus were active. Jones and Pons [30] felt that, even without sprouting, the normal arborizations of the thalamocortical projections might explain the map expansion. The normal extent of the finger representation in area 3b of the macaque somatosensory cortex is between 10 and 12 mm^2. The breath of expansion and the overlap of the adjacent projections from region of the VP nucleus representing nearby body parts was even larger. They pointed out that this divergence was great as 35%, including a substantial part of the representation of a single digit of the VPL can be destroyed before the representation in area 3b is reduced and adjacent areas begin to expand. Their findings indicate that large scale reorganization found in their study was the result of long-term, continuous, and progressive process

of thalamic atrophy and subsequent unmasking of thamocortical connections. The authors are also quick to point that intracortical mechanism, such as sprouting and cortico-cortico unmasking, have not been ruled out as contributory mechanisms even through the evidence for thalamic reorganization may be even be enough to explain the phenomena. Microsimulation of intracortical neurons also has the effect of short-term expansions of body part representations in the somatosensory cortex [30].

2.2. Motor Rehabilitation after Stroke

Current upper limb rehabilitation trainings require enormous efforts of physical therapists, and thus result in high costs and low efficiency for the treatment (Figure 2.2). Therefore, upper limb training systems have been developed for clinical applications. Many researchers [31-34] presented robot-assisted movement exercises in daily repetitive training and compared the results with those by conventional physical therapies (Figure 2.3).

(a) (b) (c)

Figure 2.2. Conventional hemiplegic rehabilitation: (a) Physical therapy, (b) Occupational therapy, (c) Elecrotherapy

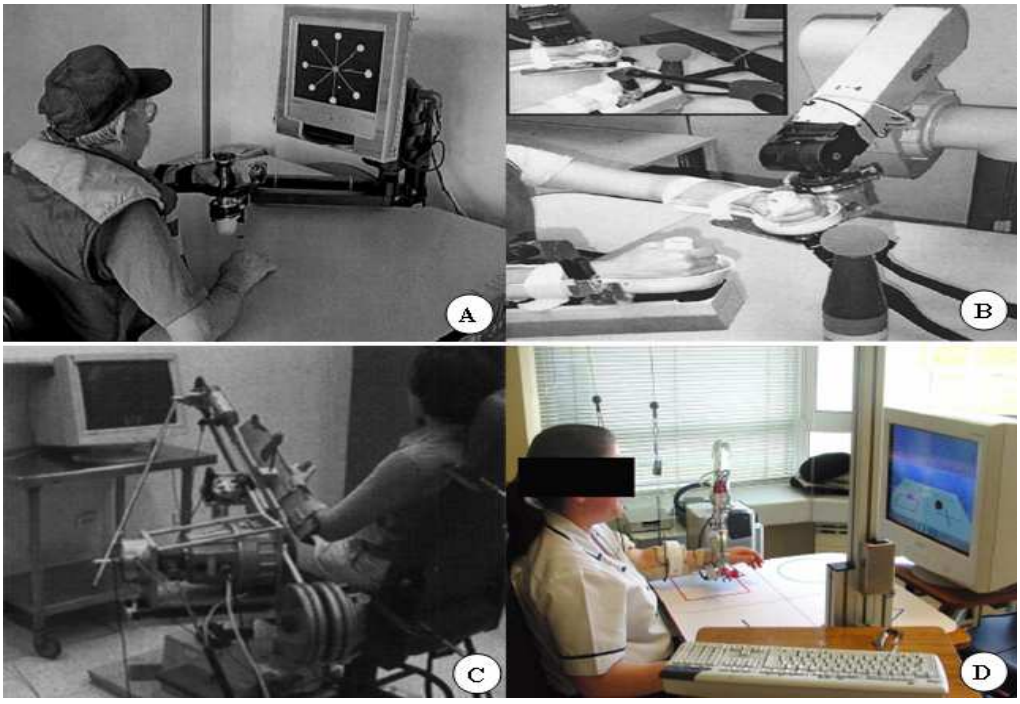

Figure 2.3. Robot-assisted hemiplegic rehabilitation: (A) Robot arm (MIT-MANUS) [31], (B) Mirror-image motion enabler (MIME) [32], (C) Assisted Rehabilitation and Measurement Guide (Arm guide) [33], (D) Robot-mediated therapy (RMT) [34].

2.2.1. Motor Task-Specific Training

A few studies have tested the effect of task-specific training on motor performance and brain function in chronic stroke patients. Carey et al. [35], using a randomized cross-over design, intensively trained stroke patients with mild to moderate impairment to track waveforms with their paretic index finger. After the training period, and not after a control period of equal duration, patients exhibited the improved tracking accuracy as well as improved hand function of grasp and release. These motor gains were associated with a shift in the laterality of activation in sensorimotor cortex (primary motor cortex, primary somatosensory cortex, premotor cortex) from largely contralesional to largely ipsilesional, detected by fMRI in the paretic index finger tracking. Normal control subjects who received the same intensive training did not improve in tracking accuracy nor exhibit a change in the predominantly contralateral sensorimotor cortex activation. In healthy adults, increasing the amplitude [36] and frequency [37] of finger movements, has been shown to increase activation in contralateral sensorimotor cortex. Therefore, better matching of waveform amplitude and frequency may have contributed to the increased activation in ipsilesional (contralateral) sensorimotor cortex observed after training in patients. Nonetheless, this study suggests that motor gains produced by task-specific rehabilitation in chronic stroke patients are associated with normalization of sensorimotor cortex laterality. Muellbacher et al. [38] examined the effect of a novel strategy for improving paretic hand motor function in chronic stroke patients. Task-specific motor practice was coupled with the modulation of ipsilesional motor cortex excitability. Previous studies in healthy adults have suggested that there is a competitive interaction between neuronal representations of the hand and upper arm in contralateral sensorimotor cortex [28]. Accordingly, Muellbacher

et al. [38] hypothesized that motor function of the paretic hand in stroke patients would be improved if the ipsilesional sensorimotor cortex representation of the paretic upper arm is inhibited, thus increasing neuronal activity of the paretic hand representation. To test this hypothesis, the paretic upper arm was transiently anesthetized so that its skin lost tactile sensation and its muscles lost strength. Under regional anesthesia, or unanesthetized, the paretic hand practiced a thumb-to-index-finger pinch grip. They found that paretic hand pinch strength and acceleration increased after the practice, more so under anesthesia than unanesthetized. Further, the gains in paretic hand pinch strength under anesthesia were correlated with the increases in the amplitude of MEP recorded from the paretic hand by TMS to the ipsilesional motor cortex. The anesthesia-induced gains in pinch force were retained 2 weeks later. These findings suggest that the excitability of the representation of the paretic hand in ipsilesional motor cortex is affected by the sensorimotor status of body parts that neighbor the hand, and thereby the efficacy of motor training of a paretic hand.

2.2.2. Task-Oriented Training

The functional gains produced in stroke patients by the task-oriented training, like those produced by neurofacilitation approaches and task-specific training, may be due to the reestablishing control exerted by ipsilesional sensorimotor cortex. Liepert et al. [39] examined the effects on dexterity and motor cortex function of a single task-oriented session focused on improving dexterity of the mildly to moderately paretic hand in patients early (4–8 weeks) after stroke. Using TMS, they observed that prior to training, the size of the representation in contralateral motor cortex was smaller for the paretic hand than the unaffected hand. Just after training, most of the patients (seven of

nine) exhibited improved dexterity. Paralleling this motor gain, the size of the representation in contralateral motor cortex of the paretic hand enlarged, whereas that of the unaffected hand was unchanged. Neither the behavioral nor the contralateral (ipsilesional) motor cortex change was retained 1 day after training.

Functional neuroimaging studies suggest that the functional gains produced in stroke patients by task-oriented training are associated with increased activity in ipsilesional primary sensorimotor cortex and redistribution of activity in several areas of the sensorimotor network. Nelles et al. [40] compared the motor outcome of subacute, severely impaired stroke patients after random assignment to 3 weeks of intensive task-oriented training directed at improving affected upper limb function or standard rehabilitation. Patients in their study showed better motor recovery in the affected upper limb, compared with the control patients. Further, after therapy the experimental patients exhibited greater increases in activation in ipsilesional primary sensorimotor cortex and secondary sensorimotor cortices (bilateral inferior parietal cortex, bilateral premotor cortex), as measured by PET during passive movement of the affected elbow, relative to the control patients. Normal control subjects did not exhibit changes in brain activation when scanned twice over the same time period. Jang et al. [41] provided a home-based, task-oriented program which was designed to improve the function of affected upper limb in chronic stroke patients. After training, the paretic hand of patients showed greater gains in dexterity and grip strength than the unaffected hand. In parallel, their fMRI studies showed that the laterality of activation in primary sensorimotor cortex, and in some cases secondary motor areas (premotor cortex, supplementary motor area), shifted from largely ipsilateral (contralesional) to largely contralateral (ipsilesional) during paretic finger movement, yet was stably contralateral during unaffected hand movement.

2.2.3. Constraint-Induced Movement Therapy

Constraint-induced movement therapy is a task-oriented approach that has gained much attention in the rehabilitation community because of significant functional gains of the paretic upper limb of chronic stroke patients [42, 43]. The therapy combines intensive practice using the affected upper limb to achieve functional goals with restricted use of the unaffected upper limb (usually by means of wearing a sling) to prevent its habitual compensatory use. This combination of strategies has been believed to be necessary to overcome the learned-nonuse that develops early after stroke from repeated failed attempts to use the affected upper limb [44]. After constraint-induced movement therapy applied to patients with mild to moderate motor impairment, the most marked behavioral gain has been in self-reported use of the affected upper limb in activities-of-daily-living; less marked gains in motor control parameters have also been found [42-44]. Several studies have applied human brain mapping technologies in an attempt to reveal changes in brain function that underlie the efficacy of constraint-induced movement therapy. Results of these studies have variously suggested changes in activity in ipsilesional sensorimotor cortex, contralesional motor cortex, and perilesional cortex, as related to the therapy-induced gains in motor function. TMS studies suggest that the normalization of activity in ipsilesional motor cortex underlies functional gains in stroke patients after constraint-induced movement therapy. Liepert et al. [39] found that before therapy, the size of the representation in contralateral motor cortex was smaller for the paretic hand than the unaffected hand. After therapy, when functional use of the paretic upper limb had improved, the size of the paretic hand representation in contralateral motor cortex was enlarged, whereas that of the unaffected hand was not chhanged, representing a return to the normal balance of excitability of the two

hemispheres. Wittenberg et al. [45] found that chronic stroke patients who received constraint-induced movement therapy showed greater gains in function of the paretic upper limb than patients who received a less intense control therapy. TMS revealed a trend toward an increased ratio in the size of the contralateral motor cortex representation of the paretic hand relative to the unaffected hand in the experimental patients as compared to the control patients. Wittenberg et al. [45] performed PET scanning as well as TMS on the patients. PET showed that activation in contralateral primary sensorimotor cortex before constraint-induced movement therapy was greater during paretic hand movement than during hand movement of normal control subjects. Experimental patients after therapy exhibited greater decreases in the activation in contralateral primary sensorimotor cortex during paretic hand movement, compared to the control patients, toward the level observed in normal control subjects. In parallel, the TMS and PET results may appear paradoxical, yet might reflect differences in the physiologic basis of these brain mapping methods. Therapy to improve paretic limb function effectively might lower the firing threshold of neurons in ipsilesional motor cortex, resulting in MEP elicited from a larger cortical territory. A lower firing threshold might also translate into more efficient recruitment of neurons during performance of the prescribed motor task during PET, resulting in less increase in regional cerebral blood flow. A role of ipsilesional secondary sensorimotor cortices in mediating the efficacy of constraint-induced movement therapy in chronic stroke patients is suggested by Johansen-Berg et al. [46]. They found that a home-based program of constraint-induced movement therapy yielded greater strength gains of the paretic hand, compared to the unaffected hand of patients. Further, the gains in paretic handgrip strength were positively correlated with increased activation in ipsilesional premotor cortex and secondary somatosensory cortex, as measured by fMRI during paretic hand

movement. This result is particularly appealing because of the graded nature of the observed relationship between motor function and activation increases on the paretic hand. Other brain mapping studies suggest that increased recruitment of contralesional sensorimotor cortices may be involved in the efficacy of constraint-induced movement therapy. Using EEG, Kopp et al. [47] found that the source location of cortical potentials associated with paretic hand movement shifted anteriorly within the ipsilesional hemisphere immediately after therapy, and into the contralesional hemisphere 3 months later. In contrast, the source location associated with the unaffected hand was unchanged over time. These authors suggested that the delayed source shift into the contralesional hemisphere may reflect the hemisphere's increased contribution on the control of paretic upper limb movement in association with progressively greater use of the limb in the daily. In an fMRI study, Levy et al. [48] evaluated two stroke patients before and after constraint-induced movement therapy. Motor gains exhibited by one of these patients were accompanied by the increased activation in both hemispheres, more contralesionally than ipsilesionally, during paretic hand movement. However, since activation patterns associated with the unaffected hand over time were not reported, it is difficult to draw conclusions from this finding. In another fMRI study, Schaechter et al. [49] found that motor gains exhibited by the paretic upper limb after therapy were associated with a trend toward a shift in the laterality of activation in motor cortex (primary motor cortex, premotor cortex, supplementary motor area) toward the contralesional hemisphere during paretic hand movements. Motor gains and laterality shift associated with the paretic upper limb were retained 6 months later. In contrast, the laterality of motor cortex activation associated with the unaffected hand of patients was unchanged over time. Cumulatively, these studies raise the possibility that in chronic stroke patients, motor gains of paretic limb produced

by constraint-induced movement therapy may be mediated by shifting the balance of activity toward sensorimotor cortices of the contralesional hemisphere. Decreased use of the unaffected limb during constraint-induced movement therapy may contribute to a relative increase in the representation of the paretic limb in contralesional sensorimotor cortices. Increased fMRI activation in perilesional cortex has been also reported in some cases after constraint-induced movement therapy. In the Levy et al. [48] fMRI study mentioned above, the increased ipsilesional activation observed in the two patients after therapy bordered their respective lesion. Similarly, Johansen-Berg et al. [46] found that the increased activation in ipsilesional secondary somatosensory cortex detected after therapy bordered the lesion in two of the seven patients. Previous fMRI studies in chronic hemiparetic patients who recovered to varying degrees have also occasionally noted increased activation in perilesional cortex during affected hand movement [50, 51]. It is possible that integration of this tissue into the sensorimotor network controlling paretic hand movement is a mechanism supporting the motor gains promoted by efficacious rehabilitation. It is noteworthy that these brain mapping studies provide no consensus of the neural mechanisms underlying the efficacy of rehabilitation, even when applying a single therapeutic approach—constraint-induced movement therapy. This may be due to several factors. One factor is that different technologies are sensitive to different neurophysiologic phenomena, as raised in regard to the Wittenberg et al. [45] TMS-PET study. TMS is sensitive to the excitability of motor cortex. This is not equivalent to the neurovascular sensitivity of functional neuroimaging methods. While both technologies provide insight into the neural effect of rehabilitation, the neurophysiologic relationship between findings based on these technologies is currently unclear. Another factor may be that the neural and behavioral sensorimotor status of a patient prior to therapy predisposes a particular neural

mechanism to mediate recovery induced by therapy. For example, therapy-induced brain plasticity may be influenced by changes in the sensorimotor network that occurred during spontaneous recovery, and the degree of damage to the ipsilesional motor cortex and its corticospinal tract. Accordingly, among a group of study patients, the detected change in brain activity after therapy may reflect the dominant neural and behavioral sensorimotor characteristics among the patients prior to therapy.

2.2.4. Bilateral Movement Rehabilitation with Chronic Stroke

The study of interlimb coordination in healthy adults has provided an important window into the psychological and neural mechanisms involved in the control of action. Of particular interest have been the interactions that occur between effectors when they move concurrently. A key principle emerging from this research is the universal tendency for synchronization among effectors. In a wide variety of bimanual coordination tasks, strong temporal and spatial interactions between the hands have been observed including: (a) a tendency toward frequency and phase locking between the limbs; (b) amplitude coupling (i.e., a tendency toward identical movement amplitudes when different amplitudes are assigned to the two hands); (c) direction coupling (i.e., a preference to move the effectors in the same direction); (d) mutual accommodation or interference between different geometric forms (i.e., circle and line) drawn concurrently with each hand [52, 53]. These studies support the view that mirror-symmetrical movements are a classic coordination mode in the human repertoire [54]. As Bernstein [55] argued, evidence clearly indicates that both arms are centrally linked as a coordinative structure unit; upper extremities function in a homologous coupling of muscle groups on both sides of the body.

A question of particular importance, therefore, is whether the apparent default organization of the motor system toward the coupling of homologous muscles can be exploited to promote functional recovery of a paretic limb in stroke patients. In healthy adults, for example, there is evidence to indicate that performance of the non-dominant limb is enhanced when in a symmetric relationship with the dominant limb during bimanual circle-tracing tasks [56]. For two movement disorders, spastic hemiparesis and Parkinson's disease, enhancement of an impaired limb's performance when coupled in-phase with an unimpaired limb has been reported [57, 58].

With stroke, neural networks are depleted because of damaged neurons. Bilateral symmetrical movements, therefore, may allow the activation of the undamaged hemisphere to increase activation of the damaged hemisphere and facilitate movement control of the impaired limb promoting neural plasticity. The results from studies of bimanual coordination in stroke patients, however, have been mixed. Cunningham et al. [59] reported improvements in the smoothness and velocity profiles of the involved limb during bilateral training with an increased inertial load for simple elbow movements. Similarly, Rose and Winstein [60] found in a ballistic movement task that, for 5 of 11 patients, the impaired limb had a shorter movement time when both hands were moved simultaneously than when the task was performed unimanually. Other studies, however, rather than finding facilitatory bimanual coupling effects have observed the impaired side exerting a negative influence on the unimpaired side degrading its performance to match that of the impaired limb, illustrating that the symmetry constraint exerts a powerful influence even when one of the limbs is severely impaired [61, 62]. Factors such as differences in task complexity and level of impairment of participants across studies may account for the lack of consistency in results. Furthermore, compensation for loss of function is easier to achieve during simple

coordination tasks than complex tasks involving the coordination of multiple degrees of freedom [63].

Consistent with this view are strong facilitation effects evident on simple wrist extension movements of the impaired limb when the intact limb is moved simultaneously in studies using electromyography-triggered (EMG) neuromuscular stimulation [64]. In stududy, chronic stroke subjects completed 360 wrist/finger extension movements under one of two rehabilitation protocols: (a) unilateral movements of the impaired limb with active neuromuscular stimulation assistance or (b) coupled bilateral movements (wrist/finger extension on both arms and assistive active stimulation on the impaired arm). Across 6 h of training over 4 days during a 2-week period, the chronic stroke subjects in the coupled bilateral movement group displayed improved motor functions in a pretest–posttest design. Indeed, the motor improvements of the bilateral group were better than the improved motor functions of the unilateral group. Higher Box and Block test scores, shorter premotor and motor reaction times, and reduced root mean square error during a sustained contraction task indicated improved motor capabilities. Moreover, the EMG activation patterns displayed in the impaired limb during wrist extension distinctly favored the coupled protocols group [64].

Further evidence of therapeutic effects from involving the undamaged hemisphere in the recovery process of the impaired limb has come from studies of the after-effects of bilateral training regimes on unimanual performance. Mudie and Matyas [65] examined the effectiveness of a bilateral isokinematic training intervention (BIT), involving the practice of synchronous bilateral actions, in three experimental studies using controlled single-case multiple baseline designs. BIT lasted for 30–40 sessions over 6–8 weeks. Each experiment involved a baseline phase involving unilateral practice of three tasks (block placement, simulated drinking, and peg targeting) with the

impaired arm followed by an intervention phase where the tasks were performed simultaneously with both arms. The data of interest were unilateral test trials of each experimental task performed at the beginning of each session by patients with their hemiplegic limb. Neither task-specific unilateral practice with the hemiplegic limb nor practice with the unimpaired limb guiding the hemiplegic limb during the baseline phase significantly improved task performance. However, the introduction of BIT produced significant and rapid improvements in the kinematic patterns of unilateral hemiplegic limb performance. The gains observed during therapy were maintained at a 6-month follow-up indicating some permanent reorganization of the motor system. Across the three studies involving 12 stroke patients significant effects with BIT were found in 35 of the 40 individual time series.

Additionally, bilateral training effects have been observed in a between-subjects design comparing unilateral and bilateral intervention groups [66]. Twelve chronic stroke patients were randomly assigned to a six-session intervention involving the performance of a task involving the placement of a wooden dowel(s) on a shelf (50 trials per session) either with the impaired arm or with the two arms moving simultaneously. Patients receiving bilateral training showed both a significant decrease in time to complete the movement and an increase in the pretest to posttest functional ability of the impaired limb. In contrast, patients receiving unilateral training showed no improvement in movement kinematics or functional ability measures.

Further, positive training effects have been reported in studies using variations of the bilateral movement protocol. Luft et al. [67] tested a repetitive bilateral arm training task with rhythmic auditory cuing (BATRAC) (Figure 2.4) in which patients grasped two independent handles and made metronome paced repetitive pushing/pulling movements, in synchrony or alternation, simultaneously with the two arms.

Figure 2.4. Bilateral arm training with rhythmic auditory cueing (BATRAC).

The intervention consisted of four 5-minute periods of bilateral training on each of 18 training sessions over a 6-week period. Twenty-one chronic stroke patients (median 50 months post-stroke) were randomly assigned to (a) a BATRAC group (n=9) or (b) a control group (n=12) involving neurodevelopment based dose-matched therapeutic exercises. The bilateral rhythmic cuing group showed significant increases in activation of the precentral and postcentral gyri as well as the cerebellum. Moreover, when three BATRAC subjects who did not show any fMRI changes were removed, functional motor performance of the hemiplegic upper limb improved more than the control therapeutic exercise group. These findings are consistent with an earlier BATRAC study conducted by Whitall et al. [68]. The earlier study reported that 13 out of 14 chronic stroke patients demonstrated significant gains in functional motor performance of the hemiplegic upper limb that was sustained at an 8-week follow-up. In another variant of bilateral training, Stinear and Byblow [69] recently reported positive effects using a novel active–passive bimanual movement therapy in which the impaired wrist was moved passively through flexion and extension by active flexion–extension movements of the unimpaired hand to produce either synchronous or

asynchronous patterns. After 60 min of active–passive bimanual therapy per day over a 4-week period, five of nine acute and chronic stroke patients showed improved upper limb motricity.

Although significant bilateral training effects have been observed across a variety of testing protocols, Mudie and Matyas [65] failed to find enhanced unilateral performance following one session of bilateral practice in a group of acute (n=15) and chronic (n=15) stroke patients with dense hemiplegia. Furthermore, a recent study by Lewis and Byblow [62] revealed limited improvement in motor function following a bilateral intervention. In a multiple baseline design similar to that used by Mudie and Matyas [66], six stroke individuals across the three phases of recovery (acute, subacute, and chronic) practiced three upper limb tasks each session over a 4-week period for a total of 20 sessions. Both behavioral and neurophysiological measures of post-training performance showed large between-subject variation with little evidence of overall beneficial effects of bilateral training. The small sample size and large diversity between participants in lesion location, degree of initial impairment, and time since stroke onset, however, may have contributed to the lack of significant effects.

2.2.4.1. Neural Mechanisms Underlying Bilateral Coupling

A basic assumption of the use of bilateral movement therapy is that symmetrical bilateral movements activate similar neural networks in both hemispheres when homologous muscle groups are simultaneously activated [71, 72]. When the upper extremity is used unilaterally there is inhibition of the ipsilateral hemisphere, and the interhemispheric inhibition is specifically directed to prevent mirror movements by the opposite upper limb [73]. However, during symmetrical bilateral tasks both hemispheres are activated

and intracortical inhibition is reduced [69]. Indeed, the primary sensory and motor cortices are organized symmetrically, especially for hand control, in the left and right hemispheres [74].

In unilateral cortical stroke, severe damage may modify transcallosal inhibition resulting in hyperexcitability of the unaffected motor cortex [75]. Whether the increased excitability of the intact hemisphere represents a compensatory mechanism involved in motor recovery or spurious activity unrelated to recovery is a matter of considerable debate [76]. However, a consequence of the overactivation is that the lesioned hemisphere may receive abnormally strong interhemispheric inhibition from the intact hemisphere [77]. Support for this view comes from the recent finding that anesthetizing the healthy hand of chronic stroke patients, thereby possibly reducing the abnormal level of inhibition to the affected hemisphere, improved the motor performance of the paretic hand [78]. Given the suggestion that balanced interhemispheric interactions are necessary for normal voluntary movements [79], perhaps practicing bilateral symmetrical movements serves to normalize transcallosal inhibitory influences and facilitate the motor output from the damaged hemisphere.

Researchers have suggested that there may be a single central regulatory mechanism controlling both limbs in the bilateral situation [80]. In particular, as the supplementary motor area (SMA) in each hemisphere projects to the ipsilateral primary cortex and to a lesser extent to homologous muscles in the contralateral primary motor cortex, Goldberg [81] proposed that an intact SMA might act alone in executing bilateral movements. Thus, when the two arms work together in such a fashion, the arms are coordinated as a unit [82]. Recent imaging studies, while confirming the role of the SMA in the higher-order control of bilateral limb movements, reveal that there is widespread activation within a large distributed neural network associated with bimanual

movements. In addition to the SMA and sensorimotor cortex, the cingulate motor cortex, lateral premotor cortex, superior parietal cortex, and cerebellum have been shown to be specifically involved in bimanual coordination [83].

2.2.4.2. Neural Crosstalk

A common assumption among most models of bimanual coordination is that facilitation and interference effects emerge because of interhemispheric crosstalk. There are at least two levels of the central nervous system at which neural crosstalk can occur [84] (Figure. 2.5).

High-level crosstalk is the result of transfer of abstract movement parameters between the cortical hemispheres via callosal connections. The SMA and premotor cortices have dense interhemispheric connections via the anterior portion of the corpus callosum and the parietal cortices via the posterior portion [85]. There is growing evidence that the corpus callosum is particularly involved in the spatial coupling between the limbs. Callosotomy patients do not exhibit the spatial interference evident in control subjects when asked to draw two different shapes simultaneously (e.g., a circle and a line) with the two hands [86]. Nevertheless, these patients do show temporal coupling between the hands suggesting that temporal parameters of movement may be controlled by subcortical neural circuitry.

Recent patient and fMRI evidence reveals that callosal connections, particularly posterior parietal fibers may play an important role in the directional coding of movement [72]. Many cortical neurons in each hemisphere are tuned to the direction of movement and local inhibition

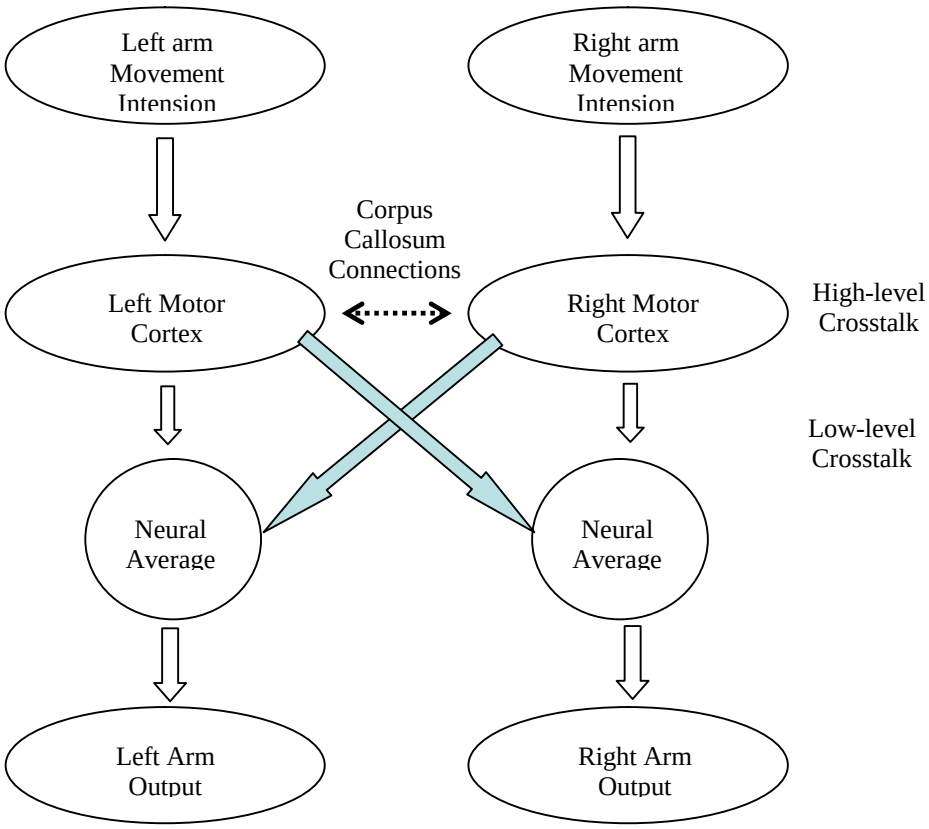

Figure 2.5. Movement intention model displaying two levels of crosstalk: (a) high level interactions between the left and right motor cortices via the corpus callosum; (b) low level subcortical interactions. The neural average signal for each arm is a consequence of the multiple interaction levels, and these interactions may cause the final efferent outputs to be more similar than originally planned.

processes are necessary to prevent mutual assimilation from interhemispheric crosstalk when incompatible movement directions are required [87]. Furthermore, some cortical neurons have been identified that specifically respond to simultaneous movements of the two arms, and these bimanually sensitive neurons appear to be directionally specific [88]. Interestingly, there is some evidence to suggest that the left hemisphere plays a dominant role in organization of mirror-symmetrical movements, whereas the right hemisphere

specializes in organization of non-mirror movements through inhibition, via the corpus callosum, of the homologous musclecoupling tendency [72]. Thus, a reasonable assumption is that when mirror-symmetrical movements are performed, as in bilateral training, identical movement parameters are specified for the two arms and reinforcement occurs through neural crosstalk.

Secondly, neural crosstalk can occur during the execution of movements that is downstream from the specification of abstract movement parameters. Although in most mammals the majority of corticospinal axons cross to the contralateral side at the level of the medullary pyramids, approximately 10% of the fibers remain uncrossed and project to the distal extremities in the ventral corticospinal tract [89]. While the role of ipsilateral pathways in the control of movement is a matter of some debate [90], they have been implicated in congenital mirror movements [91], cortical plasticity following injury [92], the recovery of motor function after stroke [93], and between-hand interference and facilitation during bimanual coordination in healthy subjects [94]. For example, Cattaert et al. [95] were able to simulate performance on a bimanual circledrawing task by a model of neural crosstalk in which some fraction of the motor command sent to the contralateral limb is dispatched as a mirror image to the homologous muscles of the ipsilateral limb. The model assumed predominating coupling influences from the dominant to the non-dominant limb. Accordingly, when bilateral symmetrical movements are performed, input to ipsilateral and contralateral pathways are consistent in reinforcing the coupling between the limbs. In stroke patients, bilateral symmetrical practice may exploit these coupling influences allowing increased use of spared ipsilateral projections in the recovery process.

2.2.4.3. Corticopropriospinal System

Some recent evidence suggests that neural plasticity following stroke may also involve a corticopropriospinal system consisting of premotorneurons that relay part of the descending motor command to upper limb motor neurons. Stinear and Byblow [69] have reported an upregulation of the propriospinal system in the impaired limb of chronic stroke patients. In addition, Mazevet et al. [96] found that a relatively greater component of the descending command to upper limb muscles transmitted through the propriospinal relay in recovering stroke patients was evident in the impaired limb compared with the intact limb. The authors suggest that the upregulation of descending commands may reflect the unmasking and/or reorganization of bilateral reticulospinal projections onto propriospinal neurons. It is possible that bilateral training promotes the increased involvement of spared corticopropriospinal pathways in the recovery process.

2.2.4.4. Sensory Feedback Contributions

Within the field of motor control, recent research has emphasized the importance of afferent information in interlimb coordination[97]. Further, given that a key process in recovery of motor function after stroke is interhemispheric sensorimotor integration, therapies promoting active use of sensory feedback may be particularly effective [90]. Consistent with this hypothesis are the positive therapeutic effects evident when external cues, such as rhythmic auditory stimuli, are used as an adjunct to pace movements of patients [98] and when active neuromuscular stimulation is coupled with bilateral movement training [99]. In the latter intervention, the active (EMG-triggered) neuromuscular stimulation requires stroke patients to voluntarily

contract a group of muscles in the impaired arm while simultaneously executing mirror-symmetrical movements with the intact arm.

Coupling active stimulation with bilateral symmetrical movements increases the likelihood that sufficient efferent and afferent signals will be generated in the impaired arm. This is important because the sensory information (i.e., proprioceptive feedback) returning to the somatosensory area may assist in establishing voluntary movement control associations with the adjacent primary motor cortex [100].

Further support for the use of augmented feedback within a bilateral training program comes from action/perception studies. Altschuler et al. [101] had chronic stroke patients move both hands/arms symmetrically while looking at a mirror reflection of the moving unimpaired limb and found improved motor functions of the hemiplegic limb. This finding suggests that functional recovery can be facilitated by visually substituting for impoverished proprioceptive input from the paretic limb [102]. The action and perception involved in executing voluntary movements activates the neural mechanisms in the association areas of the cerebral cortex, and these association areas integrate sensory and motor functions [103]. Stroke patients performing bilateral movements while watching their intact limb move in a mirror appears to activate a link between action and perception as well as related association areas. Support for the view that mirror therapy may produce cortical facilitation comes from a recent study showing that in healthy adults the excitability of the motor cortex ipsilateral to a unilateral hand movement was facilitated by viewing a mirror reflection of the moving hand [104].

2.2.4.5. Bilateral Therapy-Induced Neural Reorganization

Clearly, there are abundant neurophysiological mechanisms through

which bilateral movements may facilitate stroke rehabilitation. The considerable amount of redundancy in the central nervous system permits neural plasticity post-stroke. The limited number of studies examining neurophysiological changes associated with activity-dependent interventions in chronic stroke patients, however, has not produced consistent findings with regard to the neural mechanisms underlying therapy-induced plasticity. For example, some studies examining cortical plasticity after constrained-induced movement therapy indicate changes primarily in the affected hemisphere [46], whereas other studies suggest that increased recruitment of the contralesional cortex in the control of the paretic limb may underlie the therapy effect [47, 105]. Similarly, three recent TMS studies, involving small sample sizes, of neurophysiological changes following bilateral training have produced inconsistent findings. Lewis and Byblow [62] failed to find any consistent changes to motor cortex excitability in two (one acute, one chronic) patients following a bilateral training intervention. In contrast, Summers et al. [66] found that for two of the three chronic stroke patients on whom TMS mapping was possible, significant improvements in ratings of the functional ability of the affected upper limb following six sessions of bilateral training were accompanied by large increases in the corticomotor representation of the target muscle in the affected hemisphere. Enhanced upper arm motricity in five patients following an active–passive bilateral training intervention, however, was accompanied by a decrease in cortical excitability in the unaffected hemisphere [69]. More studies of the neurophysiological changes associated with bilateral movement training are clearly needed to identify the exact therapeutic conditions that mediate functional motor recovery post-stroke. Furthermore, recent research showing that non-invasive cortical stimulation combined with movement practice may enhance cortical neural plasticity suggests a promising new direction for neurorehabilitation research [106, 107].

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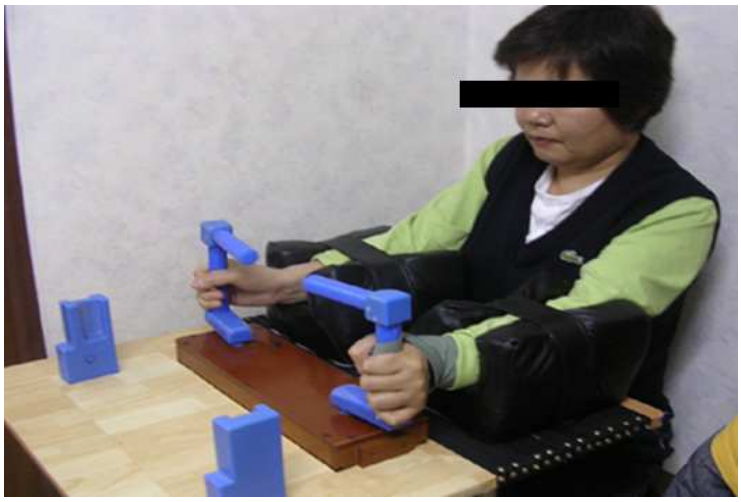
3. Experimental Setups & Hypotheses

In this study, we determined the effect of the bilateral symmetric motion trainer on the upper-limb motor recovery in chronic hemiparetic patients after the 6-week training program. For this study, we designed a bilateral symmetric arm trainer system as the training device and selected appropriate patients group. To maximize the training effects, we designed an appropriate training protocol. Finally, we established on the hypothesis that "repetitive bilateral training improves motor function in hemiparetic stroke patients". This chapter describes the experimental setup in this study. This chapter consists of four parts: '3.1. Bilateral Symmetric Arm Trainer (BSAT)' introduces the compositions, principles and characteristics of the designed BSAT. '3.2. Subjects' describes clinical characteristics and inclusion criteria of eight chronic stroke patients for this study. '3.3. Training Program' introduces the protocol of 6-weeks training program in this study. '3.4. Hypotheses' describes the hypothesis of the effect on motor function after the 6-week training.

3.1. Bilateral Symmetric Arm Trainer (BSAT)

Subjects were seated in a chair in front of a height-adjustable table, with their forearms in the mid-position between pronation and supination into an arm trough. Each hand of each subject grasped a handle that was 3cm in diameter and was tapered at the top for ease in insulting into the paretic hand. The hand was held in place by a 6cm Velcro strap. Both handles of the training system were connected to two serial spur gears. The system provides both handles with symmetrical motions such as forearm pronation/supination or wrist flexion/extension. Therefore, the affected side can be passively

controlled with the symmetrical movement according to the active motion of the unaffected side (Figure 3.1).



(a)

(b)

Figure 3.1. Bilateral symmetric arm trainer (BSAT): (a) wrist flexion/extension, (b) forearm pronation/supination.

3.2. Subjects

Eight hemiparetic patients (5 males and 3 females) participated in an open clinical study approved by written consent. Inclusion criteria were first hemorrhagic stroke with an interval of at least 20 months poststroke; severe upper-arm paresis, that is, the patients could only protract their paretic shoulder girdle, hold their extended arm while lying or flex, and extend their elbow slightly; at least moderate upper-limb flexor spasticity or joint stiffness on the affected side (modified Ashworth's scale: MAS<3, Grade 0 = no clearly, Grade 1 = barely discernible repetitive movement or increase tone, Grade 2 = either a slight but unsustained repetitive movement or a stronger but briefer repetitive movement, Grade 3 = a strong and sustained repetitive movement, Grade 4 = a movement equal to that expected of the intended hand); mild or no impairment of sensation of the affected upper extremity, tested for touch, pain as prothopatic and position sense, and dermolexia as epicrutic modalities; no additional peripheral paresis of the both upper extremities; no additional orthopedic disease (eg. Arthritis, arthrosis) of both upper extremities; no neurolytic of spasticity 3 months before of during the study; no severe impairment of cognition and communication (patients had to be able to understand the purpose of the study); no involved in other upper-limb rehabilitation in hospital or home now.

Six right-handed healthy male subjects (age: 34±5, range 24~38 years) without any history of neurological or psychiatric disease participated in this study as a control group. Stroke patients were at an age of 43.9±11.0years (range 33~67 years). The mean stroke interval was 67.5 months (range 24~142 months). Five subjects had right hemiparesis and three had left hemiparesis. All patients participated in a comprehensive impatient rehabilitation program of at 6 week training. Characteristics of eight patients are listed in Table 3.1.

Table 3.1. Demographics and pathology of 8 patients with stroke.

Patient	Age/ Sex	Lesson type	Paretic hand	Time of stroke (months)
1/KSH	44/M	ICH in right BG, TH	Lt.	38
2/MCH	37/M	ICH in right BG, TH	Lt.	58
3/YBJ	49/M	ICH in left BG, IC	Rt.	24
4/JYJ	33/M	ICH in left TH, IC	Rt.	58
5/KDH	67/M	ICH in left TH, IC	Rt.	142
6/CJS	57/F	ICH in right BG,TH	Rt.	72
7/KYS	48/F	ICH in right TH, IC	Lt.	120
8/KYH	36/F	ICH in left BG, TH	Rt.	28

ICH = Intracerebral hemorrhage, BG = basal ganglia, TH = thalamus, IC = internal capsule.

3.3. Training Program

Each training with BSAT takes at his/her home, and was performed 5 times per week during 6 weeks (30 sessions). In each session, patients were seated comfortably at a table with a custom-designed bilateral symmetric arm trainer in the following limb poison: ankle in neutral dorsiflexion, knee and hip placed at 90°, shoulders in 30° flexion, elbows in 30°, and wrist in neural position of flexion/extension. The apparatus consists of 2 independent handles that move symmetrically. Each patient grasps the handles or the affected hand is strapped to the handle depending on the severity of the deficits. Patients trained both forearm pronation/supination or wrist flexion/extension each 30 minutes, respectively. The whole training program consisted of four 15 minute session with BSAT and 10 minute rest was given at every session. Periods consisted of bilateral repetitive movements that were simultaneous for 1 and 3 and alternating for period 2 and 4. Movements were timed to a metronome set at the participant’s preferred speed that was established at the first session by

asking patients to assume a self-selected speed (Speed 1) and the other session was slow speed (Speed 2). Table 3.2 shows the training program design for this study.

Table 3.2. The training program design for this study.

Wrist flexion/extension	15 min. excercise (speed 1)	10 min. rest	15 min. excercise (speed 2)	10 min. rest
Forearm (pronation/supination)	15 min. excercise (speed 1)	10 min. rest	15 min. excercise (speed 2)	10 min. rest

3.4. Hypotheses

We made several hypotheses that repetitive bilateral training improves motor function in hemiparetic stroke. These hypotheses were suggested as follows:

1) By the 6 week training with the BSAT, the affected arm motor function as assessed by Fugl-Meyer (FM) and manual muscle test (MMT) (eg. post-stroke motor recovery test) would improve.

2) By the 6 week training with the BSAT, the spasticity of affected, wrist and forearm, assessed by modified Ashworth's scale (MAS), would decrease.

3) By the 6 week training with the BSAT, the reaction time of affected wrist flexor and extensors, measured by surface EMG activity, would decrease.

4) By the 6 week training with the BSAT, the coactivation pattern between affected wrist flexor and extensors, measured by surface EMG activity, would decrease.

5) By the 6 week training with the BSAT, the cortical map of contralateral somatosensory area (primary sensory-motor cortex (SMC), premotor cortex (PMC), supplementary motor area (SMA) and so on during affected limb movements, measured by fMRI, would change. In addition, fractional anisotropy (FA) of diffusion tensor imaging (DTI) would change.

4. Evaluation on Motor Recovery: Clinical Assessments

4.1. Introduction

Clinical evaluations have been used extensively to quantify motor recovery. They are ease to perform, inexpensive, and can be conducted usually in a short time. More importantly, the examiner can account for the confounding influencing factors that affect the state of spasticity at any given moment.

Lum et al. [1] presented robot-assisted mirror image movement exercises in the daily repetitive training and compared results with those by the conventional physical therapies. They reported that mirror image movement exercises improve strength and reaching kinematics in the arm of chronic hemiparetic subjects for a 2-month period. Fasoli et al. [2] also demonstrated that the robotic therapy could complement other treatment approaches in persons with moderate to severe chronic impairments from measuring the modified Ashworth scale (MAS), Fugl-Meyer assessment (FMA) and motor status scale (MSS) scores of the upper extremity [3]. Whitall et al. [4] reported that 6 weeks of bilateral exercises with a bilateral arm trainer improved functional motor performance of the affected upper extremity as well as small changes in isometric strength and the range of motion.

The purpose of this chapter was to determine the effect of the bilateral symmetrical motion trainer (BSAT) on the clinical motor impairment and the physical disability, as measured by FMA, MAS, and manual muscle test (MMT) scores in chronic hemiparetic patients before and after the 6-week training.

4.2. Background

4.2.1. Fugl-Meyer (FM) Scale

An alternative evaluation method based on Brunstrom's qualitative of motor recovery was developed by Fugl-Meyer and colleagues [5]. The Fugl-Meyer (FM) scale differs from that of Brunstrom in that it is qualitative and be statistically analyzed for both research and clinical work. The evaluation based on the recovery stages after the onset of the ictus. The test requires the subject to perform motor acts graduated in complexity and requires increasingly fine neuromuscular control. The items assessed are muscle tone, state of motor recovery, movement pattern (synergy), movement speed, and prehension pattern of the limb (see the Appendix A). A cumulative numerical scoring system for measurement is sued to quantify the level of motor recovery. The FM scale uses an ordinal scoring system in which detail is rated 0 (cannot be performed), 1 (can be partly performed), or 2 (can be performed faultlessly). Maximum scores rage from 0 (flaccidity) to 66 (normal motor function) [5, 6].

The FM scale has been demonstrated to valid and reliable (intra-and intertester) in the assessment of motor function in people with hemiplegia, although not necessarily in those with spasticity. It is easy to perform and takes approximately 20 minutes to conduct. It is objective and accurate. More important, Karz and coworkers showed that FM scale correlated well with other clinical measures of spasticity (eg., the Ashworh scale) [6, 7].

4.2.2. Modified Ashworth Scale (MAS)

Ashworth was the first to devise an objective means to assess the severity of spasticity. The Ashworth scale involves manually moving a limb

through the rage of motion to stretch specific muscle groups. The resistance encountered during the passive muscle stretch is documented on a five-point ordinal scale from 0 to 4, with 0 representing normal tone, and 4 depicting severe spasticity [8].

Bohannon and Smith [9] investigated the interrater reliability of a modified version of the Ashworth scale. They tested elbow flexor muscle spasticity in 30 patients with interacranial lesion. The original Ashworth scale was modified because the lower end of the scale was indiscrete (Table 4.1).

Table 4.1. Modified Ashworth scale for grading spastcity [9].

Grade	Description
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part is moved in flexion of extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the reminder (less than half) of the range of motion
2	More marked increase in muscle tone through most of the range of motion, but affected part easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part rigid in flexion or extension

Bohannon and Smith's research [9] showed that the MAS had a high interrater reliability (86.7% agreement between raters). Therefore, the MAS has become the clinical testing protocol to which all newer tests are compared.

A major difficulty with the Ashworth scale and other tests like it is that with repeated testing, both and low scores within an overall rage of scores cluster toward the mean. This tendency for scores migrate toward the mean is termed ststistical regression. Statistical regression has been identified as a major source of secondary variation or evaluation [10]. Therefore, the validity of the evaluation decrease as the number of times the test is given increases.

Clinicians should be instructed to limit the administration of these tests to as few times as possible.

4.2.3. Manual Muscle Testing (MMT)

Early clinical tests of muscular strength involved the use of manual resistance by the therapist. They have been considered an useful diagnostic and prognostic tool [11].

MMT is simple and essentially reflects anatomic and biomechanical principles. Thus, it is a measure of impairment rather than function, and while its use is most common for persons with disorders of muscles or peripheral neural systems. It has been used for patients with central nervous system problems, including brain injury [12].

Table 4.2 shows the grading system used in manual muscle testing.

Table 4.2. Grading system used in manual muscle testing (MMT).

Grading Symbols					Criteria for Muscle Grading
Normal	10	5	5.0	100%	Can move or hold against gravity and maximum resistance
Good+	9	4+	4.5	80%	Can raise part against gravity and an external resistance
Good	8	4+	4.0		
Good–	7	4–	3.66		
Fair+	6	3+	3.33	50%	Can raise part against gravity
Fair	5	3	3.0		
Fair–	4	3–	2.66		
Poor+	3	2+	2.33	20%	Produces movements with gravity eliminated
Poor	2	2	2.0		
Poor–	1	2–	1.5		
Trace	T	1	1.0	5%	A flicker or feeble contraction
Zero	0	0	0.0	0%	No contraction

Fundamentals of MMT is the notion that the muscle, either individually or as a group, has a specific action on a joint. Based on this premise and utilizing the effects of gravity and manual resistance provided by the therapist

as external forces, a patient is positioned in such a way that one muscle or group muscles is primarily responsible for moving a joint through a specific range of motion (ROM). Grading of muscle strength is then based on the arc of movement produced by the muscle and amount of external resistance to the motion. The muscle or tendon is palpated by the therapist to ensure that the muscle of interest is contracting and no substitution of muscle activity is responsible for the specific movement test.

4.3. Materials and Methods

4.3.1. Data Assessment

A pretest and posttest consisted on the following items: (1) The Fugl-Meyer upper-limb motor performance section test was selected because it assesses impairments in sensorimotor function. This test has been shown to be valid and reliable [13,14] and it correlates well with inter-joint upper-limb coordination measurements in the upper-limb of patients after stroke [15]. (2) We assessed elbow, wrist, and finger spasticity with the modified Ashworth scale (MAS). With the patient prone, passive extension of the elbow, wrist, and metacarpal finger joints were tested and rated from 0 to 5. (3) We assessed the functional strength of shoulder, elbow, forearm, wrist, and finger with the manual muscle test (MMT). It was based on a 5 point ordinal scale grading degree of independence.

During the 6-week training with the BSAT, FM, MAS, and MMT in participated patients were measured every two weeks. All tests were measured by a physical therapist.

4.3.2. Data Analysis

The initial analyses were one-way *t*-test to compare measures on the depedent reriables before and after training (at 6 weeks of training). In FM score, significant results were further investigated post hoc (Tukey honestly significant difference). Data of ordinal scales were presented as median and interquartile ranges, any within group differences before and after training were calculated within the help of nonparametric the Wilcoxon test. An alpha level of <0.05 was used as the level of significance. All statistical analyses were performed by SPSS 10.0 (SPSS, Chicago, USA).

4.4. Results

4.4.1. Fugl-Meyer (FM) Score

Table 4.3 shows changes in motor function such as FM score during the 6-week training. In all eight patients, FM (range: 0-66) of the affected hands were significantly improved after the 6-week training program ($p<0.05$) (Figure 4.1). Post hoc analysis revealed that the before-training score were higher than after-training score (increase of 44%) (Figure 4.2).

4.4.2. Modified Ashworth Scale (MAS)

Table 4.4 represents change in clinical score of MAS on the affected upper-limb of eight chronic patients before and after training. MAS scores of the affected elbow, wrist, and finger joints decreased continuously. The shoulder joint spasticity did not change considerably.

Table 4.3. Changes in clinical score of FM on the affected upper-limb of 8 chronic hemiplegic patients before, 2, 4, and 6 weeks of training with the BSAT.

Patient	FM 0-2-4-6 (week)	dFM
1/KSH	25 - 29 - 33 - 34	9
2/MCH	35 - 49 - 54 - 56	21
3/YBJ	20 - 25 - 27 - 32	12
4/JYJ	26 - 27 - 37 - 38	12
5/KDH	43 - 44 - 46 - 49	6
6/CJS	15 - 17 - 21 - 22	7
7/KYS	18 - 18 - 25 - 28	10
8/KYH	23 - 23 - 27 - 33	10
Average	25.8 - 27.8 - 33.8 - 36.5	10.9

dFM = last FM score-initial FM score.

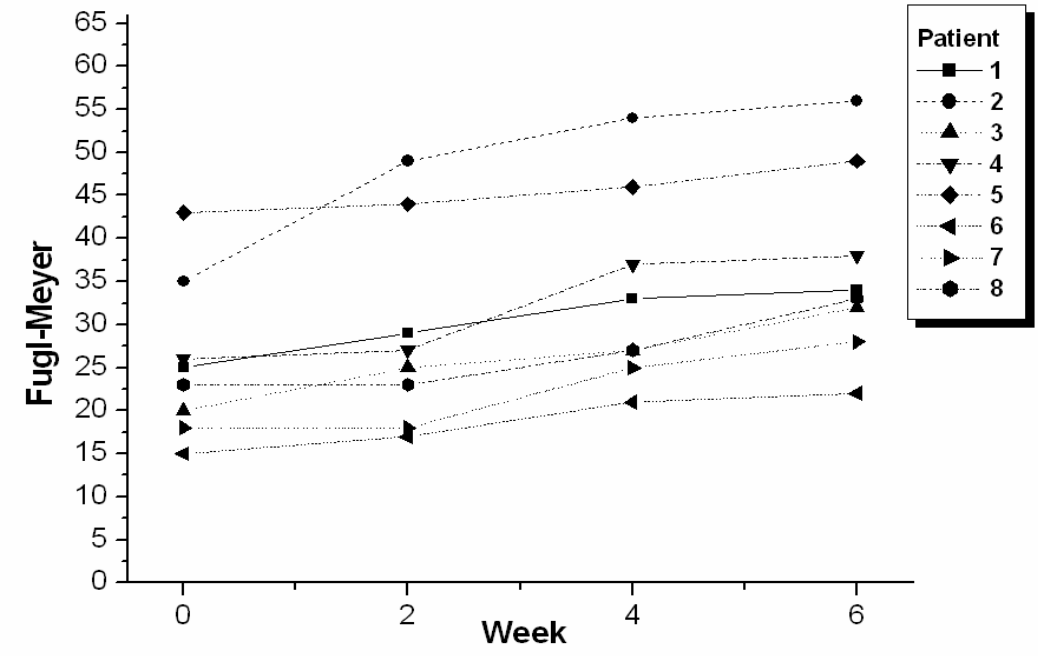


Figure 4.1. Changes in clinical score of FM on the affected upper-limb of 8 chronic hemiplegic patients.

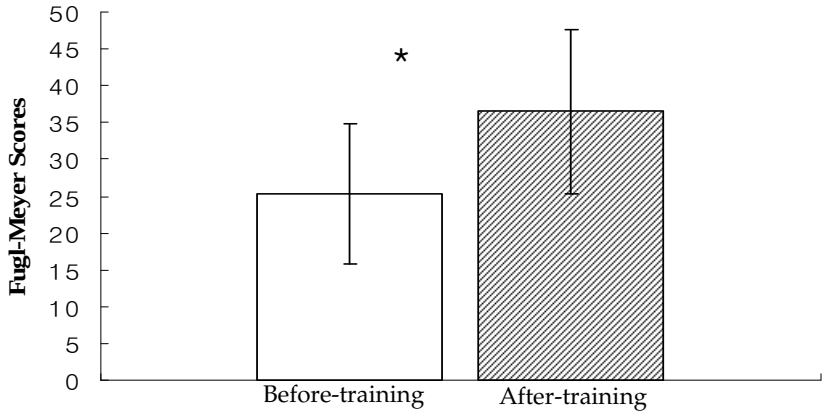


Figure 4.2. Median FM scores (range 0~66) of the affected upper-limb of 8 chronic hemiparetic subjects before and after 6 weeks of BSAT. Significant differences exist between before-training and after-training ($p<0.05$).

Table 4.4. Changes in clinical score of MAS on the affected upper-limb of 8 chronic hemiplegic patients before, 2, 4, and 6 weeks of training with the BSAT.

Patient	Shoulder		Elbow		Wrist		Finger	
	Flex.	Ext.	Flex.	Ext.	Flex.	Ext.	Flex.	Ext.
1/KSH	1^0-1^0	0-0	1^+-1^+	0-0	1^+-1^+	1^+-1^0	1^0-1^0	1^+-1^0
	1^0-1^0	0-0	1^0-1^0	0-0	1^0-1^0	1^0-1^0	1^0-1^0	1^0-1^0
2/MCH	0-0	1^0-1^0	0-0	1^+-1^+	1^+-1^+	0-0	0-0	1^+-1^0
	0-0	1^0-1^0	0-0	1^0-1^0	1^0-1^0	0-0	0-0	1^0-1^0
3/YBJ	2^0-2^0	0-0	2^0-2^0	1^+-1^+	0-0	1^+-1^+	1^0-1^0	2^0-2^0
	2^0-1^+	0-0	1^+-1^+	1^+-1^0	0-0	1^0-1^0	1^0-1^0	1^+-1^+
4/JYJ	1^0-1^0	0-0	1^+-1^+	1^+-1^+	1^+-1^+	1^+-1^+	1^+-1^+	2^0-2^0
	1^0-1^0	0-0	1^+-1^0	1^0-1^0	1^0-1^0	1^0-1^0	1^0-1^0	1^+-1^0
5/KDH	1^0-1^0	1^0-1^0	1^+-1^+	1^+-1^+	1^+-1^+	1^+-1^+	1^+-1^+	1^+-1^+
	1^0-1^0	1^0-1^0	1^+-1^0	1^0-1^0	1^0-1^0	1^+-1^0	1^0-1^0	1^0-1^0
6/CJS	2^0-2^0	0-0	2^0-2^0	1^+-1^+	1^0-1^0	1^+-1^+	1^0-1^0	2^0-2^0
	2^0-2^0	0-0	1^+-1^+	1^0-1^0	1^0-1^0	1^0-1^0	1^0-1^0	1^+-1^0
7/KYS	1^0-1^0	0-0	0-0	1^+-1^+	0-0	1^+-1^+	0-0	1^+-1^+
	1^0-1^0	0-0	0-0	1^0-1^0	0-0	1^+-1^0	0-0	1^0-1^0
8/KYH	0-0	0-0	1^+-1^+	0-0	0-0	1^+-1^+	0-0	1^+-1^+
	0-0	0-0	1^+-1^+	0-0	0-0	1^0-1^0	0-0	1^0-1^0
Average	1.3-1.3	0.3-0.3	1.8-1.8	1.5-1.5	1.3-1.3	1.8-1.6	0.9-0.9	2.4-2.1
	1.3-1.3	0.3-0.3	1.4-1.2	0.9-0.8	0.7-0.7	1.1-0.8	0.6-0.6	1.4-.1.1

Flex.= flexion, Ext.= extension.

4.4.3. Manual Muscle Testing (MMT)

Table 4.5 describes change in clinical score of MMT on the affected upper-limb of eight chronic patients before and after training. The MMT scores of the affected shoulder, elbow, wrist, and forearm joints increased continuously. The muscle strength of finger joint, distal muscle did not change considerably.

4.5. Discussion

After a 6-week training program using the BSAT, significant improvements on FM, MAS, and MMT tests with respect to the functional ability, muscle spasticity and the muscle strength were observed.

A rationale regarding the reason of the effectiveness of the active BSAT training can be found in the motor behavior and neurophysiology literature. Practicing bilateral movements in synchrony may result in a facilitation effect from the unaffected arm to the affected arm. For example, when bilateral movements are initiated simultaneously, arms act as a unit superseded individual arm action [16,17], indicating that both arms are strongly linked as a coordinated unit in the brain. In addition, it is well known that even if one arm or hand is activated with moderate force, this can produce motor overflow in the other such that both arms are engaged in the same or opposite muscle contractions although at difference level of force [18,19].

Furthermore, studies have shown that learning a novel motor skill with one arm will result in a subsequent bilateral transfer of skill to other arm [20]. The present experiments suggest a strong neurophysiological linkage in the central nervous system that explains how bilateral movements may benefit motor learning.

Table 4.5. Changes in clinical score of MMT on the affected upper-limb of 8 chronic hemiplegic patients before, 2, 4, and 6 weeks of training with the BSAT.

Manual Muscle Test 0-2-4-6 (week)									
Patient		1	2	3	4	5	6	7	8
Shoulder	Flexor	3^{+} - 3^{+}	4^{-} - 4^{+}	3^{-} - 3^{+}	4^{+} - 4^{+}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{0} - 2^{0}	3^{-} - 3^{-}
		3^{+} - 4^{0}	4^{+} - 4^{+}	3^{+} - 3^{+}	4^{+} - 4^{+}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{0} - 2^{0}	3^{-} - 3^{-}
	Extensor	3^{-} - 3^{+}	3^{0} - 4^{-}	3^{-} - 3^{-}	3^{-} - 3^{-}	3^{-} - 3^{-}	2^{0} - 2^{0}	1^{0} - 2^{0}	3^{-} - 3^{-}
		3^{0} - 3^{+}	4^{-} - 4^{0}	3^{+} - 3^{+}	3^{-} - 3^{-}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{0} - 2^{0}	3^{-} - 3^{-}
	Abductor	3^{-} - 3^{0}	4^{-} - 3^{+}	3^{0} - 3^{0}	3^{-} - 3^{-}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{0} - 2^{0}	3^{-} - 3^{-}
		3^{+} - 4^{-}	3^{+} - 4^{-}	3^{+} - 3^{+}	3^{-} - 3^{-}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{0} - 2^{0}	3^{-} - 3^{-}
	Horizontal abduction	3^{-} - 3^{+}	3^{+} - 4^{+}	3^{-} - 3^{0}	3^{-} - 3^{-}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{-} - 2^{0}	3^{-} - 3^{-}
		3^{0} - 4^{-}	4^{+} - 4^{+}	3^{+} - 3^{+}	3^{-} - 3^{-}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{+} - 2^{+}	3^{-} - 3^{-}
	Horizontal adduction	3^{-} - 3^{+}	3^{+} - 4^{+}	3^{-} - 3^{0}	2^{+} - 2^{0}	3^{-} - 3^{-}	2^{0} - 2^{0}	3^{-} - 2^{0}	3^{-} - 3^{-}
		3^{+} - 4^{-}	4^{+} - 4^{+}	3^{+} - 3^{+}	2^{0} - 2^{+}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{+} - 2^{+}	3^{-} - 3^{-}
	Internal rotation	3^{-} - 3^{-}	3^{-} - 3^{0}	2^{0} - 2^{+}	2^{0} - 2^{0}	3^{-} - 3^{-}	1^{0} - 1^{0}	2^{0} - 2^{0}	3^{-} - 3^{-}
		3^{-} - 4^{0}	3^{0} - 3^{0}	3^{-} - 3^{-}	2^{0} - 2^{+}	3^{-} - 3^{-}	2^{0} - 2^{0}	2^{0} - 2^{0}	3^{-} - 3^{-}
	External rotation	3^{-} - 3^{+}	3^{-} - 3^{0}	2^{0} - 2^{+}	2^{0} - 2^{0}	3^{-} - 3^{-}	1^{0} - 1^{0}	2^{0} - 2^{0}	2^{0} - 2^{0}
		3^{-} - 3^{0}	3^{0} - 3^{0}	2^{+} - 2^{+}	2^{0} - 2^{+}	3^{-} - 3^{-}	1^{0} - 2^{0}	2^{0} - 2^{0}	3^{-} - 3^{-}
Elbow	Flexor	3^{+} - 4^{0}	3^{+} - 4^{+}	3^{-} - 3^{+}	2^{0} - 4^{-}	3^{+} - 3^{+}	2^{0} - 2^{0}	2^{-} - 2^{0}	3^{+} - 3^{+}
		4^{0} - 4^{0}	4^{+} - 4^{+}	3^{+} - 3^{+}	4^{-} - 4^{0}	3^{+} - 3^{+}	2^{0} - 2^{0}	2^{0} - 3^{-}	3^{+} - 3^{+}
	Extensor	3^{-} - 4^{0}	3^{+} - 4^{+}	3^{-} - 3^{-}	2^{0} - 4^{-}	3^{+} - 3^{+}	2^{0} - 2^{0}	2^{-} - 2^{0}	3^{+} - 3^{+}
		4^{-} - 4^{0}	4^{+} - 4^{+}	3^{0} - 3^{0}	4^{-} - 4^{-}	3^{+} - 3^{+}	2^{0} - 2^{0}	2^{0} - 3^{-}	3^{+} - 3^{+}
Forearm	Supination	1^{0} - 2^{+}	2^{-} - 1^{0}	1^{0} - 1^{0}	1^{0} - 1^{+}	3^{-} - 3^{-}	1^{0} - 1^{0}	2^{-} - 2^{0}	2^{0} - 2^{0}
		1^{+} - 1^{+}	1^{+} - 2^{0}	1^{0} - 1^{0}	1^{+} - 2^{-}	3^{+} - 5^{0}	2^{0} - 2^{0}	2^{+} - 3^{-}	2^{0} - 3^{-}
	Pronation	2^{-} - 2^{+}	2^{0} - 3^{-}	1^{0} - 2^{-}	2^{0} - 1^{0}	3^{-} - 3^{-}	1^{0} - 1^{0}	2^{-} - 2^{0}	2^{0} - 2^{0}
		2^{0} - 2^{0}	3^{-} - 3^{0}	2^{-} - 1^{0}	1^{+} - 2^{-}	3^{+} - 3^{+}	1^{0} - 2^{0}	2^{+} - 3^{-}	3^{-} - 3^{-}
Wrist	Flexor	2^{0} - 1^{0}	3^{+} - 3^{+}	1^{0} - 2^{-}	1^{0} - 1^{+}	3^{-} - 3^{-}	2^{-} - 2^{-}	1^{0} - 1^{0}	2^{0} - 2^{0}
		1^{0} - 1^{+}	3^{+} - 3^{+}	2^{0} - 1^{+}	1^{+} - 1^{+}	3^{+} - 3^{+}	2^{+} - 2^{+}	2^{+} - 3^{-}	2^{0} - 3^{-}
	Extensor	1^{0} - 1^{0}	3^{+} - 3^{+}	1^{0} - 1^{0}	0^{0} - 1^{0}	3^{-} - 3^{-}	2^{-} - 2^{-}	1^{0} - 1^{0}	2^{0} - 2^{0}
		1^{0} - 1^{+}	3^{+} - 3^{+}	1^{0} - 1^{0}	1^{+} - 1^{+}	3^{+} - 3^{+}	2^{+} - 2	2^{+} - 2^{+}	3^{-} - 3^{-}
Finger	MP flexor	2^{-} - 2^{-}	3^{0} - 4^{-}	1^{0} - 1^{0}	0^{0} - 1^{0}	2^{-} - 2^{-}		1^{0} - 1^{0}	1^{0} - 1^{0}
		2^{0} - 2^{0}	4^{0} - 4^{0}	1^{0} - 2^{0}	1^{0} - 2^{0}	2^{-} - 2^{-}		1^{0} - 1^{0}	1^{0} - 1^{0}
	IP flexor	2^{-} - 2^{-}	3^{-} - 3^{+}	1^{0} - 1^{0}	0^{0} - 1^{0}	2^{-} - 2^{-}	Not	1^{0} - 1^{0}	1^{0} - 1^{0}
		2^{-} - 2^{0}	4^{+} - 4^{+}	1^{0} - 1^{0}	1^{0} - 2^{0}	2^{-} - 2^{-}	measured	1^{0} - 1^{0}	1^{0} - 1^{0}
	MP extensor	0^{0} - 0^{0}	2^{-} - 3^{0}	0^{0} - 0^{0}	0^{0} - 1^{0}	2^{-} - 2^{-}		1^{0} - 1^{0}	1^{0} - 1^{0}
		1^{0} - 1^{0}	3^{0} - 3^{0}	0^{0} - 1^{0}	1^{0} - 1^{0}	2^{-} - 2^{-}		1^{0} - 1^{0}	1^{0} - 1^{0}

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5. Evaluation on Motor Recovery: EMG

5.1 Introduction

Hemiparesis resulting from stroke is likely to be associated with a reduction in the numbers of functional corticospinal and corticobulbar fibers projection to the brainstem and spinal cord. Because these cortical projections carry instructions about voluntary movement to the cord, either loss of connectivity or reduced discharge in these pathways likely to limit the rage of possible voluntary movement patterns on the affected side [1].

Spasticity is attributed to increased muscle tone associated with hyperreflxexia according to Lance [1] who defined spasticity as a `velocity-dependent increase of tonic stretch reflexes with exaggerated tendon jerks'. Previous efforts to quantify spastic hypertonia have concentrated on clinical scales [2, 3], electromyographic and biomechanical analysis of limb resistance to passive or voluntary movements [4, 5], gait analysis [6] and a host of electrophysiological reflex studies [1, 7]. In spite of this broad range of techniques, no uniformly useful objective measurements have emerged in the clinical practice. An objective, quantitative measure would achieve widespread clinical acceptance only if its variations broadly paralleled an accepted clinical scale. An important criterion that objective parameters have to fulfill to gain everyday clinical acceptance is consistency and sensitivity [8]. Clinical scales, such as those proposed by Ashworth [2], offer qualitative information, but lack temporal and interexaminer reproducibility and suffer from a clustering effect in that most of the patients are grouped within the middle grades [8]. Nevertheless they have been and continue to be widely used in the study of spasticity [9] and are the present yardstick against which newer, more exact methods must be compared.

Many stroke survivors experience reasonable motor recovery of their proximal upper limb, but limitation distal recovery. For those with some hand function, evaluating their therapeutic methods such as constraint induced therapy [10] and electrical stimulation [11] may provide additional recovery. However, many stroke survivors do not experience adequate distal recovery or are unresponsive to new therapeutic techniques.

In order to expand treatment strategies, the nature of hemiparesis and its relationship to clinical outcomes must to be further elucidated using quantifiable methods. Prior electomyographic (EMG) studies among stroke survivors demonstrated significant delay in initiation [12-14] and termination of muscle contraction [12, 13], gaps in EMG interference patterns [15], abnormal co-contraction of agonist and antagonist muscles [16, 17], and abnormal co-activation of synergistic muscles [18]. However, the clinical implications of these abnormalities remain uncertain.

The purpose of this Chapter is to describe the relationship between delay in initiation/termination and co-contraction of muscle contraction in the upper limb of chronic hemiparetic subjects, and clinical measurements of motor impairment and physical disability after the BSAT training.

5.2. Materials and Methods

5.2.1. EMG Measurement

EMG activities were recorded from conductive solid-gel disposable Ag/AgCl transcutaneous recording electrodes (Noraxon, AZ, USA). Surface EMGs were recorded from the flexor carpi radialis (FCR) and the extensor carpi radialis (ECR) muscles. Active electrodes were placed over the muscle belly and the reference electrode over the muscle tendon (Figure 5.1) [19].

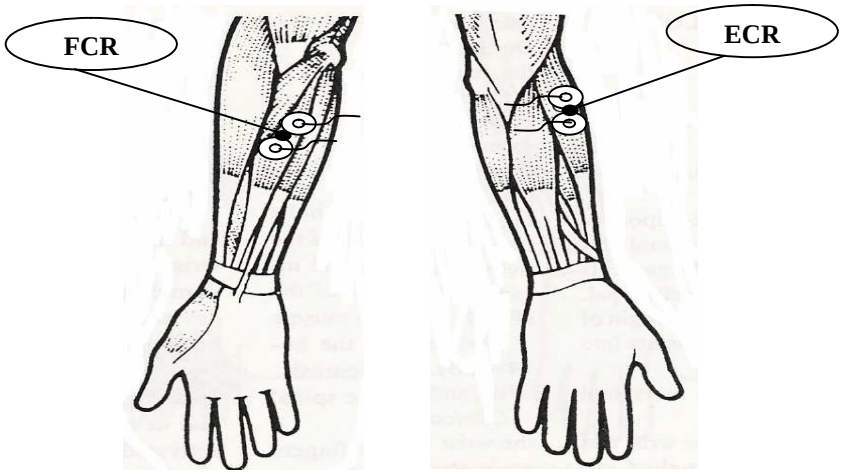


Figure 5.1. Electrode displacement for the FCR and ECR with forearm supine (left) and prone (right).

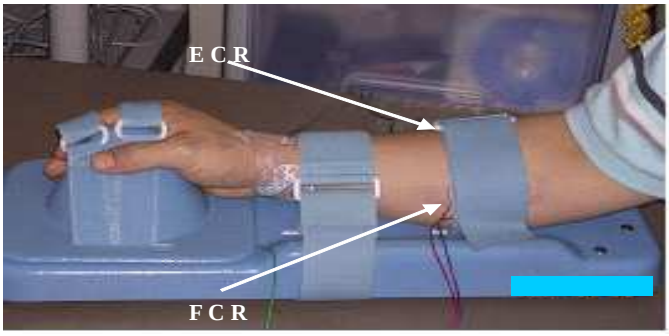


Figure 5.2. The apparatus for positioning of the arm and forearm for EMG recording during isometric wrist flexion and extension.

During the experiment, the subject's arm was placed on an apparatus that stabilized the wrist in a neutral position (Figure 5.2). However, we elected not to force the neural wrist position on the all subjects to minimize baseline EMG activity in subjects with hypertonic of wrist flexions or contractures. The apparatus allowed for adjustment of wrist angle. The elbow angle was not constrained but was maintained at approximately 120 degrees. Each subject was instructed to contract the wrist flexor or extensor as forcefully and quickly

as possible against the confinement of the apparatus in response to an audible beep, and relax the muscle as quickly as possible as soon as the beep terminated. For wrist flexion, all subjects were asked to response to seven audible beeps consisting of five trials of 3s contraction. The trials were presented in a balanced random order to minimize subject anticipation. The procedure was repeated for wrist extension.

Delay in initiation of the EMG signals was defined at the time interval between onset of the audible beep and onset the of the EMG signal. Delay in termination of the EMG signal was defined as the time interval between termination of the audible beep and termination of the EMG signal (Figure 5.3).

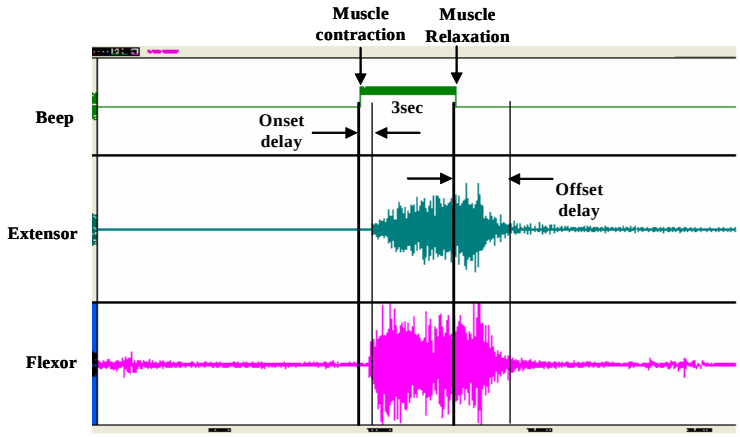


Figure 5.3. Representative EMG raw data during isometric wrist contraction. Delay in initiation of EMG signal was defined as the time interval between onset of the audible beep and onset of the EMG signal. Delay in termination of EMG signal was defined as the time interval between termination of the audible beep and termination of the EMG signal.

Data acquisition hardware included MP 150 system (Biopac system, Inc., CA, USA). Amplifier gain was set at 1,000 with sampling frequency of 1,080 Hz was used.

For determination of the delay of muscle contraction, EMG signals were band-pass filtered (10-1000Hz) and full-wave rectified. The baseline of the EMG signal was defined as the average activation level for 3 seconds prior to muscle contraction and maintained the above baseline at least during 25 milliseconds. Then, the onset was defined when the rectified signals first exceeded the baseline plus two standard deviations.

In addition, the co-contraction ratio of flexor and extensor muscles was quantified during isometric wrist flexion/extension. Since the muscle force is almost proportional to the integrated EMG (*IEMG*) [20], we first measured muscle activations in agonist and antagonist during wrist movements.

$$EMG_N = \frac{EMG_m}{EMG_{m\_rest}} \tag{5-1}$$

where EMG_N represents a normalized value of EMG signals during wrist movements. EMG_m indicates muscle activations during wrist movements; and EMG_{m_rest} indicates a value of EMG_m measured during relaxation.

$$IEMG = \sum_{n=0}^{N} \left(\overline{EMG_{Nn}} \right) \Delta t \tag{5-2}$$

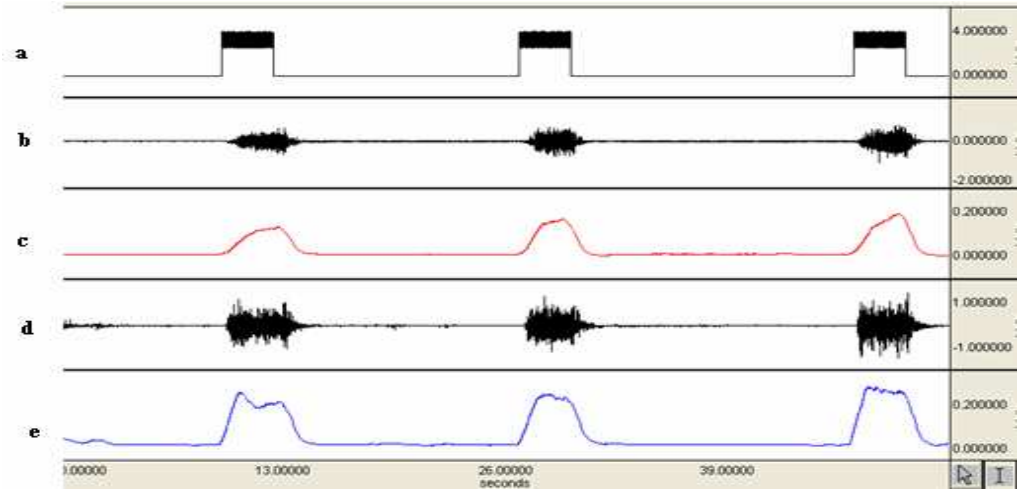
where N indicates the number of sampled data in experimental trials and Δt is a wrist contraction time.

$$Co-contraction\ ratio = \frac{IEMG_n^{ANTA}}{IEMG_n^{AGO}} \tag{5-3}$$

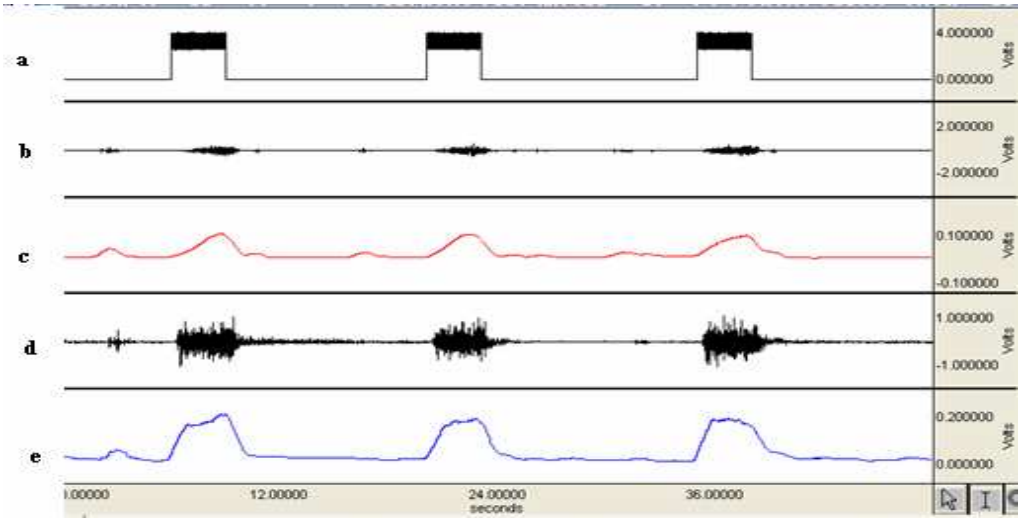
where $IEMG_n^{AGO}$ indicates a IEMG of agonist and $IEMG_n^{ANTA}$ is a *IEMG* of antagonist during wrist movements.

During the 6-week training, we measured EMG parameters in patients were measured every two weeks.

Figure 5.4~5.5 show the EMG data of different muscles during affected wrist movements.

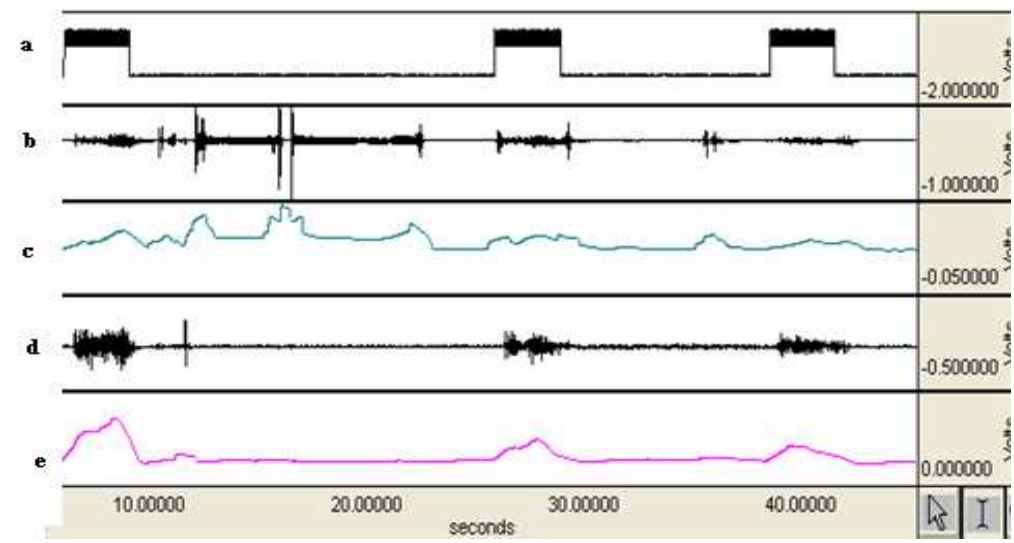


(A) EMG signal before the training

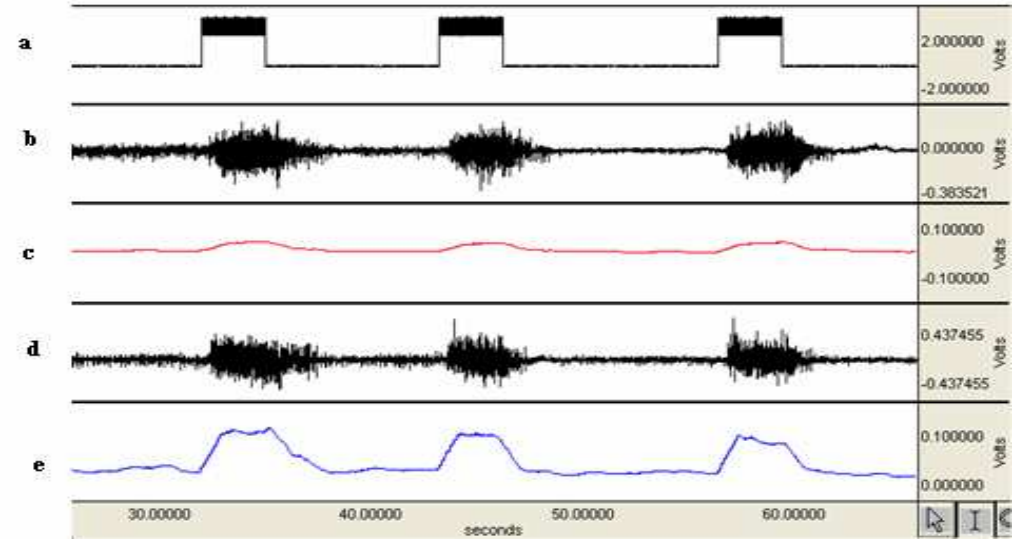


(B) EMG signal after the training

Figure 5.4. EMG data of different muscles during isometric affected wrist flexion in Patient 1. (a) beep signal, (b) wrist extensor signal, (c) *IEMG* of wrist extensor, (d) wrist flexor signal, (e) *IEMG* of wrist flexor.



(A) EMG signal before the training



(B) EMG signal after the training

Figure 5.5. EMG data of different muscles during isometric affected wrist flexion in Patient 4. (a) beep signal, (b) wrist extensor signal, (c) *IEMG* of wrist extensor, (d) wrist flexor signal, (e) *IEMG* of wrist flexor.

5.2.2. Data Analysis

EMG data was analyzed using two separate *t*-tests. The first test determined the effects of three experiment-specific factors on delay in onset/offset and co-contraction ratio, which included arm side (control, unaffected and affected), direction of wrist movement (flexion and extension) with unpired *t*-test. The second test determined the differences between delay in onset/offset included arm side (control, unaffected and affected), direction of wrist movement (flexion and extension) using in paired *t*-test. One-way repeated ANOVA was used to compare before-training and after-training (at 6 weeks of training using the BSAT). Finally, Spearman's correlation coefficients, describing the relationship between EMG parameters and motor recoveries, were obtained. We used the nonparametric test of the ordinal nature of Fugl-Meyer score (FM). An alpha level of <0.05 was used as the level of significance. Representative scatter diagrams relating EMG parameters and clinical measures were obtained. All statistical analyses were performed with SPSS 10.0 (SPSS, Chicago, USA).

5.3. Results

5.3.1. EMG Onset Delay and Offset Delay

Table 5.1 shows onset/offst delay for wrist flexion/extension movements during the 6-week training with the BSAT.

As shown in Table 5.1, after the 6-week training, the unaffected hands, as well as the control group, did not show significant changes in onset/offset

Table 5.1. Changes in EMG onset/offset delay. included control, unaffected and affected side, direction of wrist movement before, 2, 4, and 6 weeks of training.

Side	No.	Wrist flexion 0-2-4-6 (week)		Wrist extension 0-2-4-6 (week)	
		$Delay_{on}$ (s)	$Delay_{off}$ (s)	$Delay_{on}$ (s)	$Delay_{off}$ (s)
Control		0.17±0.11	0.31±0.13	0.22±0.17	0.21±0.07
Un affeced	1	0.43-0.30	0.45-0.41	0.46-0.32	0.53-0.49
		0.34-0.30	0.64-0.41	0.33-0.33	0.59-0.42
	2	0.30-0.35	0.34-0.44	0.22-0.23	0.60-0.38
		0.29-0.26	0.29-0.29	0.31-0.38	0.49-0.68
	3	0.30-0.27	1.13-0.59	0.24-0.26	0.70-0.45
		0.29-0.28	0.79-0.64	0.24-0.20	0.47-0.23
	4	0.48-0.51	0.65-0.58	0.34-0.32	0.79-0.55
		0.37-0.32	0.54-0.47	0.41-0.30	0.56-0.55
Average		0.38-0.34	0.64-0.51	0.32-0.28-	0.65-0.46
		0.32-0.37	0.52-0.46	0.32-0.28	0.52-0.47
Affected	1	0.51-0.41	0.71-0.64	0.78-0.50	1.05-0.64
		0.37-0.33	0.60-0.58	0.44-0.40	0.62-0.60
	2	0.56-0.50	1.87-0.95	0.68-0.44	0.86-0.81
		0.36-0.37	0.92-0.76	0.33-0.32	0.69-0.57
	3	0.76-0.73	1.80-1.26	1.04-0.55	1.19-1.15
		0.52-0.50	0.86-0.74	0.74-0.49	0.93-0.72
	4	0.65-0.60	1.67-0.86	1.16-0.72	1.67-1.14
		0.49-0.40	0.74-0.77	0.57-0.52	1.18-1.07
Average		0.62-0.57	1.51-0.93	0.92-0.56	1.19-0.94
		0.44-0.40	0.78-0.76	0.52-0.44	0.86-0.75

$Delay_{on}$: Onset delay on muscle contraction, $Delay_{off}$: Offset delay on muscle contraction

delays and co-contraction ratio for wrist flexion/extension. However, affected hands showed significantly decreased onset/offset delays in muscle contraction after the 6-week training in both wrist flexion and extension ($p<0.05$). Table 5.2 shows the effects of three experiment-specific factors on onset delay or offset delay in control, unaffected and affected before training.

Before the training, onset/offset delays on the affected side were significantly larger than those in the control group and unaffected side. Onset/offset delays in the unaffected side were significantly larger than those on the control group.

Table 5.2. Differences of onset/offset delay which included control, unaffected and affected as direction of wrist movement before training.

Sides	Wrist flexion		Wrist extension	
	$Delay_{on}$	$Delay_{off}$	$Delay_{on}$	$Delay_{off}$
Control	0.17±0.11	0.31±0.13	0.22±0.17	0.21±0.07
Unaffected	0.38±0.09	0.64±0.34*	0.32±0.11	0.65±0.11*
Affected	0.62±0.10*†	1.51±0.54*†	0.92±0.22*†	1.19±0.34*†

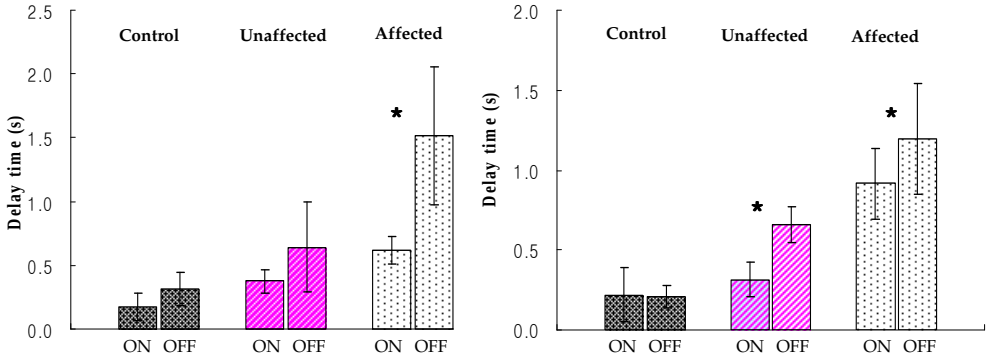
* Significantly different from control sides with independent t-test ($p<0.05$).
† Significantly different from unaffected sides with independent t-test ($p<0.05$).

Figure 5.6 shows the differences between onset/offset delay included control, unaffected and affected before training. Offset delay of affected sides was significantly larger than onset time in both wrist flexion and extension ($p<0005$). In unaffected side, offset delay was significantly larger than onset time in wrist extension (Figure 5.6 (b)).

5.3.2. Co-Contraction Ratio

Table 5.3 shows changes of the co-contraction ratio for wrist flexion/extension movements during the 6-week training with the BSAT.
Co-contraction ratio of muscle contraction in the affected side was significantly larger than those in the control group ($p<0.05$).

As shown in Table 5.3, after the 6-week training, the unaffected hands, as well as the control group, did not show significant changes in co-contraction ratio for wrist flexion/extension. However, affected hands showed significantly decreased co-contraction ratio in muscle contraction ($p<0.05$).



(a) (b)

Figure 5.6. Comparison of delay in contraction onset and offset of the wrist flexor (a) and extensor muscle (b). Values of the bar are mean±SD. ON: onset delay, OFF: offset delay.
* Significant difference between onset and offset delay ($p<0.05$).

Table 5.3. Changes of the co-contraction ratio in control, unaffected and affected side before, 2, 4, and 6 weeks of training.

Side	No.	Co-contraction ratio (CCR)	
		Wrist flexion 0-2-4-6 (week)	Wrist extension 0-2-4-6 (week)
Control		0.15±0.04	0.15±0.08
Un affeced	1	0.34 - 0.35 - 0.35 - 0.19	0.40 - 0.30 - 0.26 - 0.19
	2	0.25 - 0.23 - 0.30 - 0.16	0.30 - 0.34 - 0.33 - 0.17
	3	0.41 - 0.44 - 0.35 - 0.20	1.30 - 0.80 - 0.50 - 0.27
	4	0.30 - 0.25 - 0.25 - 0.18	0.38 - 0.35 - 0.23 - 0.18
Average		0.33 - 0.32 - 0.31 - 0.18	0.60 - 0.45 - 0.33 - 0.20
Affected	1	1.20 - 0.70 - 0.43 - 0.26	0.66 - 0.45 - 0.23 - 0.20
	2	0.92 - 0.29 - 0.19 - 0.12	0.44 - 0.41 - 0.21 - 0.19
	3	4.09 - 2.94 - 0.45 - 0.36	2.13 - 0.75 - 0.49 - 0.31
	4	1.18 - 0.87 - 0.40 - 0.23	0.58 - 0.39 - 0.20 - 0.20
Average		1.85 - 1.20 - 0.37 - 0.24	0.95 - 0.50 - 0.28 - 0.23

5.3.3. EMG Parameters and Motor Recoveries

Spearman's correlation coefficients were determined, relating each EMG parameter from wrist flexion and extension of the affected hand to FM scores. Representative scatter diagrams of delay in onset and offset during 3s wrist flexion and extension versus FM scores are shown in Figure 5.7. Onset/offset delays in muscle contraction correlated well with FM scores, except for offset delay in wrist flexion.

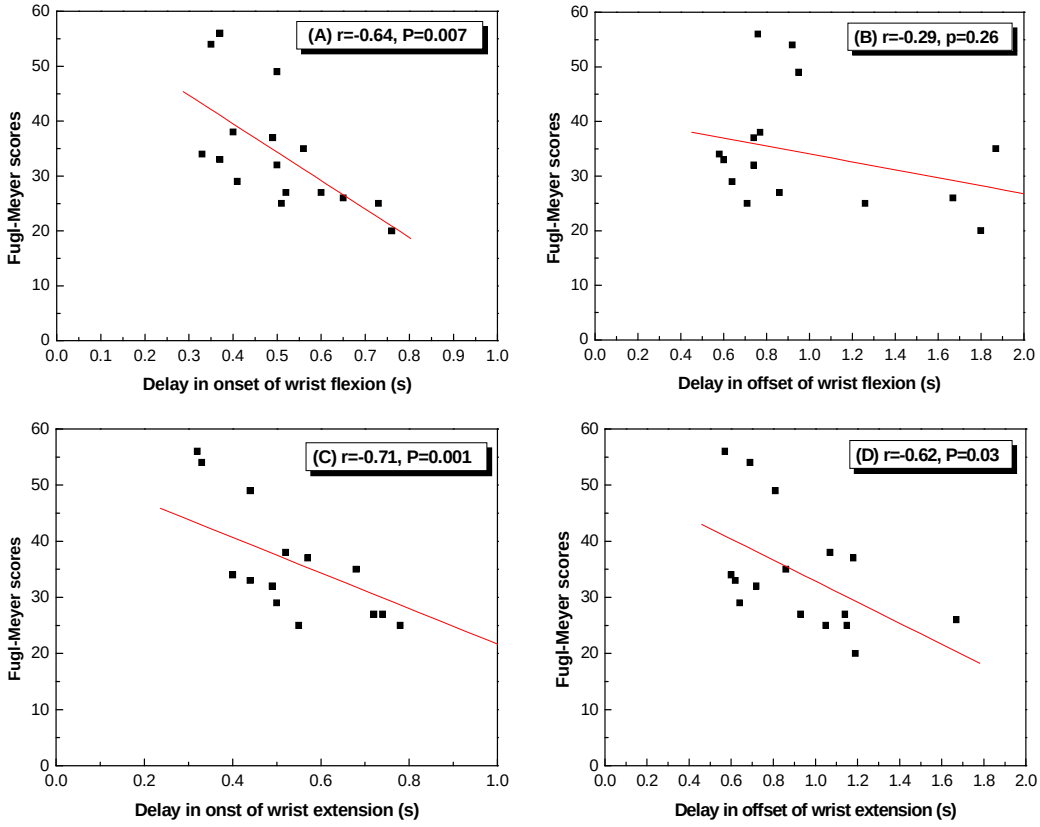


Figure 5.7. Correlations between delay of EMG responses of wrist movement and FM score. (A) Delay in onset of wrist flexion versus FM scores, (B) Delay in offset of wrist flexion versus FM scores, (C) Delay in onset of wrist extension versus FM scores, (D) Delay in offset of wrist extension versus FM scores.

In addition, as shown in Figure 5.8, the co-contraction ratio in wrist movements correlated well with FM scores.

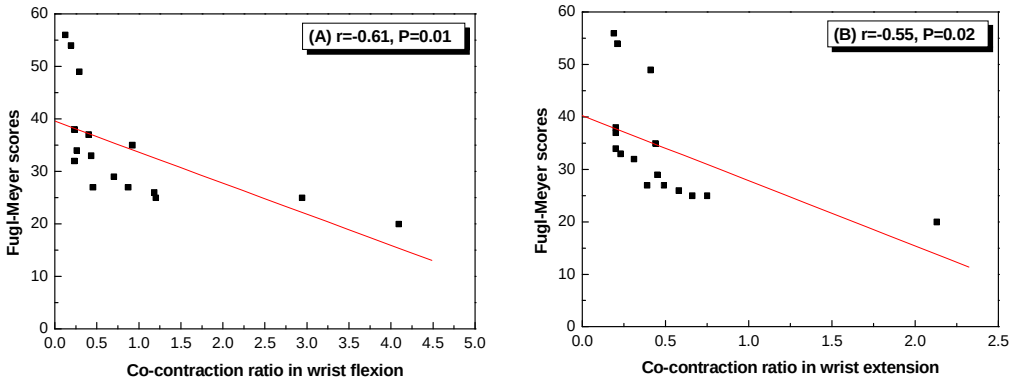


Figure 5.8. Correlations between co-contraction ratio of wrist movement and FM score. (A) Co-contraction ratio of wrist flexion versus FM scores, (B) Co-contraction ratio of wrist extension versus FM scores.

5.4. Discussion

Major findings in this chapter are: (1) there is a significant difference in onset/offset delay of muscles contraction between the affected and unaffected upper limbs; (2) there is a significant decrease in co-contraction ratio of affected hand of chronic stroke patients after 6-week training program; and (3) onset/offset delay of muscle contraction and co-contraction ratio correlates significantly with upper limb motor impairment and motor recovery.

Most quantitative EMG studies performed on impaired limbs of hemiparetic stroke patients have dealt with temporal analyses of EMG patterns during arm movements [14]. Consistent with prior studies [12, 13], we found a significant onset delay of muscle contraction of the hemiparetic upper limb compared to the unaffected upper limb. The task required of the subjects in this study represented a “simple reaction time” task in which the subject knows in advance stimulus (audible beep) will occur and which response to make isometric wrist flexion and extension. The task can be broken down into three components: signal detection, signal processing and selection of motor strategy, and task execution. Delay in simple reaction time can be attributed to lesions causing specific impairments in processing and efferent mechanisms, but not to signal detection disturbances, which are common to tasks involving affected and unaffected limbs. We excluded subjects with clinical evidence of other neurological disorders, decreasing the likelihood of lesions caudal to the brainstem contributing to onset delay of contraction. Motor processing is mediated by the posterior parietal cortex and premotor areas, whereas selection of motor strategy and motor execution are mediated by the primary motor and premotor areas [21]. However, the final motor output among stroke survivors can be modulated by changes in descending and propriospinal excitatory and

inhibitory inputs into the spinal interneurons and alpha motoneurons [22] as well as neuroplastic changes consequenct to brain injury [23].

We observed a difference of approximately 0.8 s in the inset delay of muscle contraction between the affected and unaffected limbs. How much of this difference was due to the impairment in motor processing rather than efferent mechanisms is cause hyperexcitability of the spinal motor pool and lead to loss of the orderly recruitment of motor units [24]. However, Heald et al. [25] reported difference in latency of no more than 0.1 s between the affected and unaffected limbs after activating the motor cortex with transcortical magnetic stimulation and recording thenar muscle responses. Dewald et al. [18] examined spatiotemporal abnormalities in the flexor reflex response in the impaired upper limb of hemiparetic subjects. The difference in delay in the reflex response between affected and unaffected limbs ranged between 0.1 and 0.4 s. The delay, which is attributable to deficits in the efferent mechanism, would account for only a small portion of the delay observed in this study, suggesting motor processing contributes substantially to the delay in initiation of motor activation in heniparetic muscles. Another means to evaluate the relative contributions of the processing and efferent mechanisms to the observed differences is to assess the onset difference when the muscles are pre-activated.

Consistent with prior studies [13, 18], we found a significant delay in termination of muscle contraction of the hemiparetic upper limb compared to the unaffected upper limb. Hammond et al. [14] evaluated the difference in delay in termination of muscle contraction using a similar experimental design. However, contrary to their expectations, they did not observe a significant difference between affected and unaffected upper limbs. They reported that many subjects would not maintain their contraction throughout the entire prescribed duration of contraction. Each subject underwent 12 wrist flexion

and extension trials for each limb, each lasting 3, 6, or 9 s. The inability to maintain their contraction was probably due to fatigue associated with the long duration of contraction, high number of trails, and severity of hemiparesis.

Delay in termination of contraction represents one of a constellation of clinical manifestations following nervous system injury that Jackson [26] described as “positive” signs, or stereotyped abnormalities that emerge after lesson. Other examples include spasticity, abnormal co-contraction of antagonist and agonist muscles, and abnormal co-activation of synergetic muscles. The mechanisms that account for these “positive” manifestations remain uncertain. Many researchers found significant onset delays of muscle contraction in the hemiparetic upper limb. The delay in muscle contraction can be extended when the decrease in inhibitory control of central nervous system (CNS) after stroke or brain injury causes muscle stiffness or excessive co-contraction of the antagonist muscle. It may be also extended when the function of intact reticulospinal tract is activated with the dysfunction of corticospinal tract or when the cortical reorganization is developed [24]. The co-activation of agonist and antagonist muscles is an important component of motor control in normal individuals. It participates in the regulation of joint stiffness and postural stability [14]. As regulated by a feed forward mechanism, it is modulated according to task requirements. An abnormal co-activation pattern, consisting of massive and synergistic activation of many muscles, has been reported on the affected side of hemiparetic patients during movement [27]. In the present study, we observed that onset/offset delay and co-contraction ratio, which was defined by the ratio between agonist and antagonist using IEMG, significantly decreased after the 6-week training with the BSAT.

The second objective of this Chapter was to describe the statistical relationship between a fundamental neural deficit manifested by onset/offset

delay of muscle contraction and co-contraction ratio of hemiparetic upper limb, and clinical motor recovery, as measured by the FM score. In this study, we found a statistical relationship between the degree of the onset, offset delay and co-contraction ratio of muscle contraction and clinical measures of motor impairment and physical disability. Activities of daily living require prompt and coordinated repetitive initiation and termination of muscle contractions. Many stroke survivors achieve the hand closure by isolated movements or by volitionally activating a flexor synergy pattern. Dewald et al. [18] demonstrated a similar statistical relationship between muscle co-activation patterns of synergistic muscles in the paretic upper limb and FM scores. Thus, it is possible that subjects with more prolonged delays in initiation and termination of muscle contraction also have greater degree of muscle weakness, fatigue, abnormal co-contraction of antagonist and agonist muscles, and abnormal co-activation of synergetic muscles, all of which may have more direct impact on functional activity. Although correlational studies may provide insights into mechanisms for functional deficits and potential interventions, cause-and-effect relationship can only be demonstrated by prospectively introducing specific interventions to address specific motor abnormalities in a controlled manner with assessment of functional outcome.

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6. Evaluation on Motor Recovery: fMRI

6.1. Introduction

Hemiparesis is the most common acute deficit of stroke [1]. Most hemiparetic patients experience some degree of motor recovery within the first 6 months after stroke [2]. Post stroke physical therapy or robot assisted therapy may produce gain in motor function beyond those occurring spontaneously [3]. However, the neural mechanisms mediating rehabilitation-induced motor recovery are poorly understood.

Recent development in functional neuroimaging modalities such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and transcranial magnetic simulation (TMS) have been made. Several studies have reported the cortical reorganization induced by physical interventions in hemiplegic patients [4-6]. Functional imaging and electrophysiologic brain mapping techniques have provided substantial insights into the adaptive changes of cerebral networks associated with the recovery from brain damages. These studies demonstrated the recruitment of areas adjacent to brain lesion or ipsilateral motor regions of the unaffected hemisphere after the complete recovery from the upper extremity motor impairment [5].

Furthermore, the reorganization of both motor and sensory structures occurs in parallel with the improvement of the upper extremity motor function [4, 5]. Given the close temporal correlation between these sequential alterations of cerebral activity and the return of voluntary motor control, many of the dynamic changes observed in the cerebral cortex may have a restorative capacity. Accumulated evidences in hemiparetic patients suggest that

rehabilitation techniques with repetitive training of functional movements have significant effects on the recovery of motor skills [6]. The effects of such specific rehabilitative interventions on the cortical reorganization after stroke or brain injury, however, have not been examined by functional imaging experiments to evaluate rehabilitative training systems.

The goal of current Chapter study was to evaluate cortical reorganization associated with motor recovery produced by the BSAT using fMRI. We focuced on determining reorganization in motor cortical areas, since activation changes in these areas have been previously shown to related with motor recovery after stroke.

The present study was to determine the effect of the BSAT on the cortical activation changes in chronic hemiparetic patients before and after the 6 week training using fMRI.

6.2. Backgroud

6.2.1. Magnetic Resonance Imaging (MRI) : Principles

Magnetic Resonance Imaging (MRI) is one of the least invasive methods to image internal organs of human beings and animals. It has become an important and powerful tool for clinical diagnosis since 1970s and has been applied extensively in basic researches in biology, physiology, and medicine related sciences [7, 8].

The MRI system consists of a main machine and computer system. The main machine is installed in an electrically and magnetically shielding room. It is equipped with a main magnetic coil, radiofrequency (RF) coils, gradient coils and shim coils. The computer system is located outside the shielded room

and is connected to the main machine to monitor the system and control data acquisition (Figure 6.1).

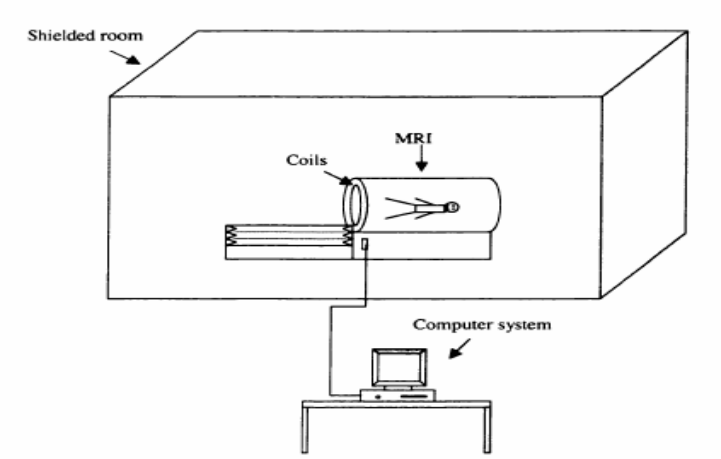

Figure 6.1. Schematic Illustration of MRI system. It includes a shielded room, a main MRI machine and a controlling computer system. The machine has a main magnet and other coils for imaging. The subject lies in the magnet bore and part of his body of interest is imaged.

The object of the standard MR imaging of humans is to extract information about the hydrogen distribution of the tissue of interest. During imaging, the main magnet applies a strong and extremely homogeneous magnetic field to the tissue being imaged. The spines of the protons in this tissue are forced to align along the magnetic field. An RF electromagnetic pulse, thereafter, is applied to the tissue by the RF coils. Since the RF pulse is chosen to have the same frequency as the Larmor frequency of the protons in the main magnetic field, the tissue protons resonate and absorb the energy, being flipped away from the direction of the main magnetic field to higher-energy states. The proton spins then process around the main magnetic field at the Larmor frequency. This causes a changing magnetic flux, which induced a current signal in the receiver coil. (The receiver coil can be the same RF coil or other one.) By superimposing linear gradient to the main magnetic field by the gradient coils, the positrons of the proton spins are phase encoded, and the

induced signals correspond to the Fourier transform of the spin density of the protons in the tissue. The signals collected in the Fourier space are called raw data. The spin density of the protons is then reconstructed form the raw data by performing the inverse Fourier transform. The distribution of the protons constitutes the imaging of the tissue being imaging [8]. Because of the relaxation effect (proton spins relax from the high energy states to the rest states), the imaging procedures are much more complex than what has been described above. These effects are described by three empirical parameters, the spin-lattice relaxation time (T_1), the spin-spin relaxation time (T_2), and a relaxation time due to the external field inhomogeneous (T_2'). The latter two are often combined as T_2^* since they cause signal loss in similar way. These relaxation times need to be taken into account when designing imaging sequences.

It is noteworthy that MRI requires an extremely homogeneous magnetic field. To achieve the requirement, the MRI machine room is magnetically shielded to minimize the noise from outside environment, and a set of shim coils is employed to eliminate the small inhomogeneities in the main magnetic field. This limitation imposes more requirements on any equipment being designed to sue with the MRI machine.

MRI is a non-ionizing imaging modality and hence a safer one when compared to X-ray, CT, and other modalities applying radioactive materials. The magnetic fields used by current MRI systems rage from 0.1 Tesla up to several Tesla. Properly administrated, these systems will not produce harmful effects on the human body, such as energy deposition in the tissue being imaged. In our experiments, subjects were required to sty inside the machine for from 20 minutes to one hour (maximally), typically around half an hour. According to our experience, this is a reasonable length of time for most of the healthy subjects and patients who participated in our experiments.

6.2.2. Functional MRI (fMRI)

Functional MRI is a method to study human brain function based on the fast MRI technology. Using the Echo Planar Imaging (EPI) sequence, a whole brain can be scanned within 2 seconds, with a spatial resolution of 2 mm. Because of its noninvasive feature and good spatial resolution, fMRI is considered as one of the most powerful probes to explore human brain function. Since its emergence in the early 1990s, it has become increasingly used in the basic and clinical researches on cognitive neuroscience, motor control, etc. [9].

In this section, the principle of fMRI is described first. Then, experimental procedures and data analysis methods for fMRI are described.

6.2.2.1. Principle of fMRI

The fundamental principle underlying fMRI is a phenomenon called the blood-oxygen-level-dependent (BOLD) effect, although other contributing effects have also been investigated [10-12]. According to the BOLD effect, changes in blood oxygenation level during brain activation play the main role in indicating functional regions of the brain. As we know, there are two types of hemoglobin (red blood cells) in the blood, oxyhemoglobin and deoxyhemoglobin. They have different molecule structures and hence have different magnetic properties. Oxyhemoglobin is diamagnetic and has little effect on the local magnetic field. Thus, it dos not affect the MRI signals. However, deoxyhemoglobin is paramagnetic relative to the surrounding tissue, thus it affects the local magnetic field. This will introduce inhomogeneties into the magnetic field, which leads to dephasing of the proton processions and hence a loss in the detected MRI signal. The more deoxyhemoglobin, the

bigger the inhomogeneties in the local magnetic field, and the bigger the signal loss. When a functional region of the brain is activated during a task, oxygenated blood in artery flows faster into this area compared to the normal or resting state. However, remarkably, it has been found that the oxygen consumption by the brain basically does not increase. As a result, the relative content of deoxyhemoglobin in this area of the brain will decrease. Therefore, this leads to an increase of the MRI signal intensity. The fast MRI technology makes it possible to record the local signal intensity changes. These changes indicate the activated area in the brain during the given task.

6.2.3. Human Brain Mapping Technologies

Our current understanding of brain plasticity underlying spontaneous motor recovery has largely come from three human brain mapping technologies: transcranial magnetic stimulation (TMS) and the functional neuroimaging technologies—positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

TMS can be applied to evaluate motor cortex excitability in stroke patients. Using TMS, a stimulating coil is placed on the scalp over where the motor cortex resides. A brief, high-current pulse is passed through the coil. This current pulse induces a magnetic field that penetrates painlessly through the scalp, skull and underlying brain tissue, resulting in an induced current in the brain tissue. This induced current activates, indirectly, pyramidal cells of the corticospinal tract. As action potentials traverse these neurons, motor evoked potentials (MEP) are detected by electromyography in a contralateral target muscle, typically a finger muscle. Several parameters of the MEP can be measured to provide indices of motor cortex excitability, including threshold, amplitude, and size of the cortical area from where the potentials are evoked.

TMS is usually done with the target muscle initially at rest. Therefore, TMS measurements are not dependent on subjects performing a particular movement. This feature makes TMS a tool amenable to studying motor cortex excitability in stroke patients, even those with hemiplegia.

Activation studies using PET or blood oxygenation level-dependent (BOLD) fMRI evaluate the brain's hemodynamic response to an "activation task" (e.g. a specified, repetitive hand movement). Brain areas with neurons actively involved in the activation task receive an increased supply of blood. PET and BOLD-fMRI exploit different aspects of this neurovascular response. PET relies directly on the increase in cerebral blood flow. A PET camera monitors emitted positrons just after intravenous injection of a radioactive tracer substance, usually ^{15}O labeled water. The distribution of the radiolabeled substance is related directly to regional cerebral blood flow. BOLD-fMRI, in contrast, provides only an indirect measure of cerebral blood flow changes, relying on a complex and not yet fully understood set of physiologic events. BOLD-fMRI relies on the fact that oxygen consumption by active neurons is less than the increase in cerebral blood flow, resulting in a local net increase in oxygenated blood and net decrease in deoxygenated blood. The net decrease in deoxygenated hemoglobin iron in blood produces a change in magnetic susceptibility, resulting in an increase in magnetic resonance signal (T2*) in brain tissue. Using PET or fMRI, brain areas with statistically significant increases in signal during the activation task, as compared to baseline (e.g. no movement) are interpreted as areas involved in processing information related to the activation task.

PET and fMRI have their particular advantages as methods for evaluating brain activation related to motor recovery after stroke. Functional MRI has the advantage of being non-invasive (i.e. no exposure to a radiolabeled substance). Further, the images collected using fMRI are of higher

spatial and temporal resolution than PET (approximately 3mm3 versus 8mm3; approximately 2 s versus 5 min, respectively), permitting a more refined assessment of the spatial and temporal dynamics of brain activation associated with motor performance in stroke patients. However, the PET scanning environment is advantageous because it provides more physical space for subjects to perform limb movements and for ancillary equipment to monitor these movements. Further, the PET scanning environment provides more flexibility in the design of ancillary equipment because of the lack of high magnetic fields.

Other human brain mapping technologies have also begun to contribute to our understanding of brain plasticity associated with motor recovery after stroke, and each holds particular advantages that will be helpful in piecing together a complete understanding of the recovery process. Near-infrared spectroscopy (NIRS) is an emerging technology that non-invasively measures brain activation by monitoring changes in the absorption of near-infrared light by hemoglobin-containing species in cerebral blood. To its advantage, NIRS can be designed to be relatively insensitive to head motion, and uses compact instrumentation that makes it feasible for application in stroke patients at the bedside or in the rehabilitation facility. The temporal resolution of NIRS is similar to that of fMRI (approximately 1 s), though the sampling rate is typically several orders of magnitude greater than this, thereby allowing for more accurate detection of the evolution of the hemodynamic response. The disadvantages of NIRS, as compared to PET and fMRI, are its relatively poor spatial resolution (approximately 3 cm) and depth penetration (approximately 1 cm beneath the skull). Magnetoencephalography (MEG) and electroencephalography (EEG) are methods that record the electromagnetic fields and induced electrical currents, respectively, generated by neuronal activity. Whereas all the previously mentioned methods rely on a relatively

slow hemodynamic response, MEG and EEG measures derive directly from neural activity signals that are significantly faster. MEG and EEG allow for measurement of brain activity with a high temporal resolution (approximately 1 ms), and like NIRS can be sampled at a much higher frequency. The spatial resolution of MEG/EEG, however, is relatively poor (approximately 5–10 mm). Efforts are currently being made to develop robust methods for combining from individual subjects high spatial resolution information of fMRI with high temporal resolution information of MEG/EEG. Such technical developments will aid in understanding the spatiotemporal processes underlying motor recovery in stroke patients.

6.2.4. Response during Movement

Voluntary motor activity is exerted by the striated muscles. Contractions and relaxations from striated muscles are required to induce all forms of voluntary motor behavior. These impulses, which lead to muscle contractions, must pass through the motor neurons located in the anterior horn of the spinal cord, or to the cranial nerve nuclei. Motor neurons, or spinal motor neurons, are the final common pathway to voluntary behavior. Spinal motor neurons and motor neurons for the cranial nerves in the brain stem are influenced by a multitude of inputs from many parts of the central nervous system. All voluntary motor activities are preceded by the activation of many anatomical structures, some of which are connected to the spinal and bulbar motor neurons. Some of the terminals stem from neurons in the brain with somatosensory functions or from neurons receiving impulses from sensory end organs in the skin and muscle itself [13].

The motor system is made up of several descending pathways. While each of these tracts plays an important role in the total integration of motor

capabilities, cortical plasticity after deafferentation have been most studied in the corticospinal tract.

The corticospinal tract contains over a million axons originating from three sources: one third descend from Betz pyramidal neurons in the primary motor cortex (Brodmann area 4), one-third from somatosensory cortex (Brodmann area 3, 1 and 2) and the other one-third from premotor cortex (Brodmann area 6) (Figure 6.2).

Each of the individual motor structures cannot act alone, thus each structure and their interconnections act together to form an output system for the brain. The question should then be restarted: how do the distinct motor areas in the brain work together effectively to produce movement?

At the instant the desire to move is formulated in the brain, it is rarely in the form that permits immediate motor execution. Once a person decides to put a plan into action, they have an intention to act. Intention for motor action has been defined as a recruitment of those cortical areas whole participation is necessary for the information processing between the idea of a goal for action and motor execution [14]. The organization of voluntary action, from the intension to the execution, is dependent on the type of voluntary behavior the subject wishes to express. The organization also depends on whether the motor task is novel of has been previously learned [14].

Normally executed voluntary movement requires information from nonmotor structures in the brain. Voluntary motor acts are the results of either thoughts or desires formulated by other brain areas or reactions to events in the environment. Theses are coactivated with the motor structures in the brain that are relevant to the task at hand. In this way, motor and nonmotor structures work together, in the principle of economy, to utilize only those structures that are needed to produce the desired movement in the correct context.

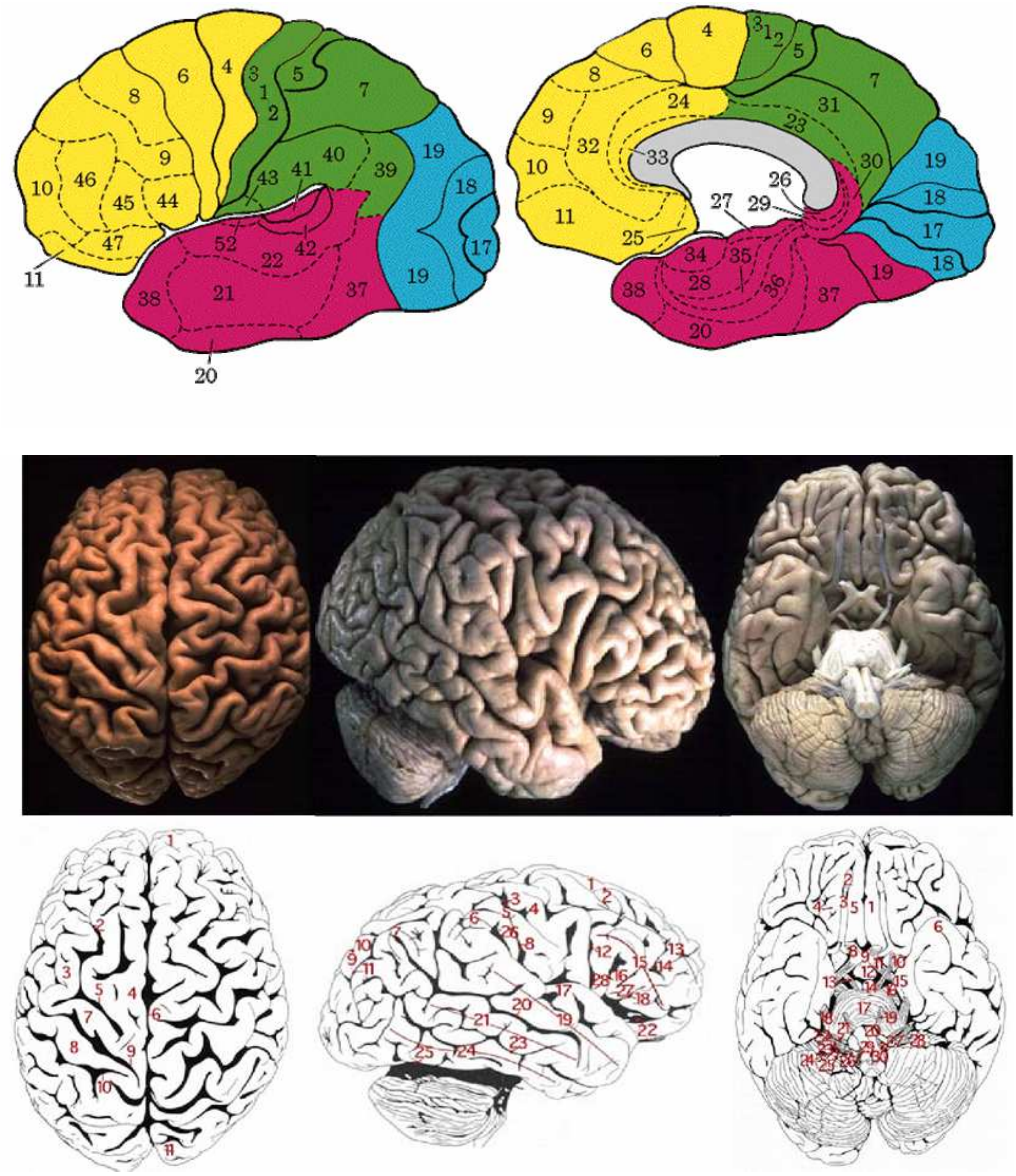

Figure 6.2. Broadmann′s areas. 1. Motor area (Brodmann′s area 4, 6): primary motor cortex (area 4), supplementary motor cortex (area 6), premotor cotex (area 6), posterior periatal cortex (area 5, 7), prefrontal cortex (area 9-11, 46-47), 2. Somatosenory area (Brodmann′s area 3, 1, 2, 5, 7): primary somatosensary cortex (area 3, 1, 2).

6.2.5. Cortical Areas in the Motor System

The key cortical areas in the motor system include the primary motor area (M1), premotor area (PMA), supplementary motor area (SMA), parietal cortex and the basal ganglia. Each area contributes necessary motor structures to the representation and actualization of motor output and does so in a somatotopic fashion. There seems to be at least one complete somatotopic representation of the body in each of theses areas. The cerebellum will be examined although will not be focused due to a lack of somatotopic in this area. Figure 6.3 shows the location of primary and secondary cortical motor areas.

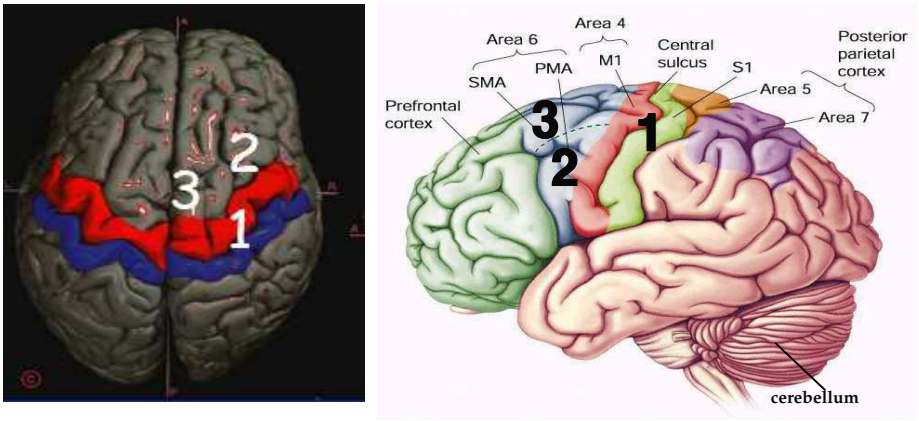

Figure 6.3. Location of primary and secondary cortical motor areas. 1: M1, 2: PMA, 3: SMA.

6.2.5.1. Primary Motor Area (M1)

The primary motor cortex (M1) runs along the length of the precentral gyrus and contains a spatially distinct motor homunculus [15]. Muscle of the face, tongue and mouth are controlled by neurons in the ventral position of the

precentral gyrus. The remainder of the body is representation in successive more dorsal portions of the gyrus, with the leg representation expending onto the medial wall of the hemisphere. This resulting body map is termed the motor homunculus and is what is meant by somatotopic reorganization (Figure 6.4). These also exists a sensory homunculus on the postcentral gyrus. The neurons in the primary motor cortex make both excitatory and inhibitory connections with spinal and bulbar motoneurons. In addition, M1 receives input from premotor, supplementary motor area, and cerebellum via the ventral lateral nucleus of the thalamus. These connections are thought to be the predominant influences increasing the metabolism and regional cerebral blood flow (rCBF) in M1.

Research indicated that all voluntary movement increases regional cerebral blood flow in M1. This is to say that in order to perform a motor task, the appropriate somatotopic area of primary motor cortex is required.

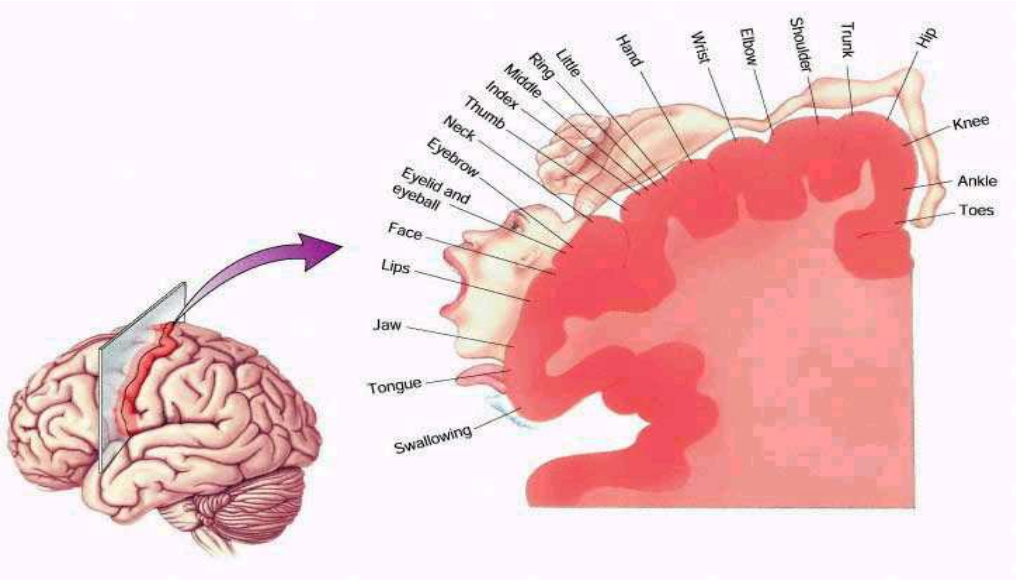

Figure 6.4. Somatotopic map of the human precentral gyrus.

6.2.5.2. Supplementary Motor Area (SMA)

The supplementary motor area is situated on the medial side of the hemisphere just in front of M1 and superior to the lateral premotor areas. SMA was originally discovered during direct stimulation during surgery of an awake patient. The patient was rehearing the alphabet and reached the letter H, the stimulation made him repeat the H continuously until the stimulation ended [16]. Other more recent studies have found SMA involved in speech arrest preceded by acceleration or slowing of speech, movements of upper extremity, often rhythmic finger tapping, vocalizations, aversion of head and eyes, and movements of lower extremity [17].

Studies have shown that repetitive movement of the same finger in which flexions automatically followed extensions activated SMA. SMA has also been shown to have a role as a programmer of motor subroutines [18]. This is apparent in the fact that pure internal rehearsal of motor sequences activates SMA [19].

6.2.5.3. Premotor Area (PMA)

The premotor cortex is difficult to define anatomically. Positron emission tomography (PET) studies have located it above the frontal eye fields, and limited posteriorly by the fundus of the central sulcus. The premotor area shares Brodmman area 6 with the supplementary motor area, but is located below the SMA in a more lateral position.

Premotor cortex seems to be specifically involved when sensory information is necessary to build the motor program or when the motor program is modulated by incoming sensory information, such as in early stages of motor learning. Premotor cortex becomes active when voluntary movements

are carried out under the guidance of somatosensory, auditory, or visual information or when sensory information is necessary for the execution of the movements. In experiments ranging from shape discrimination to performance of a maze task in which individuals performed navigation on a paper and pencil maze, premotor cortex was strongly activated [20].

6.2.5.4. Cerebellum (CRB)

The cerebellum, a large and conspicuous part of the motor system, sits on top of the brainstem and is clearly visible just behind the cerebral cortex. The cerebellum is divided into two hemispheres, as is the cerebral cortex. A small lobe called the flocculus projections from its ventral surface. Despite the cerebellum′s relatively small size, it contains about one-half of all the neurons of the nervous system. As Figure 6.5 shows, the cerebellum can be divided into several regions, each of which specialized in a different aspect of motor control. The flocculus receives projections from the vestibular system, which will be described shortly, and takes part in the control of balance and eye movements. Many of its projections go to the spinal cord and to the motor nuclei that control eye movements. The hemispheres of the cerebellum can be subdivided as shown by the white line in the Figure 6.5. The most medial part controls the face and the midline of the body. The more lateral parts are connected to areas of the motor cortex and are associated with movements of the limbs, hands, feet, and digits. The pathways from the hemispheres project to nuclei of the cerebellum, which in turn project to other brain regions, including the motor cortex.

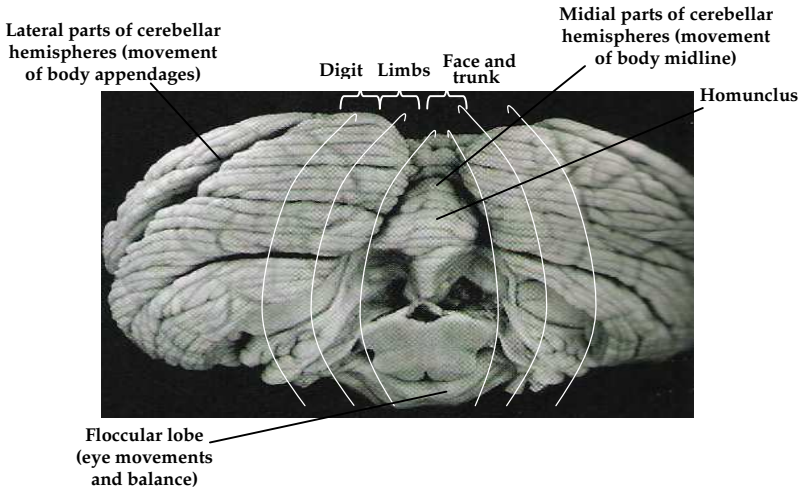

Figure 6.5. The cerebellum consists of the cerebellar hemispheres and the flicculus. The hemispheres control body movements, and the flicculus controls balance. The cerebellum is topographically organized, with its more medial parts representing the midline of the body and its more lateral parts representing the limbs and digits.

To summarize the cerebellum′s topographic organization, the midline of the homunculus is represented in the central part of the cerebellum, whereas the limbs and digits are represented in the cerebellum′s lateral parts. Tumors or damage to midline areas of the cerebellum disrupt balance, eye movements, upright posture, and walking but do not substantially disrupt other movements such as reaching, grasping, and using the fingers. For example, a person with medial damage to the cerebellum may, when lying down, show few symptoms. Damage to lateral parts to the cerebellum disrupts arm, hand, and finger movements much more than movements of the body′s trunk.

6.3. Materials and Methods

6.3.1. Subjects

During fMRI experiments, two environment tasks were assigned to every subject: Environment 1 was task with nonferritic device inside the magnet and Environment 2 was the task without device.

Six control group and patient 1~4 were participated in Environment 1, and other patients were examined in Environment 2.

6.3.2. fMRI Acquisition

Before and after the 6-week training program, the blood oxygen level dependent (BOLD) fMRI measurements employing the echo planar imaging (EPI) technique (TR/TE/α=1900/40/90°, FOV=240mm, matrix size=64×64 and slice thickness=5mm), were performed using a 3T MR scanner (GE Medical System, Milwaukee, USA) with a head coil. A T2-wighted anatomical volumetric images (FSE, TR/TE/α=4500/104/90°, FOV=240mm, matrix size=256×256 and slice thickness =5mm) were obtained.

Echo-planar images were realigned to the first image of each time series to remove residual head movements. Images were then resized into the standard anatomic space defined by the atlas of Talairach and Tournoux [21]. The images were then soothed with an 8 mm isotropic Gaussian kernel.

6.3.3. Motor Tasks

6.3.3.1. Motor Task with the BSAT

For the motor task paradigm, eyes-closed resting state for 20s was defined as the rest state, and self-paced wrist flexion-extension movements at frequencies of 1-2Hz using the nonferritic device inside the magnet another 20s was defined as the active state. Each task protocol was to alternate rest-active states (40s), repeating three times (Figure 6.6).

For this study, a bilateral symmetric motion system was made of an insulating material for MR environments to reproduce the training environment (Figure 6.7 (A)).

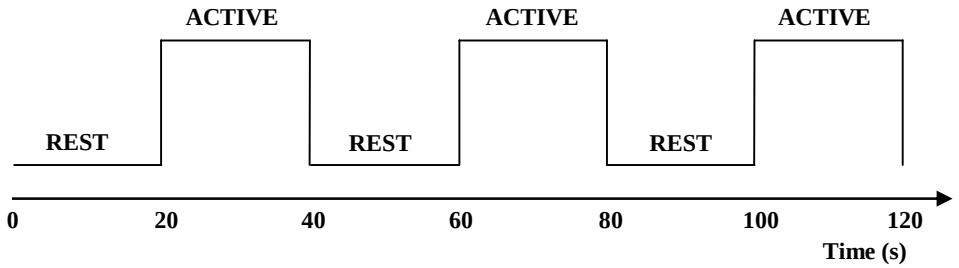

Figure 6.6. The paradigm for fMRI experiments. It consisted of recurrent Rest and Active sessions. In the Rest sessions, the subject remained still his/her brain images were collected as rest images. In the Active sessions, the subject performed the required motor tasks while active brain images were collected.

During fMRI experiments, two motor tasks were assigned to every subject: Task 1 was an active wrist movement only on the unaffected side and Task 2 was the passive wrist movement of the affected hand driven by an active wrist movement of the unaffected side.

6.3.3.1. Motor Task without the BSAT

Task paradigm was the same as above motor task. During fMRI experiments, three motor tasks were assigned to every subject: Task 1 was wrist movement only on the unaffected side, Task 2 was wrist movement only

on the unaffected side, and Task 3 was bilateral wrist movement. Figure 6.7(B) shows the experimental set-up for these tasks.

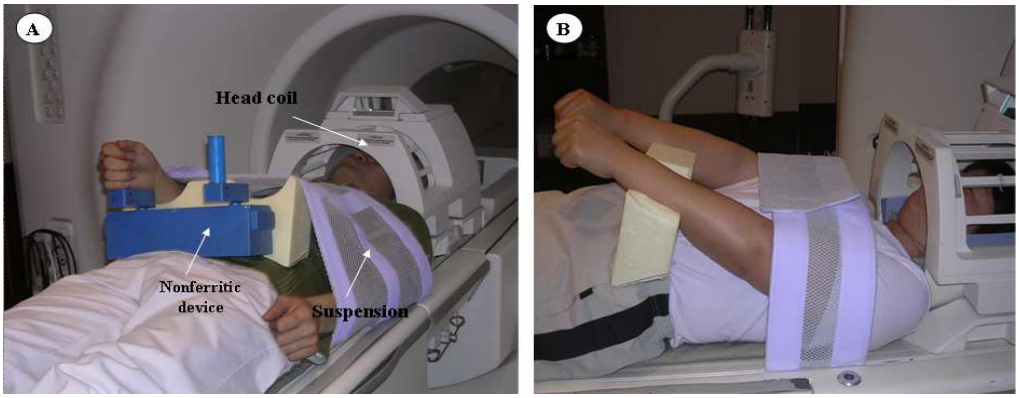

Figure 6.7. Experimental set-up for fMRI acquisition. (A) Environment 1: task with nonferritic device, (B) Environment 2: task without device.

The laterality index (LI) for SMC was calculated to compare the relative in the ipsilateral versus the contralateral SMC. LI was defined as below.

$$LI = \frac{(contralateral\ SMC\ voxel - ipsilateral\ SMC\ voxel)}{(contralateral\ SMC\ voxel + ipsilateral\ SMC\ voxel)} \qquad (6.1)$$

It could range from 1.0 (all activity in the contralateral hemisphere) to -1.0 (all activity in the ipsilateral hemisphere).

6.3.4. Statistical Analysis

To analyze fMRI data, SPM99 software (Welcome department of Cognitive Neurology, London, UK) was used. Regions of interest were selected as the primary sensorimotor cortex (SMC), the premotor area (PMA), the supplementary motor area (SMA) and cerebellum (SRB), since these areas has been reported to have neuroplastic recovery potential [22]. Significance of

the activation between the rest and the task was threshold at $p<0.001$, uncorrected. In motor task without system, we used non-parametric Wilcoxon signed rank test to validate interval changes of LI, because the medical status of the subjects was variable and there only four subjects. In order to test correlations of the two variables, we calculated the interval changes of each variable, and then performed the non-parametric Spearman's correlation analysis. A sifnificance in the difference was defined as $p < 0.05$.

6.4. Results

6.4.1. Motor Task with the BSAT

In the control group, activations in primary contralateral SMC, SMA and ipsilateral CRB were observed in Task 1, with only dominant wrist movement. On the other hand, in Task 2, the passive wrist movement of the non-dominant hand by the active wrist movement of the dominant hand, activations in primary bilateral SMC, PMA, SMA and CRB were observed (Figure 6.8).

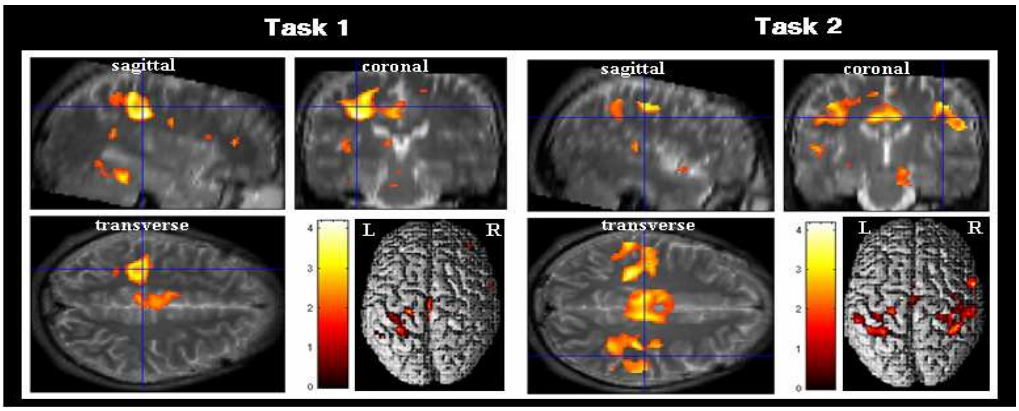

Figure 6.8. Cortical activations in control group.

Figure 6.9 shows cortical activations for both tasks before and after the 6-week training. In fMRI results with Task 1, a cortical activation in the contralateral of the affected side was observed after the training. The ipsilateral SMC activation disappeared in Patient 1 and 4. In Patient 1, The contralateral CRB activation disappeared. It is noted that activations in the contralateral SMC for all patients' unaffected wrist had disappeared and then increased after training.

However, Task 2 showed that the contralateral PMA of the unaffected wrist and the bilateral SMA were newly activated and activations in contralateral SMC increased in Patients 1 and 3, whose ipsilateral SMC and ipsilateral PMA of unaffected wrist were activated in fMRI measurements before the training. However, cortical activations in contralatral SMC of unaffected wrist, bilateral PMA and bilateral SMC were newly activated in Patient 1, 2 and 3 whose ipsilateral SMC of the unaffected wrist was only activated site before training. In Patient 4, bilateral SMC, PMA was the only activated before training, bilateral SMA was newly activated. In the CRB region, bilateral and ipsilateral site were activated in Patient 1 and 2 before the training, respectively. On the other hand, medial CRB was activated in Patient 3 and 4 before the training. After the training, bilateral and medial CRB of all patients were activated (Table 6.1).

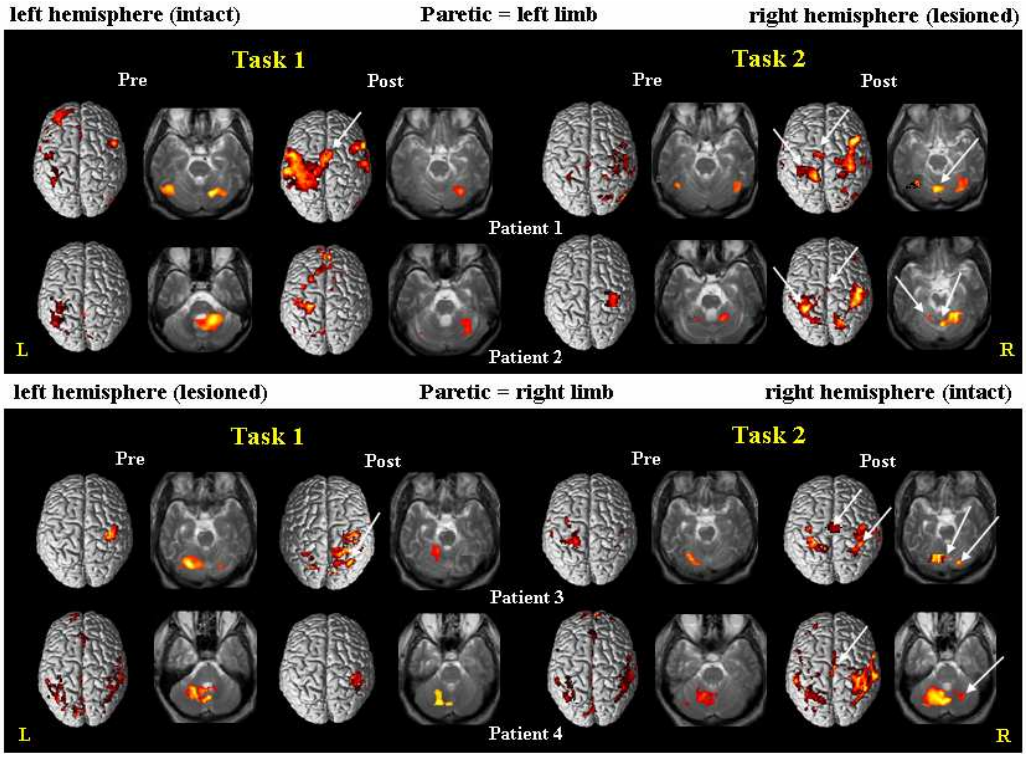

Figure 6.9. Cortical activations before and after training during Task 1 and Task 2 (p<0.001), newly activated (white arrow) areas compared before the training.

Table 6.1. Changes in cortical activation with system.

Patient	Task 1		Task 2	
	Pre-training	Post-training	Pre-training	Post-training
1	SMC^{B}, PMA^{C} CRB^{B}	SMC^{C}, PMA^{C}, SMA^{C}, CRB^{I}	SMC^{C}, PMA^{C} CRB^{B}	SMC^{B}, PMA^{B} SMA^{B}, CRB^{B}
2	SMC^{C}, CRB^{I}	SMC^{C}, PMA^{C}, CRB^{I}	SMC^{C}, CRB^{B}	SMC^{B}, PMA^{B} SMA^{B}, CRB^{B}
3	SMC^{C}, CRB^{B}	SMC^{C}, CRB^{I}	SMC^{I}, PMA^{I} CRB^{I}	SMC^{B}, PMA^{B} SMA^{B}, CRB^{B}
4	SMC^{B}, CRB^{I}	SMC^{C}, CRB^{I}	SMC^{B}, PMA^{B} CRB^{C}	SMC^{B}, PMA^{B} SMA^{B}, CRB^{B}

C=contralateral, I=ipsilateral, B=bilateral.

6.4.2. Motor Task without the BSAT

Figure 6.10 shows cortical activations for both tasks before and after the 6-week training. In Task 1, ipsilateral primary sensorimotor cortex (SMC) activity disappeared in Patient 8 and contralateral SMC was newly activated in Patients 5 at after-training. In Task 2, ipsilateral SMC activity disappeared in Patients 5, 6 and 7. In Task 3, a great degree of bilateral movement was significantly associated with more bilateral primary sensorimotor cortex activation. In Patients 6 and 8, ipsilateral SMC of the affected side was newly activated. While, contralateral SMC of the affected side was newly activated in Patients 7 (Table 6.2).

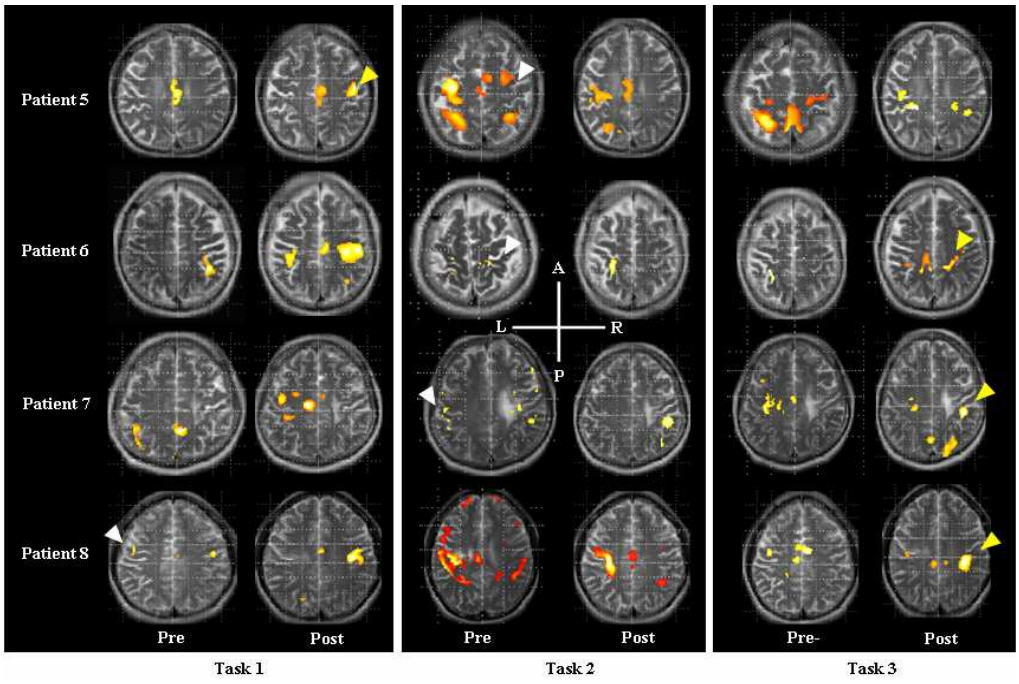

Figure 6.10. Images at the pre-training fMRI and at the post-training fMRI during Task 1, 2 and 3. Newly activated (yellow arrow) areas and disappeared (white arrow) compared before the training.

Table 6.2. Changes in cortical activation without system.

Patient	Task 1		Task 2		Task 3	
	Pre	Post	Pre	Post	Pre	Post
5	SMA^{C}	SMC^{C} SMA^{C}	SMC^{B} SMA^{I}	SMC^{C} SMA^{C}	SMC^{B}	SMC^{B}
6	SMC^{C}	SMC^{B} SMA^{C}	SMC^{B}	SMC^{C}	SMC^{I}	SMC^{B}
7	SMC^{C}	SMC^{C} SMA^{C}	SMC^{B}	SMC^{C}	SMC^{C}	SMC^{B}
8	SMC^{B}	SMC^{C} SMA^{C}	SMC^{B}	SMC^{B}	SMC^{I}	SMC^{B}

C=contralateral, I=ipsilateral, B=bilateral.

6.4.3. Laterality Index (LI)

In all patients, LI of the affected hand significantly increased ($p<0.05$) (Table 6.3).

Table 6.3. The changes of laterality index (LI) during Task 1 and Task 2.

Patient	Task 1			Task 2		
	Pre-LI	Post-LI	LI Change (%)	Pre-LI	Post-LI	LI Change (%)
5	NA	1.00	NA	0.96	1.00	4
6	1.00	1.00	0	0.47	1.00	53
7	1.00	1.00	0	0.58	1.00	42
8	0.87	1.00	13	0.67	0.86	19
Average	0.97±0.07	1.00	3.25±6.50	0.67±0.21	0.97±0.07	30.0±22.13

Pre-LI: LI at pre-training, Post-LI: LI at post-training, NA: not available due to no activation in SMC.

Figure 6.11 Shows the changes of LI during Task 1 and Task 2. In Task 1, LI was not significantly increased, however, in Task 2, LI was significantly increased ($p<0.05$).

6.4.4. Laterality Index (LI) and Motor Recovery

The relationship between FM and LI of the affected hand was showed in Figure 6.12. A significant correlation was found between the change of LI and the motor recovery (r=0.71, p=0.05)

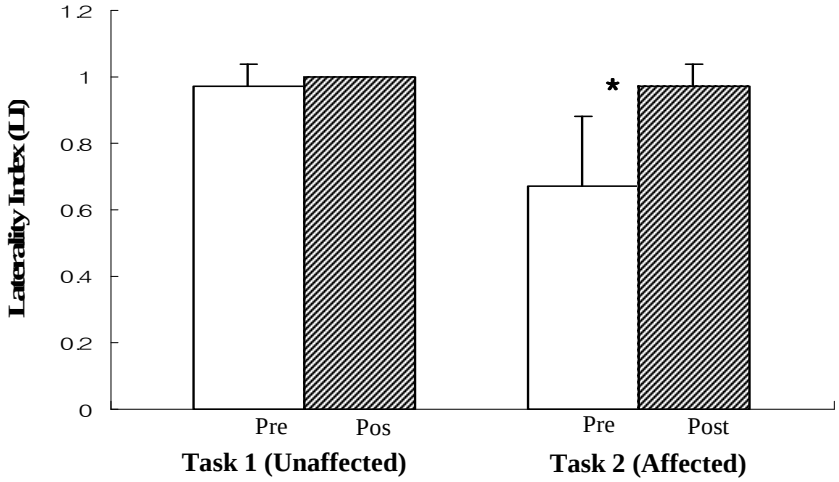

Figure 6.11. Mean laterality index for the sensorimotor cortex (SMC) for the chronic stroke patients (n=4) during both Task 1 and Task 2. In Task 2, there was a significant difference between before and after training ($p<0.05$).

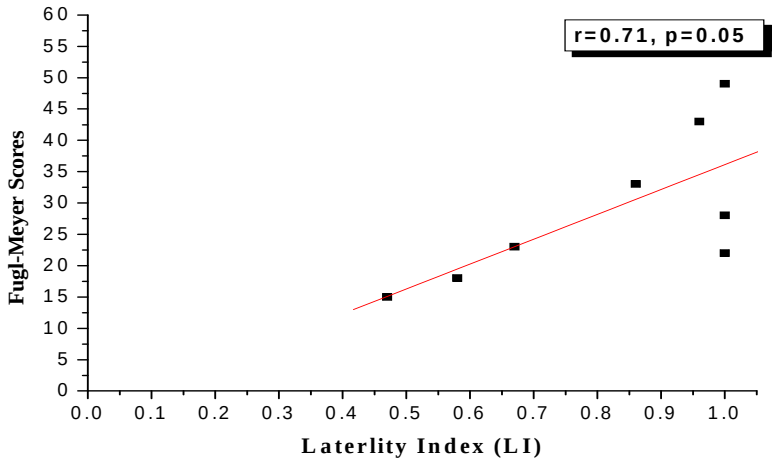

Figure 6.12. The relationship between FM and LI of the affected hand.

6.5. Discussion

Functional neuroimaging studies have been previously conducted on the cortical activation changes occurring with hand function recovery over time in brain injury patients [1]. Accordingly, no standardized motor task paradigm or analytic methods exist. The first study upon cortical activation changes according to hand function recovery over time was performed [18]. These workers followed up eight subcortical stroke patients for 3-6 months using fMRI. They estimated LI for the SMC, and demonstrated that activity of the damaged SMC increased significantly over time as the paretic hand regained function. However, this study was criticized because the motor task paradigm is important in studies of interval motor function changes by functional neuroimaging [6].

For exact performance of motor task, we adopted simple movements (wrist flexion-extension) and a fixed rate as the motor task paradigm. We set up the SMC, SMA, PMA and CRB as ROIs because these areas have been reported to have the neuroplastic potential for motor recovery in brain-injured patients [22].

Biological changes accompanying stroke recovery are thought to occur in ipsilateral brain regions adjacent to the lesion site and in contralateral homologous regions [6]. Other regions, including the PMA, CRB, putamen and parietal cortex have been postulated to play a role in recovery [3]. Few studies have used functional neuroimaging to support the notion that, a task-oriented training can induce cortical reorganization in stroke patients [23]. They demonstrated that functional recovery by physical intervention was associated with increased the ratio of contralateral SMC activity during movement of the affected hand.

In this Chapter, all eight patients showed cortical activation changes with significant motor recovery during 6 weeks training with the BSAT. We believe that cortical reorganization with motor recovery by the BSAT training in chronic hemiparetic stroke patients. In Task 2, movements of the affected hand resulted in changes in SMC in all patients and changes in the secondary motor areas. The activation of SMC was not changed by the unaffected hand movements (Task 1) in all patients. The activity of the ipsilateral SMC disappeared in three patients but contralateral SMC activity newly appeared. The LI for SMC of the affected hand significantly increased. Therefore, we believe that the the main cortical activation changes occurred in the SMC, as the contralateral SMC activity compared with that of ipsilateral SMC by the affected hand movements, was markedly increased in accordance with the motor recovery. These results are in agreement with those from previous functional neuroimaging studies. It has been believed that the clinical recovery in stroke patients is related with the increased contralateral SMC activity [2]. In addition, transcranial magnetic stimulation (TMS), study [3] demonstrated that clinical recovery in stroke patients is directly correlated to the enlargement of the hand motor area on the contralateral motor cortex .

The secondary motor, SMA and PMA may be activated by the mere imagination of complex movements [22]. However, the correlation between the changes of secondary motor area and the function recovery still remains a controversy [24]. Zaman et al. [25] reported that bilateral SMA activation disappeared and PMA activation of contralateral cortex newly appeared with a function recovery in a passive finger movement task. On the contrary, Loubinoux et al. [22] reported that SMA was activated bilaterally after arm trainings in stroke patients.

The present study demonstrated that activation in the CRB was a significant correlation with behavioural recovery. Activation of ipsilateral

CRB increased in the unilateral movements, and those of bilateral CRB was increased in the bilateral movements, which explains a underlying mechanism with motor recovery.

Moreover, several studies have been conducted to find pathophysiological mechanism of bilateral movements, and results in the present study are largely in agreement with the previous studies [26, 27]. Cohen et al. [26] was the first to prove the presence of bilateral motor cortex activation in two patients with congenital bilateral movements, using PET. Using fMRI and TMS in a patient with perinatal unilateral brain injury, Nirkko et al. [27] demonstrated that the direct ipsilateral coticospinal tract is involved in functional recovery with bilateral movements. Jang et al. [28] confirmed this it in patient with congenital brain disorder and Kim et al. [29] also reported that bilateral SMC was activated during bilateral movements of finger in all post-stroke patients in their fMRI experiments.

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7. Evaluation on Motor Recovery: DTI

7.1. Introduction

An impaired upper limb function is one of the most serious disabling sequent of stroke. Therefore, predicting the extent of motor dysfunction in the hemiplegic upper limb is important for stroke rehabilitation. Many studies have attempted to predict the prognosis of the hemiparetic hand following a stroke using clinical assessment, electrophysilogical studies or brain imaging methods as mentioned in prior Chapters. Of the various brain imaging methods, diffusion tensor imaging (DTI), a relatively new MRI technique, allows the orientation and the integrity of the white matter tracts to be determined by virtue of its ability to image water diffusion characteristics [1]. In the normal white matter, water molecules move relatively freely parallel to the nerve fiver tract, but their movements are restricted across the tracts, causing the diffusion anisotropy (DA) of the white matter. In MR diffusion, fractional anisotropy (FA), relative anisotropy (RA), the volume ratio (VR), and lattice index (LI) are commonly used to characterize the DA of a tissue [2]. Among them, FA is most widely referred as an anisotropic index. A tissue is considered to be fully isotropic when its FA is equal to 0, and fully anisotropic when its FA equal to 1.

An impairment of water diffusion in the white matter tracts may be correlated with the degree of damage to its structure. DTI can provide a quantitative measure of DA, and thus it can be used to obtain quantitative information about the microstructural integrity of the white matter tracts [3]. Since the introduction of DTI, several studies have shown that DA impairment may be correlated with motor dysfunction in stroke patients [4]. However, few

studies have shown that the degree of impairment of DA in the early stages of stroke can be used to predict the motor outcome of hemiparetic upper limb in stroke patients [5, 6].

3D white matter tractography is a powerful approach to anisotropic diffusion using DTI data set. Fiber white tract maps can be created, based on similarities between neighbouring voxels in the shape and orientation of the diffusion ellipsoid, and can be used for in analysis of axonal networks in the brain [7].

Some studies on human stroke analyzed invariant anisotropy demonstrated the reduced diffusion anisotropy in white matter ischemia [8, 9]. It is of interest, however, whether stroke affects an important axonal projection such as the corticospinal tract when neurological deficits suggest its involvement. Precise imaging localization of stroke reinforces neurological findings, and demonstration of stroke and neuronal fiber tracts on the same images might be helpful. 3D white matter tractography can used to show axonal projections and other brain components simultaneously, but previous discussions have rather been confined to technical aspects in healthy subjects.

Therefore, the aim of this Chapter was to measure diffusion anisotropy to examine changes of FA of chronic stroke patients before and after 6-week training with the BSAT. In addition, we examined changes amount of fiber tracking using 3D white matter tractography before and after 6-week training. Finally, we determined the correlation with these parameters and upper-limb motor function recovery.

7.2. Background

7.2.1. Diffusion Tensor Imaging (DTI): Principles

Diffusion tensor imaging measures the water diffusion tensor using diffusion-weighted pulse sequences sensitive to microscopic random water motion. The resultant diffusion-weighted images (DWI) display and allow for quantification of how water diffuses along axes or diffusion encoding directions. In the simplest case of a single diffusion value (D), the DWI signal intensity (S) that results in a pixel following application of the diffusion gradients is $S = S_o \exp(-bD)$, which requires the signal intensity in the same pixel from a different image with no diffusion gradient applied (So) and b, or the gradient "b value," which is a function of the diffusion sensitizing gradient strength and duration. Single diffusion value (D) can thus be easily calculated from the DWI and a non– diffusion-weighted reference image.

White matter may exhibit remarkable differences in diffusion, depending on which direction the diffusion sensitizing gradients are applied and also on the direction of the white matter tracts imaged [1]. Diffusion-weighted images are bright where diffusion (measured as the apparent diffusion coefficient [ADC]) is small and dark where diffusion is greater. As shown in Figure 7.1, the splenium of the corpus callosum, in which the tracts are oriented in the left-right direction near the center of the image, gets dark if the gradients are in the left-right direction, since the ADC is large along that direction; however, the same region is bright if the gradients are in the front-back direction, perpendicular to the tract, since the diffusion is reduced in that direction. This demonstrates that water diffusion in the brain is anisotropic; that is, water diffusion is constrained by microscopic structures such as myelin sheaths and white matter tracts. This results in a directional diffusion of water.

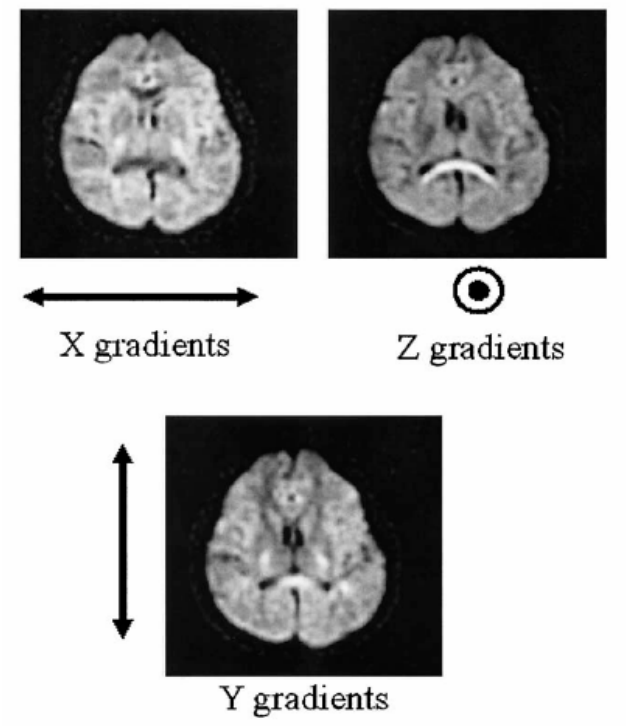

Figure 7.1. Diffusion-weighted images in which brighter regions indicate reduced diffusion values, showing the effect of different directions for the diffusion sensitizing gradients. The splenium of the corpus callosum is aligned mainly with the x direction and has a large diffusion coefficient in that direction. It is thus dark when the gradients are in the x direction (upper left). When the gradients are perpendicular to the x direction (upper right and below), the central region is bright, since diffusion is reduced in those directions.

The simplest model of such a phenomenon is to think of the diffusion in each image pixel as being like a footballshaped ellipsoid that is tilted in different directions, depending on the local diffusion coefficients (Figure 7.2). The ellipsoid has three principal diffusion values: D1, D2, and D3, which correspond to the diffusion of water in three main directions. If the tissue is isotropic and water can freely diffuse, then D1 = D2 = D3. Otherwise, the tissue is anisotropic with the convention that D1 is the largest diffusion coefficient, D1 > D2 > D3.

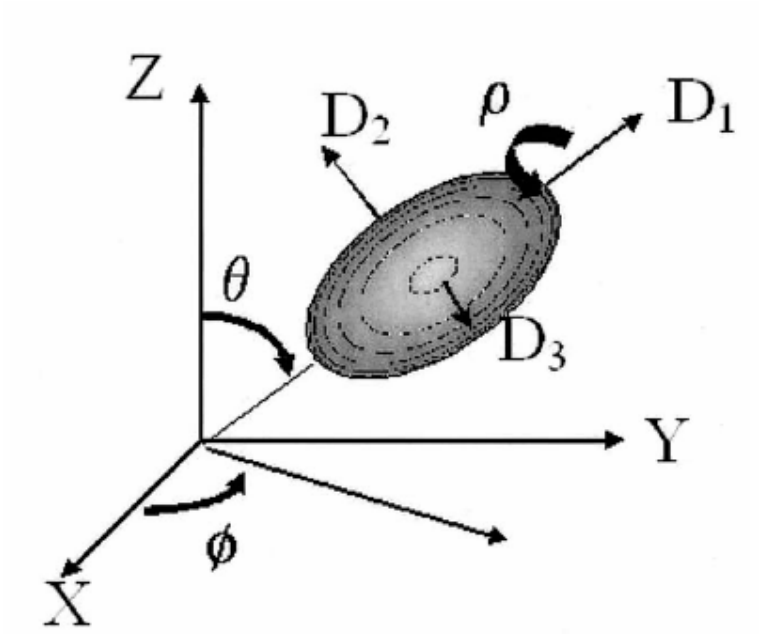

Figure 7.2. Diagram of the diffusion ellipsoid showing the principle diffusivities: D1, D2, and D3. The eigenvectors are the arrows that point along the direction of D1, D2, and D3. The ellipsoid is rotated from the scanner coordinate system (X, Y, Z) by angles (ρ, θ, ϕ).

For an oriented, anisotropic tissue, such as white matter, cartilage, or myocardium, there will be one direction, such as along the axon in white matter, where water has the largest diffusion coefficient. There will be less diffusion along the other directions. Although actual tissue is much more complex and may be oriented in more than one major direction, this model has proven useful to better describe the properties of oriented tissues [2].

If the diffusion ellipse is oriented such that D1 is along the x axis, D2 is along the y axis, and D3 is along the z axis, then the diffusion coefficient (Dx) measured with a diffusion gradient along the x axis will be Dx = D1 and Dy = D2 and Dz = D3. In this simple case, the diffusion tensor (**D**) is described as a matrix:

$$D = \begin{bmatrix} D1 & 0 & 0 \\ 0 & D2 & 0 \\ 0 & 0 & D3 \end{bmatrix} \qquad (7.1)$$

The values D1, D2, D3 are the eigenvalues of the tensor. There are also three eigenvectors of the matrix that describe the vectors pointing along the principal directions of diffusivity. The form of the matrix is simple, since the natural coordinate system of the ellipse is aligned with the scanner coordinate system. In the above case, the three eigenvectors point along x, y, and z.

The ellipse in a given pixel is described in the scanner coordinate system so we have a common coordinate system for each pixel, since the diffusion tensor may rotate to different angles in different pixels. This might be the case for a white matter tract that rotates as it moves from pixel to pixel. Rotations along ρ, θ, and ϕ result in a rotated matrix (**D***r*). Rotation of specific angles, such as θ, is accomplished using a rotation matrix, R(θ).

$$\begin{aligned} Dr &= R(\theta)R(\phi)R(\rho)DR^{-1}(\rho)R^{-1}(\varphi)R^{-1}(\theta) \\ &= \begin{bmatrix} Dxx & Dxy & Dxz \\ Dxy & Dyy & Dyz \\ Dxz & Dyz & Dzz \end{bmatrix} \end{aligned} \qquad (7.2)$$

The elements of the matrix are functions of the original values D1, D2, and D3 and the rotation angles. The eigenvectors, which always point along the major diffusion directions, would now also be rotated.

Thus, in general, there are six quantities to be calculated in each pixel: the diffusivities D1, D2, and D3 and the rotation angles ρ, θ, and θ that describe the direction of the eigenvectors. These measures depend on the

gradient b value, which is a function of the diffusion sensitizing gradient strengths and duration; in a diffusion tensor situation, this is expressed as a gradient b-value matrix (**b**). Diffusion tensor measurement requires that images be acquired with six different b-value matrices **b**. In addition, a seventh measurement is required with no diffusion weighting to provide a reference measure of signal intensity without a diffusion gradient (So) [2]. These seven measurements are the minimum needed to calculate the full diffusion tensor, although more are often used to improve the stability of the calculation. It is important that the measurements be taken with gradient directions that are independent and not coplanar. The gradient direction "scheme" used for calculation can differ among various MR scanner manufacturers. It is important to know what directions were used to properly calculate the diffusion tensor. A popular way to distribute the gradient directions is to use vectors in which the endpoints are uniformly distributed on a sphere centered at the origin. With other models, other schemes are possible. In a cylindrical model of diffusion, we would have the simplified case that D1 > D2, D3 and D2 = D3. In this case, only four measurements are needed [7].

Once a gradient direction scheme has been chosen and suitable measurements taken, the diffusion tensor eigenvalue calculation will yield values of D1, D2, and D3 and the three eigenvectors that correspond to these diffusion values in each pixel. The ADC value in each pixel is easily calculated as ADC = (D1+D2+D3)/3 = Trace (**D**)/3. It is an interesting result of the mathematics of tensors that the Trace is an invariant, or the same in all coordinate systems. Thus, the ADC calculated this way is independent of head rotation, for example.

There are several different proposals on how to calculate the anisotropy (A) in a pixel (Table 7.1, Figure 7.3) [8, 9]. The simplest measure is the ratio A = D3/D1, where the minimum eigenvalue is divided by the maximum value.

Table 7.1. Anisotropy measures.

Anisotropy Measure	Formula	Comment
Fractional Anisotropy (FA)	$FA = \sqrt{\frac{3}{2}}\sqrt{\frac{(D1-D)^2+(D2-D)^2+(D3-D)^2}{D1^2+D2^2+D3^2}}$	Independent of sorting of eigenvalues
Relative Anisotropy (RA)	$RA = \sqrt{\frac{1}{3}}\sqrt{\frac{(D1-D)^2+(D2-D)^2+(D3-D)^2}{D^2}}$	Independent of sorting of eigenvalues
Volume Ratio (VR)	$VR = \frac{D1 \cdot D2 \cdot D3}{D^3}$	Independent of sorting of eigenvalues
Minimum/Maximum Ratio (A)	$A = \frac{D^3}{D^1}$	Dependent of sorting of eigenvalues

D=Apparent Diffusion Correlation (ADC)=(D1+D2+D3)/3.

Isotropic material would have A = 1 and anisotropic material would have A <1. Such ratios depend on "sorting" the eigenvalues into size order, which can introduce a bias that is avoided by sorting independent measures [8]. Most authors have begun to use fractional anisotropy (FA) due to its simple scaling between 0 and 1 and its use of all of the eigenvalues.

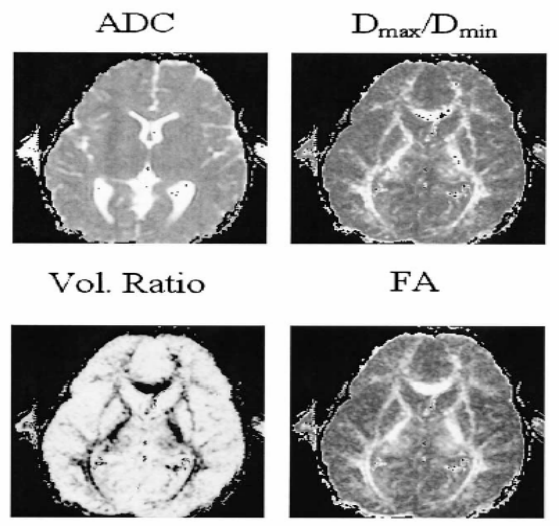

Figure 7.3. Images illustrating various ways of expressing the diffusional anisotropy. The upper left image shows the apparent diffusion coefficient image. Other images, showing anisotropy, are the ratio of the maximum and minimum eigenvalues of the diffusion tensor (upper right), the volume ratio (lower left), and the fractional anisotropy (lower right).

It is also of interest to display the direction of the eigenvectors in each pixel to visualize the fiber directions. Authors have displayed small lines [8] to indicate the projection of the principle eigenvector onto the plane of the picture, small ellipsoids [1] to show all of the directions, and color map schemes [2], where different hues indicate different directions.

7.2.2. Diffusion Tensor Tractography: Principles

7.2.2.1. Reconstruction Algorithm

The 3-D tract reconstruction was performed using the FACT (Fiber Assignment by Continuous Tracking) method (Figure 7.4), which performs a straightforward linear line propagation based on the v_1 vector angle. An anisotropy threshold of FA > 0.2 was used, while the angle of progression was restricted by using an inner product of more than 0.75 between consecutive eigenvectors [10].

Figure 7.5 shows a schematic diagram of the fiber reconstruction process. Suppose there is a tract with structure shown in Figure 7.5A. DTI measurement provides the fiber orientation information shown in Figure 7.5B. For fiber reconstruction, a tract of interest first needs to be identified and marked by a region of interest (ROI). Two possible reconstruction approaches are demonstrated. In first, the so-called ‘from-ROI′ approach (Figure 7.5C), tracking orientates from the ROI. The ROI contains only one pixel and, as a result, only 1 line is produced in the ″from-ROI″ approach, which restricts the labeling to merely a segment of the tract. In the second, so-called ″brute-force″ approach, all pixels are visited and examined and all tracts originating from such pixels and penetrating the ROI are tracked. This approach is much more time-consuming but leads to more comprehensive delineation of the tract.

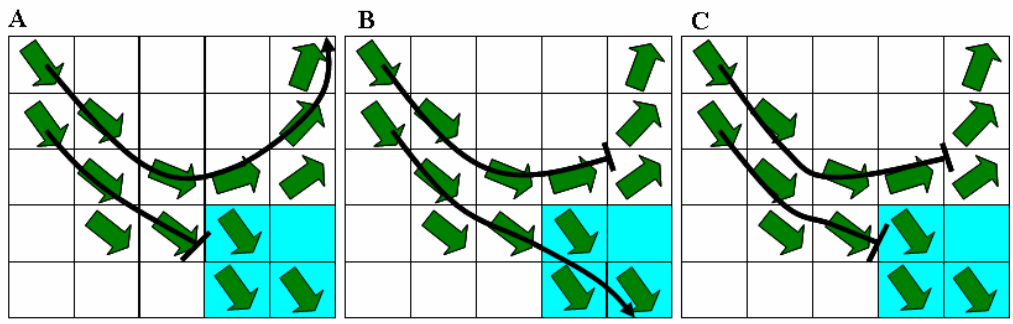

Figure 7.4. Schematic diagram of FACT fiber tract reconstruction based on DTI data. Once the fiber orientation (v_1) is estimated at each pixel, putative projections are traced by propagation a line along the estimated fiber orientations. The propagation terminates either when it enters an area with anisotropy lower than a threshold (A: dark boxes) or when the trajectory has a turn judged as too sharp by an inner product between two connected pixels (B). In FACT, both criteria are applied (C).

7.3. Materials and Methods

7.3.1. DTI Acquisition

Stroke patients in section 3.2 of Chapter 3 were participated in this study. DTI was performed before and after the 6-week training program with the BSAT. For the anatomic image, conventional T2-weighted images were acquired, and a single shot spin echo planner imaging DTI sequence was used to produce diffusion tensor images. For diffusion tensor imaging, 33 contiguous axial images were acquired at the internal capsule level and the imaging parameters were: TR/TE/NEX=12000ms/93ms/1, slice thickness=4mm, matrix= 256×256, FOV= 250×250mm^2 and b=1000s/mm^2. Fractional anisotropy (FA) maps were obtained by using dTVII, Version 1.72 (VOLUME-ONE, University of Tokyo Hospital, Tokyo, Japan).

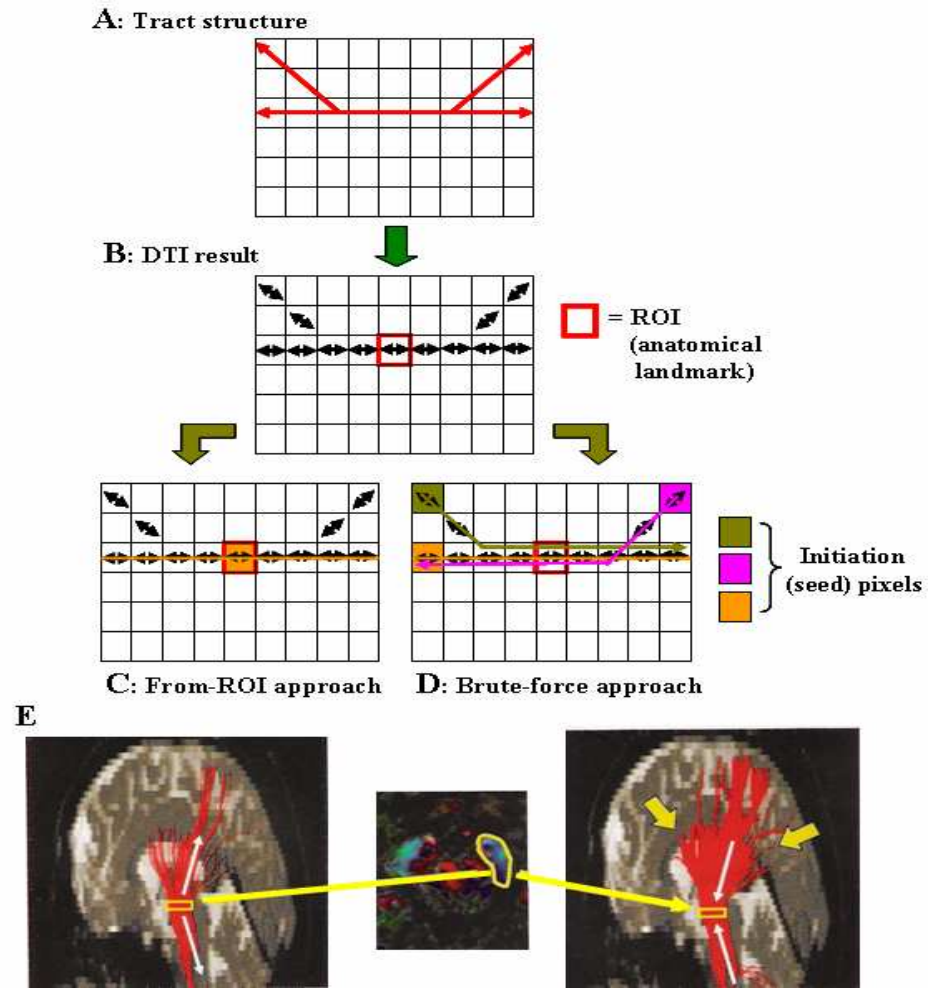

Figure 7.5. Principles of tract reconstruction using the "from ROI" and the "brute-force" approaches. (A) Example of a tract structure with 2 branching points. (B) Results of DTI measurement, a vector field that shows the fiber orientation at each pixel. A bold box shows the anatomical landmark where a ROI is defined. (C) Results of the tract reconstruction using the "from ROI" approach, in which tracking is started from the ROI. This generally leads to an incomplete delineation of the tract. (D) Results of the "brute force" approach, in which tracking is started from all pixels. Several initiation (seed) pixels from which the tracking can lead to same ROI are demonstrated. (E) Results of actual tracking using the cerebral peduncle as a reference ROI. The left and right panels show results for the "from ROI" and "brute force" approaches, respectively.

7.3.2. ROI (Region of Interest)

The FA for analyzing to extent of the injured corticospinal tract was determined by measuring the region of interest (ROI) in the FA map. The FA was measured in the posterior limb of the internal capsule (Plic) in an unaffected site (a) and in the affected site (b) (Figure 7.6). The Figure 7.7 show two-dimensional atlas of brain white matter. The injury to the internal capsule at the affected site was determined by calculating the ratio of the affected site to the unaffected site using both FAs. In other words, the FA ratio was calculated from 'FA ratio (FAR) (%)=b/a×100', and this reflected the conserved FA level of the affected site's posterior limb of the internal capsule.

7.3.3. 3-Dimensioanl Fiber Tracking

From the DTI, brain fiber tracking was performed using the free software Volume-One and TVII (VOLUME-ONE, University of Tokyo Hospital, Tokyo, Japan) to composed the tractography. The seed area was set as the ROI was drawn around the posterior of the internal capsule on the axial image of the axially reformatted FA map. Fiber tracking was stopped when the FA values was <0.18. On these images, injured nerve fibers of the affected site could be compared to those of the unaffected site by dimensional visualization. We measured the amount of seed point, tract line, draw line in ROIs of the affected site and unaffected site, respectively.

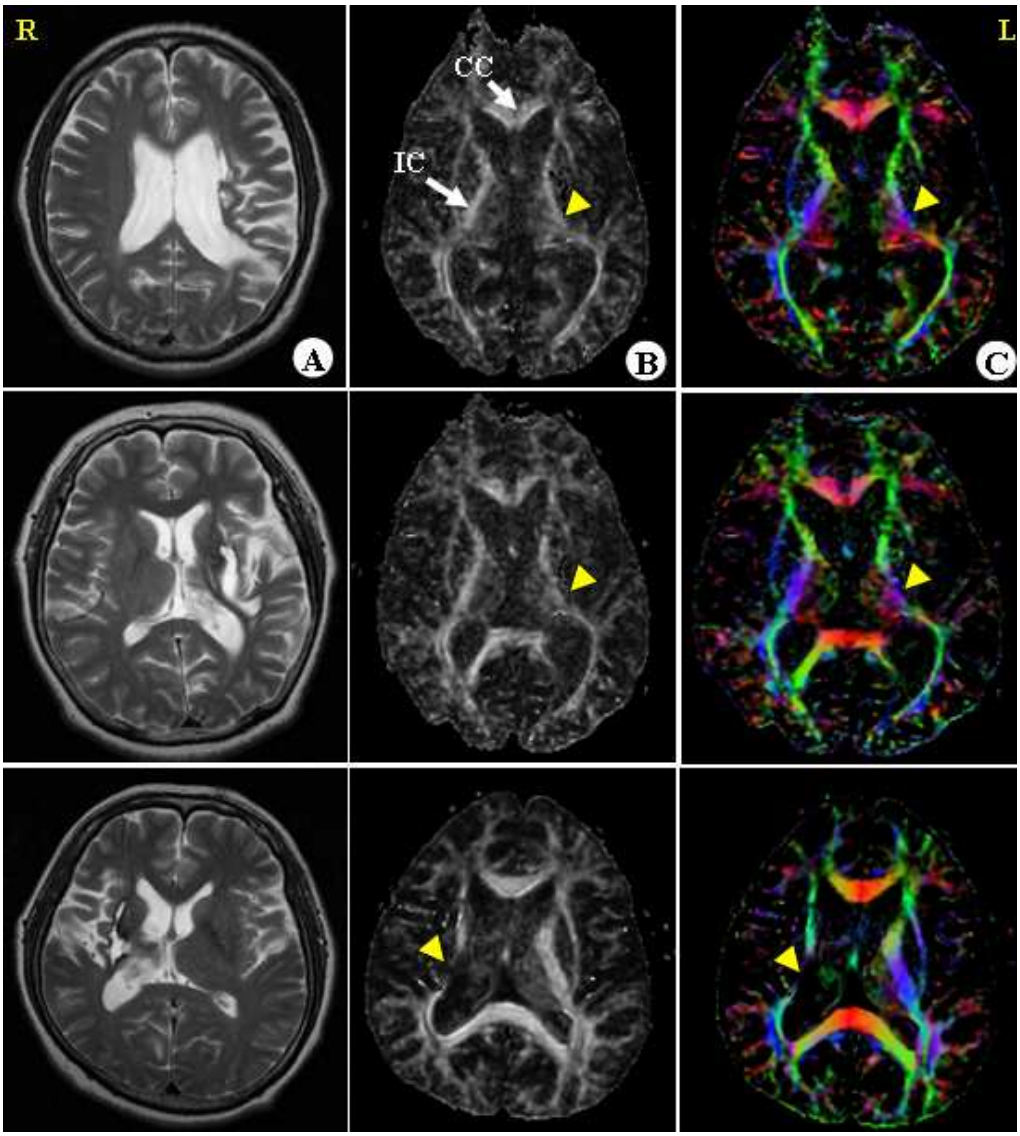

Figure 7.6. T2-weighted MR images (A), axial fractional anisotropy (FA) maps (B) and axial color maps (C) showing the locations of typical regions of interest used in this study. On diffusion tensor image, it reveals deceased signal intensity on posterior limb of internal capsule (arrow head) and it means decreased fractional anisotropy of that lesion. IC: internal capsule, CC: corpus callosum.

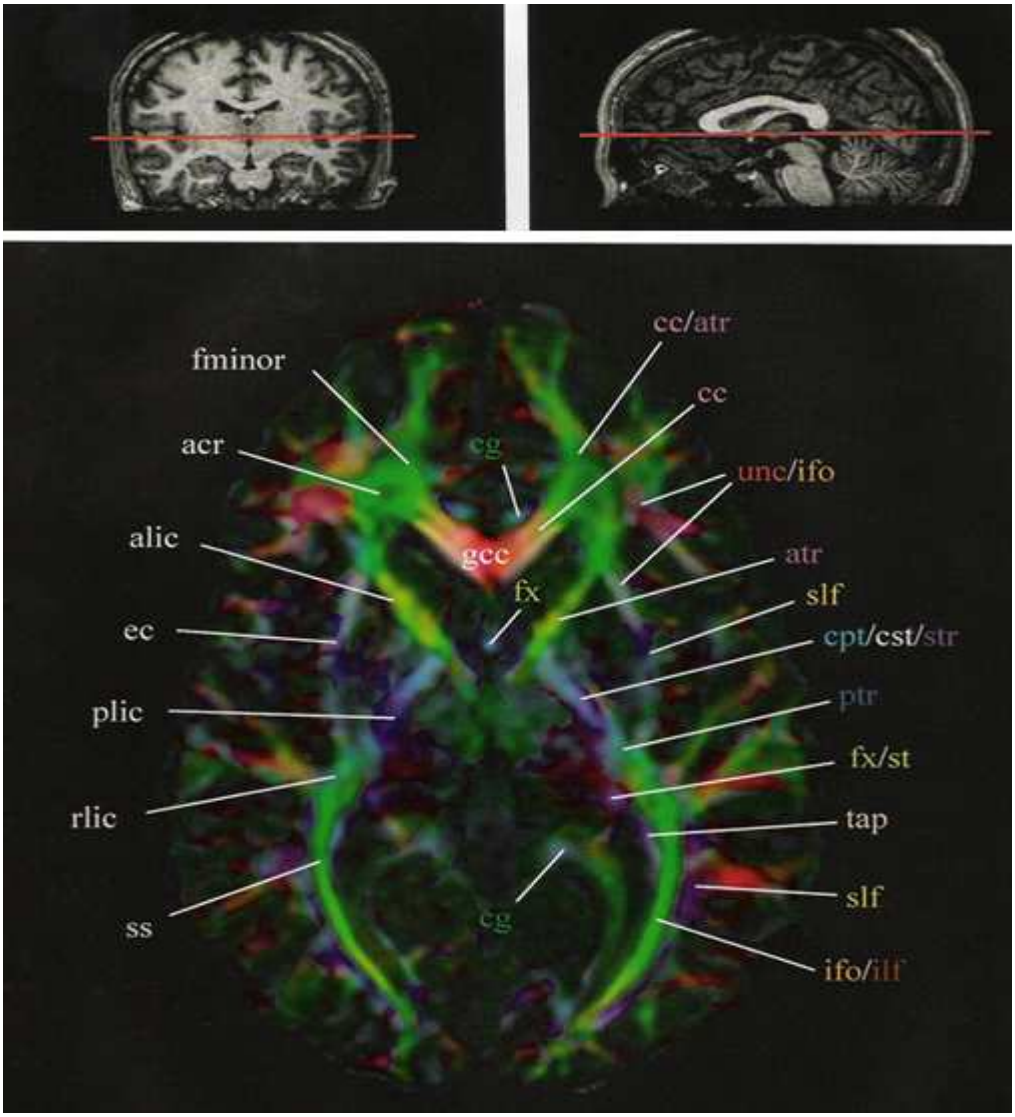

Figure 7.7. Two-dimensional atlas of brain white matter in axial color map.
acr: anterior corona radiate, alic: anterior limb of the internal capsule, atr: anterior thalamic radiation, cc: corpus callosum, cg: cingulum, cpt: corticopontine tract, cst: corticospinal tract, ec: external capsule, fminor: forceps mimor, fx: fornix, gcc: genu of the corpus callosum, ifo: inferior fronto-occipital fasciculus, ilf: inferior longitudinal fasciculus, plic: posterior limb of the internal capsule, ptr: posterior thalamic radiation, rlic: retrolenticular part of the internal capsule, slf: superior longitudinal fascisulus, ss: sagittal stratum, str: superior thalamic radiation, tap: tapetum, unc: uncinate fasciculus.

7.3.4. Statistical Analysis

In order to illustrate the impact of a stroke on the unaffected hemisphere of the patient group, the FA in the Plic was also measured in the unaffected hemisphere.

To investigate changes of the FAR and white matter fiber tract before and after training (at 6 weeks of training using the BSAT), one-way repeated ANOVA was used. Spearman's correlation coefficients describing the bi-variate relationship between FA ratio and motor recovery were calculated. In addition, we estimated the correlation with the amount of draw line and motor recovery in white matter fiber tracking. An alpha level of <0.05 was used as the level of significance.

7.4. Results

7.4.1. Changes of FA Ratio Before and After the Training

Table 7.2 shows FA ratio before and after the training with the BSAT. In all patients, the FA ratio significantly increased after the training ($p<0.05$).

7.4.2. Correlation Between FAR and Motor Recovery

The relationship between FM and FA ratio of the patients was examined. As shown in Figure 7.8, the FM of patient 6 was the lowest at 15 and 22 points before and after training, respectively, but FAR, measured by 55.00% and 62.38%, was not lower than patient 3, 7, and 8. On the other hand, patient 6 had the lowest FM at 15 points, but higher FAR than patient 3, 4, 7, and

Table 7.2. Changes of FA ratio before and after training with the BSAT.

Patient	Before			After			dFAR
	FA unaf.	FA aff.	FAR (%)	FA unaf.	FA aff.	FAR (%)	
1	0.61	0.33	54.10	0.61	0.41	67.21	13.11
2	0.62	0.34	54.84	0.62	0.48	77.42	22.58
3	0.66	0.25	37.88	0.66	0.35	53.03	15.15
4	0.65	0.25	38.46	0.66	0.32	48.48	10.02
5	0.60	0.49	81.67	0.58	0.50	86.21	4.54
6	0.60	0.33	55.00	0.61	0.38	62.30	7.30
7	0.62	0.28	45.16	0.68	0.39	57.35	12.19
8	0.62	0.28	45.16	0.69	0.36	52.17	7.01
Mean	0.62	0.32	51.53	0.64	0.40	63.02	12.49

unaf.=unaffected side, aff.=affected side, FRA=fractional anisotropy ratio ((affected side FA/unaffected side FA) ×100), dFAR= last FAR-initial FAR.

8. FA ratio from the initial and final DTI did not show a linear correlation with motor impairment.

Figure 7.9 shows the relationship between the initial FA ratio and the upper-limb motor recovery after 6-week training with the BSAT. In patients 5 and 6, whose initial FA ratios were 81.67% and 55.00%, respectively, motor recovery was not found in the upper limb, with scores of 6 and 7 points, respectively. Initial FA ratio did not show a linear correlation with motor recovery.

However, in patients with higher change of FA ratio, like patients 2 and 3, motor recovery was greatly improved by 21 and 12 points, respectively. A significant correlation was found between the change of FA ratio and the motor recovery in the posterior limb of IC ($r=0.88$, $p=0.002$) (Figure 7.10).

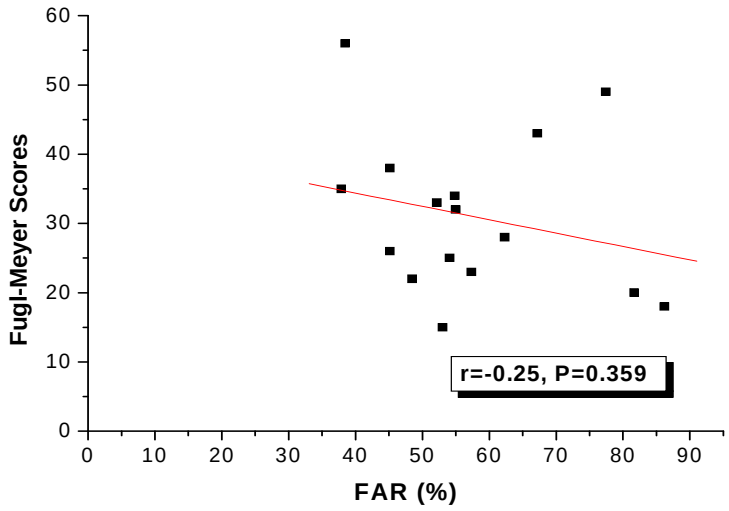

Figure 7.8. The relationship between the fractional anisotropy ratio and FM is graphically represented. The FA ratio did not show a proportional relationship to FM scores.

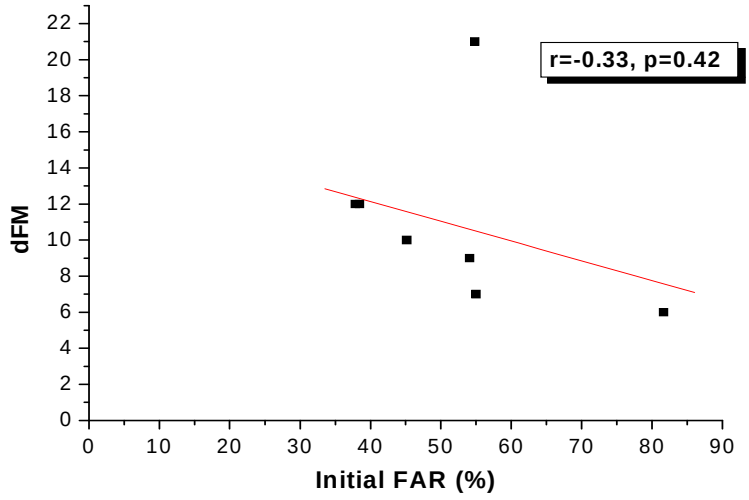

Figure 7.9. The relationship of the initial fractional anisotropy ratio to the extent of improvement after 6weeks training is represented. The extent of improvement was calculated by subtracting the score on initiation from the score after 6 weeks. The initial FA ratio is not proportional to the extent of improvement.

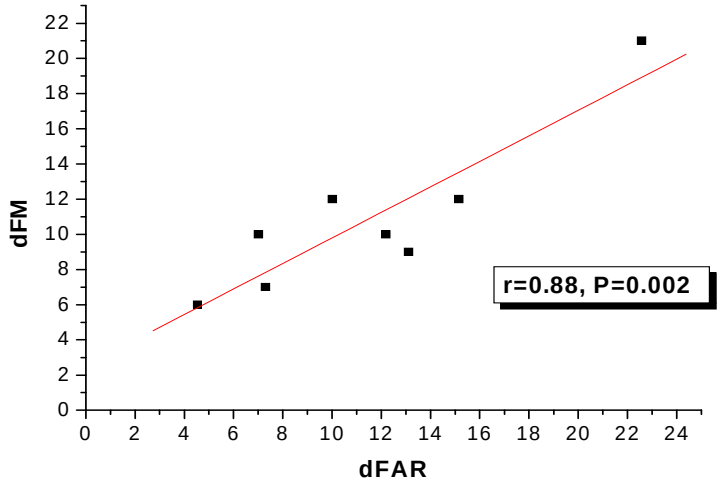

Figure 7.10. The relationship of the fractional anisotropy ratio change to the extent of improvement after 6weeks training is represented. The initial FA ratio change is proportional to the extent of improvement: the higher change of the FA ratio, the larger the extent of improvement.

7.4.3. Three-Dimensional Fiber Tracking Analysis

Table 7.3 shows the amount of fiber pass through plic before and after the training with the BSAT, when seed point were selected as 161 point. In all patients, the fiber tracking ratio (FTR) significantly increased after the training (p<0.05).

7.4.4. Correlation Between FTR and Motor Recovery

Figure 7.11 shows the relationship between the fiber tracking (FT) ratio and FA ratio before and after 6-week training with the BSAT. A significant correlation was found between the change of FT ratio and FA ratioin the posterior limb of IC (r=0.80, p=0.001).

Table 7.3. Amount of fiber pass through plic before and after the training with the BSAT (seed points = 161).

Patient	Before			After			dFTR
	FT unaf.	FT aff.	FTR (%)	FT unaf.	FT aff.	FTR (%)	
1	161	73	45.34	161	110	68.32	22.98
2	161	89	77.02	161	150	93.17	37.89
3	161	69	42.86	161	113	70.19	27.33
4	161	52	32.30	161	98	60.87	28.57
5	161	115	71.43	161	143	88.82	17.39
6	161	63	39.13	161	109	67.70	28.57
7	161	53	32.92	161	94	58.39	25.47
8	161	62	38.51	161	101	62.73	24.22
Mean	161	72.00	47.44	161	114.75	71.27	26.55

unaf.=unaffected side, aff.=affected side, FTA=fiber tracking ratio ((affected side FT/unaffected side FT) ×100), dFTR= last FTR-initial FTR.

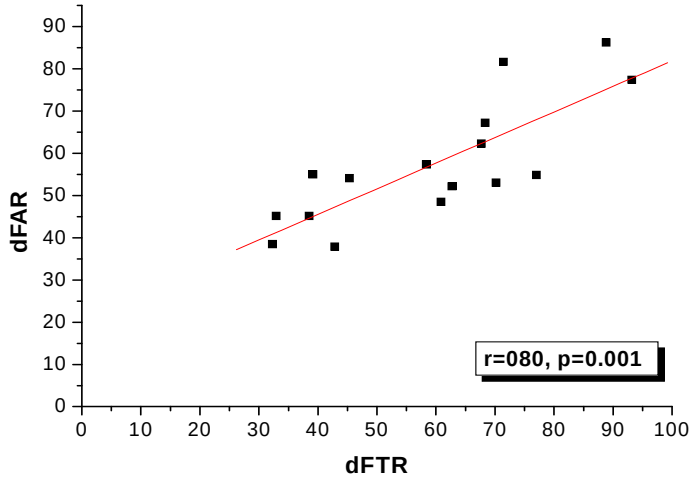

Figure 7.11. The relationship of the fiber tracking ratio and fractional anisotropy after 6weeks training is represented. The extent of change was calculated by subtracting the ratio on initiation from the score after 6 weeks. The change of FT ratio is proportional to the change of FA.

Figure 7.12 shows the relationship between the fiber tracking (FT) ratio and the upper-limb motor recovery after 6-week training with the BSAT. In patients 1 and 5, whose initial FT ratios were 22.98% and 17.39%, respectively, motor recovery was found in the upper limb, with scores of 9 and 6 points, respectively. Therefore, FTR show a linear correlation with motor recovery (r=0.87, p=0.05).

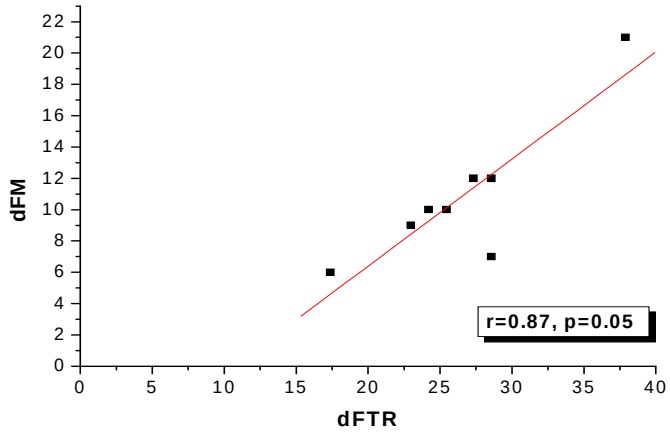

Figure 7.12. The relationship of the fiber tracking ratio to the extent of improvement after 6weeks training is represented. The extent of improvement was calculated by subtracting the ratio on initiation from the ratio after 6 weeks. The FT ratio is proportional to the extent of improvement.

Figure 7.13~7.16 show 3-dimensional tractography before and after 6-weeks training with the BSAT. Tactography shows the corticospinal tract form various angles such as the axial, sagittal and coronal view. In eight patients, 3D fiber tract maps showed corticospinal tract in close proximity to the hemorrhage but not to pass through it. Before the training, there was little corticospinal tract in the affected side relative to the unaffected side in all patients. After 6 weeks trainng, almost all sides of the corticospinal tract were conserved in Patient 2, 5, and 8, although there was a little displacement by hemorrhage. The conservation of the corticospinal tract by motor cortex did not correlation with the motor recovery.

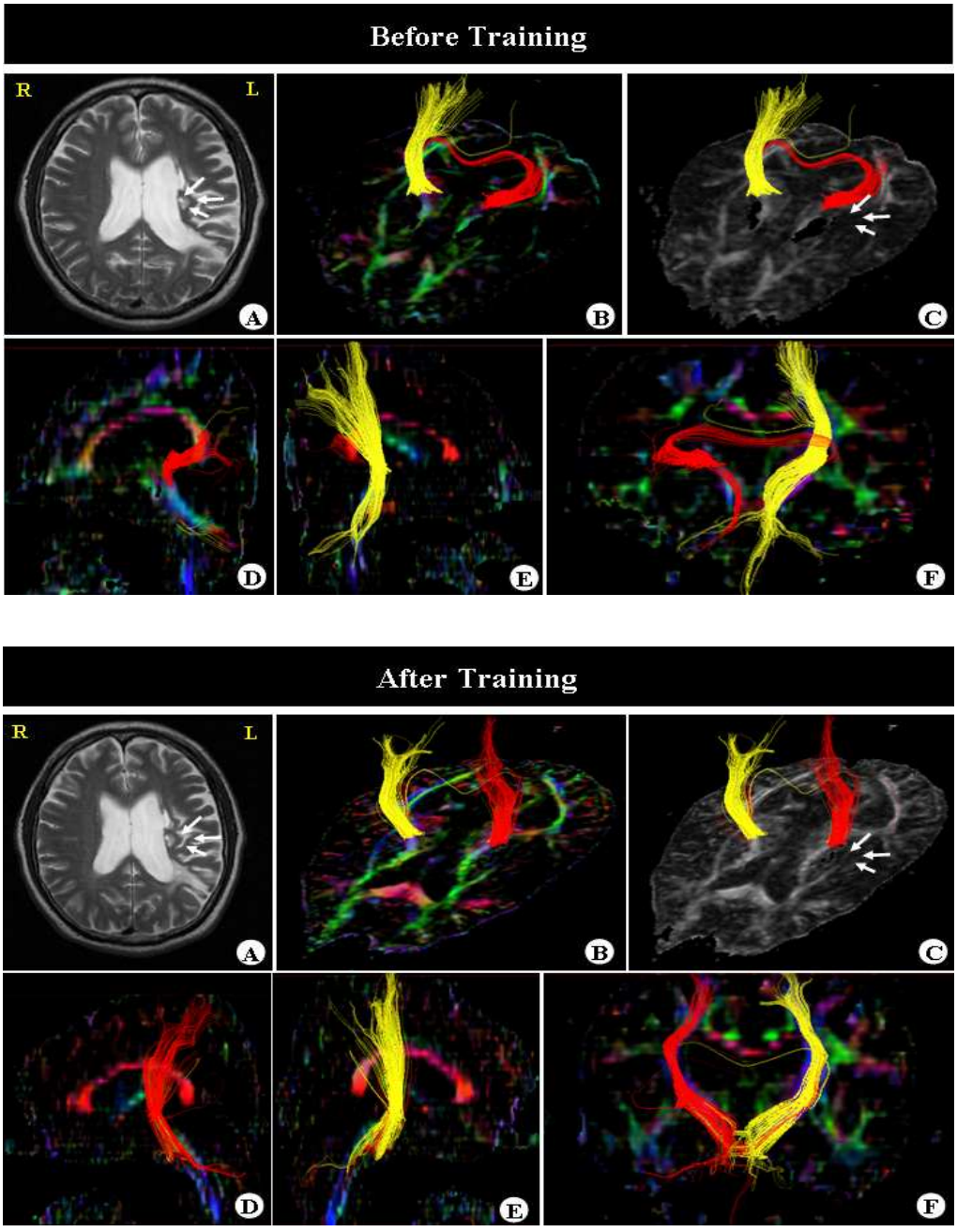

Figure 7.13. Tractography in Patient 5, A: axial T2-weighted image, B: 3D tractograpy superimposed on an axial color map, C: 3D tractograpy superimposed on an axial FA map, D: 3D tractograpy superimposed on a left sagittal color map, E: 3D tractograpy superimposed on a right sagittal color map, F: 3D tractograpy superimposed on a coronal color map.
Corticospinal tract of the affected side: red lines, unaffected side: yellow lines.

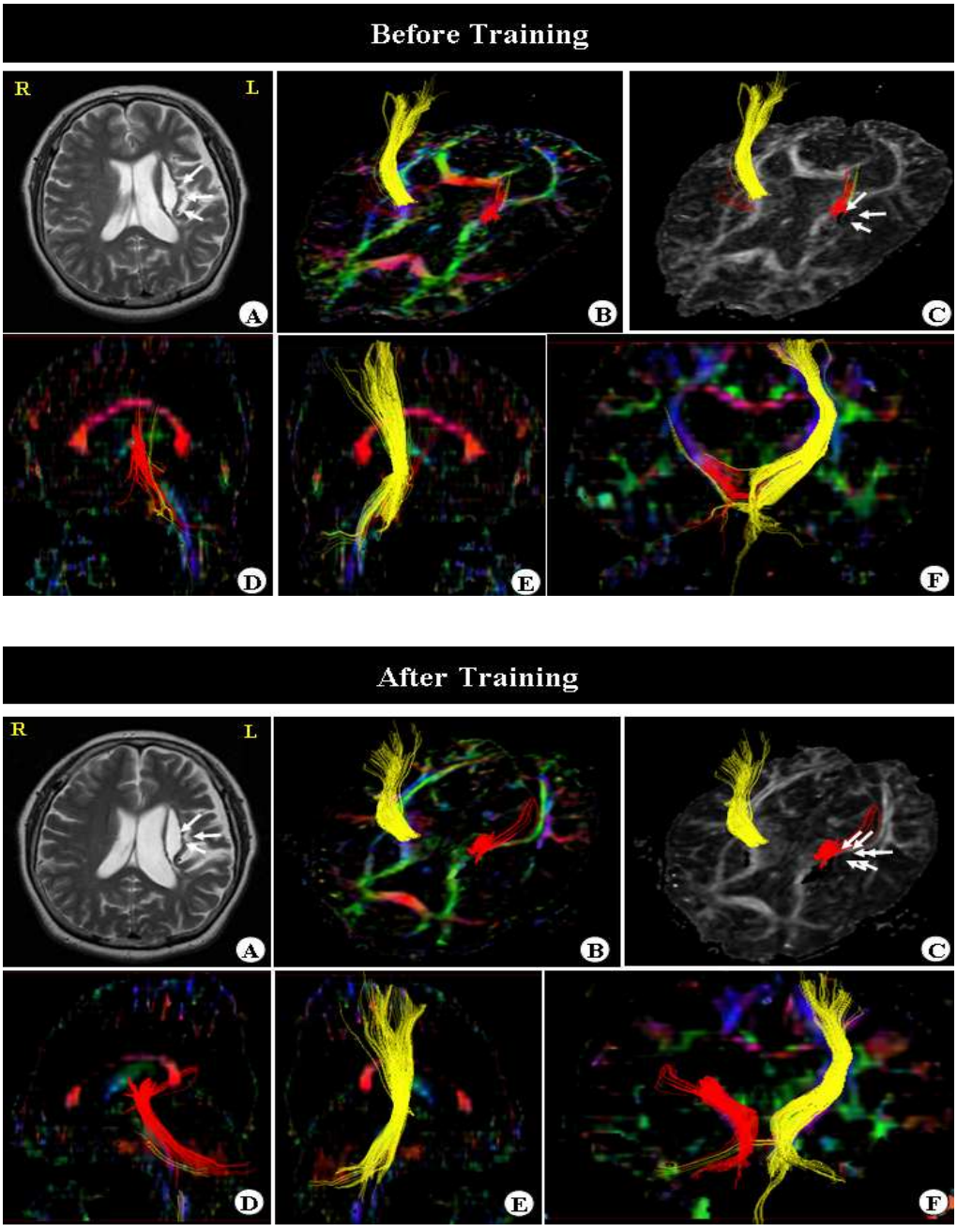

Figure 7.14. Tractography in Patient 6, A: axial T2-weighted image, B: 3D tractograpy superimposed on an axial color map, C: 3D tractograpy superimposed on an axial FA map, D: 3D tractograpy superimposed on a left sagittal color map, E: 3D tractograpy superimposed on a right sagittal color map, F: 3D tractograpy superimposed on a coronal color map.
Corticospinal tract of the affected side: red lines, unaffected side: yellow lines.

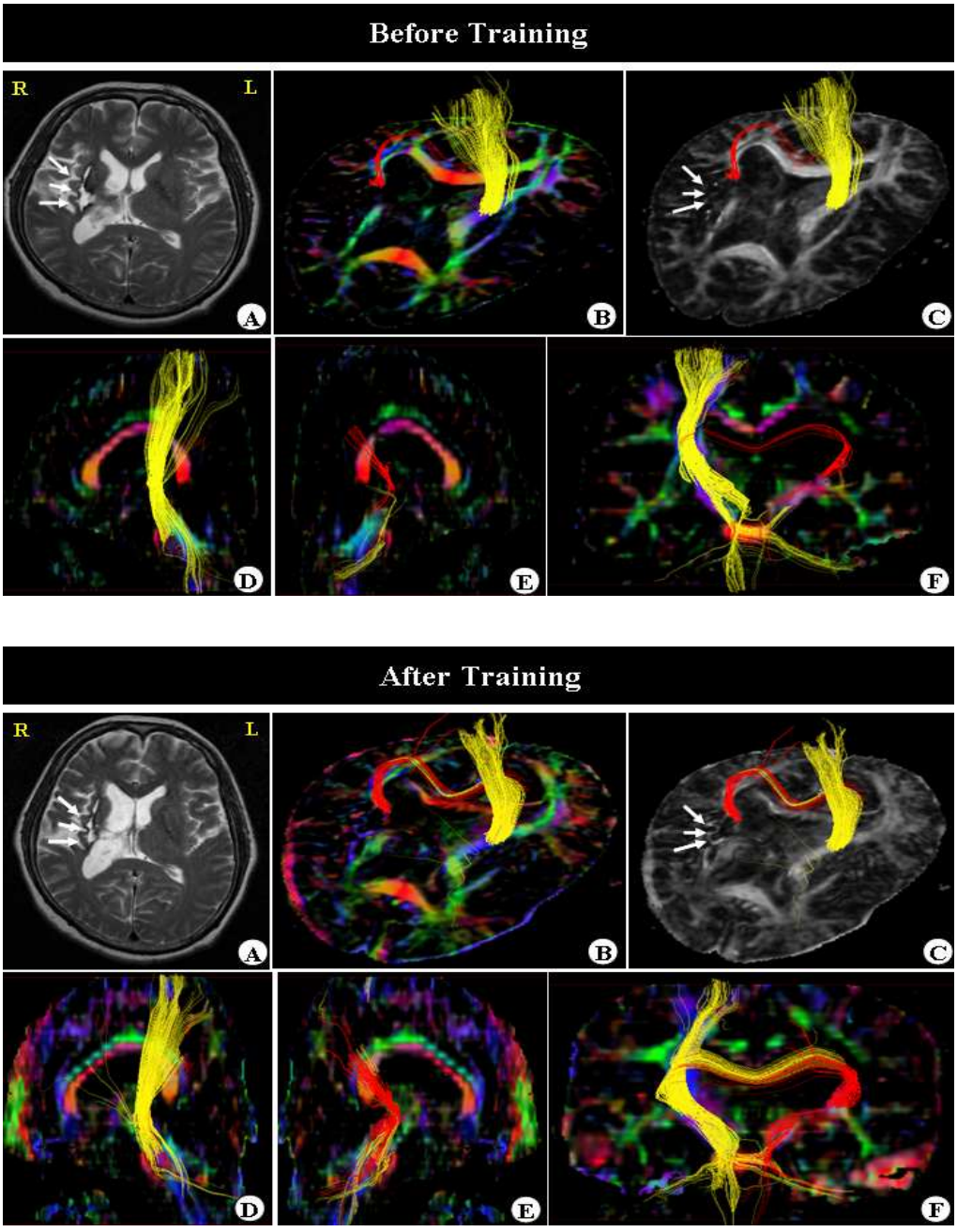

Figure 7.15. Tractography in Patient 7, A: axial T2-weighted image, B: 3D tractograpy superimposed on an axial color map, C: 3D tractograpy superimposed on an axial FA map, D: 3D tractograpy superimposed on a left sagittal color map, E: 3D tractograpy superimposed on a right sagittal color map, F: 3D tractograpy superimposed on a coronal color map.
Corticospinal tract: of the affected side: red lines, unaffected side: yellow lines.

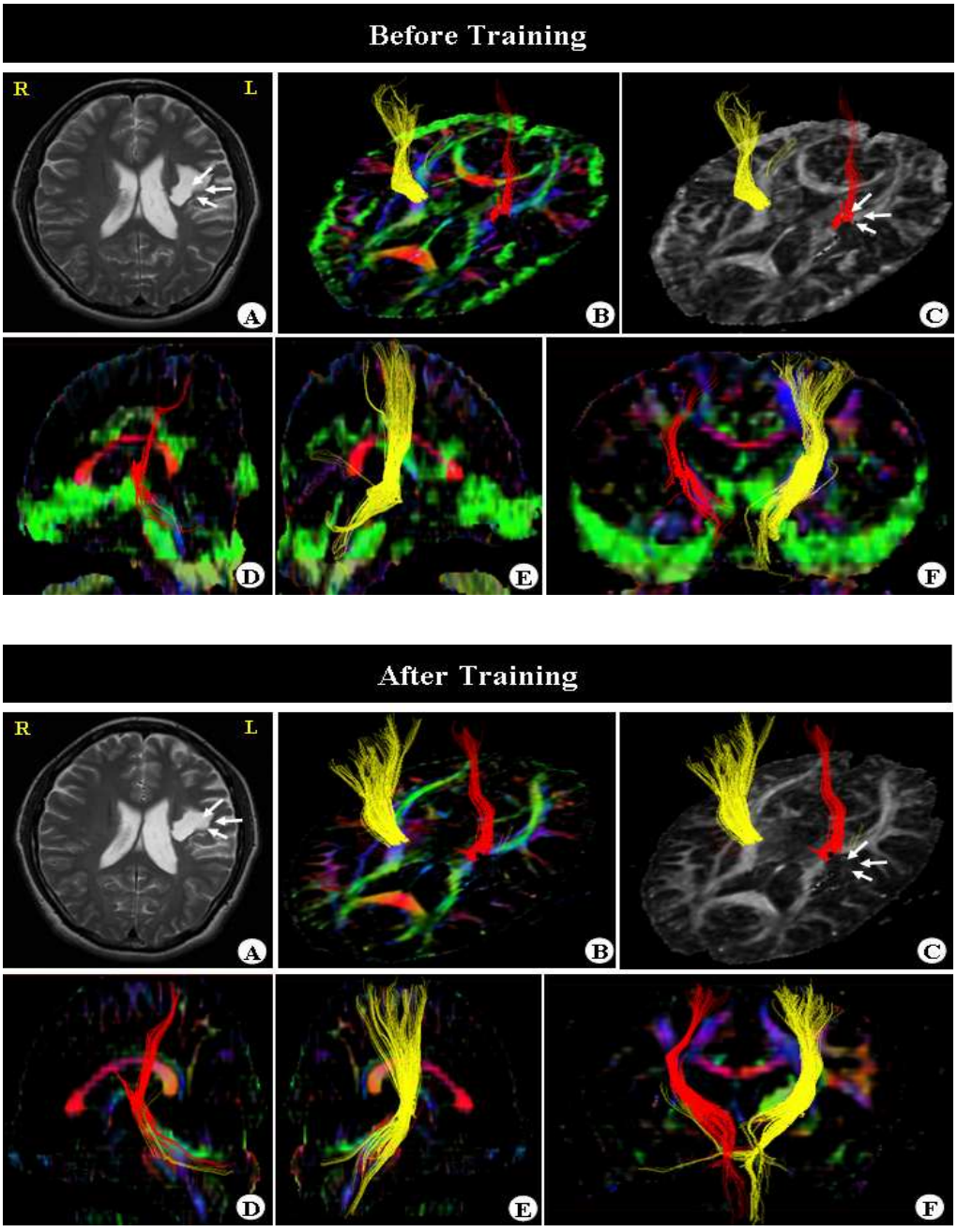

Figure 7.16. Tractography in Patient 8, A: axial T2-weighted image, B: 3D tractograpy superimposed on an axial color map, C: 3D tractograpy superimposed on an axial FA map, D: 3D tractograpy superimposed on a left sagittal color map, E: 3D tractograpy superimposed on a right sagittal color map, F: 3D tractograpy superimposed on a coronal color map.
Corticospinal tract: of the affected side: red lines, unaffected side: yellow lines.

7.5. Discussion

It is well known that the corticospinal tract is essentially required for the fine motor activity of the hand, and that motor recovery of the hand is correlated with the amount of the functional corticospinal tract [11, 12]. Figure 6.17 show pathway of the corticospinal tract.

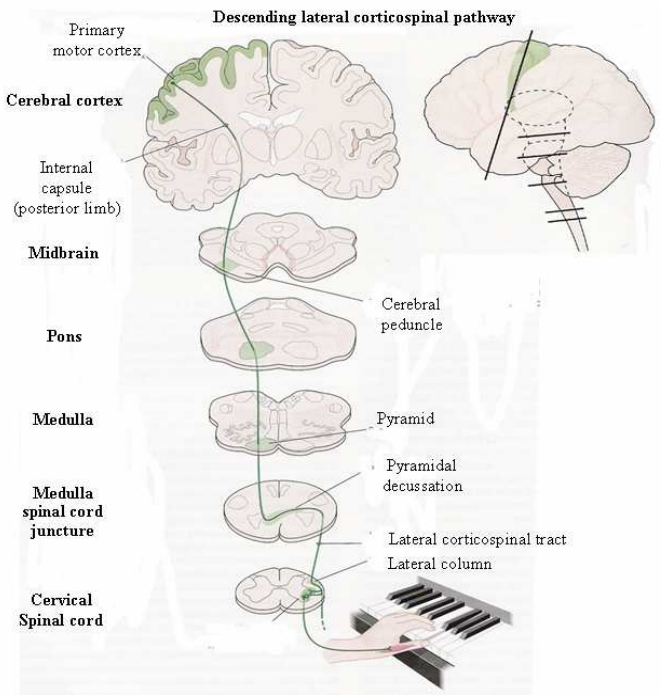

Figure 7.17. Fibers that orientate in the primary motor cortex and terminate in the ventral horn of the spinal cord constitute a significant part of the corticospinal tract. The same axons are at various points in their projection part of the internal capsule, the cerebral peduncle, the medullary pyramid, and the lateral corticospinal tract.

The FA is a popular index to quantify degree of DA, and has been used as an indicator of white matter integrity at the microstructural level [3]. In this study, the FA in the affected side was significantly smaller than that in the unaffected side.

Several investigators have tried to demonstrate that the microstructural abnormalities, such as the degree of DA impairment, reflect motor dysfunction at the time of DA evaluation in stroke patients [4, 13]. More recently, the role of DTI as a potential marker to predict motor outcome in stroke patients has been suggested [5, 6]. Watanabe et al. [5] demonstrated that a three dimensional axonograph using the DTI method in the early stages of stroke may be useful to predict the prognosis of motor function. The FA of the unaffected side in hemiparetic patients was significantly smaller than that of control subjects. Reasons for this phenomenon might be the inter-hemispheric influence of the motor system or the immobilization effect. Many studies have demonstrated that the affected motor cortex can affect the unaffected contralateral motor cortex via transcallosal pathway or by some other pathways [6]. Schmithorst and Wilke [14] have demonstrated that the long-term forced use of a hand can increase the DA of white matter. Jang et al. [15] and Cho et al. [16] demonstrated the degree of impairment in diffusion anisotropy during the early stages of stroke appears to have the potential to predict motor outcome.

3D white matter tractography, the first method which allows us to show axonal projections non-invasively in living human beings, is currently being used to assess normative functional connections. Application to certain types of pathology such as brain tumors or stroke haves begun [17, 18].

We showed the corticospinal tract repeatedly and symmetrically in involved of uninvolved hemispheres. Its cause was consistent with anatomical descriptions, and we inferred that what we were showing did indeed represent the corticospinal tracts and that 3D white matter tractography was thus suitable for demonstrating it. The technique provided unique information which could not be obtained from axial images alone, displaying the corticospinal tract and infarcts or hemorrhages simultaneously, so that the involvement of the former

could be assessed by eye. This may be useful in stroke, which frequently affects the internal capsule and corona radiate. The observed correlation between involvement of the tract and prognosis indicates that amount of fiber tracking relationships of the corticospinal tract to an infarcts or hemorrhage might affect with recovery of motor function.

In this Chapter, we demonstrated both FA ratio and FT ratio in DTI were significant increase after 6 week training with the BSAT. In addition, changes of FA ratio and FT ratio show a linear correlation with motor recovery. However, some technical limitations should be noted. We used 256×256 matrix in plane resolution and 4 mm, contiguous slices for DTI, leading to substantial orientations volume averaging of multiple fibers with different orientations in a voxel for which interpolation could not compensate. The tract shown reflects only major trajectories with abundant fiber bundles and does not necessarily represent the whole tract. We traced the corticospinal tract based on its known anatomical charateristics. What we showed seemed to correspond reasonably with the corticospinal tract, but we have to recognize there is no any other noninvasive way of validating this; the tract could be incomplete or incorrectly traced. Accurate tracking is more difficult in the brain stem because of both susceptibility and fiber crossing. Using high in-plan resolution and thin slice images may be one way to solve these problems, but it takes longer and is more subject to motion artifacts.

In DTI, despite these limitations, the clinical correlations we have shown are encouraging. Although further studies are needed, it seems likely that favorable recovery of gross motor functions could be expected in patients without obvious involvement on 3D white matter tractography. The technique seems suitable for qualitative assessment of quantitative or spatial relationships of the corticospinal tract an infarcts or hemorrhages, which might be helpful in prognosis of patients with stroke.

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8. Summary: Conclusion and Perspective

In this dissertation, motor recovery of upper-limb function in chronic hemiparetic patients after 6 week motor training with a bilateral symmetric arm trainer (BSAT) was evaluated. For this study, we used various techniques, which measure clinical assessment such as FMA, MAS, MMT, EMG characteristics and neuroimaging methods such as fMRI and DTI.

Clearly, there are abundant neurophysiological mechanisms through which bilateral excises may facilitate stroke rehabilitation. A considerable amount of redundancy in the central nervous system permits neural plasticity post-stroke. Based on these facts and many literatures, we designed bilateral symmetric arm trainer (BSAT) system, which provides both handles with symmetrical motions such as forearm pronation/supination or wrist flexion/extension. Eight chronic stroke patients were trained with the BSAT during 6 weeks.

Clinical evaluation such as FM, MAS and MMT have been used extensively to quantify motor recovery. The above clinical scales, offer qualitative information, but lack temporal and interexaminer reproducibility and suffer from a clustering effect that most of the patients are grouped within the middle grades. We proposed the onset/offset delay and co-contraction ratio methods in EMG during isometric movements of stroke patients. Functional magnetic resonance imaging (fMRI) provides the cortical reorganization induced by physical interventions in hemiplegic patients. In addition, diffusion tensor imaging (DTI), a relatively new MRI technique, allows the orientation and the integrity of the white matter tracts to be determined by virtue of its ability to image water diffusion characteristics. In this dissertation, we evaluated motor recovery using these technologies, and examined the

correlation with each parameter (clinical assessments, onest/offset delay, co-contracion ratio, LI, FAR and FTR) and motor recovery of the chronic stroke patients.

In summary, results of the present study have shown the following:
1) BSAT improved upper limb motor function and ability in all three patients with chronic hemiparesis. In this study, the clinical motor impairment and physical disability, as measured by the FMA, MMT scores increased significantly; 2) Affected hands showed significantly decreased onset/offset delays in muscle contraction after the 6-week training. Co-contraction ratio of agonist and antagonist muscles also significantly decreased after the 6-week of training; 3) Main changes in cortical activation in affected or unaffected hand movements were a decrease in ipsilateral SMC, an increase in contralateral SMC and ipsilateral CRB. Bilateral movement clearly showed cortical reorganization in bilateral SMC, PMA, SMA and CRB. In addition, LI was significantly increased in affected hand movement after training. 4) DTI studies also demonstrated that FA ratio and amount of fiber tracts run through corticospinal tract significantly increased after the training. 5) It seemed that the cortical reorganization was induced by the 6 week training with the BSAT. 6) Finally, in all parameters proposed this study, a significant correlation was found between these parameters (clinical assessments, onest/offset delay, co-contracion ratio, LI, FAR and FTR) and motor recoveries.

We could conclude that the 6 week-short term BSAT therapy produced changes in motor function and functional organization of motor network after stroke, but the clinical assessment, EMG and the area and pattern of reorganization were patient dependent. This plasticity of the motor network might be considered as a neural basis for the improvement of the affected

upper-limb by BSAT therapy. The results of this study confidently support the effectiveness of BSAT therapy in a clinical setting by providing a neurophysiological basis for the therapy-induced effects on the neural network. Understanding the neural mechanisms of motor recovery may be useful to improve the current therapeutic strategies of motor rehabilitation of chronic hemiparetic patients.

The major limitation of this study is the lack of a control group to receive a conventional treatment. The study does not answer the highly relevant clinical question of whether the arm trainer could accelerate and increase the amount of upper-limb recovery in acute or sub-acute stroke survivors. Also, we do not know the optimal dose of BSAT or the number of joints and movements that need to be practiced to maximize functional benefits, and therefore, we selected an arbitrary administration schedule. It makes possible the early, intensive, and individually adjusted practice of elbow and hand movement. Another limitation is no simultaneous measurements during fMRI study, because EMG measurement in the magnet is technically difficult.

Further studies with long-term follow up and precise evaluation on the pretreatment status, degree of functional change, and type and location of the lesions may give more insight.

Appendix A. Questionaire for Fugl-Meyer (FM) Score in Chapter 3

Name: _____
Pretest date: _____
Post-test date: _____

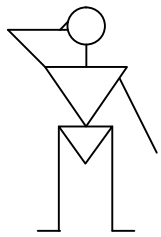
A. Shoulder/Elbow/Forearm in a seated patient

1. Reflex: Biceps
Finger flexors
Triceps
Total (max=4)

0 = no flexion
2 = reflexs present

2. Volitional movement in synergy

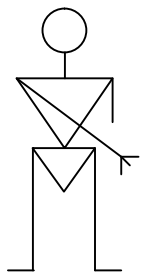
1) Flexor synergy: supinated forearm to ipsilateral ear with elbow flexed, and shoulder abducted 90°, externally rotated, retracted and evevated.



Shoulder				
retraction	_____	_____	_____	_____
elevation	_____	_____	_____	_____
abduction	_____	_____	_____	_____
ext. rotation	_____	_____	_____	_____
Elbow flexed	_____	_____	_____	_____
Forearm supinated	_____	_____	_____	_____

0 = unable to perform
1 = partially perform
2 = full

2) Extensor synergy: from flexor synergy pattern above, adduct and internally rotate the shoulder, extend the arm, pronate the forearm and reach for the contralateral leg.

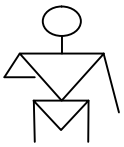


Shoulder retraction	_____	_____	_____	_____
Elbow elevation	_____	_____	_____	_____
Forearm abduction	_____	_____	_____	_____

0 = unable to perform
1 = partially perform
2 = full

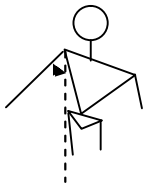
Total (max=18)	_____	_____	_____	_____

3. Volitional motion mixing dynamic flexor and extensor synergy.



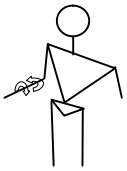
1) Hand to lumbar spine _____ _____ _____ _____

0 = unable to perform
1 = hand passes ant. iliac spine
2 = full



2) Flex shoulder 90° with elbow extended and forearm neutral _____ _____ _____ _____

0 = no flexion
1 = reflexs present
2 = full

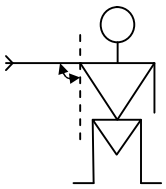


3) Forearm supination / pronation (elbow at 90° and shoulder at 0°) _____ _____ _____ _____

0 = shoulder and elbow out off position and or can't pronate / supinate
1 = limited pronation / supination with Correct elbow / shoulder position
2 = full

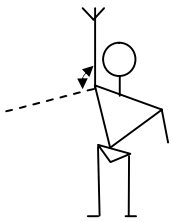
Total (max = 6) _____ _____ _____ _____

4. Volitional movement with little or no synergy dependence.



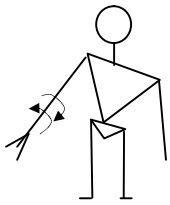
1) Shoulder abduction to 90° (elbow extended, forearm pronated) _____ _____ _____ _____

0 = initial elbow flexion or loss of forearm pronation
1 = abduction only in part or if elbow flexion or loss of forearm pron. occurs
2 = full



2) Shoulder flexion from 0° ~ 180° _____ _____ _____ _____

0 = arm abduction or elbow flexed at onset
1 = arm abduction or elbow flexed later in motion
2 = full

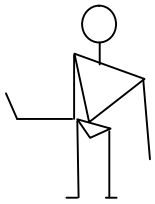


3) Forearm pronation / supination (elbow extended, shoulder 80° ~ 90°) _____ _____ _____ _____

0 = incorrect shoulder and elbow position or unable to pronation / supination
1 = correct shoulder and elbow position but only limit pronation / supination
2 = full

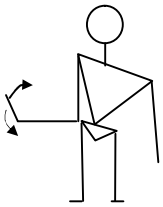
Total (max = 6) _____ _____ _____ _____

B. Wrist



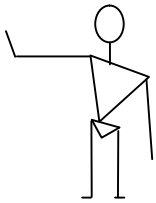
1) Wrist stability: wrist poison at 15° dorsiflexion with shoulder at 0° elbow at 90° and forearm pronated _____ _____ _____ _____

0 = can't dorsiflexion to above position
1 = dorsiflexion to 15° but without against slight resistance
2 = full



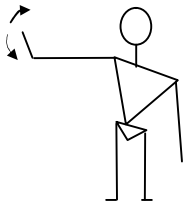
2) Wrist flex/ext: repeated full flex/ext with above elbow, forearm and shoulder position _____ _____ _____ _____

0 = no volitional movement
1 = volitional movement but not full range
2 = full



3) Wrist stability: wrist position at 15° dorsiflexion with shoulder flexed and or abducted, elbow at 0° and forearm pronated _____ _____ _____ _____

0 = can't dorsiflexion to above position
1 = dorsiflexion to 15° but without resistance
2 = can dorsiflex and maintain against slight resistance



4) Wrist flex/ext: repeated full flex/ext with above elbow, forearm and shoulder position _____ _____ _____ _____

0 = no volitional movement
1 = volitional movement but not full range
2 = full

5) Circumduction _____ _____ _____ _____

0 = no circumduction
1 = jerky or incomplete circumduction
2 = full

Total (max = 10) _____ _____ _____ _____

C. Hand

1) Mass flexion: flex all finger _____ _____ _____ _____

0 = no flexion
1 = some but not full active finger flexion
2 = full active flexion compared to the other side

2) Mass extension: from the position of full active of passive flexion, extend all fingers _____ _____ _____ _____

0 = no extension
1 = can release an active mass flexion grasp
2 = full active extension compared to the other side

3) Grasp A (hook grasp): extend the MCP joint and flex PIP and DIP joints of digits 2~5, test grasp against resistance _____ _____ _____ _____

0 = position cannot be attained
1 = grasp is weak
2 = grasp maintained against strong resistance

4) Grasp B: radial grasp (thumb to 1st side of 2nd digit) _____ _____ _____ _____

0 = cannot perform
1 = paper between the thumb and second metacarpal can be kept in place but not with resistance
2 = paper held well against tug

5) Grasp C: pincer grasp (oppose thumb pulpa against (pulpa of the second finger and pencil is interposed) _____ _____ _____ _____

0 = cannot perform
1 = can hold pencil but not with resistance
2 = pencil held well against resistance

6) Grasp D: grasp a cylinder with volar surface of the 1st and 2nd fingers _____ _____ _____ _____

0 = cannot perform
1 = can hold but not with resistance
2 = held well against resistance

7) Grasp E: spherical grasp _____ _____ _____ _____

0 = cannot perform
1 = can hold but not with resistance
2 = held well against resistance

Total (max = 14) _____ _____ _____ _____

D. Coordination / speed : Finger to own nose in rapid succession 5 times, blind folded. Measure time and compare with opposite side.

1) Tremor _____ _____ _____ _____

0 = marked tremor
1 = slight tremor
2 = no tremor

2) Dysmetria _____ _____ _____ _____

0 = pronounced or unsystematic dysmetia
1 = slight and systematic dysmetria
2 = no dysmetria

3) Speed _____ _____ _____ _____

0 = at least 6 seconds slower on the affected UE than the unaffected
1 = 2 to 5 second slower on the affected UE
2 = less than 2 seconds different

Total (max = 6) _____ _____ _____ _____

UE Total (max = 66) _____ _____ _____ _____

Abstract (in Korean)

양측 대칭형 상지 운동기구 훈련에 의한 만성 편마비 환자의 운동회복 검증

연세대학교 대학원

태기식

편마비는 뇌졸중이나 뇌손상에 의해 흔히 발생되는 문제이며 80% 이상은 급성이지만 이중 40% 이상은 만성 편마비 상태가 지속된다. 뇌졸중 발병 이후 2~5 개월만에 자발적인 기능회복이 가능하다. 특히 만성 환자들에 있어서 편마비에 의하여 상지의 기능이 현저히 저하되므로, 만성 편마비 환자의 재활을 위한 기능 평가가 중요하다.

본 학위 논문에서는 8 명의 만성 편마비 환자를 대상으로 양측운동의 장점을 활용하여 고안된 양측 대칭형 상지 운동기구를 이용한 6 주간의 훈련 프로그램에 의해 임상적인 상지기능 회복 검사인 Fugl-Meyer, 근 강직도 검사, 근력 검사와 근전도 반응검사, 기능적 자기공명영상을 이용한 뇌 피질의 활성도 변화와 확산텐서영상을 이용한 백질의 변화를 관찰하여 훈련 전후의 기능 변화를 평가하고자 하였다. 본 연구에서 6 주간 일주일에 5 일 하루에 1 시간 운동으로 구성된 훈련 프로그램을 제안하였다.

실험에 참가한 모든 환자에 있어 양측 대칭형 상지 운동기구를 이용한 6 주간의 훈련에서 Fugl-Meyer, 근 강직도 검사, 근력 검사에서

향상을 보였다. 근전도 검사에서 손목의 최대 등척성 굴곡, 신전운동을 유도하여 신호를 분석한 결과 근수축 개시 및 종료 지연이 유의하게 감소하였으며 길항근과 주동근의 비를 구한 동시수축비가 현저하게 감소하였다. 제시한 과제에 대한 뇌 활성도 변화를 관찰한 기능적 자기공명영상 실험에서는 한쪽 (건측 또는 환측) 손목 운동 시 운동 쪽에 대한 대측 주감각운동 영역에 활성도가 증가하였고 동측 주감각운동 영역의 활성도가 감소하였으며 동측 소뇌의 활성도가 증가하였다. 또한 양측 손목 운동 시 양측 주감각운동 영역, 전운동 영역, 보조운동 영역 및 소뇌의 활성도가 훈련 후 증가함을 관찰하였다. 대뇌 백질의 변화를 관찰한 확산텐서영상 연구에서 훈련 이후 내포 후각에서의 환측과 건측에 대한 비등방도율 및 겉질척수로를 지나는 백질섬유가 유의하게 증가함을 보였다. 이러한 뇌 재조직화는 개발된 양측 대칭형 상지 운동기구에 의한 훈련에 기인한다고 볼 수 있다. 또한, 다양한 평가 방법에서 제시한 여러 기법들은 환자의 상지 기능회복과 유의한 상관관계를 보여주었다.

본 학위논문에서 제시된 임상적 상지 기능평가, 근전도, 기능적 자기공명영상, 확산텐서영상 기법들은 만성 편마비 환자의 기능회복을 예측하는 데 유용하게 쓰일 것으로 기대된다.

핵심되는 말: 만성 편마비 환자, 기능회복, 양측 대칭형 상지 운동기구, 임상적 상지평가, 근전도, 기능적 자기공명영상, 확산텐서 영상