

CASE REPORT

EFFICACY OF BRAIN-COMPUTER INTERFACE-DRIVEN NEUROMUSCULAR ELECTRICAL STIMULATION FOR CHRONIC PARESIS AFTER STROKE

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Objective: Brain computer interface technology is of great interest to researchers as a potential therapeutic measure for people with severe neurological disorders. The aim of this study was to examine the efficacy of brain computer interface, by comparing conventional neuromuscular electrical stimulation and brain computer interface-driven neuromuscular electrical stimulation, using an A-B-A-B withdrawal single-subject design.

Methods: A 38-year-old male with severe hemiplegia due to a putaminal haemorrhage participated in this study. The design involved 2 epochs. In epoch A, the patient attempted to open his fingers during the application of neuromuscular electrical stimulation, irrespective of his actual brain activity. In epoch B, neuromuscular electrical stimulation was applied only when a significant motor-related cortical potential was observed in the electroencephalogram.

Results: The subject initially showed diffuse functional magnetic resonance imaging activation and small electroencephalogram responses while attempting finger movement. Epoch A was associated with few neurological or clinical signs of improvement. Epoch B, with a brain computer interface, was associated with marked lateralization of electroencephalogram (EEG) and blood oxygenation level dependent responses. Voluntary electromyogram (EMG) activity, with significant EEG-EMG coherence, was also prompted. Clinical improvement in upper-extremity function and muscle tone was observed.

Conclusion: These results indicate that self-directed training with a brain computer interface may induce activity-dependent cortical plasticity and promote functional recovery. This preliminary clinical investigation encourages further research using a controlled design.

Key words: brain computer interface; stroke; hemiparesis; neuromuscular electrical stimulation; rehabilitation.

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INTRODUCTION

Brain-computer interface (BCI) technology is a newly developed technique that is attracting much attention. Recent studies have shown that brain signals measured using electroencephalography (EEG) or magnetoencephalography (MEG) provide information for the presumption of motor intention (1). Using BCI technology, real-time feedback concerning cortical activity can be provided to the patient through visual and somatosensory information.

In the present study, we developed a BCI system controlling neuromuscular electrical stimulation (BCI-driven NMES) as a closed-loop feedback system for use with severe paresis, and examined whether there were advantages of a closed-loop BCI system compared with an open-loop NMES system to restore motor ability. We used a single-subject A-B-A-B experimental design, and employed a series of neurological and clinical assessments to comprehensively evaluate improvement of the motor system. Upstream to downstream measures were used, including regional cerebral electric and blood oxygenation responses, corticospinal connectivity, voluntary muscle activity, kinetic performance, and muscle tone. The reproducibility of neurophysiological changes simulated by BCI was also evaluated.

CASE REPORT

A 38-year-old right-handed Japanese male, with severe chronic left hemiplegia due to right putaminal haemorrhage 14 months earlier, was the subject of this study. The patient had already received 7 months of inpatient rehabilitation after the onset of putaminal haemorrhage, including the last 2 months in Keio Tsukigase Rehabilitation Center (KTRC), and following 7 months of outpatient rehabilitation. Rehabilitation examination at hospital admission revealed that the patient's upper limb section of the Fugl-Meyer assessment (FMA) score for testing physical motor performance at the paralysed upper extremity

was 27 (range 0–66), and his modified Ashworth scale (MAS) score for testing muscle spasticity at the paralysed finger was 2 (range 0–4). These scores were unchanged from those acquired 8 months prior to admission to the present study, including 30 days of previous inpatient rehabilitation in KTRC. His hand function was severely impaired, and surface electromyogram (EMG) activity from the affected extensor digitorum communis (EDC) was absent. Sensory examination showed a mild decrease in position sense in all fingers. Pin-prick and touch senses were also mildly impaired. He was independent in activities of daily living, and used a T-cane and plastic ankle-foot orthosis. His cognitive abilities were intact. Before the experiment, the patient gave written informed consent to participate in this study. The only medication that the patient received was hypnotic, and no anti-spasticity drugs were used during inpatient rehabilitation.

The experimental design described below followed the Declaration of Helsinki on medical protocol and ethics, and was approved by the Keio University School of Medicine ethics committee.

Experimental design

The study incorporated a within-subject A-B-A-B withdrawal design in which we alternated epochs A (control) and B (BCI). During epoch A, the patient was asked to attempt finger opening for 3 s at maximal voluntary effort. During this period, simultaneous NMES (see Appendix S1¹) was applied to the paralysed finger-opening muscle. Next, a 3-s rest period was given, and stimulation was halted. The trial lasted for 6 s and was repeated for 60 min, and was conducted on weekdays for 2 weeks (10 days in total).

During epoch B, the patient was similarly asked to attempt finger opening for 3 s at maximal voluntary effort. The BCI monitored motor-related cortical potential in the electroencephalogram (EEG) recorded over the sensorimotor area in the affected hemisphere, and NMES was given only if the amplitude of motor-related cortical potential reached a pre-determined threshold, and amplitude was maintained for 1 s (Fig. 1). A relative power decrease in the sensorimotor rhythm from baseline, called event-related desynchronization (ERD), is known as a biomarker of the excitability of the primary motor area (2). We used ERD as a trigger source of NMES to form the closed-loop structure, which couples continuous motor-related brain activity with somatosensory activity by NMES. The detailed settings for the EEG recordings and the calculation have been described previously (3), and are summarized in Appendix S1¹. As the training settings of the BCI-NMES and the NMES were different, the subject was not blinded to the training contents.

The experiment was discontinued for the day if the patient reported exhaustion. The subject ended the treatment early on 3 days: 2 in the first BCI epoch and 1 in the second BCI epoch. In both epochs, traditional occupational therapy (OT) was performed 40 min/day after each intervention, which included thermotherapy, continuous muscle stretch, and practicing functional activities (i.e. wiping or holding paper down).

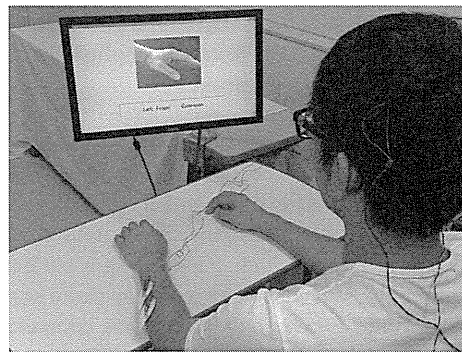


Fig. 1. Training with brain computer interface–neuromuscular electrical stimulation. The subject attempted to extend his fingers according to the instructions presented on the monitor. Electrical stimulation was triggered if the amplitude of the motor-related cortical potential reached a pre-determined threshold.

The patient cancelled OT only once, in the first BCI epoch; he did not end OT early during the NMES epochs. No additional exercise apart from OT was performed during the epochs.

Outcome measures

The following functional magnetic resonance imaging (fMRI), EEG, surface EMG of the affected EDC muscle, and clinical evaluations were performed before the first session and at the end of each training epoch. The researchers involved in the analyses of fMRI, EEG and EMG were blinded as to the training contents.

fMRI data acquisition. Whole-brain fMRI (Excelart/Vantage, Toshiba Medical Systems, Tokyo, Japan) was performed at 1.5 T, with standard scanning software, on the day of admission and the last days of each training period. The following parameters were used for 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 s).

Motor task paradigm. The paradigm was a block design (5 rest and 5 task blocks, 30 s each). We employed a self-paced movement paradigm at 1 Hz, in which the subject was directed to employ self-paced finger-extension movements with the affected hand for 30 s with maximal effort (4). To observe unintentional movement of other muscles, direct observation was performed, as described previously.

fMRI data analysis. Data were processed using a general linear model using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK). The detailed methods for fMRI data analysis are shown in Appendix S1¹.

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

¹<http://www.medicaljournals.se/jmm/content/?doi=10.2340/16501977-1785>

To examine the change in the RMS ratio, we used the Kruskal-Wallis and Mann-Whitney *U* tests and applied Bonferroni's correction for multiple comparisons.

Corticomuscular coherence. Corticomuscular coherence (CMC) measures the functional coupling between the cortex and muscle. (5) The details of the coherence calculation are shown in Appendix S1¹. 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 within >95% confidence limits computed from the number of epochs (epochs 100; limit 0.030).

Clinical evaluation. For evaluation of motor function, the upper extremity section of FMA was performed. Finger spasticity was measured using the MAS. Evaluation was performed by a physician and an occupational therapist who were both blinded to the experimental design.

RESULTS

Functional magnetic resonance imaging changes

fMRI activation during affected hand movement prior to training sessions was associated with extensive participation

of active areas in both hemispheres, including the bilateral primary motor cortex, primary sensory cortex, supplementary motor area (SMA), and the bilateral premotor cortices (Fig. 2A). The total activated area gradually decreased through the training epochs, and in the BCI-NMES epochs (B1 and B2), lateralization of the activated area was observed. The calculated laterality index (LI) of voxels in the bilateral precentral gyrus and hemisphere was unchanged or decreased during the NMES epoch, while it was markedly increased during the BCI-driven NMES epoch (Fig. 2B–G).

Neurophysiological changes

The ERD in the right primary sensory-motor cortex (SM1) gradually increased during the training epochs, both in the alpha (μ) and beta bands (Fig. 3A). In the time-frequency map before the training epochs, the generation of ERD was not evident by motor intention. In contrast, the time-frequency map on the last day clearly showed ERD in alpha (μ) and beta bands (Fig. 3B). Similar to the fMRI study, the LI of the bilateral SM1 markedly increased only during the BCI-NMES epoch (Fig. 3C). The success rate of triggering NMES by ERD gradually increased during the BCI-NMES epoch (Fig. 3D).

The change in the averaged ratio of RMS of surface EMG activity on the EDC during the task to initial baseline was cal-

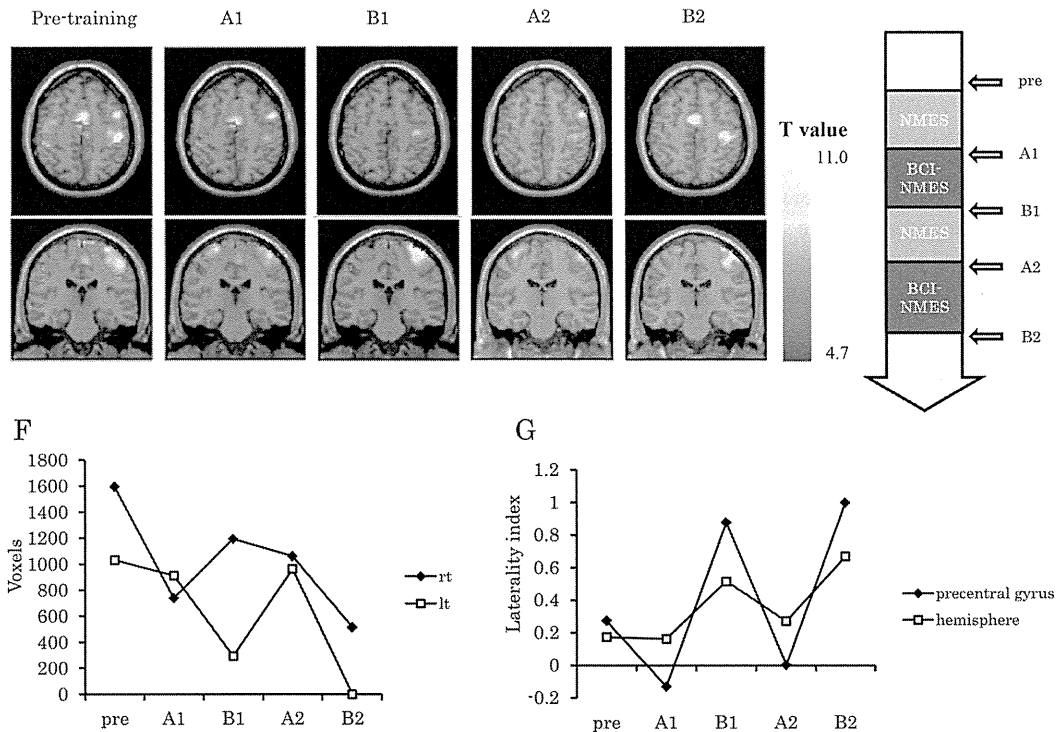


Fig. 2. Change in the pattern of functional magnetic resonance imaging (fMRI) activation during finger movement. (A) Before the start of intervention, fMRI showed diffuse activation including bilateral primary motor cortex, primary sensory cortex, supplemental motor area (SMA), and part of the frontal and parietal lobes. (B) After the first epoch A (NMES), no changes were observed. (C) After the first epoch B (brain computer interface–neuromuscular electrical stimulation; BCI-NMES), brain activity was lateralized to the right hemisphere. (D) However, lateralization of activity was cancelled during the second epoch A. (E) After the second epoch B, fMRI activation was mostly localized to the right primary cortex and SMA. (F) The activated area in the bilateral primary motor area gradually decreased. Laterality index (LI) markedly increased during the BCI-NMES epoch, whereas it decreased during the NMES-only epoch. Hemispheric LI showed a similar pattern, and a tendency of gradual increase (G). MRI Images (A–E) are displayed in neurological convention (left is left).

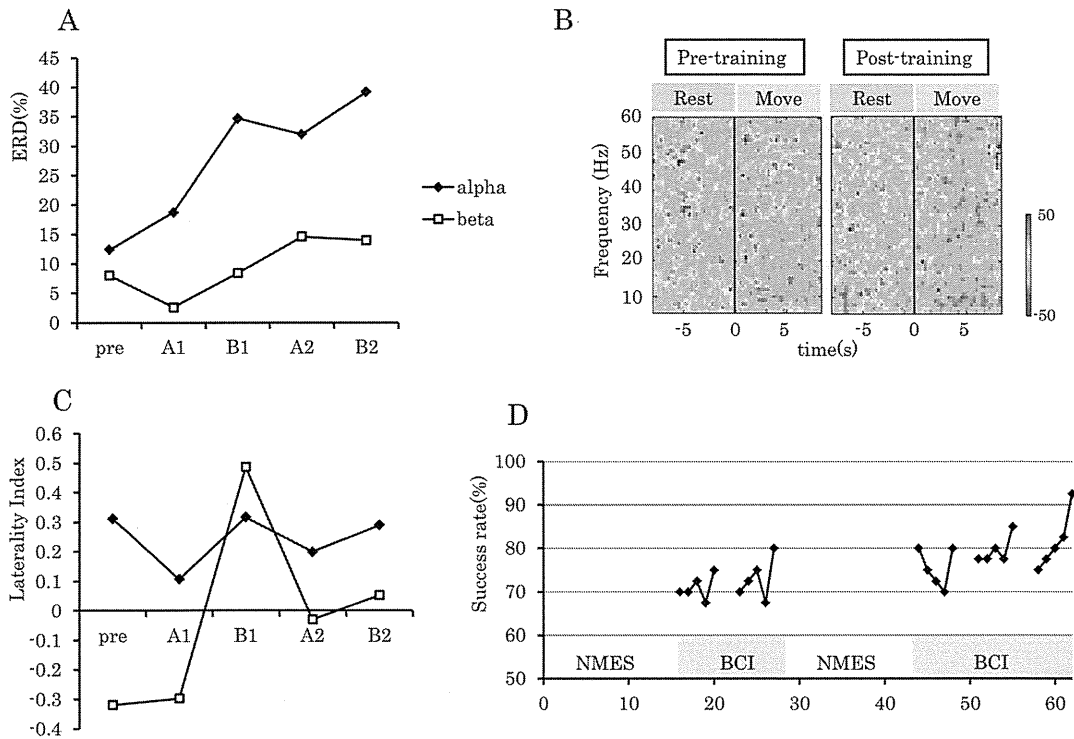


Fig. 3. Time course of electroencephalogram activity. (A) The extent of event-related desynchronization (ERD) in the alpha (μ) and beta bands around SM1 was gradually increased through the training periods. (B) The time-frequency map of ERD over the right cortex before the session started showed limited ERD at both bands during motor intention, while the occurrence of ERD was markedly clear in the map at the end of the whole experiment. The colour bar shows the power spectrum density. Blue indicates low power and red high power. (C) The laterality index of ERD was increased during the brain computer interface–neuromuscular electrical stimulation (BCI–NMES) epoch, showing movement of activity to the right hemisphere. In contrast, laterality index was decreased during the NMES epoch. (D) The success rate of the task gradually increased through the BCI–NMES epoch.

culated (Fig. 4A). There was very little increase (3%) in EMG activity of the EDC by the “extend finger” instruction on the day before training started. After the first NMES epoch, there

was a 37% increase in RMS value. After the first BCI epoch, the value reached a 132% increase compared with baseline. However, the RMS ratio on the last day of the second NMES

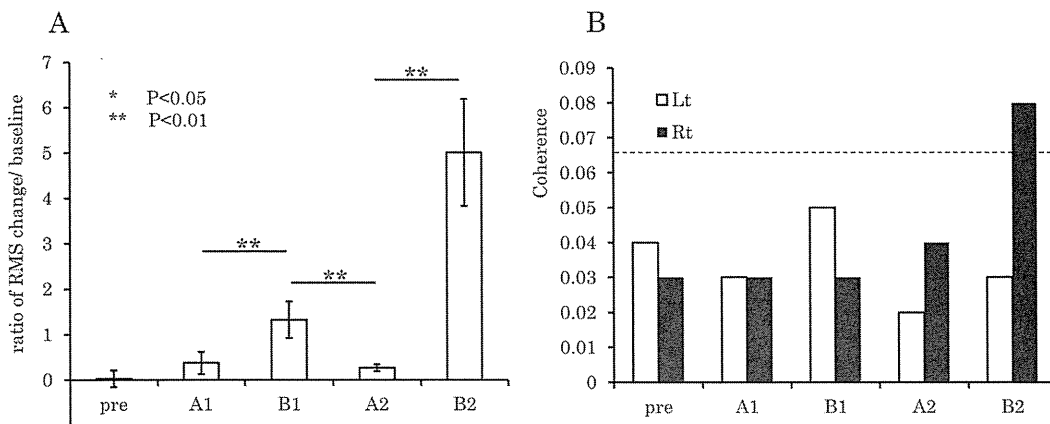


Fig. 4. Change in electromyogram (EMG) activity of extensor digitorum communis (EDC), and corticomuscular coherence (CMC). Prior to the neuromuscular electrical stimulation (NMES) epoch, almost no increase in root mean square (RMS) was observed for attempted finger extension. After the first NMES epoch, a slight increase in RMS was observed, while the second NMES session resulted in a decreased RMS value. (A) In contrast, a marked increase in RMS was observed during the NMES epoch. CMC was calculated using the EEG of SM1 and the EMG of EDC, and was not significant at the start of the training sessions. (B) After the second brain computer interface–neuromuscular electrical stimulation (BCI–NMES) epoch, CMC was significantly increased. Pre: before the start of intervention; A1: after the first epoch A (NMES); B1: after the first epoch B (BCI–NMES); A2: after the second epoch A; B2: after the second epoch B.

Table 1. Clinical scores during conventional neuromuscular electrical stimulation and brain computer interface–neuromuscular electrical stimulation (BCI-NMES) training

	Before	A1	B1	A2	B2
MAS	2	2	1+	1+	1
FMA U/E	26	27	31	31	34

MAS: modified Ashworth Scale; FMA U/E: upper extremity section of Fugl-Meyer assessment; Before: before the start of intervention; A1: after the first epoch A (NMES); B1: after the first epoch B (BCI-NMES); A2: after the second epoch A; B2: after the second epoch B.

epoch decreased to 27%. Finally, after the second BCI session, the ratio was increased to 500% relative to the reference EMG.

The CMC in the beta band was calculated using EEG and EMG of the affected EDC (Fig. 4B). The coherence of the EEG in contralateral SM1 and the EMG of upper limb muscles have been shown to be related to functional recovery after stroke (6). Before the sessions started, CMC was not significant. At the end of all sessions, CMC of the left EDC and EEG of the contralateral SM1 exceeded the 95% confidence level.

Clinical changes

The result of the clinical examination of motor function is shown in Table I. The FMA score increased to 34 in the final evaluation, which was mostly achieved during BCI-NMES epochs. This increase in FMA score was not due to improvement in finger function, but was mostly due to improvement in proximal muscle movement in the paretic limb, which was not directly involved in the experimental design. Despite improvement in EMG and EEG activity, no practical finger movement was regained. However, the patient was able to keep his fingers extended and to hold paper down while writing, which was not possible before the intervention. Finger spasticity was reduced from 2 to 1 on the modified Ashworth scale, and this improvement was seen during BCI-driven NMES epochs.

DISCUSSION

The effect of BCI training is often explained by the mechanism of motor learning with closed-loop feedback (7). In our model, the real-time feedback of brain activity was provided with NMES as strengthened proprioceptive feedback. Temporary re-establishment of closed-loop feedback by a BCI system may support the retention of motor-related brain activity after corticospinal tract injury. Furthermore, this BCI-driven NMES system, without visual feedback of brain activity, may indicate the importance of proprioceptive feedback contingent on motor-related brain activity.

Recently, several studies have shown a robust effect of EMG-triggered NMES, which provides closed-loop biofeedback for paralysed limbs (8–10). However, severely hemiplegic patients who show less voluntary EMG cannot use this method. The

BCI-NMES could be a substitute for those patients, and may allow some restoration of motor control.

It is possible that the observed changes in EEG or fMRI reflect the simple learning of emerging ERD-like activity, which is independent of practical motor function. However, the observed lateralization of brain activity without any laterality feedback implies that such a simple biofeedback mechanism is not enough to explain the observed changes.

In conclusion, BCI-driven NMES was associated with improvement in motor function and plasticity of the motor cortex in our patient, which was superior to that achieved by NMES only. Although this was a single-subject study, the present data strongly suggest the feasibility of using BCI technology, which accesses the plasticity of the motor system as a whole, from brain to muscle, in stroke rehabilitation. These results encourage further examination with more controlled studies for training with BCIs, especially for severe motor paresis.

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APPENDIX S1. Additional information on the experimental settings

Neuromuscular electrical stimulation neuromuscular electrical stimulation (NMES)

A pair of self-adhesive electrodes was placed over the muscle belly of the extensor digitorum communis (EDC) on the paralysed side. NMES (20 Hz, single pulse width 100 μ s, 3 s ON, 3 s OFF) was delivered through an electrical stimulator (MEB-2200, Nihon Kohden, Tokyo, Japan). Every day before intervention, the intensity of electrical stimulation was adjusted and fixed at just over motor threshold for evoking visible contraction of EDC muscles (15–20 mA).

Electroencephalography recordings

Electroencephalography (EEG) recordings were made from the scalp near the sensorimotor cortex using 5 silver–silver chloride (Ag–AgCl) surface electrodes with a diameter of 10 mm placed at C3 (left) and C4 (right), defined by the international 10–20 system, and their 20 mm front, back, left lateral, and right lateral positions. The reference electrode was placed at A2 (right earlobe). An additional electrode was placed at A1 (left earlobe) as a ground electrode. EEG was amplified ($\times 50,000$) and band-pass filtered (0.5–100 Hz) using a commercially available bioamplifier (g.USBamp, g.tec, Graz, Austria). A Laplacian transformation with 5 electrodes in each hemisphere was used to produce a signal of estimates of current source density for precise cortical activity detection. Signals produced from the left and right hemispheres were digitally sampled at a sample frequency of 1,024 kHz with 12-bit resolution, and were stored on the hard disk of a personal computer.

Calibration of brain computer interface in epoch B

At the beginning of the intervention in epoch B, 40 trials of the cue-based motor task were conducted as a rehearsal, and the parameters of the event-related desynchronization (ERD) detection algorithm in brain computer interface (BCI) were calibrated using the obtained data. During the rehearsal, an arrow pointing to the left ("attempting paretic finger extension") or no arrow (rest) was displayed for 1 s over a cross-shaped icon in the centre of a monitor, and the subject performed the cued task for the next 4 s. Twenty trials per class were given in a randomized order. A 4-dimensional feature vector (the power spectrum densities in alpha (μ) and beta frequency bands in the left and right hemispheric EEGs) was calculated every 30 ms, with a time-sliding window of 1 s during the task. The feature vectors with annotations of either "attempting finger extension" or "during rest" were mapped onto the feature space, and the parameters in the linear discriminant analysis (LDA) algorithm were optimized using g.BSanalyze software (g.tec Guger Technologies, Graz, Austria) to separate the features into appropriate classes. Consequently, the LDA returned either the value "+1" (resting) or "-1" (finger extension) every 30 ms according to the EEGs.

Outcome measures

Functional magnetic resonance imaging analysis. The first 5 images (for 15 s) of each set were discarded, because they showed irregular contrasts acquired before the MRI signal had reached an equilibrium state. Next, motion correction was performed by realigning all the functional volumes to the first volume of the functional series, and by co-registration to the anatomical volume. All co-registered images were normalized to the Montreal Neurological Institute template. After normalization, images were smoothed with a Gaussian kernel (full-width at half-maximum, 8 mm). We estimated the task-specific effects using the general linear model with a delayed boxcar waveform. The boxcar waveform was convolved with the canonical haemodynamic 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 blood oxygenation level dependent signal enhancement, caused by changes in blood oxygenation, occurred in accordance with the task. Laterality index (LI) was calculated for the voxels within the whole hemisphere and precentral gyrus.

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

$$\text{ERD}(f,t) = \frac{R(f) - A(f,t)}{R(f)}$$

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. Using this definition, ERD was expressed as a positive number in this study.

As stated above, the computer program returned the result of LDA, either "+1" (resting) or "-1" (finger extension) according to the EEGs. Classification accuracy during training was calculated.

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

$$|R_{xy}(i)|^2 = \frac{|f_{xy}(i)|^2}{|f_{xx}(i) \times f_{yy}(i)|}$$

In this equation, $f_{xx}(i)$ and $f_{yy}(i)$ are autospectra of the EEG and EMG signals, x and y , for a given frequency (i), and the $f_{xy}(i)$ is the cross-spectrum between them.

