A Thesis for the Degree of Ph.D. in Engineering

A Study on Brain-Machine Interface Rehabilitation for Stroke Hemiplegia

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Graduate School of Science and Technology
Keio University

Takashi Ono
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Chapter 1

1. General Introduction

1.1. Objectives of the dissertation

Stroke leads to a rapid loss of brain function through a disturbance in the blood supply to the brain. A stroke lesion in motor cortex or a related network usually causes hemiparesis. The results of several randomized, controlled trials have indicated that the intensive practice of important motor tasks, while constraining the non-paretic limb, can substantially improve upper limb function in individuals whose movements have been mildly impaired by stroke (Grotta et al., 2004; Mark et al., 2006; Taub et al., 2006; Lin et al., 2010). In the case of moderate impairment, assisted voluntary movement with functional electrical stimulation through surface electrodes is effective in improving motor functions finger and wrist (Peckham et al., 1980; Kimberley et al., 2004). By 2000, Nudo et al. and Taub et al. reviewed the principle of functional recovery and cortical reorganization such as use-dependent recovery or learned-nonuse (Nudo et al. 2001; Taub et al. 2002). These conventional rehabilitation techniques, however, are applied to a patient while performing voluntary movement, because they need minimal movement to intensively use the paralyzed limb (Taub et al. 1999).

There has been much interest in developing Brain-Machine Interface (BMI) technology for rehabilitation (Daly and Wolpaw 2008). A BMI records brain activity to translate the user’s intention into an output (e.g. cursor movement) without actual movement. Thus, BMI techniques enable new real-time communication to external control devices depending on the user’s intention.

Electroencephalogram (EEG) signals obtained from the scalp have been tested in BMI systems. EEG-based BMI is expected to easily develop into a commercial application because EEG recording is a non-invasive method. The various features of EEG (e.g. P300, mu rhythm) have also been translated into commands that control an external device, such as word-processing software, wheelchair, or neuroprosthetic limb.
BMI in rehabilitation use has become increasingly popular nowadays. Some researchers proposed that BMI technique could induce a change in cortical activation even in patients who cannot completely move their limb, because BMI can control and train their cortical activation without actual movements. (Pfurtscheller and Neuper 2001; Wolpaw et al. 2002). In fact, long-term BMI use lead to changes in brain signal (Neuper et al. 2003; Pineda et al. 2003) and suggests that the brain is able to adjust to changes in the environment. By 2006, several studies proposed that BMI technology might be useful for chronic stroke patients with severe motor deficits as a new rehabilitation tool (Birbaumer 2006; Daly and Wolpaw 2008; Pfurtscheller et al. 2008). Indeed, multiple studies showed that EEG-based BMI training improved motor function in stroke patients (Daly et al. 2009; Prasad et al. 2009; Broetz et al. 2010; Caria et al. 2011; Shindo et al. 2011; Ramos-Murguialday et al. 2013; Mukaino et al. 2014).

The main EEG feature for BMI rehabilitation is mu rhythm. The mu rhythm, including a dominant 8–13 Hz component, is observed over primary sensorimotor cortex (SM1), and is frequently used as a potential EEG marker representing motor output signals. It is well known that two types of pattern in the change of the mu rhythm are observed following a sensorimotor process: event-related desynchronization (ERD), which is defined by amplitude attenuation of mu rhythm; and event-related synchronization (ERS), which is characterized by an enhancement of mu rhythm (Pfurtscheller and Lopes da Silva 1999). Such self-induced brain potential changes can be used as control signals of electronics (Wolpaw and McFarland 2004; Birbaumer 2006; Nijholt and Tan 2008). However, the large inter-subject variability limits the practical use of BMI. Therefore, training users to control a BMI will help achieve higher classification accuracy (Neuper et al. 1999; Wolpaw et al. 2002; Hwang et al. 2009).

The cerebral cortex is the main center for the control of voluntary movement. The cortex integrates all sensory information for the design and planning of movements (Haas 2010). Since motor imagery does not require with actual sensory information, the design and planning of movements can be unclear. Therefore, for the current study, the author investigated the difference in ERD value and reproducibility between various feedback types after 5 days of training. Visual feedback may be an effective tool for accomplishing these objectives, which are described in Chapter 2. For instance, there is some evidence that a realistic visual representation of the feedback signal, such as in a 3-dimensional video game or virtual reality environment, enhances the learning process in a BMI task (Pineda et al. 2003; Leeb et al. 2007; Hashimoto et al. 2010). This suggests that realistic and engaging feedback scenarios that are closely related to a
specific target application assist users in motor imagery (Neuper et al. 2009). Thus, it seems plausible to expect that different types of visual feedback may improve the controllability of BMI. This study has implications for understanding the influence of feedback type on BMI performance and the reactivity of ERD during motor imagery to elucidate the complex interplay between motor imagery and feedback processing.

Most EEG-based BMI studies uses ERD values recorded over SM1. However, it is unclear whether ERD observed during attempt of motor execution could be regarded as a neural marker representing the primary motor area (M1) excitability not only in healthy subjects but also in chronic stroke survivors with severe impairments. Neural activity in stroke patients is different from that of healthy subjects when they attempt to move, as confirmed by functional magnetic resonance imaging (fMRI) studies (Ward et al. 2006; Arya et al. 2011; Ward 2011). Although BMI training for stroke patients was performed with the assumption that ERD reflects excitability of M1, this assumption has not been validated. Therefore, the author investigated the correlation between ERD value and blood oxygenation-level dependent (BOLD) signal in fMRI to confirm the source of ERD, which is described in Chapter 3.

In general, BMI rehabilitation uses a robotic or prosthetic device (Broetz et al. 2010; Caria et al. 2011; Shindo et al. 2011; Ramos-Murguiadlay et al. 2013) or electrical stimulation (Daly et al. 2009; Mukaino et al. 2014). Daly and Wolpaw proposed two BMI training strategies (Daly and Wolpaw 2008). The first strategy translates specific features of brain activity into an action (e.g. cursor movement) and uses that action as feedback to train patients to produce more normal brain activity. The second strategy uses specific features of brain activity to actuate a device that assists movement to compensate for the patient’s impaired neuromuscular control during motor tasks. Therefore, two different types of feedback (i.e., visual feedback and somatosensory feedback with robotic movement assistance) contingent to motor-related EEG were tested in stroke patients with chronic hemiplegia to assess which strategy was more effective in improving motor function of a paretic limb, which is described in Chapter 4.

In the remainder of Chapter 1, the principles of human physiology and an outline of BMI technology are reviewed to facilitate the reader’s comprehension. In Chapter 2, the investigation of the differences of trainings with various feedbacks is described. In Chapter 3, cerebral blood flow changes after BMI training and the relation between BOLD signal and an ERD value are investigated. In Chapter 4, the efficacy of two feedback types is compared. Finally, Chapter 5 describes a general summary of the findings of this dissertation.
1.2. Neurophysiology of Sensorimotor Function

Through this section, the principle of physiology related to the following chapter is described. The nervous system especially related to somatosensory and somatomotor functions are focused on.

1.2.1. Central nervous system

The central nervous system (CNS) integrates the information that it receives from all body parts of bilaterian animals. It contains the majority of the nervous system and consists of the brain and the spinal cord. Some classifications also include the retina and the cranial nerves in the CNS. Together with the peripheral nervous system, it has a fundamental role in the control of behavior. The CNS is contained within the dorsal cavity, with the brain in the cranial cavity and the spinal cord in the spinal cavity.

Voluntary movement is organized in the cerebral cortex. The motor areas of the cortex are subdivided into a primary motor area and several premotor areas. Primary motor cortex (M1) proved to be the area in which the lowest intensity stimulation elicited movements. M1 is projected by some areas in primates, ventral premotor area, dorsal premotor area, supplementary motor area (SMA), presupplementary motor area, primary sensory cortex (S1) and cingulated motor area. Similar premotor areas exist in humans, but differences in size and sulcal patterns make it difficult to identify homologous areas with precision (Kandel et al., 2013; Figure 1–1). All the premotor areas project to both M1 and the spinal cord (Figure 1–2), although there are fewer projections from the premotor areas to the spinal cord than from the primary motor cortex (Kandel et al., 2013). This connection suggests that the premotor neurons can control movements independently of the primary motor cortex. Stimulation of the SMA can give rise to bilateral movements, suggesting that this area has a role in coordinating movements on the two sides of the body (Kandel et al., 2013).
Figure 1–1. Motor related cortices. Numbers mean Brodmann’s cytoarchitectural areas (Kandel et al., 2013).
The major inputs to the primary motor cortex. PMd = dorsal premotor area; PMv = ventral premotor area; S1 = primary sensory cortex; SMA = supplementary motor area; CMA = cingulated motor area (cited from Kandel et al., 2013).
Each premotor area contributes to different aspects of motor planning. When a finger is pressed repeatedly against a spring, increased blood flow is detected in the hand-control areas of the primary motor and sensory cortices (Figure 1–3 A). During a complex sequence of finger movements the increase in blood flow extends to SMA and preSMA (Figure 1–3 B). During mental rehearsal of the complex sequence of finger movements, blood flow increases only in the medial motor area (Figure 1–3 C) (Kandel et al., 2013).

The cerebellum and basal ganglia influence the motor systems by estimating imbalances between intention and action and by coordinating the operation of motor centers in the cortex and brain stem (Figure 1–4). The cerebellum and basal ganglia do not project directly to the spinal cord. Three aspects of the cerebellum’s organization underlie the function (Kandel et al., 2013). First, the cerebellum is provided with extensive information about the goals, commands, and feedback signals associated with the programming and execution of movement. Second, the output projections of the cerebellum are focused mainly on the premotor and motor systems of the cerebral cortex and brain stem, systems that control spinal interneurons and motor neurons directly. Third, synaptic transmission in the circuit modules can be modified, a feature that is crucial for motor adaptation and learning. Characteristic oscillations of the EEG signals are suggested to depend on the membrane properties of the single neurons and on the organization and interconnectivity of networks to which they belong (Lopes da Silva 1991). The cortical activation can result in phasic changes in synchrony of cell population due to externally or internally paced events and can lead to characteristic EEG patterns (Pfurtscheller 2006).

Voluntary movements need the design and planning of the movement by motor-related cortices. These cortices will use previous experiences in the planning of movements and project a motor command confirming to this plan into muscles. After movements, sensory receptors will provide feedback about the movement to the cortices. Those cortices can refine movement according to its feedback (Figure 1–5).
Figure 1–3. Different cortices are activated during different finger tasks. (A) M1 and S1 (green) are activated during simple finger movement. (B) SMA (blue) and M1 are activated during complex finger movement. (C) Only SMA is activated during mental rehearsal of complex finger movement. (edited from Kandel et al., 2013).
Figure 1–4. The relationships of motor-related areas to the primary motor area. (edited from Kandel et al., 2013).
Figure 1–5. The motor-related cortices in movement control. (cited from Haas 2010)
Cortical excitability of human can be measured by applying the external stimulation. Transcranial magnetic stimulation (TMS) is known to activate pyramidal neurons indirectly via synaptic inputs rather than at the axon of pyramidal neurons (Di Lazzaro et al. 2004). Therefore the size of motor evoked potential (MEP) elicited by the same strength of TMS was used to estimate the cortical activation of pyramidal neurons in the motor cortex (Liang et al. 2008). The former study showed the augmented MEP from the contralateral primary motor area of the hand area during the motor imagery of the hand muscles. Motor threshold (MT), the minimum strength of the TMS that can evoke the MEP, is also used to estimate the cortical activation and the MT of the contralateral hand area was decreased during the motor imagery of hand muscles (Facchini et al. 2002). In addition, the increment of blood flow in SMA during the motor imagery was reported with functional magnetic resonance imaging (fMRI) (Ritter et al., 2008) and regional cerebral blood flow (Decety 1996; Oishi et al. 2007).

A neural activity leads subsequent changes in cerebral blood flow. That relationship is referred to as neurovascular coupling (Figure 1–6). The energy metabolism of neurons is influenced by changes in synaptic activity or synaptic strength. Several investigations have showed what CBF depends on, local field potential (LFP) or spikes (Mathiesen et al. 1998; Gandhi et al. 1999; Logothetis et al. 2001; Viswanathan and Freeman 2007; Rauch et al. 2008). These results suggest that the vascular response can be considered to reflect strongly synaptic activity and the CBF response is typically delayed by 1–2 s and peaks 4–6 s after the neural response (Figure 1–7). The vascular response can not reflect the fast neural activity modulation because of the slow reaction.
Figure 1–6. Some of the suspected mediators of neurovascular coupling. (cited from D’Esposito et al. 2003)
Figure 1–7. Responses of LFP, MUA and BOLD signal to 12-s stimulation. The blue trace measures the LFP, the green trace measures the MUA, and the red-shaded trace measures the BOLD response. Gray bar on x-axis indicates stimulation period (modified from Logothetis and Wandell 2004).
1.3. Brain-Machine Interface

1.3.1. Motor imagery

The former researches represented the motor imagery as the result of conscious access to the content of the intention of movement (Decety 1996; Lotze and Cohen 2006), which is usually performed unconsciously during movement preparation (Lotze and Cohen 2006). Several studies suggested that motor imagery and unconscious motor preparation share common mechanisms because of the high overlap of active brain region such as cerebellum, basal ganglia, parietal cortical area, premotor cortex and SMA and are functionally equivalent (Decety 1996; Lotze and Cohen 2006).

Generally motor imagery strategy can be categorized into the kinesthetic motor imagery and the visual motor imagery (Stinear et al. 2006). Kinesthetic motor imagery involves imaging the feeling that actual task performance produces. Visual motor imagery involves imaging seeing yourself performing the task. Former studies suggested that kinesthetic motor imagery have the similar strategy to the motor execution than the visual motor imagery (Neuper et al. 2005; Stinear et al. 2006).

1.3.2. Feature extraction

Since motor imagery results in somatotopically organized activation patterns, mental imaginings of different movements can be an efficient strategy to operate a BMI (Pfurtscheller et al. 2006). An idling activity of the thalamo-cortical loop in the sensorimotor nervous system changes its temporal structure along with mental motor imagery. Its state change can be detected by means of various brain activity recording such as needle electrodes, electrocorticogram, EEG, Near Infrared Spectroscopy and others. ECoG and other intracortical measurements have good topographical resolution (1.25–1.4 mm; Schalk and Leuthardt 2011) and fewer artifacts, and thus implanting of electrode arrays over the cortical surface has been highly recommended to record brain activity precisely. EEG is a noninvasive way of brain activity recording, allowing non-neurosurgeon researchers to handle BMI. EEG is usually contaminated by some artifacts (e.x. eye blink or body movement) and has less topographical resolution. Experience of BMI research in humans has so far primarily involved non-invasive EEG-based investigations in the fields of signal processing and human interface to establish noise-robustness communication channels (Daly and Wolpaw 2008).

Mu (8–13 Hz) and beta (18–30 Hz) rhythms in EEG are the spontaneous characteristic features. These rhythmic waves appear maximally over the central Rolandic or SM1 during relaxing state (Kuhlman 1978; Arroyo et al. 1993) and can be
blocked by the movement of the contralateral hand or arm (Kuhlman 1978; Kozelka and Pedley 1990), passive movements of the contralateral hand or arm (Kuhlman 1978), and by the attention to or preparation for the activity (Chatrian et al. 1959; Schoppenhorst et al. 1980). Movement or preparation for movement is typically accompanied by a decrease in mu and beta rhythms, particularly contralateral to the movement. This decrease has been labeled “ERD” (Wolpaw et al. 2002). Conversely an increase in mu and beta rhythms is called an ERS.

BMI systems use the classifier to judge whether a subject images motor execution or not. The classification algorithms are mainly divided into two different categories: linear classifiers and nonlinear classifiers (Lotte et al. 2007). The most popular algorithm is linear discriminant analysis (LDA). LDA technique has a very low computational requirement which makes it suitable for online BMI system and LDA is simple to use and generally provides good results (Lotte et al. 2007). Support vector machine is a popular method in nonlinear classifiers. It is possible to create both linear and nonlinear decision boundaries, with only a low increase of the classifier’s complexity, by using the “kernel trick” (Lotte et al. 2007).

1.3.3. Potential Clinical Applications

A stroke is the loss of brain functions due to lack of the blood supply to the brain. Strokes have two major types. One is ischemic stroke which is caused by a interruption of the blood supply. Another type is hemorrhagic stroke which is caused by rupture of a blood vessel or an abnormal vascular structure. Those stroke lead unable to function (e.g. inability to move one or more limbs on one side of the body). Annually, fifteen million people worldwide suffer a stroke (World Health Organization, 2002). The prevalence of stroke increases as one grows older (Figure 1–8).
Figure 1–8. Prevalence of stroke by age and sex. (Rosamond et al. 2008)
Stroke can cause some of the physical disabilities, paralysis, numbness, pressure sores, pneumonia, incontinence, apraxia (inability to perform learned movements), difficulties carrying out daily activities, appetite loss, speech loss, vision loss, and pain. Intensive practice of meaningful motor tasks with constraint of the non-paretic limb can substantially improve upper limb function in individuals who have been mildly impaired by stroke (Taub et al. 1999; Grotta et al. 2004). In case of moderate impairment, assistance of voluntary movement by functional electrical stimulation through surface electrodes is known to be effective to improve finger and wrist motor function (Kimberley et al. 2004).

Though most stroke lead to motor deficit, all nerves from a brain to a muscle cannot transmit cortical signal. There are some surviving and bypass pathways that are not used naturally. Activating those pathways results in motor recovery. Therefore, BMI techniques give appropriate visual and/or somatosensory feedbacks and could improve motor function by inducing cortical reorganization.
Chapter 2

2. Daily training with realistic visual feedback improves reproducibility of event-related desynchronisation following hand motor imagery

* This chapter was based on my original article, “T. Ono, A. Kimura, and J. Ushiba, Daily training with realistic visual feedback improves reproducibility of event-related desynchronisation following hand motor imagery, Clin Neurophysiol, vol. 124, no. 9, pp. 1779–1786, Sep. 2013.”. I have a right to use this dissertation.

Event related desynchronization (ERD) in electroencephalogram (EEG) is observed during motor execution, and its spatial pattern is clearly different for finger and foot movement (Pfurtscheller et al. 2000b), each corresponding to the location of the respective somatosensory and motor areas in the cortex. In addition to actual motor behaviour, mental motor imagery can also alter neural activity in the primary sensorimotor cortex (SM1) and result in ERD (McFarland et al. 2000; Neuper and Pfurtscheller 2001; Neuper et al. 2005). Such brain potential changes can be used as communication signals with electronic devices, as in Brain Machine Interface (BMI) (Wolpaw and McFarland 2004; Birbaumer 2006; Nijholt and Tan 2008). Although ERD during motor imagery has been successfully applied in BMI (Pfurtscheller et al. 2000a), large inter-subject variability of ERD value limits the practical use of BMI (Hashimoto et al. 2010). Therefore, training users to improve volitional ERD performance will help achieve a high classification accuracy (Neuper et al. 1999; Wolpaw et al. 2002; Hwang et al. 2009).

Visual feedback may be an effective tool for accomplishing these objectives. For
instance, there is some evidence that a rich visual representation of the feedback signal, such as in a 3-dimensional video game or virtual reality environment, enhances the learning process in a BMI task (Pineda et al. 2003; Leeb et al. 2007; Hashimoto et al. 2010). This suggests that realistic and engaging feedback scenarios closely related to a specific target application assist users in motor imagery (Neuper et al. 2009). Thus, it seems plausible to expect that use of different types of visual feedback may improve the controllability of BMI.

The goal of the present study was to explore which types of visual feedback promote robust ERD in ERD feedback-regulated motor imagery training. In this experiment, I prepared 3 types of visual stimuli; bar feedback (BAR) with changing bar length on the screen, anatomically incongruent feedback (INCONGRUENT) in which the hand open/grasp picture was animated on the screen in front of the participant, and anatomically congruent feedback (CONGRUENT) in which the same hand open/grasp picture was animated on the screen overlaying the participant’s hand. A motor imagery task with no feedback (NONE) was used as a control. I investigated the difference in ERD value and reproducibility among the feedback types after 5 days of training. This study has implications in the understanding the influence of feedback type on ERD performance during the complex interplay between motor imagery and feedback processing.
2.1. Methods

2.1.1. Participants

A total of 32 (22 men and 10 women, aged 21–35 years, mean 26.6 years, all right-handed) in good health with no history of neurologic disease participated in an experimental session conducted daily for 5 consecutive days. The participants were experimentally naïve, and also had no history of similar motor-imagery experience in exercise and sports. The informed consent after the experimental procedure was explained to them. The experimental protocol used in the study was in accordance with the Helsinki Declaration and was approved by the ethical committee of Keio University.

2.1.2. Electroencephalogram recording

EEG was recorded with 7 sintered Ag/AgCl scalp electrodes over centroparietal areas (Figure 2–1 A). The closely spaced electrodes with distances of approximately 2 cm placed in a configuration including the electrode positions C3, C4, Cz of the international 10-20 system. The channels placed anterior to C3, C4 were called C3a, C4a and posterior were called C3p, C4p in this study. Electrode impedance was kept lower than 10 kΩ throughout the experiment. The EEG signals were amplified and bandpass filtered between 2 and 100 Hz by Neuropack (Nihonkohden, Tokyo, Japan) and then sampled at 256 Hz. The subjects were instructed to keep their arms and hands relaxed during recordings.
Figure 2–1 Experimental design. (A) Electrode setup. (B) Time course of a single trial of the feedback session.
2.1.3. Experimental paradigm

The subjects sat in a comfortable armchair. Each subject participated in a series of two experimental sessions: one screening and one feedback sessions. In screening session, participants were asked to imagine grasping with their right hand following a fixed repetitive time scheme (Figure 2–1 B). The trial was initiated with the presentation of the word “Relax” on the monitor, and a 5-s countdown was presented at the bottom of the monitor for readying to image a movement. The word and countdown disappeared 5 s later, and the participants were asked to imagine a movement. After 5 s of EEG feedback exposure, the participants were asked to relax for 5 s. This 15-s trial was repeated for 20 trials. The EEG montage and the frequency band for deriving ERD in the subsequent BMI feedback session were determined from the results for the ERD results in this screening session (see also EEG Analyses section below). This protocol was followed because the EEG results are dependent upon the participant’s mental state; the exact positions of the electrode shifted from day to day, although they were set as precisely as possible according to the code of the international 10-20 system. These selection method of the EEG montage and the frequency band from the obtained results in screening session were formerly established elsewhere (Neuper et al. 1999; Wolpaw and McFarland 2004) and used in this study.

In the feedback session, the time course of the trial was the same as in the screening session. ERD was calculated during motor imagery by a 1-s window of the EEG every 100 ms (again, see also EEG Analyses section below). During the right hand motor imagery, the feedback stimulus depending on ERD value was displayed in the centre of the monitor. The coupling of ERD to the resulting feedback action was determined. Participants generally achieved ERS via passive relaxation and ERD via a continuous grasping movement imagery with the right hand. Participants were randomly assigned to 1 of 4 experimental groups of different types of visual feedback as described below.

(I) NONE

The monitor was placed approximately 1 m in front of the participant at eye level and no stimulus was presented during the feedback period. Such paradigm has been used in previous BMI studies (Pfurtscheller and Neuper 1997; Neuper and Pfurtscheller 2001).

(II) BAR

The monitor was placed approximately 1 m in front of participant at eye level. A bar was presented on the monitor. This bar lengthened toward the right of the monitor.
with increasing ERD and shortened with decreasing ERD. The participants’ task was to extend the bar horizontally which resulted from ERD value while hand motor imagery toward the right monitor edge and to keep it as long as possible (Figure 2–2 A). BAR feedback paradigm was found elsewhere in previous BMI studies (Neuper et al. 1999; Townsend et al. 2004; Chatterjee et al. 2007).

(III) INCONGRUENT

The monitor was placed approximately 1 m in front of the participant at eye level. The hand open/grasp picture from the first person’s perspective was animated on the monitor, according to the amplitude of ERD caused by hand motor imagery. I prepared 20 hand pictures with different hand positions from full hand grasp to full hand open. The hand images presented in association with increasing ERD were continuous hand grasping motor imagery, whereas hand opening motor imagery was associated with decreasing ERD (Figure 2–2 B). INCONGRUENT feedback paradigm was found elsewhere in previous BMI studies (Neuper et al. 2009).

(IV) CONGRUENT

The form and animation manner of the CONGRUENT visual feedback were the same as the INCONGRUENT visual feedback, but the display monitor was placed over the participant’s hand. Thus, the participants saw their own hand-grasping animation overlaid on top of their hand (Figure 2–2 C). It is noted here that this realistic feedback was a novel paradigm in BMI study.

The participants in each feedback group were asked the same motor imagery task (i.e. a kinaesthetic hand grasping imagination) with maximal efforts without overt muscle contraction.
Figure 2–2 Assignment of EEG to visual stimuli in feedback. The feedback figures both when small ERD in alpha and beta band is observed (left) and when significant ERD (right) is observed are shown. (A) The bar extended toward the right in association with increasing ERD, whereas shortening was associated with decreasing ERD. (B) The hand open/grasp picture from the first person’s perspective was animated on the monitor which was placed in front of participant, according to the amplitude of ERD
caused by hand motor imagery. (C) The hand open/grasp picture from the first person’s perspective was animated on the monitor which was placed over the participant’s hand, according to the amplitude of ERD caused by hand motor imagery.
2.1.4. Analysis of electroencephalogram

In a first step of analysis all EEG trials were visually controlled for artifacts and contaminated trials were discarded. Three independent montages were performed on three different bipolar electrode combinations: anterior-central (a-c), central-posterior (c-p), anterior-posterior (a-p) in same side of hemisphere. The band power of each mu and beta rhythm of each bipolar montage was estimated from ongoing EEG by digital band-pass filtering with a Butterworth filter of order 4, squaring, and averaging the samples over 1 s. The processing was done sample by sample. Other studies of healthy subjects have confirmed that the processed signal by this manner somatotopically changes its amplitude by motor imagery of the hands (Neuper et al. 1999; McFarland et al. 2000; Müller-Putz et al. 2005; Halder et al. 2011). I computed the ERD with following equation:

\[
ERD(f, t) = \frac{R(f) - A(f, t)}{R(f)} \times 100
\]

where \( A \) is the power spectrum of the EEG at frequency \( f \) at time \( t \) with reference to the onset of motor imagery and \( R \) is the power spectrum of a 2-s epoch of the reference rest period (-3 s to -1 s) in each trial. By using this definition, ERD was expressed as positive numbers in this study.

In the screening session, ERD in each frequency was calculated using a 1-s window of the EEG every 100 ms and averaged across the trials offline. This averaged time-frequency data of ERD was used to manually select the most reactive frequency band for each participant (within 8–35 Hz which includes both mu and beta rhythm) and the bipolar montage (Hashimoto et al. 2010). As reported previously, most reactive frequency bands and EEG montages slightly differ each day and for each participant (Aftanas et al. 2002; Ward et al. 2003; Neuper et al. 2006a; Hashimoto et al. 2010). Thus, the frequency bands and EEG montage for the BMI training were the ones that showed the highest ERD during right hand motor imagery in the time-frequency map by visual inspection as reported previously (Müller-Putz et al. 2005; Hashimoto et al. 2010). ERD in the selected frequency band was computed by the following equation:

\[
ERD(t) = \frac{1}{f_{\text{high}} - f_{\text{low}}} \sum_{f_{\text{low}}}^{f_{\text{high}}} ERD(f, t)
\]

where \( f_{\text{low}} \) and \( f_{\text{high}} \) are the upper and lower bounds of the manually selected frequency region. In case ERD was not observed at the beginning of BMI training, I used EEG power at a base frequency with a bipolar montage of C3a-C3, which was the best electrode scheme in general (Neuper et al. 2006a). This reactive frequency band was
used both for feedback session and for offline analysis of subject-specific mu or beta rhythms.

For the experiments with BAR, INCONGRUENT, and CONGRUENT in feedback session, ERD in the selected frequency was calculated with a 1-s time window every 100 ms at on-line, as in the screening session, and used it as the signal source of the visual feedback. For offline analysis to see the difference of ERD with the feedback types, the most reactive ERD during the imagery period was segmented with a 1-s time window every 100 ms from every trial. The average and the standard deviation (s.d.) of the representative value were calculated.

2.1.5. Classification and Accuracy Analysis

In offline analysis of feedback sessions, Fisher’s linear discriminant analysis (LDA) was applied to the ERD data for calculation of accuracy in 2-class discrimination: right hand imagery versus rest states. First, the power spectrum of EEG was calculated from a 1-s time window every 100 ms during both the resting and imagery periods as in real-time feedback. EEG derivation and frequency range selected were also equivalent to those used for calculation of ERD in the screening and feedback sessions. Here, I had 150 data points with annotation of either ‘Rest’ (100 data) or ‘Imagery’ (50 data) at each trial, since the task consisted of 5-s rest, 5-s imagery, and 5-s rest. The entire data from all included trials were used to set the LDA parameters, and the error rate of the classification was calculated by 10-fold cross-validation as follows. All data were mixed randomly and divided into 10 small packets. Then, 9 packets were used as training data to set the LDA parameters, and the remaining packet was classified by the LDA. This operation was done 10 times with different combinations of packets, and finally, I calculated the accuracy. I used this 10 × 10 cross-validation procedure since it is known to enhance the generalization of classification results (Neuper et al. 2009). Linear regression analysis was performed to investigate the influence of ERD parameter (effect size) on accuracy.
2.2. Results

A parallel group comparison design was performed in this study to abolish the interference effect between the experimental groups. There was no systematic biases on participants’ sex, age, and handedness among the experimental groups (sex: $p > 0.05$, the test of independence. Age: $p > 0.05$; one-way ANOVA. Handedness: all participants were right-handedness. In addition, the participants to the groups equally such that ERD at the first day without feedback (screening session) does not have systematical biases to one group ($p > 0.05$, one-way ANOVA)).

Feedback experiments used participant-specific features (bipolar and frequency). These parameters were described in Table 2–1.
Table 2–1. Participant-specific features.

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<th>Age</th>
<th>Site</th>
<th>Frequency (Reference Power/(Y))</th>
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<th>Accuracy, %</th>
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*a* indicates the anterior channel of C3.

*ac* indicates the C3.

*ac* indicates the posterior channel of C3.
2.2.1. Electroencephalogram change in the first day

Figure 2-3 A shows typical data of the inter-trial average time-frequency conventional representation of ERD values in the feedback session on the first and last days. ERD values in the first session for each condition are as follows: 7.9% ERD in NONE, 20.3% ERD in BAR, 18.8% ERD in INCONGRUENT, and 17.9% ERD in CONGRUENT. The ERD value in the NONE condition was significantly different from all 3 feedback types \((p < 0.01)\), and no significant differences were observed between the feedback groups.

In addition to average ERDs, the inter-trial variance of ERDs should be examined, since reproducibility of ERD is determined by both its average and variance. Averages and 95% confidence intervals (equivalent to the inter-trial variance) of ERDs from representative subjects participants in each feedback condition (Participant 2 from NONE, Participant 12 from BAR, Participant 17 from INCONGRUENT, and Participant 25 from CONGRUENT) on the first day are showed in Figure 2–4 A. The BAR, INCONGRUENT, and CONGRUENT conditions had large ERDs and small inter-trial variance of ERD trajectory for a short time interval.

2.2.2. Training effect

Here, I describe the effect of 1-h daily training on ERD reproducibility. Representative data from all groups are shown in Figure 2–3 B and Figure 2–4 B. During the last day, BAR, INCONGRUENT, and CONGRUENT showed both prolonged ERDs and small inter-trial variances during the task period. Representative participants’ data of ERD and accuracy time courses are displayed in Figure 2–3 C. Data from the BAR, INCONGRUENT, and CONGRUENT conditions showed the tendency of increases in the mean of ERDs and decreases in ERD variance to covary with increases in accuracy. Figure 2–5 A presents a detailed overview of the mean ERD values and s.d. for all feedback groups. Five-day training induced more robust ERD than that seen in the first session in all groups (None: 12.7%, BAR: 25.5%, INCONGRUENT: 28.3%, CONGRUENT: 32.0%). Bartlett’s test was performed to examine the homogeneity of variance, and significant differences in variance were observed among all conditions \((p < 0.05)\). Therefore, Friedman’s test was used to test the null hypothesis. Friedman’s test revealed significant differences between both sessions \((p < 0.01)\) and feedback types \((p < 0.05 \text{ between NONE and BAR}; \ p < 0.05 \text{ between NONE and INCONGRUENT}; \ p < 0.05 \text{ between NONE and CONGRUENT})\). In addition, The effect size which was the mean value divided by the standard deviation in CONGRUENT group was the smallest.
Figure 2–3. The repetitive data of across-trial average. (A) Time-frequency representations of ERD values (coloured blue) over trials in the feedback session on the first day. (B) Time-frequency representations of ERD values (coloured blue) over trials in the feedback session on the last day. The highlighted period on the X-axis indicates the period of motor imagery. (C) Representative data of ERD and accuracy across days. NONE: Participant 2, BAR: Participant 12, INCONGRUENT: Participant 17, CONGRUENT: Participant 25.
Figure 2–4. **Band power time courses from each feedback.** Solid line: grandaverage. Dashed line: ±95% confidence interval. (A) Time courses at the first day. (B) Time courses at the last day. The highlighted time period on the x-axis indicates the period of motor imagery. NONE: Participant 2, BAR: Participant 12, INCONGRUENT: Participant 17, CONGRUENT: Participant 25.
Figure 2–5. ERD (A) and accuracy (B) for the subjects in each feedback group by session. Open bars: first session, filled bar: last session. X-axis shows the participant number. Only the ERD data but not accuracy data are presented with error bars.
2.2.3. Accuracy changes

The classification accuracy was obtained over all participants. Figure 2–5 B presents a detailed overview of the accuracy for the participants in each feedback group during the first and last sessions. The sessions × feedback types (2 × 4) factorial analysis of variance revealed a significant difference between the feedback groups ($F_{3,56} = 7.67; p < 0.001$) as well as a significant interaction between the feedback groups and session ($F_{3,56} = 4.01; p < 0.05$). Subsequently, Multiple comparisons of the feedback groups using t-tests were performed and revealed significant differences of accuracy between the MIRROR condition and all other feedback types ($p < 0.001$ between NONE and CONGRUENT; $p < 0.01$ between BAR and CONGRUENT; $p < 0.01$ between INCONGRUENT and CONGRUENT).

2.2.4. Relation between the change of brain wave and accuracy

Linear regression analysis was performed to investigate the predictability of effect size of ERD (mean divided by s.d.) on accuracy. There was a significant correlation between the accuracy and the effect size that is the mean divided by the deviation ($p < 0.01$; Pearson correlation; Figure 2–6).
Figure 2–6. Relationship between accuracy and effect size.

$r = 0.520; p < 0.01$
2.3. Discussion

The present study showed the learning effect of ERD following right hand imagery through any types of visual feedback control (BAR, INCONGRUENT, and CONGRUENT) in healthy individuals. ERD value in the NONE showed significant differences among other feedback types, although the participants were randomly assigned to one of four types (NONE, BAR, INCONGRUENT and CONGRUENT). Moreover, the NONE group showed no progressive changes during the training. From these findings, it can be said that any types of visual information representing temporal amplitude of ERD might be helpful for the subjects to test various strategies to manipulate the visual feedback object and related EEG activity, and presumably, promoted larger ERD after 5-day of training.

2.3.1. Feature extraction

I used visual inspection to decide subject-specific features (channel montage and frequency) in accordance with a previous BMI rehabilitation study (Ramos-Murguialday et al. 2013). The previous review summarizes the results of a comprehensive survey of different signal processing schemes that have been used in BMI systems and proposes the genetic algorithm (GA) as one of the most widely used methods to select a subject-specific feature (Bashashati et al., 2007). Thus, I compared my method with the GA algorithm.

At first, 100 genomes were randomly generated to form an initial population. One genome had 35 genes that were binary values, for example, the first binary indicated whether an ERD value of 5 Hz was used by the following process, and the 35th binary indicated whether an ERD value of 40 Hz was used by the following process. A grand average ERD value was calculated by using all trials of the imagery task period (from 6 to 10 s) and a selected frequency whose binary value was one. This value was regarded as a fitness score. The fitter individuals were selected from the current population, and each individual's genome was modified to form a new generation. This selection and modification process was iterated 200 times. After iteration, the genome that had the highest fitness score was stored. At the next step, a new set of 100 genomes was generated to form an initial population again, and the iteration was performed in the same way. Since this method was performed 30 times, 30 genomes were stored. Finally, these 30 genomes were added up to form each gene. Figures 2–7 shows feature frequencies selected by histograms of GA results and by visual inspection. This figure suggests that most features selected by GA were similar to those selected by visual inspection. Therefore, GA can substitute visual inspection as a more objective method.
Figure 2–7. Features by GA and visual inspection. (A) Left panel shows time-frequency representations of ERD values (colored blue) on the first day. Right panel shows the features selected by GA (blue bins) and visual inspection (green shade). (B) Other participants’ data. Since ERD of participants 1 and 2 was not observed at the beginning of BMI training, EEG power at a base frequency (8-12 Hz) was used.
2.3.2. Feedback effects

Interestingly, only CONGRUENT feedback, which involved strong perception of illusory hand movement, induced smallest inter-trial variance among the groups after 5-day training. Not surprisingly, accuracy on BMI performance by 2-class classification of ‘Rest’ and ‘Imagery’ was highest in CONGRUENT feedback. From these results, I concluded that CONGRUENT was most appropriate for effective training to motor imagery based BMI among the tested visual feedback types.

Since the aftereffect of the 5-day training can not be washed out for subsequent 5-day training with different conditions, the present study employed a parallel group comparison design. To minimize the effects from potential confounding factors, sex, age, and handiness were matched among the groups. All the participants had no history of similar motor imagery experiment and no experience in sports, expecting that individual’s learning capacities were the same among the groups. I also assigned the participants to the groups equally such that ERD at the first day does not have systematical biases to one group. It is therefore considered reasonable to assume that differences of individual’s physiological properties between are negligible in this study. For more detailed analysis in testing visual feedback conditions, a repeated measure design with exclusion of possible learning and retention effects on ERD is required.

2.3.3. Motor imagery

Motor imagery seems to be a suitable strategy to achieve discernible EEG patterns for BMI. The main advantage is the possibility to exploit EEG responses that are directly related to motor functions (Neuper et al. 2009). Movement or preparation for movements is typically accompanied by ERD in mu and beta rhythms, particularly contralateral to the movement (Manganotti et al. 1998; Keinrath et al. 2006). The ERD pattern is interpreted as a thalamocortical mechanism to facilitate cortical activation and information processing (Sherman and Guillery 1996). For example, a transcranial magnetic stimulation study reported increased motor evoked potentials and oscillations in the mu and beta frequencies during active retrieval of the motor memory trace (Hummel et al. 2002). Thus, ERD patterns might reflect certain aspects of the interaction between the thalamic nuclei and cortical areas, probably controlled by the interplay of thalamic relay cells with cells of the reticular thalamic nucleus (Bishop 1995). Therefore, ERD by the hand motor imagery applied in this experiment was considered to have some relationship with the excitability of the SM1. CONGRUENT visual feedback by a first-person perspective that involved strong perception of illusory
hand movement is, therefore, considered to help recall kinaesthetic motor imagery resulting in significant, reproducible ERD by voluntary motor imagery.

Another possible explanation for the effect of realistic visual feedback on improvement of ERD reproducibility is the contribution of mirror neurons. For example, recent studies suggest that modulation of SMR is linked to the activity of the human mirror neuron system, referring to an action observation/execution matching system, which is capable of performing an internal simulation of the observed action (Neuper and Pfurtscheller 2001; Tominaga et al. 2009). Based on indirect evidence of functional imaging and electrophysiological studies, a functional correspondence between action observation, internal simulation, or motor imagery and execution of the motor action has been proposed (Neuper et al. 2005; Filimon et al. 2007). The mu rhythm has been considered to reflect the downstream modulation of primary sensorimotor neurons by visuomotor mirror neurons in the premotor cortex (Neuper and Pfurtscheller 2001). In this study, CONGRUENT feedback causing perception of hand movement might have supported image motor action by maintaining significant ERD through the mirror neuron system.

2.3.4. Training to induce cortical activations

BMI is a communication system in which messages or commands that a subject sends to the external world do not pass through the normal corticomuscular tract BMI changes cortical activity from mere reflections of central nervous system activity into the intended devices. Successful BMI operation requires that the user develops and maintains the distinguished cortical activity, i.e., whether user images motor execution or not. The brain’s adaptive capacities extend to control of various electrophysiological signal features was initially suggested by studies exploring therapeutic applications of the EEG (Niedermeyer and Lopes Da Silva 2005). The mu rhythm is particularly well suited to an effort to develop an EEG-based BMI. In addition, ERD following motor imagery or execution indicates the cortico-spinal excitability (Neuper and Pfurtscheller 2001). The reason is that humans can gradually increase mu rhythm amplitude over the EEG feedback training that enhances cortical activity (Kuhlman 1978; Zhuang et al. 1997). This experiment investigated the training effect of four different EEG-feedback types. A realistic feedback was the most useful training to build up a reproducibility of ERD. As the result, the feedback training can also build up an accuracy rate. Therefore this ERD-based training can enhances the cortical activity depending on subject’s motor imagery exactly.
2.3.5. Insight for brain-machine interface rehabilitation

Activity-dependent neural plasticity can occur even in adult brains with neurological disorders such as traumatic injury or stroke (Stroemer et al. 1995; Dancause et al. 2005; Cramer et al. 2006). It has been recently suggested that the motor imagery-based BMI can enhance motor-related cerebral and cerebellar activities (Caria et al. 2011), and therefore is promised to improve functional reorganization in the sensorimotor system in stroke patients. Actually, it has been recently suggested that BMI can restore motor control in persons with hemiplegia due to stroke (Broetz et al. 2010; Caria et al. 2011; Shindo et al. 2011). Our preliminary study with healthy individuals has an impact to the further design of such BMI for therapeutic purposes. Realistic visual feedback, consistent with the participant’s mental motor imagery, might be helpful for accomplishment of successful motor imagery, presumably resulting in effective functional recovery.
Chapter 3

3. Multimodal sensory feedback associated with motor attempts alters BOLD responses to paralyzed hand movement in chronic stroke patients


The precise nature of the signals seen by electroencephalogram (EEG) has recently become clearer through developments in transcranial magnetic stimulation (TMS), brain imaging technology (e.g. blood-oxygen-level-dependent based functional magnetic resonance imaging [BOLD-fMRI], and functional near infrared spectroscopy [fNIRS]). The alpha oscillations found over the primary sensorimotor cortex (SM1) during resting state are known to reflect the activity of the thalamo-cortical loop (Lopes da Silva 1991) and their amplitude is negatively correlated with motor evoked potentials (MEPs) (Zarkowski et al. 2006; Sauseng et al. 2009). In addition, an event-related desynchronization (ERD) seen in an EEG during motor imagery is regarded as a marker of cortical excitability because MEPs induced by single-pulse TMS over the primary motor cortex (M1) increase when an ERD occurs (Hummel et al. 2002). Additionally, intra-cortical inhibition in M1 becomes disinhibited when an ERD occurs (Takemi et al. 2013). The association between the task-induced changes seen in BOLD signals recorded by fMRI and the changes seen in alpha/beta-band EEG signals also supports
this interpretation (Yuan et al. 2010). As a result of these findings, there is increasing interest in using an ERD-based BMI as a potential tool to train volitional regulation of corticomuscular drive for patients who have severe hemiplegia due to stroke (Neuper et al. 2006a; Buch et al. 2008; Daly and Wolpaw 2008; Pfurtscheller et al. 2008; Prasad et al. 2009; Broetz et al. 2010; Wang et al. 2010; Ang et al. 2011; Shindo et al. 2011; Caria et al. 2011; Ramos-Murguialday et al. 2013; Mukaino et al. 2014).

However, it is unclear whether ERD observed while attempting motor execution can be regarded as a neural marker that represents M1 excitability in not only healthy but also in survivors of severe stroke. This is because the neural activities of stroke patients are different from those of healthy subjects when they attempt to move (Ward et al. 2006; Arya et al. 2011; Ward 2011). Stroke leads to the loss of the peri-infarct hand territory due to learned nonuse, in addition to the exaggeration of the intracortical and intercortical inhibition in M1 (Murase et al. 2004; Honaga et al. 2013). Disinhibition of intracortical inhibition in M1 following attempts at motor action is rarely observed, and force-related signal changes were also not seen in M1 (Ward et al. 2007).

While former studies have so far tested BOLD-fMRI (Caria et al. 2011; Ramos-Murguialday et al. 2013) in patients who have received EEG-based BMI training, association of ERD and BOLD in M1 remains unclear due to limitation of the experimental paradigms. Task required in these studies was repetitive grasping and opening of the paralyzed fingers. Since most severe stroke patients can control flexor muscles in general, the results could be contaminated by BOLD responses to voluntary contraction of the flexor muscles. Moreover, they assessed the spatial configuration of activated areas in response to finger movement, but did not assess the correlation of the signal intensity between ERD and BOLD.

According to these facts, the physiological integrity of ERD needs to be carefully assessed in stroke patients themselves. The present study tested the relationship between ERD and BOLD signal in stroke patients who have chronic severe hemiplegia while they attempted movement of a paralyzed finger. The present study directly demonstrated that one month of training using an EEG-based BMI for finger extension movements led to the up-conditioning of ERD over the SM1 in the damaged hemisphere that resulted in the associated increase of the BOLD signal in the same region. Such a longitudinal within subjects designed experiment suggests that ERD observed in patients who have chronic injury from stroke is associated with M1 activation, as inferred in previous studies of healthy individuals. An additional whole-brain MRI also revealed activation of SM1 and supplementary motor areas in the damaged hemisphere after 1 month of BMI training, which supports the feasibility of BMI for motor stroke rehabilitation.
3.1. Methods

3.1.1. Participants

We recruited 12 participants. Since three participants were not chronic state, the study group consisted of 9 participants who had had a stroke (4 with right and 5 with left hemiplegia) and met the following inclusion criteria: (1) the first episode was a subcortical stroke; (2) they had severe upper limb paralysis and a score < 2 for finger movement on the SIAS; Table 3–1 (Chino et al. 1994), indicating very clumsy finger movement and absence of isolated individual finger movement; In the sense of SIAS-M score, the subjects whose SIAS score is < 2 are usually called “severe”. Fugl-Meyer assessment and ARAT test are a strong emphasis on the evaluation of muscle synergies, but the SIAS-M in the present study scores simple muscle impairment. Such discrepancy may be the reason for the reviewer to have a different impression from our description; (3) they had no contraindications to MRI; (4) they had no cognitive impairment; and (5) chronic stroke more than 18 weeks before the study that further neurological and clinical recoveries are less likely (Nakayama et al. 1994b; Jørgensen 1995; Duncan et al., 2000). Detailed clinical information of the 9 participants is shown in Table 3–2. All participants provided written informed consent prior to participating in the study.
Table 3–1. SIAS finger function. (modified from Chino et al. 1994)

<table>
<thead>
<tr>
<th>Motor function (finger)</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Finger test: Individual finger movements are tested. The patient flexes each digit from the thumb to the little finger, in that order, and then extends them from the little finger to the thumb.</td>
<td></td>
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<tr>
<td>0 No voluntary finger movement</td>
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<tr>
<td>1a Minimal voluntary movement or mass flexion</td>
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<tr>
<td>1b Massextension</td>
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<tr>
<td>1c Minimal individual movement</td>
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<tr>
<td>2 Individual movement of each finger is possible, but flexion or extension is not complete</td>
<td></td>
</tr>
<tr>
<td>3 Individual movement of each finger is possible, with adequate flexion and extension of the digits; however, the patient carries out the task with severe or moderate clumsiness</td>
<td></td>
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<tr>
<td>4 The patient carries out the task with mild clumsiness</td>
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</tbody>
</table>
Table 3–2. Summary of clinical data of subjects
3.1.2. Experimental Paradigm

The experimental protocol was conducted in accordance with the Helsinki Declaration and was approved by the ethical committee of Keio University. The experiment consisted of BMI training and brain activity assessment using both EEG and BOLD-MRI. The BMI training protocol was similar to that reported previously (Neuper et al. 1999). Briefly, EEG signals were recorded using 10 Ag/AgCl disc electrodes placed on both the cortices (Figure 3–1 A). The reference electrode was placed at the left auricle. The signals were amplified (g.USBamp; Guger Technologies, Graz, Austria), band-pass filtered (2–60 Hz), and digitized (sampling frequency, 256 Hz). EEGs were recorded in both the cortices for assessment, but only the EEG in the damaged cortex was used as a signal source for BMI training. The mechanisms involved in the motor recovery of stroke patients in the chronic stroke have yet to be fully known (Nudo 2013). However, M1 in the damaged hemisphere might have an important role for functional recovery in a distal upper limb (Braun et al. 2007; Ward 2007; Caria et al. 2011) and actually, Ramos-Murgualday et al., achieved functional recovery in stroke patients by BMI using only ipsilesional cortical activity (Ramos-Murgualday et al. 2013) Thus, the present study also employed ERD on the damaged hemisphere in the BMI system. To obtain reference-free EEG data, bipolar signals were calculated (see EEG Analyses section). The surface electromyogram (EMG) of the extensor digitorum communis and flexor digitorum superficialis muscles on both upper limbs were monitored during the experiment because increased EMG activity for the affected or unaffected limb was expected during imagining of affected finger movement. Participants were instructed to relax when surface EMG signal was recorded. Surface EMG was amplified (g.USBamp), band-pass filtered (5–500 Hz), and digitized (sampling frequency, 1200 Hz).

The trial was initiated with the presentation of the word “Relax” on the monitor, and a countdown was presented at the bottom of the monitor for preparing to image an affected finger movement. The word and countdown disappeared 5 s later, and 6 participants without motor-driven orthosis received visual feedback stimulus of the EEG in the form of a picture of the affected hand on the monitor. The ERD value to the resulting action of the feedback was determined before training as follows. First, the participants generally achieved an increase in SMR during passive relaxation and an ERD while imagining maximal finger extension effort on the paralyzed side. Pictures of the hand with varying degrees of hand movement were then mapped according to ERD magnitude. I prepared 20 hand pictures with different hand positions, ranging from a full-hand grasp to a fully open hand. For 3 of the 4 participants, they were asked to attempt their affected finger extension and a hand opening in the picture was associated
with increasing ERD. In these patients, pictures of a hand closing were associated with decreasing ERD because the participants’ hands were normally positioned in a more grip-like posture during the passive state, caused by the spasticity (Figure 3–1 B). For only participant number 4, he was asked to attempt his affected finger flexion and a hand closing in the picture was associated with increasing ERD, whereas a hand opening was associated with decreasing ERD because that participant’s hand was normally positioned in a more open posture in the passive state. The ERD was divided into 20 parts from 0–80 %, and each part was assigned 1 hand picture. The hand picture on the screen then remained stable, and the participants were asked to relax for 5 s. The other five participants who did not receive visual feedback during the task period were asked to attempt their affected finger extension. They received passive finger extension by a motor-driven orthosis when ERD was observed at the end of the task period (Figure 3–1 C). This was designed to provide additional reward for completing the task. This 15-s trial was repeated for approximately 1 h, and a total of 100 trials were performed. This training was conducted on weekdays for 1 month. The experiment was discontinued for the day if the participant complained of exhaustion. Because some participants complained of exhaustion during multiple sessions, the training time was shortened, and the participants were asked to perform at least 60 trials on that day.
Figure 3–1. Design of this experiment. (cited from Shindo et al., J Rehbil Med 2011, partially revised.) (A) Electrode setup. (B) Visual feedback (C) Motor-driven feedback system
Every day before BMI training, 20 trials of the same paradigm were conducted for each participant to determine the extent of ERD. In this screening session, the participants performed the task of imaging paretic hand finger movement but did not receive feedback. The EEG montage and frequency band for deriving ERD in the subsequent BMI training session were determined from the ERD results obtained in these sessions. This was done because the EEG results depend on the participant’s mental condition and the exact electrode positions, which may vary even if they were set as precisely as possible according to the international 10-20 system (Aftanas et al. 2002; Ward et al. 2003; Neuper et al. 2006b). This calibration was formerly established elsewhere (Neuper et al. 1999; Wolpaw and McFarland 2004).

3.1.3. Neurophysiological assessments

Before and after the 1-month BMI training period, brain activity during attempting affected finger movement was assessed using EEG and BOLD-fMRI. The participants received 80 trials with the same paradigm as the BMI training for ERD assessment. Whole-brain BOLD-fMRI (Excelart/Vantage, Toshiba Medical, Japan) was performed at 1.5 T with standard scanning software on the day before and after BMI training. The following parameters were used for BOLD-fMRI experiments: repetition time (TR), 3000 ms; echo time (TE), 40 ms; flip angle, 90°; field of view, 256 mm; matrix size, 96 × 96; and slice thickness, 5 mm (slice gap, 1 mm). Between repetitions, 23 axial sections (slices) were acquired in an interleaved manner (i.e., 23 slices/3 s). These protocols were the same as that described previously (Park et al. 2004), except for the number of slices.

The paradigm was a block design (5 rest and 5 task blocks, 30 s each). The participants practiced self-paced grasping tasks with the affected hand before BOLD-fMRI measurement. The tasks were practiced with a metronome until the rate could be maintained around 1 Hz. After the participants practiced self-paced grasping movements, they were placed in the MRI machine and verbally instructed to rest for 30 s, and then make self-paced grasping movements with the affected hand for 30 s with maximal effort. The entire procedure was repeated 5 times. I could not confirm whether patients actually moved their hand at 1 Hz in compliance with our direction, since their severely paralyzed finger movement was too weak to measure it even in terms of EMG recording. The previous studies in stroke participants with severe motor disorder (which is same severity level as the ones in our study) also confronted with the same technical difficulties (Marshall et al. 2000; Foltys et al. 2003). These studies used the video recording and motor performance during MRI scanning were assessed Therefore, I used
“self-paced movement” design, according to previous study for stroke (Jaillard et al. 2005). In healthy subject, self-paced frequency variations of a simple motor task in the 0.2–2 Hz range are not a relevant source of the variability of the BOLD-fMRI results (Diciotti et al. 2007). So even if the patients in our study could not attempt to perform 1 Hz-grasping exactly, and the actual rate was slower, its effect on BOLD-fMRI result was considered to be minimum.

3.1.4. Electroencephalogram Analyses

EEG signals were processed using MATLAB (MathWorks Inc., USA). First, all bipolar combinations were calculated from 5 electrodes over each cortex. Feedback was generated on the ERD value calculated for predefined participant-specific frequency bands (Pfurtscheller and Neuper 1997) by following equation:

\[
ERD(f,t) = \frac{R(f) - A(f,t)}{R(f)} \times 100
\]

where \(A(f,t)\) is the power spectrum of the EEG at frequency \(f\) in Hertz at time period of [-3 -2] in second, with reference to the onset of motor task, and \(R(f)\) is the power spectrum of a 1-s epoch of the reference period (2–3 s) in each trial. By using this definition, ERD was expressed as a positive number. This time-frequency data was used to select the most reactive frequency band and a bipolar montage. I selected most reactive frequency band and channel around the SM1 at every day, since I considered that most reactive ERD around the SM1 may reflect the peak activity of the SM1. If ERD was not observed at the beginning of BMI training, I used EEG power at a base frequency (9–12 Hz) with a bipolar montage of C3a-C3, which was the best electrode scheme in general (Neuper et al. 2006). The artefact was not removed in on-line session.

3.1.5. BOLD-fMRI Analysis

Data were processed with a general linear model using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK). Data analysis comprised of motion correction, co-registration, normalization, statistical analysis of the activated pixels, and calculation of the activated volumes. The first 5 images (for 15 s) of each set were discarded because they showed irregular contrast acquired before the MRI signal had reached equilibrium. Next, motion correction was performed by realigning all functional volumes to the first volume of the functional series and by coregistration to the anatomical volume. Direct observation was
made by an investigator as reported previously (Ward et al. 2003). The self-paced frequency variations of a simple motor task in the 0.2–2 Hz range are known to be irrelevant sources of BOLD-fMRI result variability (Diciotti et al. 2007). Therefore, the obtained BOLD-fMRI data was useful for further analysis, even if the actual rate of self-paced movement attempts was slower than expected. All functional volumes were normalized to the Montreal Neurological Institute (MNI) template. I used a lesion mask created with MRICro software (Chris Rorden, Columbia, SC, USA. www.mricro.com) because the general normalization process may result in incorrect normalization due to lesion irregularity. I performed this procedure in accordance with a previous study that registered to MNI space (Ward et al. 2003). Functional images were smoothed with a Gaussian kernel (full width at half-maximum, 8 mm), and I estimated task-specific effects using a general linear model with a delayed boxcar waveform (Friston et al. 1994), which was convolved with the canonical hemodynamic response function. Significance was determined on a voxel-by-voxel basis using a t-statistic, which was then transformed to a normal distribution. The resulting sets of spatially distributed Z-values constituted statistical parametric maps (SPM[Z]), which show regions of significant condition-associated signal changes. These regions were then displayed with a statistical threshold based on the amplitude (p < 0.05 corrected for multiple comparisons). Voxels with a greater Z-value were regions for which BOLD signals were enhanced due to changes in blood oxygenation in accordance with the task. Contrast images that showed activated volumes for both conditions before and after BMI training were created for each participant. These images were then used in a second-level (random-effects) analysis in order to generalize the inferences across the participants to the population.

I performed between-subject analysis of correlations between ERD and regional BOLD changes in a before-and-after experimental design. First, in every participant, I set regions of interest (ROIs) that covered both pre- and post-central gyrus at individual hemisphere. This method was the same as that described previously (Yuan et al. 2010), except the value of the non-activated area was defined as 0. Next, correlations between ERD and BOLD signal for the same regions before and after BMI training were calculated. In short, each participant had 4 BOLD-fMRI values (left/right ROIs and before/after training).
3.2. Results

3.2.1. Neurophysiological representations on the first day

In all participants, ERD was detected over both the damaged and undamaged SM1 in a 9–26 Hz frequency band throughout the experiment, and the EEG montage and reactive frequency band that showed the highest ERD while attempting movement of an affected finger differed only slightly on each day and for each participant (Table 3–3). ERD values below were calculated by using those parameters.

I observed BOLD responses in 10 of 18 SM1 before BMI training (6 in damaged cortices and 4 in undamaged cortices). There was no correlation between ERD and BOLD responses (Pearson’s correlation).
### Table 3-3. The most reactive frequency band and channels

<table>
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<tr>
<th>Frequency (Hz)</th>
<th>Participant</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>Before</td>
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<td>17 - 20</td>
<td>20 - 22</td>
<td>19 - 16</td>
<td>17 - 20</td>
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<tr>
<td>After</td>
<td>Damage</td>
<td>22 - 26</td>
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<td>13 - 20</td>
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<tr>
<td>Before</td>
<td>ERD, % Measured</td>
<td>21.2 ± 4.6</td>
<td>11.4 ± 6.2</td>
<td>14.8 ± 3.2</td>
<td>26.9 ± 16.9</td>
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<td>After</td>
<td>ERD, % Measured</td>
<td>19.9 ± 21.9</td>
<td>7.6 ± 5.5</td>
<td>6.4 ± 8.4</td>
<td>24.7 ± 11.4</td>
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<td>Before</td>
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<td>22.9 ± 6.5</td>
<td>28.8 ± 5.9</td>
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<td>After</td>
<td>ERD, % Measured</td>
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<td>15.6 ± 5.3</td>
<td>8.6 ± 4.7</td>
<td>22.8 ± 8.7</td>
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<tr>
<td>Before</td>
<td>Damage</td>
<td>6 - 1</td>
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<tr>
<td>After</td>
<td>Damage</td>
<td>6 - 1</td>
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<tr>
<td>Before</td>
<td>Damage</td>
<td>16.5 ± 6.6</td>
<td>13.5 ± 7.6</td>
<td>10.7 ± 6.7</td>
<td>12.8 ± 8.8</td>
<td>9.2 ± 4.9</td>
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<tr>
<td>After</td>
<td>Damage</td>
<td>37.3 ± 15.3</td>
<td>15.8 ± 5.4</td>
<td>14.2 ± 4.4</td>
<td>16.2 ± 6.0</td>
<td>8.3 ± 7.3</td>
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<tr>
<td>Before</td>
<td>Damage</td>
<td>26.7 ± 8.4</td>
<td>22.2 ± 8.9</td>
<td>22.4 ± 5.6</td>
<td>21.3 ± 9.2</td>
<td>21.1 ± 9.2</td>
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<tr>
<td>After</td>
<td>Damage</td>
<td>40.3 ± 13.3</td>
<td>14.3 ± 4.9</td>
<td>21.2 ± 8.3</td>
<td>28.4 ± 6.1</td>
<td>17.3 ± 6.2</td>
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</table>
3.2.2. The changes of electroencephalogram across training

After the BMI training period, ERD while attempting movement of an affected finger became stronger. Figure 3–2 A shows representative data of the time-frequency map of ERD before and after BMI training. Statistical evaluation of the ERD values revealed significant enhancement over both damaged and undamaged hemispheres after BMI training in participants (Figure 3–2 B, \( p < 0.01 \), paired \( t \)-test). The ERD time-courses of all participants are shown in Figure 3–2 C. ERD recorded over the damaged hemisphere tended to increase in the first week. ERD and BOLD responses obtained from the 4 participants who did not have motor-driven orthosis and the 5 participants who did have motor-driven orthosis were combined for further analysis.
Figure 3–2. Changes in ERD across BMI training. (A) Typical time-frequency map during motor execution, before and after BMI training (Participant 7). ERD time-frequency maps for the undamaged cortex (left column) and damaged cortex (right column) were computed, both before (upper row) and after (lower row) BMI training. The highlighted time period on the x-axis indicates the period of motor intention. (B) ERD change of all participants. (C) Longitudinal ERD changes at all days.
3.2.3. Correlation between hemodynamic response and electroencephalogram change

Figure 3–3 shows the correlation between BOLD response and ERD. I observed BOLD responses in 15 of 18 cortices before and/or after BMI training. After training, of these 15 hemispheres, 8 hemispheres showed an increase in BOLD response with increasing ERD, and 2 hemispheres showed a decrease in BOLD response with decreasing ERD. Another 3 hemispheres showed a decrease in BOLD response with increasing ERD, and 1 hemisphere showed an increase in BOLD response with decreasing ERD. Different slopes among participants are not a concern because the ERD while attempting movement of an affected finger is different for each participant. A steep slope when the hemisphere did not activate before or after BMI training is not unexpected because of a zero value in the non-activated hemisphere. In the case of correlation between BOLD response and ERD only on activated areas by BOLD-fMRI, a larger BOLD response was associated with a larger ERD in the same cortical region (Pearson’s correlation, $p < 0.05$).
Figure 3–3. The correlation between BOLD signal changes on SM1 and ERD activation.

\[ y = 0.01x + 0.48 \]
\[ R^2 = 0.23, p < 0.05 \]
3.2.4. Individual analysis about hemodynamic response across training

MRI images with an overlay of the BOLD regions of activation for all participants while attempting a finger movement of the paretic hand are shown in Panel A in Figure 3–4 to Figure 3–12. Panel B and C in Figure 3–4 to Figure 3–12 show time courses of BOLD signal before and after trainings.

Before BMI training, Participant 1 showed activation of the bilateral SMA while attempting a finger movement of the paretic hand. After the BMI training, activation of the SM1 contralateral to the affected hand was observed, in addition to the activation of the SMA contralateral to the affected hand observed while imaging a finger movement of the paretic hand.

Before the BMI training, Participant 2 exhibited activations of both SMA and bilateral SM1 while imaging a finger movement of the paretic hand. After the BMI training, the activations of the SM1 and SMA contralateral to the affected hand was observed while imaging a finger movement of the paretic hand.

Before BMI training, Participant 3 showed activations of the bilateral SMA while imaging a finger movement of the paretic hand. After the BMI training, activation of both SM1 was observed while imaging a finger movement of the paretic hand.

Before BMI training, Participant 4 exhibited activations of both SM1 while imaging a finger movement of the paretic hand. After the BMI training, only activation of the SM1 contralateral to the affected hand was observed while imaging a finger movement of the paretic hand.

Before the BMI training, Participant 5 exhibited activations of bilateral SMA and SM1 contralateral to the affected hand while imaging a finger movement of the paretic hand. After the BMI training, the activations of the SM1 and SMA contralateral to the affected hand was observed while imaging a finger movement of the paretic hand.

Participant 6 exhibited activations of bilateral SMA and bilateral SM1 while imaging a finger movement of the paretic hand before and after the BMI training.

Before the BMI training, Participant 7 exhibited activations of bilateral SMA and bilateral SM1 while imaging a finger movement of the paretic hand. After the BMI training, the activations of the SM1 contralateral to the affected hand and bilateral SMA were observed while imaging a finger movement of the paretic hand.

Before BMI training, Participant 8 did not show activation in any brain area while imaging a finger movement of the paretic hand. After the BMI training, activation of the SM1 and SMA contralateral to the affected hand was observed while imaging a finger movement of the paretic hand.

Before BMI training, Participant 9 showed activations of the SM1 contralateral to the affected hand and the bilateral SMA while imaging a finger movement of the paretic hand.
hand. After the BMI training, activation of both SM1 was observed while imaging a finger movement of the paretic hand.

Table 3–4 depicts the activated regions for each participant during attempting affected finger movement observed using BOLD-fMRI.
Figure 3–4. BOLD-fMRI result of Participant 1.
Figure 3–5. BOLD-fMRI result of Participant 2.
Figure 3–6. BOLD-fMRI result of Participant 3.
Figure 3–7. BOLD-fMRI result of Participant 4.
Figure 3-8. BOLD-fMRI result of Participant 5.
Figure 3–9. BOLD-fMRI result of Participant 6.
Figure 3–10. BOLD-fMRI result of Participant 7.
Figure 3–11. BOLD-fMRI result of Participant 8.
Figure 3–12. BOLD-fMRI result of Participant 9.
Table 3–4. Activated area of each participant.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Visual</th>
<th>Orthosis</th>
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<tr>
<td></td>
<td>Undamaged SM1</td>
<td>Damaged SM1</td>
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<tr>
<td>Pre 1</td>
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<tr>
<td>Post 1</td>
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<tr>
<td>Pre 2</td>
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<td>Post 2</td>
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<td>+</td>
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<tr>
<td>Pre 3</td>
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<td>+</td>
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<tr>
<td>Post 3</td>
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<tr>
<td>Pre 4</td>
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<tr>
<td>Post 4</td>
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<td>+</td>
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<tr>
<td>Pre 5</td>
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<td>+</td>
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<tr>
<td>Post 5</td>
<td></td>
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<tr>
<td>Pre 6</td>
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<tr>
<td>Post 6</td>
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<tr>
<td>Pre 7</td>
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<tr>
<td>Post 7</td>
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<td>Pre 8</td>
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<td>Post 8</td>
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<td>Pre 9</td>
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<tr>
<td>Post 9</td>
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</table>

Figure 3–4. Activation maps and BOLD signal. (A) The activation maps of each subject. Red: the activation area before BMI training. Green: the activation area after BMI training. The left of the figure indicates the undamaged cortex. (B) BOLD signal in each ROI before training. Participants attempted finger movement during shaded periods, while participants relaxed during other periods. (C) BOLD signal in each ROI after training.
3.2.5. Group Analysis about BOLD response across training

In group analysis, bilateral SM1 and supplementary motor area (SMA) activation was observed while attempting movement of an affected finger before BMI training (Figure 3–13, red). The number of voxels and signal change in both the SM1 increased after BMI training (Figure 3–13, green, Before: undamaged = 349 voxels, damaged = 118 voxels; After: undamaged = 577 voxels, damaged = 900 voxels). Before BMI training, various regions (both SM1, both SMA, and both premotor areas) were activated during attempts at movement of an affected finger. Cortical activation represents the different patterns observed among participants. After BMI training, 3 cortical activation patterns were observed during attempts at movement of an affected finger: 1) only damaged SM1 was activated, 2) both the SM1 and only the damaged SMA were activated, 3) both the SMAs were activated. No participants exhibited only undamaged SM1 and SMA activation while attempting movement of an affected finger.

Although differences in the EEG and BOLD-fMRI results were observed after BMI training, no significant improvement was observed in the clinical assessment (SIAS scale) or EMG activity recorded from the extensor and flexor digitorum muscles.
Figure 3–13 Activation map during imaging to move affected hand. The activation map in group-analysis. Red: the activation area before BMI training. Green: the activation area after BMI training. The left of figure indicates the undamaged cortex.
3.3. Discussion

In this study, chronic stroke patients with severe hemiplegia performed ERD-regulated motor imagery training in a BMI framework for 1 month, and I observed that ERD enhancement while attempting paralyzed finger movement was associated with increased BOLD responses in both the damaged and undamaged SM1. Moreover, statistical parametric mapping of BOLD changes confirmed that the neural reorganization involved the SM1 and SMA in the damaged cortex in many cases, and, in a few cases, it involved the SM1 and SMA in the unaffected cortex. Despite changes in neural activity, no physical improvement was observed in any participants. A previous BMI-training study showed that the combination of EEG-based BMI with conventional physical therapy induced functional upper limb recovery (Broetz et al. 2010; Ramos-Murguialday et al. 2013), suggesting that EEG-based BMI promotes subthreshold levels of activation in a wide range of sensorimotor-related areas. Our findings provide neuroimaging evidence to support these previous findings.

3.3.1. The change of electroencephalogram during action observation

Action observation of hand movement generates ERD over the somatosensory cortex. Therefore, such effect may also contribute to change in ERD over time. Since the activity of the somatosensory cortex is tightly coupled with that of the primary motor cortex, our experimental paradigm consisted of a positive closed-loop of ERD. In this BMI, once the participant attempts to perform hand movement, ERD over SM1 first occurs. Then, visual feedback of hand movement, triggered by this ERD, promote further ERD in S1 due to the mechanism you pointed out, resulting further increase of net ERD. Changes in ERD and BOLD-fMRI over time in the present study may be thus promoted by such a positive closed loop system of our BMI. Therefore both “motor imagery” and “action observation” may be possible factors for promoting ERD and BOLD-fMRI change.

3.3.2. Physiological relevance of change of electroencephalogram in stroke survivors

First, I will discuss the physiological relevance of ERD enhancement, especially in the damaged cortex, when chronic stroke patients, who had received one month of BMI training for severe hemiplegia, imagined movement of the affected finger. ERD reflects certain aspects of interactions between thalamic nuclei and cortical areas that
are controlled by the interplay between thalamic relay cells and reticulo-thalamic pathway cells (Steriade and Llinás 1988). The cortical network involved in this interaction is thought to be in an activated state and ready for information processing (Neuper and Pfurtscheller 2001). It has been confirmed in healthy participants that ERD during hand motor imagery is co-localized and co-varied with SM1 BOLD signal (Fox and Raichle 2007; He and Liu 2008). Studies in healthy participants using transcranial magnetic stimulation (TMS) also revealed an association of ERD with corticospinal tract excitation (Hummel et al. 2002) and disinhibition of the intra-cortical inhibition in M1 (Takemi et al. 2013). From these findings in healthy individuals, the feedback of ERD can be regarded as an explicit representation of neural activity including M1 (Pfurtscheller 2006). It should be noted here that brain activity while attempting an affected finger movement in stroke patients is assumed to be similar to that during motor execution (Lotze and Cohen 2006; Sharma et al. 2006), but the difficulty in cognitive screening and compliance in motor imagery studies is particularly pronounced in stroke patients (Sharma et al. 2006). Thus, if the relevance of ERD can also be confirmed in chronic subcortical stroke patients, ERD feedback during motor attempt in a BMI paradigm guarantees a surrogate of motor execution training to induce brain activity similar to the one needed for motor execution under high compliance.

At the end of the EEG-based BMI training period, our stroke patients could voluntarily produce significant ERD over the ipsi-lesional SM1 despite severe, chronic paralysis. Furthermore, the BOLD response in the ipsi-lesional SM1 was associated with this phenomenon. Compared with the results of Yuan’s study (Yuan et al. 2010), ERD in stroke patients was smaller than that in healthy subjects, and the BOLD response of stroke patients was between the values during motor imagery and during motor execution of a healthy subjects. These results suggest that while neural activity during motor attempt is decreased in stroke patients, BOLD responses in stroke patients do not differ from that during motor execution in healthy subjects.

In view of these results and the argument mentioned above, I maintain that ERD observed in stroke patients is a relevant marker representing cortical excitability similar to healthy individuals. The observed ERD enhancement after EEG-based BMI training could thus be interpreted as the result of the acquisition of an efficient mental strategy for voluntary cortical drive. The ability to generate ERD over the damaged cortex in both acute and subacute phases of stroke is known to be correlated with clinical motor outcome (Platz et al. 2002); thus, the present result encourages us to employ EEG-based BMI to facilitate clinical improvement, as tested previously (Broetz et al. 2010; Caria et al. 2011; Shindo et al. 2011; Ramos-Murgualday et al. 2013).

A previous study has shown that the BOLD response in M1 during motor imagery is weaker than that during motor execution (Porro et al., 1996). This difference arises
because the motor imagery task is too obscure and represents a mental process without actual movement. This suggests that motor attempt of a stroke patient is similar to motor imagery of a healthy person. BMI rehabilitation with feedback enhanced cortical activity during motor attempt, and could explain why the BOLD response changed after BMI training.

3.3.3. Neural activity assessed by hemodynamic responses

Next, I discuss the use of whole-brain BOLD-fMRI to identify brain regions associated with EEG-based BMI training of finger opening movement. Previous studies have so far tested BOLD-fMRI (Caria et al. 2011; Ramos-Murguialday et al. 2013), but the task required in these studies was repetitive grasping and opening of the paralyzed fingers. It is a common sense that most stroke hemiplegia lacks volitional control in extensors, but not in flexors, implying finger flexor muscle activity in a grasping phase during such a BOLD-fMRI task might have dominant influence on the result. To exclude such BOLD response contamination of the finger flexor muscle activity, I employed simple finger extension and relaxation (and not flexion or grasping) paradigm. The result obtained in this study can be therefore interpreted as the BOLD response to the finger extensor muscle activity that was trained by EEG-based BMI rehabilitation.

Recent studies on healthy participants have shown that successful BMI use enhances SMA activation during motor imagery (Halder et al. 2011; Hermes et al. 2011). Similarly, I observed that chronic stroke participants’ ERD values increased after BMI training, and 8 of the 9 participants showed SMA activation while imagining an affected finger movement. This SMA activation may play a role in increasing damaged SM1 activity, resulting in the increase in ERD and BOLD.

Previous imaging studies of stroke patients with mild hemiparesis suggest that 3 processes are associated with motor recovery: (1) increased activation of the damaged and/or undamaged SM1 (Chollet et al. 1991; Cramer et al. 1997; Levy et al. 2001; Carey et al. 2006), (2) increased activation of motor-related areas (Chollet et al. 1991; Cramer et al. 1997; Levy et al. 2001), and (3) increased activity at the edge of the infarction in cortical strokes (Cramer et al. 1997). Although a previous study showed that neurological changes diminish a few months after stroke (Delvaux et al. 2003), 11 of the 12 participants in this study exhibited activation in the damaged SM1 and an activation shift in the SMA while attempting affected finger movement following BMI training. Because there are no successful rehabilitative measures for severe upper extremity hemiplegia, no data is available on the brain regions engaged by intervention.
training in such cases. The present study employed EEG-based BMI to provide intervention for severe cases and is the first to demonstrate that the cortical activation pattern was similar to that observed during recovery in mild hemiparetic patients. This finding substantiates EEG-based BMI training as a possible rehabilitative measure for more severe hemiplegia. Although I did not observe motor recovery, BMI training induced activity in motor-related areas. Even a subthreshold level of activation in sensorimotor-related areas promoted by BMI may facilitate functional recovery when combined with other means. In fact, several studies have suggested that a combination of BMI training and physiotherapy can induce actual functional recovery (Broetz et al. 2010; Ramos-Murgualday et al. 2013).
Chapter 4

4. Brain-Machine Interface with somatosensory feedback improves functional recovery from severe hemiplegia due to chronic stroke

* This chapter was based on my original article, “Ono T, Shindo K, Kawashima K, et al. (2014) Brain-Computer Interface with somatosensory feedback improves functional recovery from severe hemiplegia due to chronic stroke. Front Neuroeng 7:19. doi: 10.3389/fneng.2014.00019.”. I have a right to use this dissertation.

Studies about rehabilitation training for stroke patients suggest that practicing or observing movements that are highly similar to normal movements helps to improve motor functions (Ertelt et al. 2007; Garrison et al. 2010; Arya et al. 2011). Experience-based plasticity mechanisms, that involve the relative re-weighing of synaptic inputs, are constantly shaping network organization and are more likely driven by the formation and elimination of dendritic spines (Johnston 2004; Carmichael 2006; Murphy and Corbett 2009). Some animal studies suggest that such plasticity occurs at both the peri-lesion and remote areas (Nudo 2006). The results of several randomized, controlled, trials have indicated that the intensive practice of important motor tasks, while constraining the nonparetic limb, can substantially improve upper limb function in individuals whose movements have been mildly impaired by stroke (Grotta et al. 2004; Mark et al. 2006; Taub et al. 2006; Lin et al. 2010). In the case of moderate impairment, assisted voluntary movement with functional electrical stimulation through surface electrodes is effective in improving finger and wrist motor functions (Peckham et al. 1980; Kimberley et al. 2004).

Recently, electroencephalogram (EEG)-based Brain-Machine Interface (BMI) has been regarded as a new rehabilitation technique for patients with severe impairment
after stroke, who cannot use the other above-mentioned rehabilitation strategies owing to a lack of volitional muscle activity (Buch et al. 2008; Daly et al. 2009). Motor imagery is often used in EEG-based BMI, because it is defined as the mental rehearsal of a motor act without overt movement (Alkadhi et al. 2005). BMI estimates the patients’ motor imagery from the amplitude of the arc-shaped waveform on an EEG, or a magnetoencephalogram recorded over the primary sensorimotor cortex (SM1) and translates it into feedback (e.g., visual guidance, electrical stimulation of muscles, or motor-driven orthosis). Imagery, or an actual hand movement, activates the SM1 and rhythmic activity in the alpha and beta band in EEG over the hand region results in amplitude attenuation or event-related desynchronization (ERD). This enables movement observation or provides afferent feedback in the BMI, and such feedback is believed to help direct brain reorganization, resulting in some functional recovery from stroke hemiplegia (Daly and Wolpaw 2008). The prolonged use of this BMI training induces plastic changes in the brain activity of patients with stroke (Rozelle and Budzynski 1995; Buch et al. 2008) and clinical improvement of upper limb function (Prasad et al. 2009; Caria et al. 2011; Shindo et al. 2011; Ramos-Murguialday et al. 2013; Mukaino et al. 2014).

However, specifications of the BMI paradigm that are needed for functional recovery are as yet unknown. As Daly and Wolpaw speculated, neural plasticity will be guided in different ways depending on the feedback modality. Visual feedback of ongoing SM1 excitability trains patients to produce normal SM1 activity, whereas robotic assistance of paretic movement following SM1 excitation will produce sensory input that induces neural plasticity to restore more normal motor control. To date, different types of feedback have been separately tested in some research groups. Thus, the validation of feedback type and protocol standardization in a BMI rehabilitation context will be beneficial for further research development.

In this paper I compared two different types of feedback (i.e., visual feedback and sensory feedback with robotic movement assistance) contingent to motor-related EEG in stroke patients with chronic hemiplegia with a view toward functional recovery, using the Stroke Impairment Assessment Set (SIAS) which is a known standard scoring test, consisting of 22 subcategories, and has high reliability. BMI settings, except feedback and the task design, were shared between the two paradigms in order to minimize the potential influences of factors such as training intensity, duration, and adaptation to the EEG classification rules. Since such an experiment was first designed as a pilot trial, the experiments were conducted as a group comparison study to minimize participants' burden from an ethical point of view. I note here that data in this BMI paradigm (sensory feedback) was previously reported elsewhere as a preliminary case series study (Shindo et al. 2011). On the other hand, the goal of our study was to compare two
different types of feedback. Thus the same data was used for another research purpose in this article.
4.1. Methods

4.1.1. Participants

The study group consisted of 12 participants who had had a stroke (3 with right and 9 with left hemiplegia) and met the following inclusion criteria: (1) the first episode was a subcortical stroke; (2) they had severe upper limb paralysis and a score ≤2 for finger movement on SIAS (Table 3–1) (Chino et al. 1994), indicating very clumsy finger movement and absence of isolated individual finger movement; (3) they had no cognitive impairment; and (4) their chronic stroke injury occurred more than 13 weeks prior to the study to ensure that further neurological and clinical recovery were less likely (Nakayama et al. 1994a; Jørgensen et al., 1995; Duncan et al., 2000). Detailed clinical information of the 12 participants is shown in Table 4–1. Twelve participants had little or no detectable surface electromyogram (EMG) activity from the affected extensor digitorum communis (EDC) when they attempted to extend their fingers. All participants provided written informed consent prior to participating in the study.
Table 4–1. Summary of clinical data of subjects.
4.1.2. Experimental Paradigm

The experimental protocol was conducted in accordance with the Helsinki Declaration and was approved by the ethical committee of Keio University. The experiment consisted of BMI training and brain activity assessment using EEG. The BMI training protocol was similar to that reported previously (Neuper et al. 2009). Participants were seated in a comfortable chair with their arms supported and relaxed on the armrests in pronation. A 15.4-inch computer monitor was placed about 60 cm in front of their eyes. EEG signals were recorded using 10 Ag/AgCl disc electrodes (φ = 10 mm) placed on both hemispheres (Figure 4–1 A). The reference electrode was placed at the left auricle. The signals were amplified (g.USBamp; Guger Technologies, Graz, Austria) and digitized (sampling frequency, 256 Hz). The surface EMG was recorded bilaterally from the EDC muscles (high-pass filter 5Hz; sampling rate 256 Hz). Impedance of EMG electrodes was kept under 10 kOhm.

EEG signals were processed using MATLAB (MathWorks Inc., USA). Firstly, all bipolar combinations were calculated from 5 electrodes over each hemisphere. Secondly, all EEG trials were visually controlled for artifacts and contaminated trials were discarded (Neuper et al. 2009). EEG spectra were estimated by fast Fourier transformation, using 1-s window lengths, 90% overlap, and a Hanning window. Feedback was generated on the ERD value calculated for predefined participant-specific frequency bands (Pfurtscheller et al. 1997) using the following equation:

\[
ERD(f,t) = \frac{R(f) - A(f,t)}{R(f)} \times 100
\]

where \( A(f,t) \) is the power spectrum of the EEG at frequency \( f \) at time \( t \), with reference to the onset of the motor task (see BMI training below), and \( R(f) \) is the power spectrum of a 1-s epoch of the reference period (2–3 s) in each trial. By using this definition, ERD was expressed as a positive number. The time-frequency map of each bipolar signal was calculated from a 1-s EEG window after every 125 ms. This time-frequency data was used to select the most reactive frequency band and a bipolar montage. If an ERD was not observed at the beginning of BMI training, I used EEG power at a base frequency (9–12 Hz) with a bipolar montage of C3a-C3, which was the best electrode scheme in general (Neuper et al. 2006a). A three-factor (time (pre-, post-training), side (damaged, undamaged hemisphere), feedback type (visual, somatosensory)) analysis of variance (ANOVA) for the ERD

4.1.3. Brain-Machine Interface Training Session

In this study, there were two feedback groups. Six participants performed BMI
training with visual feedback and 6 participants performed BMI training with somatosensory feedback.

**Visual feedback**

The trial was initiated upon presentation of the word “Relax” on a monitor, and a countdown was presented at the bottom of the monitor to prepare participants to attempt extension of an affected finger. The word and countdown disappeared 5 s later. Six participants received a visual feedback stimulus from the EEG in the form of a picture of the affected hand on the monitor. The ERD value in response to the resulting action of the feedback was determined before training as follows: firstly, participants generally achieved an increase in SMR during voluntary relaxation and an ERD while imagining maximal finger extension on the paralyzed side. Pictures of the hand with varying degrees of hand movement were then mapped according to ERD magnitude. I prepared 20 pictures depicting different hand positions, ranging from a full-hand grasp to a fully open hand. A hand opening in the picture was associated with increasing ERD (Figure 4–1 B). Pictures of a hand closing were associated with decreasing ERD because the participants’ hands were normally positioned in a more grip-like posture during the passive state, caused by spasticity. The ERD was divided into 20 parts from 0–80%, and each part was assigned 1 hand picture. The hand picture on the screen then remained stable, and the participants were asked to relax for 5 s. This 15-s trial was repeated for approximately 1 h, and a total of 100 trials were performed. This training was conducted on 5 weekdays for 1 month. The experiment was discontinued for the day if the participant complained of exhaustion. Because some participants complained of exhaustion during multiple sessions, the training time was shortened; however, these participants were asked to perform at least 60 trials on that day.

**Sensory feedback**

The participants had to imagine the paretic hand opening or at rest for 5 s according to the task cue. The height of the cursor reflected the accumulated value of the output of classification of ERD performed every 30 ms since the beginning of the task. Thus, the cursor fluctuated around the baseline if diminution of ERD was not clearly seen. The cursor went down if the diminution of ERD was continuously observed. The gain of cursor movement was within approximately one-tenth of the vertical range of the monitor during the resting phase in the calibration experiment. From the 4th training day, when the cursor reached the lower half on the right edge of the monitor, the motor-driven orthosis was triggered to extend the paralyzed fingers from 90 to 50 degrees (Figure 4–1 C). Each training run consisted of 10 trials, with 5 trials per class, presented in randomized order. Ten training runs were recorded per day,
with a total of 100 trials.

**Outcome assessment**

Surface EMG activities of the affected EDC muscle and ERD were compared between the first and last training days. The task was slightly modified from the BMI training paradigm in order to easily perform paretic finger movements. The cursor moved from the left to right over a period of 8 s on the monitor, and the task cue was presented 5 s after the cursor had appeared. Participants were instructed to perform “unaffected hand opening” or “affected hand opening” voluntarily for 3 s. This training run consisted of 10 trials with 5 trials per class, alternately.

In assessing improvement of finger movement impairment, SIAS was used at pre- and post-BMI training. It consists of a scale from 0 to 5, with 0 indicating complete paralysis and 5 no paresis.
Figure 4–1. Design of this experiment. (cited from Shindo et al., J Rehabil Med 2011, partially revised. (A) Electrode setup. (B) Visual feedback (C) Motor-driven feedback system
4.2. Results

4.2.1. Neurophysiological Changes

ERD in most participants was detected over both the damaged and undamaged hemispheres, in alpha and/or beta frequency bands throughout the experiment. Figure 4–2 showed the ERD value before/after trainings in both hemispheres. Statistical evaluation of ERD values revealed significant enhancement over both damaged and undamaged hemispheres after BMI training in participants in both feedback categories (ERD values were shown in Table 4–2). Three-way ANOVA showed no significant differences of side and feedback type, but it became significantly greater over both hemispheres ($p < 0.05$; three-way ANOVA). Figure 4–3 shows BMI performance. BMI performance increased in both feedback groups, while there was no significant difference between feedback groups ($p < 0.05$; two-way ANOVA).

Figure 4–4 showed EMG activities of affected EDC before/after trainings. Four participants in the somatosensory feedback group, who had little or no muscle activity before training, showed EMG activity voluntarily, while no participants in the visual feedback group improved their EMG activity. These results indicated that participants in the sensory feedback group improved in finger function and/or voluntary EMG activity. Note here that the visual feedback group did not show any improvement even when they received a longer training period.
Figure 4–2. ERD evaluation over both primary sensorimotor areas. White bars represent ERD values before training and black bars represent the ERD values after training. Numbers on x-axis represent participant numbers.

Table 4–2. ERD values of each hemisphere.

<table>
<thead>
<tr>
<th></th>
<th>Visual</th>
<th>Somatosensory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before, %</td>
<td>After, %</td>
</tr>
<tr>
<td>Undamaged</td>
<td>12.1 ± 8.3</td>
<td>20.0 ± 9.2</td>
</tr>
<tr>
<td>Damaged</td>
<td>13.6 ± 10.4</td>
<td>27.9 ± 5.0</td>
</tr>
</tbody>
</table>
Figure 4–3. BMI performance accuracy. The open bars represent ERD values before training, and the filled bars represent the ERD values after training. Numbers on x-axis represent participant numbers.
Figure 4–4. Comparison of EMG activity before and after BMI. The horizontal bars represent the period during which participants opened their paralyzed hands.
4.2.2. Clinical Behavioral Changes

Figure 4–5 showed scores of SIAS finger function test. While no participants in the visual feedback group showed improvement in their finger function, 3 participants in the sensory feedback group showed improvement in finger function. All participants felt that they could relax more easily, although no participants in the visual feedback group improved on any scores. In addition, participants in the somatosensory feedback group indicated that they became more aware of the use of their paretic upper extremity in daily activities.
Figure 4–5. SIAS finger function scores.
4.3. Discussion

These results show that EEG-based BMI training with visual or sensory feedback enhanced ERD following attempted motor activity, but only sensory feedback improved motor function. Though only a limited number of patients participated in the current study, the results of this preliminary study suggest that a randomized controlled trial to complement these results be completed in the future.

4.3.1. The change of brain wave and Finger Function

Participants in this study learned to increase ERD after training. In addition, BMI performance also increased in both groups. These results follow those of previous studies (Pfurtscheller and Neuper 2001; Buch et al. 2008; Hwang et al. 2009; Broetz et al. 2010; Hashimoto et al. 2010; Shindo et al. 2011; Cincotti et al. 2012; Mukaino et al. 2014). However, in the visual feedback group, no functional improvement was seen in any participants. From these results, I can say that ERD may not be a direct correlate of functional recovery in finger movement. ERD likely reflects desynchronized neural assembly as a result of the interaction between the thalamic nuclei and cortical areas, that are controlled by the interplay among thalamic relay cells and reticulo-thalamic pathway cells (Steriade and Lopes da Silva 1991). Desynchronization that is not directly related to motor output is potentially learned by visual feedback BMI.

ERD may reflect SM1 excitability during the relevant motor task (Takemi et al. 2013), thus a proper sensory feedback which engages the participant in the task may facilitate motor reorganization. Moreover, since the nature of neural activity is nonlinear, a supplemental neural excitation factor, i.e., timing-dependent cortical excitation by contingent somatosensory feedback to the motor cortex, may promote further excitation of the SM1, resulting in functional recovery. These possibilities could explain why only sensory feedback BMI had a tendency to promote functional recovery in stroke hemiplegia.

4.3.2. Training Interval

Due to a limitation in hospital regulations, visual feedback training was done on 5 weekdays for one month and somatosensory feedback training was done once or twice a week for a period of 4–7 months. Of course, the training schedule should be the same between groups, however the results and remarks remain valid, since even intensive (everyday) and longer (one month) training with visual feedback BMI did not show functional recovery. This suggests that sensory feedback following a motor attempt may be essential for reorganization of motor function. Intensive bodily sensation of the
paralyzed limb may also be helpful to regain body awareness (or ownership), which is needed for motor planning. Such a compound effect may make sensory feedback more advantageous than visual feedback BMI.
Chapter 5

General Conclusion

In this dissertation, a series of studies was conducted in order to measure the effect of BMI training with various types of feedback on brain activity in healthy (Chapter 2) and hemiplegic stroke subjects (Chapters 3 and 4).

In Chapter 2, I examined the effect of realistic visual feedback of hand movement associated with the mu rhythm in EEG, a representative feature of cortical excitability in BMI paradigms. Participants were randomly assigned to one of four experimental groups receiving different types of visual feedback, while ERD was measured over the contralateral SM1: no feedback as a control, bar feedback with changing bar length, anatomically incongruent feedback, in which the hand open/grasp picture on the screen was animated at eye level; and anatomically congruent feedback, in which the same hand open/grasp picture was animated on the screen overlaying the participant’s hand. As a result, I confirmed that realistic feedback training is a suitable method to acquire the skill to control a BMI system. Daily training with visual feedback induced more robust ERD than the no-feedback condition. In addition, the anatomically congruent feedback produced the highest reproducibility of ERD with the smallest inter-trial variance.

In Chapter 3, I investigated the relation between the ERD and BOLD signal during attempted paralyzed finger movement in stroke patients to clarify whether the ERD observed during attempted motor execution could be regarded as a neural marker representing M1 excitability in severe chronic stroke survivors. As a result, increased ERD over the damaged cortex was confirmed in all participants during attempted extension of the affected finger after one month of training and was associated with BOLD response in SM1. ERD reflects the BOLD responses of both primary motor cortices while attempting paralyzed finger movement in severe hemiplegic stroke patients.

In Chapter 4, I performed ERD-regulated motor imagery training in a BMI
framework in stroke patients, who had chronic and severe hemiplegia, and observed ERD enhancement. Somatosensory feedback rather than visual feedback of ERD tended to restore paretic finger movement. These results revealed the importance of peripheral bodily sensation contingent with voluntary excitation of the cortical motor system, which is a key in promoting behavioral improvement. This is a serial case study with clinical limitations. Although the small number of participants, the differences in training intervals, and the time from onset of stroke are limiting factors, the current study provided interesting and positive results, which strongly indicate that a future, large-scale clinical trial be undertaken, which I expect would support these preliminary findings.

In this dissertation, I demonstrated that ERD related to motor attempt can be changed efficaciously by long-term BMI use with realistic feedback, and that somatosensory feedback such as prosthesis-assisted finger movement was needed to improve the affected finger function in stroke patients. Daly and Wolpaw proposed two BMI-based training strategies (Daly and Wolpaw 2008). The first strategy translates specific features of brain activity into an action (e.g., cursor movement) and uses this action as feedback to train patients to produce more normal brain activity. The visual feedback training was based on this strategy. The second strategy uses specific feature of brain activity to actuate a device that assists movement to compensate for the patient’s impaired neuromuscular control during motor tasks. The somatosensory feedback training was based on this strategy. The present study suggests that both strategies enhanced cortical activation during motor imagery, but only BMI with somatosensory feedback improved actual motor function. Thus, BMI with somatosensory feedback may restore central nervous system function, while BMI with visual feedback enhanced only cortical activation and not the neuromuscular system. Visual information may assist the motor system to recall information for voluntary movements by activating it. On the other hand, somatosensory feedback may induce first-person body cognition and Hebbian-like plasticity by activating both motor-related cortices and afferent signals from affected hand. Synapse-based learning rules can be divided into two broad conceptual mechanisms: homeostatic plasticity and Hebbian plasticity (Murphy and Corbett 2009). Homeostatic plasticity mechanism is based on a negative feedback-mediated form of plasticity. This mechanism might reset the level of neuronal activity at existing synapses or create new connections that occurs after injury; it includes post-stroke hyperexcitability that develops over the first week to one month of recovery. The mechanisms of Hebbian plasticity is based on a positive feedback-mediated form of plasticity. Hebbian mechanisms are engaged when presynaptic and postsynaptic neurons are coincidently active. Such coincident activity might show that a particular surviving circuit is functioning correctly with sufficient drive to produce postsynaptic
action potentials that are paired with incoming presynaptic signals. Therefore, a feedback training that exerts such effects on the nervous system can improve motor function of the paralyzed upper limb.

Clinical research consists of various phases to assess efficacy and safety:
1. Testing of intervention training in healthy persons
2. A single case report about a patient
3. A case series report about a few patients
4. A study with dozens of patients
5. A report of randomized controlled trials with a few hundred patients

The studies in this dissertation were designed according to these procedures, and Chapter 3 and 4 correspond with Phase 4. There has been little evidence about the efficacy of BMI rehabilitation; this dissertation can support previous research, although patients with many individual factors were recruited in these studies. In addition, I showed that cortical excitability changed after BMI rehabilitation by using fMRI. This evidence will direct BMI rehabilitation research to the next phase.

Through this dissertation, some possible neuroscientific mechanisms underlying BMI rehabilitation were theoretically and practically described. The significance of these results is twofold: First, ERD in EEG reflects activity of M1 even if patients are at a chronic stage where neurological and functional recovery might not be expected. Second in these chronic patients, BMI training improved both neurological and motor functions. To establish more practical ways to use BMI rehabilitation in clinical settings, a combined protocol with electromyogram-driven, neuromuscular electrical stimulation (known as HANDS therapy) is one promising approach; the regeneration of voluntary electromyogram in a paralyzed muscle by BMI helps to use HANDS for more intensive training without any medical gaps (Horie et al., 2014). These findings encourage further understanding and development of BMI as a neurorehabilitation system to maximize neural plasticity in a novel form of therapy.
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