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Functional recovery in upper limb function in stroke survivors by using brain-computer interface
A single case A-B-A-B design*

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Abstract— **Resent studies suggest that brain-computer interface (BCI) training for chronic stroke patient is useful to improve their motor function of paretic hand. However, these studies does not show the extent of the contribution of the BCI clearly because they prescribed BCI with other rehabilitation systems, e.g. an orthosis itself, a robotic intervention, or electrical stimulation. We therefore compared neurological effects between interventions with neuromuscular electrical stimulation (NMES) with motor imagery and BCI-driven NMES, employing an ABAB experimental design. In epoch A, the subject received NMES on paretic extensor digitorum communis (EDC). The subject was asked to attempt finger extension simultaneously. In epoch B, the subject received NMES when BCI system detected motor-related electroencephalogram change while attempting motor imagery. Both epochs were carried out for 60 min per day, 5 days per week. As a result, EMG activity of EDC was enhanced by BCI-driven NMES and significant cortico-muscular coherence was observed at the final evaluation. These results indicate that the training by BCI-driven NMES is effective even compared to motor imagery combined with NMES, suggesting the superiority of closed-loop training with BCI-driven NMES to open-loop NMES for chronic stroke patients.**

T. Ono and M. Mukaino contributed equally to this work.

I. Introduction

Stroke leads to rapid loss of brain functions through disturbance in the blood supply to the brain and causes. Normal movement is often not possible after a stroke, and therefore needs to be practiced using other methods. The results of several randomized controlled trials have showed that 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 [1]. Although there are several rehabilitative treatments used to restore upper limb motor function, such as passive facilitation, neuromuscular electrical stimulation, constrain-induced movement therapy, rehabilitation after stroke must continue to address serious functional limitations for patients with severe paresis [2]. For these patients, some studies suggested that brain-computer interface (BCI)-based rehabilitation has been believed to be useful for developing functional recovery of paretic hand movement [3-5].

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BCI system uses brain signals to enable a real-time interaction between the user and the outside world. The user receives feedback on this output, which reflects the user's brain activity and influences subsequent output. One of BCI techniques uses the amplitude of the arc-shaped waveform on an electroencephalogram (EEG) during motor imagery of paretic hand recorded over the primary sensorimotor cortex (SM1) that includes mu and/or beta rhythms. The change of amplitude of ongoing EEG within the motor cortex decreases (event-related desynchronization [ERD]) and increases (event-related synchronization [ERS]) during movement or motor imagery. BCI provided a closed-loop system and such a system is believed to help direct brain reorganization. Indeed, the prolonged use of this closed-loop solution induces plastic changes in the brain waves of patients with stroke [6], [7]. In addition, some studies suggest that BCI rehabilitation is useful for promoting functional recovery of paretic hand movement [3]–[5].

However, it remains unclear how closed-loop training with BCI systems induces clinical and neurophysiological changes in stroke patient. We therefore investigated the efficacy of closed-loop training with BCI by comparing with the conventional open-loop training by using ABAB experimental design.

II. Method

A. Subject

An inpatient with subcortical stroke with severe motor deficit participated in this study. He was a 38-year-old Japanese male who suffered from a putaminal hemorrhage for 14 months. He was right-handed and had a left hemiparesis. His hand function was severely impaired, and surface electromyogram (EMG) activity from the affected extensor digitorum communis (EDC) was absent. The score of fugl-meyer assessment (FMA) was 27/66, and modified Ashworth scale (MAS) at the paretic finger was 2. He was independent activities of daily living, using T-cane and plastic ankle-foot orthosis. His cognitive abilities are intact. The study was approved by institutional review board.

B. ABAB design

This study incorporated a within-subject ABAB withdrawal design in which we alternated epoch A (NMES with motor attempting) and B (BCI-driven NMES). Figure 1a shows the time-course of ABAB experimental design. Each epoch was performed for two weeks, except the last epoch B was performed for three weeks. During epoch A (Fig. 1b), subject received the intermittent electrical stimulation (3 s stimulation followed by 3 s rest) for 60 min a day. The subject was indicated to attempt finger extended with his own effort along with the stimulation. Stimulator run automatically,

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independed of brain activation. Thus we defined that epoch A was an “open-loop” training. In the epoch B (Fig. 1c), BCI-NMES training (see below) is performed. Each training was performed 5 times a week. Concurrently. Traditional occupational therapy was performed 40 min a day, 5 times a week during all the sessions. We monitored his motor function and brain activity at the end of each session with surface EMG, EEG, functional Magnetic Resonance Imaging (MRI) and clinical valuables.

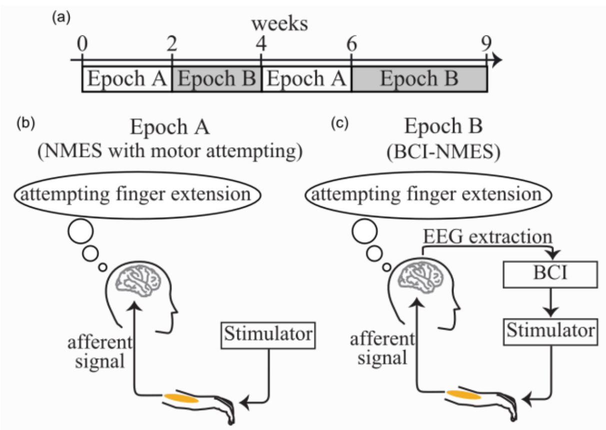

Figure 1 Overview of epoch A and B

(a): ABAB design time course. (b): Procedure of epoch A. Electrical stimulator run automatically. This is an open-loop training. (c): Procedure of epoch B. Electrical stimulator was driven when the BCI system detected motor-related EEG.

C. Electrical stimulation for NMES

NMES (20 Hz, single pulse width 100 μs, 3 s ON, 3 s OFF) was delivered by an electrical stimulator (MEB-2200, Nihon-Kohden, Tokyo, Japan) by Matlab (The MathWorks, America), using self-adhesive electrodes on affected EDC. The electrical stimulation was delivered at an intensity of 15–20 mA. Within this range, the current necessary for sufficient muscle contraction was adapted.

D. BCI-based NMES training

Subject was seated in a chair with the arm relaxed on the armrest in pronation. A 14 inch computer monitor was placed about 60 cm in front of their eyes. EEG to control NMES was recorded with 10 Ag/AgCl electrodes (5 on each hemisphere) placed around C3 and C4 according to the international 10-20 system. It was filtered between 2 and 100 Hz, and digitized 256 Hz using a biosignal amplifier (g.tec Guger Technologies, Graz, Austria). Each BCI training consisted of 2 sessions: a calibration session and an NMES-feedback training session.

The calibration session was performed to calculate the EEG classifier parameters. Subject performed either imagine paretic hand opening or rest according to the indication on the monitor. After 40 trials with 20 trials per class presented in randomized order, alpha band and beta band components of EEG in the bilateral hemispheres were used to determine the parameters for linear discriminant analysis (LDA). This processing of EEG was performed according to the previous study [4].

In the training session, the subject was indicated to attempt to follow the instruction on the monitor, to “Paretic hand opening” or to “Rest”. ERD was calculated from bilateral hemispheric EEGs every 30 ms, with a time-sliding window of 1 s during the task. The pairs of electrodes which showed the largest change during motor attempting for calculation were selected after the calibration session. The parameters for LDA were used to judge whether the patient was in “Paretic hand opening” or “Rest” state. When the computer judged the subject state “Paretic hand opening” for 1 s, the NMES on the affected EDC was provided until the computer judged the subject state “Rest”. Each training runs consisted of 20 trials, with 10 trials per class, presented in randomized order. Ten training runs were recorded per day, with a total of 200 trials. No visual feedback was provided.

E. EEG evaluation

The time-frequency map of ERD at the day admission and the last day of each training periods was calculated, to examine the change in the value of ERD. ERD was defined as the decrease in the power spectum relative to the reference period, and the ERD value was defined by the following equation:

$$ERD\,(f,t) = \frac{R(f) - A(f,t)}{R(f)} \times 100 \cdot \tag{1}$$

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

F. fMRI evaluation

Whole-brain fMRI (Excelart/Vantage, Toshiba Medical, Japan) was performed at 1.5 T, with standard scanning software, on the day admission and the last days of each training periods. The following parameters were used for the fMRI experiments: repetition time (TR)/echo time (TE)/flip angle, 3000 ms/40 ms/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 a continuous manner (i.e., 23 slices per 3 seconds). This protocol was the same as that described previously [8], except for the number of slices.

The paradigm was a block design (five rest and five task blocks, 30 s each). We employed “the self-paced movement” paradigm with 1 Hz in accordance with the previous study [9], [10]. The patient was directed for self-paced finger-extension movements with the affected hand for 30 s with maximal effort. To observe unintentional movement of the other muscles, direct observation was performed as described previously.

Data were processed with a general linear model using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK). The first 5 images (for 15 s) of each set were discarded, because they showed irregular contrast acquired before the MRI signal had reached an equilibrium state. Next, motion correction, coregistration, normalization and smoothing were performed. We estimated the task-specific effects using the general linear model with a delayed boxcar waveform [11]. The boxcar waveform 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 constitute 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). The voxels with a greater Z-value were regions for which BOLD signal enhancement, caused by changes in blood oxygenation, occurred in accordance with the task. Laterality index (LI) was calculated by the voxels within the whole hemisphere and precentral gyrus , respectively.

G. EMG and cortico-muscular coherence evaluation

Surface EMG was measured with the electrodes on affected EDC. The percent change in root mean square (RMS) after the task cue to reference RMS was calculated.

Cortico-muscular coherence (CMC) shows a functional coupling between the cortex and muscle. Therefore, CMC can clarify a mechanism of functional recovery in stroke patients after BCI training.

EEG and EMG signals during "finger extension" state were segmented into artifact-free epochs of 1 s in duration without overlapping (totally 100 epochs). To measure the linear correlation between EEG and EMG, coherence was calculated with a fast Fourier transform algorithm with a frequency resolution of 1 Hz, according to the following equation:

$$\left|R_{xy}(f)\right|^2 = \frac{\left|P_{xy}(f)\right|^2}{P_{xx}(f)\cdot P_{yy}(f)}. \quad (2)$$

In this equation, $P_{xx}(f)$ and $P_{yy}(f)$ are autospectrum of the EEG and EMG signals, x and y, for a given frequency (f), and the $P_{xy}(f)$ is the cross-spectrum between them. Coherence is expressed as a real number between 0 and 1, with 1 indicating a perfect linear association. EEG-EMG coherence was considered significant when it was >95% confidence limits computed from the number of epochs (epochs 100; limit 0.030).

E. Clinical Evaluation

For evaluation of motor function, upper extremity section of FMA score was performed. Spasticity for fingers was measured with the MAS.

III. Results

A. EEG evaluation

The ERD on right SM1 was gradually increased during the training epochs, both in the alpha and beta bands (Fig. 2a). In the time-frequency map before the training epochs, the generation of ERD was not evident by the motor intention. In the contrast, time-frequency map at the last day clearly showed ERD at alpha and beta bands. The LI of bilateral SM1 didn't change or rather decrease during NMES epoch, however, both of them markedly increased during BCI-NMES epoch (Fig. 2b).

B. fMRI evaluation

fMRI activation during affected hand movement prior to training sessions showed an extensive participation of active areas in both hemispheres, including bilateral primary motor cortex, primary sensory cortex, supplementary motor area (SMA), bilateral premotor cortices (Fig. 3). After NMES epoch, no obvious change was observed in active areas. The active area at the ipsilateral primary motor cortex was rather enlarged. After the first and second epochs of BCI-driven NMES, active areas in ipsilateral hemisphere are reduced (Fig. 4a).

At the pre-training evaluation calculated laterality index of voxels in bilateral precentral gyrus was 0.27, and hemispheric laterality index was 0.17. These laterality indexes wouldn't change or rather decrease during NMES epoch (Fig. 4b). Laterality index of precentral gyrus reached to 1.0, and hemispheric laterality index was 0.67 at the last evaluation after the whole training epochs.

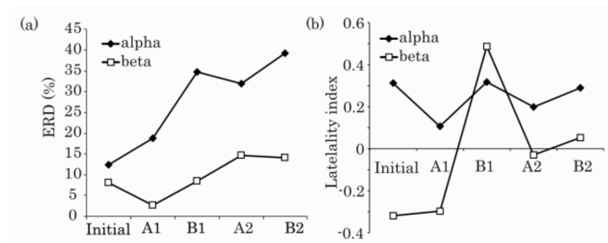

Figure 2 Time course of ERD

(a): ERD value in alpha and beta band. (b): laterality index of ERD in alpha and beta band. Positive value indicates ipsilesional (right) hemispheric dominance.

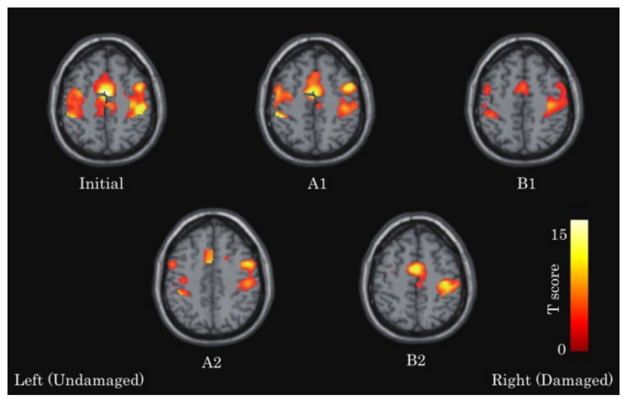

Figure 3 Activation map on MNI anatomical brain.

C. EMG and cortico-muscular coherence evaluation

The change in the averaged ratio of RMS of surface EMG activity on EDC during the task to initial baseline, was calculated (Fig. 5a). There was little difference between "Rest" and "Paretic hand opening" at the day before the training started. After first NMES epoch, there was 37% of slight increase in RMS value. The examination after the following first BCI epoch, the value reached to 132% increase compared to baseline. However, the RMS ratio at the last day of second NMES epoch was decreased to 27%. Finally, after the second BCI session, the ratio was increased to 500% relative to reference EMG.

The CMC in the beta band was calculated with EEG around bilateral SM1 and EMG of affected EDC (Fig. 5b). Before the session started, CMC was not significant. At the end of whole sessions, CMC of left EDC and EEG of contralateral SM1 were significantly increased to 0.09.

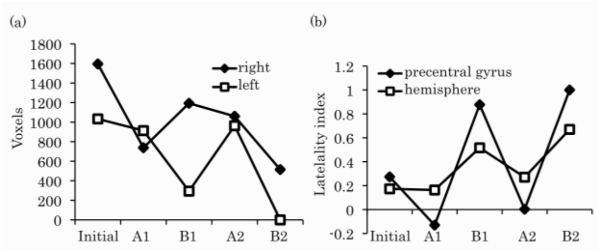

Figure 4 Time course of fMRI parameters
(a): Number of voxels on right and left M1. (b): laterality index of activation voxels in fMRI. Positive value indicates ipsilesional (right) hemispheric dominance.

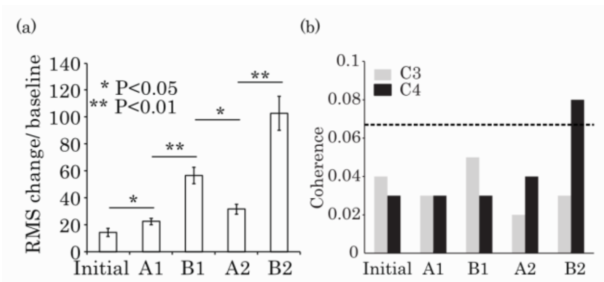

Figure 5 Time course of fMRI parameters
(a): Number of voxels on right and left M1. (b): laterality index of activation voxels in fMRI. Positive value indicates ipsilesional (right) hemispheric dominance.

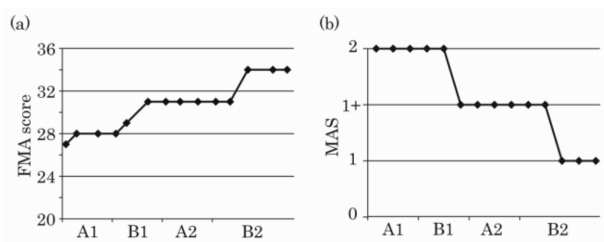

Figure 6 Time course of fMRI parameters
(a): Number of voxels on right and left M1. (b): laterality index of activation voxels in fMRI. Positive value indicates ipsilesional (right) hemispheric dominance.

D. Clinical evaluation

Epoch A was associated with no improvement except for a slight increase in FMA score during the first epoch A. Improvement in both clinical scores were seen in both Epoch B1 and B2 (Fig 6).

IV. DISCUSSION

This study showed that closed-loop rehabilitation by BCI was useful for chronic stroke patient. Previous studies show that the closed loop feedback of limb movement contribute to the improvement of motor function [12] [13]. Stroke patients with mild paralysis improve their motor function by using a NMES only rehabilitation [14], since they can activate motoneurons and move by themselves and this makes the closed-loop circuit. However, stroke patients with severe paralysis can not activate the motoneuron and motor cortex exactly. In this study, we asked the subject to attempt his affected hand opening during receiving the stimulation. However, he might not activate the motor cortex along the stimulation. Thus NMES rehabilitation was not closed-loop system. On the other hand, BCI-NMES is controlled according to the emergence of ERD. This indicates that the realtime feedback of brain activities was provided with NMES and BCI-NMES made the closed-loop feedback system. In conclusion, the BCI-NMES can make the closed-loop system and improve a brain activation and motor function of the stroke patient with severe paralysis.

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