Event-related desynchronization reflects down-regulation of intracortical inhibition in human primary motor cortex

Mitsuaki Takemi¹, Yoshihisa Masakado², Meigen Liu³, Junichi Ushiba³.⁴*

¹School of Fundamental Science and Technology, Graduate School of Keio University, Kanagawa, Japan
²Department of Rehabilitation Medicine, Tokai University School of Medicine, Kanagawa, Japan
³Department of Rehabilitation Medicine, Keio University School of Medicine, Tokyo, Japan.
⁴Department of Biosciences and Informatics, Faculty of Science and Technology, Keio University, Kanagawa, Japan

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*Corresponding author: Junichi Ushiba, Ph.D.
3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa, Japan
Tel/Fax: +81-45-563-1141; E-mail: ushiba@bme.bio.keio.ac.jp
Abstract

There is increasing interest in electroencephalogram (EEG)-based brain-computer interface (BCI) as a tool for rehabilitation of upper limb motor functions in hemiplegic stroke patients. This type of BCI often exploits EEG mu and beta oscillations recorded over the sensorimotor areas, and their event-related desynchronization (ERD) following motor imagery is believed to represent increased sensorimotor cortex excitability. However, it remains unclear whether the sensorimotor cortex excitability is actually correlated with ERD. Thus, we assessed the association of ERD with primary motor cortex (M1) excitability during motor imagery of right wrist movement. M1 excitability was tested by motor evoked potentials (MEPs), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) using transcranial magnetic stimulation (TMS). Twenty healthy participants were recruited. The participants performed 7 seconds of rest followed by 5 seconds of motor imagery, and received online visual feedback of the ERD magnitude of the contralateral hand M1 while performing the motor imagery task. TMS was applied to the right hand M1 when ERD exceeded predetermined thresholds during motor imagery. MEP amplitudes, SICI and ICF were recorded from the agonist muscle of the imagined hand movement. Results showed that the large ERD during wrist motor imagery was associated with significantly increased MEP amplitudes and reduced SICI, but no significant changes in ICF. Thus, ERD magnitude during wrist motor imagery represents M1 excitability. This study provides electrophysiological evidence that motor imagery task involving ERD may induce changes in corticospinal
excitability similar to changes accompanying actual movements.

Keywords: Electroencephalogram, Transcranial magnetic stimulation, Cortical excitability
Introduction

There is increasing interest in the use of electroencephalogram (EEG)-based brain-computer interface (BCI) as a tool for rehabilitation of upper limb motor functions in hemiplegic stroke patients (Ang et al. 2011; Broetz et al. 2010; Caria et al. 2011; Daly et al. 2008, 2009; Pfurtscheller et al. 2008; Prasad et al. 2010; Shinto et al. 2011; Wang et al. 2010). This type of BCI often exploits the oscillations in EEG mu and beta (7–26 Hz) bands recorded over the sensorimotor areas. The amplitudes of these oscillations typically decrease during actual movements, as well as during motor intention or motor imagery (Formaggio et al. 2008, 2010; Gerloff et al. 2006; Hummel et al. 2002; Neuper et al. 2005; Pfurtscheller and Lopes da Silva 1999; Yuan et al. 2010). As such, BCI can be used to operate visual display, orthosis action and neuromuscular electric stimulation.

This motor-related EEG pattern, generally referred to as event-related desynchronization (ERD), reflects the result of phasic changes in the synchrony of cell populations (Pfurtscheller 2006), and is a reliable marker of increased neuronal excitability in thalamo-cortical systems (Steriade and Llinas 1988). There is evidence that the changes in motor imagery- and actual movement-induced ERD and blood-oxygen-level-dependent (BOLD) signal by functional magnetic resonance imaging (fMRI) co-localize at the sensorimotor cortex, and that the magnitude of ERD and BOLD co-vary (Formaggio et al. 2008, 2010; Yuan et al. 2010). In addition, Hummel et al. (2002) reported evidence of both an increase of the motor evoked potentials (MEPs) induced by single-pulse transcranial magnetic stimulation (TMS) over the
primary motor cortex (M1) and ERD at 11–13 Hz during active retrieval of the motor memory trace. MEP amplitudes induced by single-pulse TMS have been suggested to reflect fluctuations in cortical and spinal motor neuron excitability (Brasil-Neto et al. 1992; Kiers et al. 1993), as well as motor neuron response desynchronization (Bühler et al. 2001; Magistracy et al. 1998). Therefore, ERD following motor imagery is believed to represent increased activation of the sensorimotor cortex. However, it remains unclear (1) whether the sensorimotor cortex excitability actually covaries with ERD over several hundred milliseconds to seconds, and (2) what parts of the intracortical circuits involved in motor output change their activity following ERD during wrist motor imagery.

There are several reasons why the two issues described above remain outstanding. For example, the BOLD signal used in numerous studies (Formaggio et al. 2008, 2010; Yuan et al. 2010) is inferior in time resolution (2–3 s (Poldrack et al. 2011)) compared with the mu and beta bands in EEG (in the order of 100 ms). Further, the BOLD signal indicates hemodynamic cortical activity, but not necessarily electric cortical excitability. Hummel et al. (2002) also reported a difference of MEP amplitude in two conditions with and without ERD, although the correlation between MEP amplitude (i.e., corticospinal excitability) and ERD magnitude remains unknown. Finally, although Maki et al. (2010) reported a negative correlation between Rolando beta oscillation and MEP amplitude using at least 60 times of single-pulse TMS, it would be difficult to use this procedure in our experiment because of the large number of the magnetic stimuli. Thus, we examined the relationship between
ERD magnitude (calculated from online EEG) and cortical excitability using TMS, which was triggered by the instantaneous ERD magnitude, in three different predetermined ERD magnitudes. ERD-triggered TMS may require fewer stimuli than the non-triggered TMS. Furthermore, we applied the paired-pulse TMS technique to determine which parts of the intracortical circuits involved in motor output change their activity following ERD during wrist motor imagery. The paired-pulse TMS technique can document intracortical interactions within M1 (Chen et al. 1998, 2004; Kujirai et al. 1993; Nakamura et al. 1997; Sanger et al. 2001), while MEP amplitudes induced by single-pulse TMS can indicate corticospinal tract excitability but not the independent excitabilities of the M1 and spinal motor neuron pool. Intracortical interactions within M1 can be studied using a combination of a subthreshold conditioning stimulus with a suprathreshold test stimulus at different short (1–20 ms) interstimulus intervals (ISIs) through the same TMS coil. The test responses are inhibited at ISIs of 1–6 ms and are facilitated at ISIs of 8–30 ms (Kujirai et al. 1993). Herein, we refer to these phenomena as short interval intracortical inhibition (SICI) and intracortical facilitation (ICF), respectively. Of note, there are contrasting results on the effect of agonist contraction on the corticospinal excitability modulation to the upper limb flexor and extensor (Chye et al. 2010; Izumi et al. 2000). Thus, we also evaluated the differences in corticospinal excitability modulation to the upper limb flexor and extensor induced by ERD during motor imagery of the agonist muscle contraction.
The aims of this study were to assess the association of EEG changes reflected by an ERD with M1 excitability during motor imagery of wrist flexion and extension using TMS, and to determine what parts of the intracortical circuits involved in motor output change their activity following ERD during wrist motor imagery from the outcomes of SICI and ICF.
Methods

Participants

Twenty healthy participants (aged 21.8 ± 1.2 years; 15 men, 5 women) joined this study. All were right-handed, without any medical or psychological disorders (according to self-reports), and had normal vision. All participants were initially naive to the experiment. The purpose and experimental procedure were explained to the participants, and written informed consent was obtained. The study was approved by the institutional ethics review board and performed in accordance with the Declaration of Helsinki.

Data acquisition

EEG was recorded from five Ag/AgCl electrodes (\( \phi = 10 \) mm) placed at C3 and 2 cm anterior (C3a), posterior (C3p), medial (C3m) and lateral (C3l) to C3 to cover the contralateral hand sensorimotor area (SM1) (Fig. 1a). In two randomly selected participants, an additional 18 electrodes were placed over the whole head for verification of spatial configuration of ERD during wrist motor imagery, and which confirmed the observed ERD during wrist motor imagery (Fig. 1b). Impedance for all channels was maintained below 10 k\( \Omega \) throughout the experiment. EEG signals were band-pass filtered (0.1–256 Hz with 2\(^{nd}\) order Butterworth) with a notch (50 Hz for avoiding power line contamination), and digitized at 512 Hz using a biosignal amplifier (g.USBamp; Gouger Technologies, Graz, Austria).
Surface electromyogram (EMG) activity was recorded from the right flexor carpi radialis (FCR) or extensor carpi radialis (ECR) muscle by using bipolar Ag/AgCl electrodes (\( \varnothing = 10 \text{ mm} \)). The cathode electrode was placed over the belly of the FCR or ECR muscle and the anode electrode was placed 20 mm distal from the cathode electrode. Impedance for all channels was maintained below 20 k\( \Omega \) throughout the experiment. EMG signals were band-pass filtered (5–1000 Hz with 2\textsuperscript{nd} order Butterworth) with a notch (50 Hz for avoiding power line contamination), digitized at 2 kHz using a biosignal amplifier (Neuropack MEB-9200; Nihon Kohden, Tokyo, Japan), and monitored throughout the experiment. Recording of each trial started 50 ms prior to the TMS pulse and finished after 150 ms.

**TMS**

TMS was applied using a figure-of-eight shaped coil (outer diameter of each coil: 7 cm) connected to the Magstim 200 magnetic stimulator (Magstim; Whiteland, UK). To apply paired-pulse, two stimulators connected by the Bistim module (Magstim) were used. The optimal coil position where MEPs in FCR or ECR muscle could be evoked with the lowest stimulus intensity was marked with ink to ensure an exact repositioning of the coil throughout the experiment. Identification of the optimal coil position was performed prior to each experimental condition. At this coil position the motor threshold intensity was defined as the lowest stimulator output intensity capable of inducing an MEP of at least 50 \( \mu \text{V} \) peak-to-peak amplitude in relaxed muscles in at least half of the 10 trials. Stimulus intensities
are expressed as a percentage of the maximum stimulator output. Single pulse TMS was applied with an intensity of 120% of the individual motor threshold. Paired-pulse TMS was used to investigate SICI and ICF. A subthreshold conditioning stimulus was set at 80% of the motor threshold, and was delivered through the same magnetic coil at 2, 3, 10 or 15 ms prior to the suprathreshold test stimulus adjusted to 120% of the motor threshold. The stimulus intensity remained constant throughout the whole experiment for each subject.

**Experimental protocol**

The participants were randomly assigned one of two conditions: kinesthetic motor imagery of sustained wrist extension and kinesthetic motor imagery of sustained wrist flexion. Surface EMG was recorded from the agonist muscle of imagined movement. Each participant participated in a series of four experimental sessions in the following order: Screening session, TMS Conditions 1, 2 and 3. The screening session and TMS Conditions 1, 2 and 3 were performed on the same day.

In the Screening session, the participant sat in a comfortable armchair, put their hand with palm side down on the table and performed kinesthetic motor imagery of sustained wrist extension or wrist flexion in the fixed repetitive time scheme (Fig. 1c). A 20-inch computer monitor was placed 60 cm in front of the participants’ eyes. Each trial started with the presentation of the word “Rest” at the upper left of the monitor. Six seconds later, the word ‘Ready’ was presented for 1 s. The participant then was asked to perform motor imagery
of wrist extension or wrist flexion for 5 s. The monitor showed the word “Image” during motor imagery. After a short pause, the monitor shows the word “Rest”, and the next trial started. Screening session consisted of 20 trials.

TMS Condition 1 was conducted as a control for TMS Conditions 2 and 3. We applied single and paired-pulse TMS (ISIs; 2, 3, 10 and 15 ms) to the contralateral hand M1 during the rest condition. The background EMG activity was monitored during the experiment, and trials contaminated by more than ±20 μV in background EMG activity were discarded. Each stimulus was applied at least ten times in random order at intervals of 6 s ± 500 ms, and fifty MEPs were collected in this session. In TMS Conditions 2 and 3, we used the ISIs obtained during TMS Condition 1 that showed a strong effect on SICI and ICF, respectively.

TMS Condition 2 was performed using the same time scheme as the screening session (Fig. 1c). A continuously moving feedback bar was displayed on the center of the screen during motor imagery. This feedback bar appeared after the task cue, and was presented for a 5 s period. According to the ERD or event-related synchronization (ERS) magnitude (band power decrease or increase) caused by the required motor imagery, the feedback bar in the screen was continuously moving. The feedback bar changed its length in a linear fashion from the center to the right and left edge of the monitor, corresponding to 0% to 30% of the ERD and ERS, respectively. The participants’ task was to extend the bar horizontally toward the right edge of the monitor at maximal voluntary effort. The participants were informed that a successful wrist motor imagery would shift the bar to the right, and an unsuccessful wrist
motor imagery would shift the bar to the left. The methods to calculate ERD and the online algorithm for controlling the length of bar extension in the screen are described below (ERD analyses). We applied either single or paired-pulse TMS, with an ISI of 2 or 3 ms or an ISI of 10 or 15 ms, to the contralateral hand M1 immediately after the ERD exceeded 5% during motor imagery (Fig. 1d). The background EMG activity was monitored during the experiment, and trials contaminated by more than ±20 μV in background EMG activity were discarded.

Each stimulus was applied ten times in a random order, and MEPs were collected. To minimize the effect of slow intrinsic oscillations around 0.1 Hz (Mayer waves) in blood pressure, heart rate and (de)oxyhemoglobin on the excitability level in the brains’ motor areas (Pfurtscheller et al. 2012), TMS Condition 3 was performed using the same conditions as in TMS Condition 2, except that TMS was applied immediately after ERD exceeded 15% during motor imagery.

**ERD analyses**

EEG data was segmented into successive 512-point (1,000 ms) windows with 480-point overlapping, and a fast Fourier transformation with a Hanning window was applied in each segment. Power spectrum density was estimated from the square of the absolute value of the fast Fourier transformation. ERD/ERS was defined as the decrease/increase of power spectrum in relation to 3 s reference intervals before representing the word ‘Ready’. ERD was
calculated at each segment (time resolution of 62.5 ms) with a frequency resolution of 1 Hz, according to the following calculations:

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

where \( A \) is the power spectrum density of the EEG at time \( t \) with the onset of motor imagery and frequency \( f \), and \( R \) is the mean power spectrum of the reference intervals. A large positive value indicates a large ERD (i.e., a large decrease in EEG power during motor imagery in comparison with the rest condition). ERD was typically found over the SM1, although the most reactive frequency band displaying the ERD and EEG montage were slightly different for each participant (Pfurtscheller et al. 2006). Thus, we determined the best electrode setup and frequency band within a given frequency range (mu and beta bands: 7–26 Hz (Hari et al. 1997) in the screening session. Pairs of C3 and 2 cm anterior, posterior, medial and lateral to C3 of bipolar derivations of EEG were then used to check existence of ERD following wrist motor imagery, and to define the electrode pair and 3 Hz width frequency band displaying the largest ERD. Herein, this frequency band is referred to as “the most reactive frequency band displaying ERD” (Pfurtscheller et al. 2006). The selected bipolar EEG that displayed the strongest ERD was used for the sessions of TMS Conditions 2 and 3. To avoid sudden movements of the feedback bar, the moving bar feedback was updated every segment (62.5 ms) by an averaged ERD of the last 16 segments (1,000 ms).

In the offline analysis, two participants whose EEG signals were obtained from 23 electrodes were used to reconstruct the topographical brain images of ERD magnitude.
Nineteen channels of the EEG signals (excluding the 2 cm anterior, posterior, medial and lateral to C3) were re-referenced using a four neighbors Laplacian spatial filter (Hjorth 1975). All EEG trials were visually controlled for artifacts and were discarded in cases of artifact-contaminated trials. These EEG signals were then used to calculate ERD as described above. Spatially interpolated topographic ERD maps were plotted according to their channel locations over the scalp using an average ERD magnitude, just prior to the magnetic stimulation. Both moving bar feedback and all off-line analyses (described above) were performed by MATLAB 2010a (MathWorks, Natick, MA, USA).

**MEP analyses**

Each single sweep was inspected visually, and the trials with artifacts (pre-stimulus EMG activity more than ±20 μV) were rejected. The artifact-free MEP amplitudes were then measured peak-to-peak. Paired-pulse TMS was performed to investigate SICI and ICF, which were expressed as a percentage of the ratio between the conditioned MEPs and the unconditioned MEPs (mean conditioned MEP / mean unconditioned MEP × 100%). Herein, this value is referred to as %unconditioned MEP, where 100 in %unconditioned MEP indicates absence of facilitation or inhibition, while values more than 100 and less than 100 in %unconditioned MEP indicate facilitation and inhibition, respectively. The peak-to-peak amplitudes and %unconditioned MEP were analyzed with Bistim Tracer (Medical Try System, Tokyo, Japan).
Statistical analyses

We analyzed the peak-to-peak MEP amplitudes induced by single-pulse TMS and %unconditioned MEP of SICI and ICF using one-way analysis of variance (ANOVA). If ANOVA yielded a significant F value, a post-hoc test was performed by the Bonferroni test. The Type I error was set to 0.05.
Results

Spectral power of the EEG

In the screening session, all participants showed the ERD during right wrist motor imagery around C3. The characteristics of ERD such as the most reactive frequency band and bipolar channels in the screening session are summarized in Table 1.

One-way ANOVA was performed in the most reactive frequency band displaying ERD of each participant with regard to power values during the reference period in TMS Conditions 2 and 3 and during 1.5-4.5 s of each trial in TMS Condition 1, which correspond to the reference period in TMS Conditions 2 and 3. There was no significant difference in the reference power values between TMS Conditions 1, 2 and 3 in both the experimental group of EMG recording from the FCR muscle ($F = 0.20, P = .81$) and the ECR muscle ($F = 0.10, P = .91$) indicating similar means of reference power values for the resting and motor imagery conditions.

Figure 2 represents the ERD topographic maps in the TMS Conditions 1 (at rest), 2 (at ERD 5% during right wrist motor imagery) and 3 (at ERD 15% during right wrist motor imagery) from the 19-channel EEG signals of participant A. The colors on the topographic maps indicate ERD magnitudes calculated from the four neighbors Laplacian deviation of the EEG signals. The ERD magnitudes of the maps were constructed from the most reactive frequency band displaying ERD in the screening session, as shown in Table 1. Results showed that ERD magnitude at C3 in the experimental condition of ERD 15% was stronger than that
of ERD 5% (27.2% and 6.9%, respectively). In addition, ERD magnitude at Cz was the second largest in the experimental condition of ERD 15%, while the ERD magnitude at P3 was the second largest in the experimental condition of ERD 5% (16.9% and 4.8%, respectively). Participant B also showed that ERD magnitudes at C3 were the largest in the both experimental conditions of ERD 5% and 15% (25.6% and 8.4%, respectively). These data indicate that the observed ERD during right wrist imagery was likely to localize at the contralateral SM1 in this experimental procedure. The other 18 participants were recorded EEG from 5 channels over the contralateral sensorimotor area for the convenience of the experimental duration using TMS.

**Changes of intracortical excitability**

To test M1 excitability at certain magnitudes of ERD during right wrist motor imagery, we applied single and paired-pulse TMS during the rest condition and during wrist motor imagery at ERD 5% and ERD 15%, and then assessed the changes of MEP, SICI and ICF.

Figure 3 shows MEP responses of the agonist muscle of motor imagery in all experimental conditions from participant A. MEP amplitudes evoked by the single pulse TMS were facilitated during motor imagery (Rest = 0.56 mV, motor imagery at ERD 5% = 1.03 mV, motor imagery at ERD 15% = 1.42 mV). As an increase in the %unconditioned MEP reflects both “reduced SICI” and “increased ICF”, both SICI and ICF were reduced in accordance with the ERD magnitude (SICI: Rest = 16.1%, motor imagery at ERD 5% =
36.7%, motor imagery at ERD 15% = 59.9%; ICF: Rest = 231%, motor imagery at ERD 5% =
185%, motor imagery at ERD 15% = 158%). Furthermore, the increase of MEP amplitudes
induced by the single pulse TMS and SICI was related to ERD magnitude.

Figure 4a represents MEP amplitudes induced by the single pulse TMS, SICI and ICF
from the FCR muscle in the resting condition during motor imagery of right wrist flexion at
ERD 5% and ERD 15%. One-way ANOVA showed that the effect of ERD for MEP
amplitudes ($F = 14.5, P < .001$) and SICI ($F = 4.01, P = .03$) were statistically significant, but
not for ICF ($F = 0.06, P = .94$). Post-hoc analysis revealed that MEP amplitudes were
significantly larger at ERD 5% ($P = .002$) and ERD 15% ($P < .001$) compared with the resting
condition. SICI was significantly reduced at ERD 15% compared with the resting condition
($P = .001$), and tended to reduce at ERD 15% compared with ERD 5% ($P = .068$).

Figure 4b represents the MEP amplitudes induced by the single pulse TMS, SICI and
ICF from the ECR muscle in the resting condition during motor imagery of right wrist
extension at ERD 5% and ERD 15%. One-way ANOVA showed that the effect of ERD for
MEP amplitudes ($F = 6.44, P = .005$) and SICI ($F = 11.8, P < .001$) were statistically
significant, but not for ICF ($F = 0.90, P = .42$). Post-hoc analysis revealed that MEP
amplitudes were significantly larger at ERD 5% ($P = .016$) and ERD 15% ($P = .009$)
compared with the resting condition. SICI was significantly reduced at ERD 15% compared
with both conditions of rest ($P < .001$) and ERD 5% ($P = .022$).
Discussion

The purpose of this study was to examine the physiological relationship between motor imagery-induced EEG changes (termed ERD) and cortical excitability using paired-pulse TMS, which was contingent on the instantaneous ERD magnitude. We found that the magnitude of ERD during right wrist motor imagery was associated with a significant increase in MEP amplitudes and a significant decrease in SICI, but no significant changes were found in ICF.

Relationship between ERD and cortical excitability

Numerous studies have examined the changes of corticospinal excitability during wrist or hand motor imagery by using single pulse TMS (Kasai et al. 1997; Patio et al. 2003; Rossi et al. 1998; Rossini et al. 1999; Stinear et al. 2006; Yahagi and Kasai 1998), and have reported that wrist/hand motor imagery significantly increases corticospinal excitability. Furthermore, Patio et al. (2003) showed that SICI was significantly reduced during hand motor imagery, but not ICF. Our results are in agreement with those studies. ERD during right wrist motor imagery led to a significant increase in MEP amplitudes induced by single pulse TMS and significant decrease in SICI, but not ICF. In addition, and most importantly, we found that the increase of MEP amplitudes and the reduction of SICI were positively related to the increase of ERD magnitude. While MEP amplitude induced by single pulse TMS is thought to be related to contralateral corticospinal tract excitability, SICI and ICF seem to reflect the
excitability of distinct inhibitory and excitatory interneuronal circuits within M1 (Chen et al. 1998; Chen 2004; Kujirai et al. 1993). As it was reported that GABA$_A$ agonists enhance SICI (Ziemann et al. 1996) and $N$-methyl-D-aspartame antagonists abolish ICF (Ziemann et al. 1998), we suggest that ERD magnitude during motor imagery is associated with an increase in contralateral M1 excitability, which is mediated by a down-regulation of GABAergic activity.

We noted here that the MEP amplitude in response to the test stimulus was different between the experimental conditions; i.e., the MEP amplitude in TMS Condition 3 (wrist motor imagery at ERD 15%) was significantly larger than that of TMS Condition 1 (resting condition). One concern is that the decrease in the amount of SICI was influenced by the increase of the test MEP amplitude rather than changes in the activity of GABAergic neurons. However, whereas Sanger et al. (2001) reported a positive correlation between the amount of SICI and MEP amplitude, our results showed a reduction of SICI with an increase of MEP amplitude. Therefore, reduction of SICI in the present study likely reflects down-regulation of GABAergic activity in the M1.

In TMS Condition 2 and 3, MEPs during motor imagery were recorded in a completely different condition as compared with rest (TMS Condition 1) in that the subjects were asked to perform motor imagery and also received online feedback of their own ERD modulation. According to this protocol, it was likely that the observed MEP size increase and the SICI changes were related to the motor imagery task and/or
to the neurofeedback context. However, Holper & Wolf (2010) illustrated that motor
cortical activity was not different between motor imagery with positive fake feedback,
motor imagery with negative fake feedback and motor imagery without feedback. This
previous study suggests that the neurofeedback context had little effect on the motor
cortical excitability. Thus, the present study indicated that the cortical excitability (i.e.,
MEP size increase and SICI changes) was related to the ERD magnitude during motor
imagery, not neurofeedback context.

Our results are also comparable to previous reports investigating changes in cortical
excitability during human voluntary movement. MEPs in response to single pulse TMS were
strongly augmented in a period of 90–100 ms before the onset of voluntary EMG activity
(Nikolova et al. 2006). In addition, whereas ICF augmentation was small, SICI decreased
gradually and disappeared 60 ms before voluntary EMG (Nikolova et al. 2006). Reynolds and
Ashby (1999) reported that the increase of MEP in response to single pulse TMS and the
decrease of SICI were significant before the onset of voluntary movement, while the decrease
of SICI appeared in advance of the increase of MEP by single pulse TMS. Alegre et al. (2003)
also demonstrated that a decrease in beta band EEG activity began contralaterally
approximately 1.5 s prior to the onset of movement, and that the decrease began in the alpha
band at 1 s before the movement. Thus, overall, these results suggest that ERD during motor
imagery may induce changes in cortical excitability, which is similar to the changes
accompanying actual movements and their anticipation.
Motor imagery of wrist extension versus wrist flexion

Our data obtained from ten subjects showed that large ERD magnitudes during motor imagery of wrist extension were associated with increased MEP amplitude and decreased SICI recorded from the ECR muscle. Furthermore, our data obtained from another ten subjects showed that large ERD magnitudes during motor imagery of wrist flexion were associated with increased MEP amplitude and decreased SICI recorded from the FCR muscle. These results indicate that ERD during motor imagery of wrist flexion and wrist extension modulates the M1 excitability by a similar mechanism. Hashimoto and Rothwell (1999) also reported that the TMS-evoked descending volley to the FCR muscle was facilitated during the period of imagined movement of wrist flexion, and that the size of the descending volley to the ECR muscle was similarly facilitated during the period of imagined movement of wrist extension. However, anatomical studies in non-human primates found differences in the wrist extensor and wrist flexor cortico-motoneuronal cells (Fetz and Cheney 1980; Kisser and Cheney 1985). In human subjects, Izumi et al. (2000) reported that the degree of facilitation observed during agonist contraction was greater for the FCR muscle than for the ECR muscle. By contrast, Chye et al. (2010) reported that the degree of facilitation was greater for the ECR muscle than for the FCR muscle during agonist contraction. Vargas et al. (2004) verified that MEP amplitude recorded from intrinsic hand muscle was influenced by hand finger posture. We therefore ensured that the hand/arm position was the same between participants and
experimental conditions. Although the differences in the characteristics of the FCR muscle and ECR muscle remain unclear, our results extend previous work by showing that ERD during motor imagery of wrist movement changes the M1 excitability of agonist muscles regardless of whether flexor or extensor.

Physiological interpretation for ERD during wrist motor imagery

The neural network that generates rhythmic EEG activity consists of four elements: the thalamic reticular nucleus (TRN) neurons, inhibitory local circuit neurons in thalamus, thalamocortical relay (TCR) neurons and corticothalamic neurons (Klimesch et al. 2007). In particular, TRN neurons, which express GABA_\text{A} receptors (Widen et al. 1992), play a key role in the control of rhythmic EEG activity in the mammalian brain (Steriade and Llamas 1988). The mu and beta bands EEG occur over the sensorimotor areas, indicating motor quiescence and a functionally inhibitory mode of the thalamocortical loops (Sherman et al. 1962). Motor imagery or motor action decreases the mu and beta bands EEG recorded over the sensorimotor areas (termed ERD). ERD is considered to reflect a decrease in synchrony of the underlying neuronal populations (Pfurtscheller 1992).

Based on these findings, Pfurtscheller and Lopes da Silva (1999) created a model of ERD involving a relationship between TRN neurons, TCR neurons and cholinergic excitatory modulatory input from the brain stem. Furthermore, using a computational model of thalamo-cortical networks, Suffczynski et al. (1999) reported that increased modulating input
from the brain stem induced ERD, with an increase of TCR cells excitability and a decrease of TRN cells excitability (i.e. GABA<sub>A</sub> transmission was inhibited). In addition to these studies, our data using TMS suggest that ERD during wrist motor imagery led to a down-regulation of GABA<sub>A</sub> transmission in human M1.

A possible mechanism for the generation of ERD during wrist motor imagery is depicted schematically in Figure 5. The TCR neurons send excitatory input to the TRN neurons and the M1, and receive cholinergic excitatory modulatory input from the brain stem. The TRN neurons project GABAergic inhibitory fibers to the TCR neurons. Therefore, the negative feedback loop formed by the TCR neurons and TRN neurons is involved in controlling basic rhythmic activities of the EEG during a rest condition (Fig. 5a). When a participant begins to perform motor imagery or anticipate movement, the excitatory modulatory input from the brain stem and ascending afferent is increased. Increased excitatory input enhances TCR cells excitability, and this augmentation of the excitatory inputs to the M1 induces a change in the ongoing EEG in the form of an ERD. As TMS stimulates cortical pyramidal neurons indirectly via cortical interneurons, which produce indirect corticospinal waves (I-waves) (Lemon 2002), our results suggest that ERD during motor imagery induces a significant disinhibition of the I-wave generating neurons and a significant enhancement of cortical pyramidal neuron excitability (Fig. 5b). However, motor imagery can also activate non-primary motor areas such as the supplementary motor cortex and premotor cortex (Halder et al. 2011). As M1 receives direct excitatory inputs from
primary somatosensory cortex and these non-primary motor areas (Krakauer et al. 2000), it is highly probable that the pyramidal neurons in M1 are influenced by neurons in the primary somatosensory cortex and the non-primary motor areas during motor imagery with ERD.

Previous studies have proposed that TCR neurons, TRN neurons and pyramidal neurons in the cortex are predominantly involved in generating ERD. Our data suggest that ERD during motor imagery increases cortical excitability by decreasing the activity of GABAergic inhibitory interneurons. In addition, we found that ERD magnitude during wrist motor imagery represents contralateral M1 excitability. This study provides electrophysiological evidence that motor imagery task involving ERD may induce changes in corticospinal excitability similar to changes accompanying actual movements.
Acknowledgments

We thank Prof. Dr. Niels Birbaumer for his valuable comments, and Ms. Sayoko Ishii and Ms. Sawako Ohtaki for their technical support.

Grants

This study was partially supported by the Strategic Research Program for Brain Sciences from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author contributions

M.T. and J.U. conception and design of research; M.T. performed experiments; M.T. analyzed data; M.T., Y.M., and J.U. interpreted results of experiments; M.T. prepared figures; M.T. drafted manuscript; M.T., Y.M., M.L., and J.U. edited and revised manuscript; M.T., Y.M., M.L., and J.U. approved final version of manuscript.


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Figure captions

Figure 1. Experimental setup and paradigm. (a) In 18 participants, five EEG electrodes were placed to cover around the right hand SM1, as designated according to the International 10/20 system, and 2 cm anterior, posterior, medial and lateral to C3 (termed C3a, C3p, C3m and C3l, respectively). (b) In two participants, 23 EEG electrodes were placed over the whole head, as designated according to the International 10–20 System, and 2 cm anterior, posterior, medial and lateral to C3. The ground electrode was placed over the forehead, and the reference electrodes were located at the left earlobe. (c) Timing of the paradigm used in the screening session and TMS Conditions 2 and 3. (d) Experimental system of the TMS Conditions 2 and 3.

Figure 2. Representative topographies of ERD during (a) the resting condition, (b) wrist motor imagery at ERD 5% and (c) ERD 15% from 19-channel EEG data of participant A. Topographic maps are illustrated in the frequency range of 9–11 Hz, which was the most reactive frequency band displaying ERD of participant A. Electrode positions are shown by dots. Positive values (blue colors) indicate strong ERD.

Figure 3. Example MEP traces induced by single and paired-pulse TMS recorded from ECR muscle during the resting condition, and during motor imagery of right wrist extension at ERD 5% and ERD 15% of participant A. Thin lines represent 10 MEP traces.
overlaid per condition. Thick lines represent mean of the 10 MEP traces. The triangle and
below vertical line indicate the onset of stimulus. As the ERD increased, MEP amplitudes
induced by the single pulse TMS were markedly facilitated, while SICI and ICF were
markedly reduced.

Figure 4. MEP amplitudes induced by the single pulse TMS, SICI and ICF changes
recorded from (a) FCR and (b) ECR muscle in the resting condition, and during motor
imagery of right wrist flexion at ERD 5% and ERD 15%. Each line shows the result
obtained from a representative participant (N=10). * P < .05, ** P < .01, *** P < .001.

Figure 5. Schematic diagram of the possible mechanism for the generation of ERD
during motor imagery. (a) Rest condition. (b) ERD during motor imagery. ERD during
motor imagery induced a significant inhibition of GABA_A transmission in both the thalamus
and M1, and a significant facilitation of the excitatory modulatory input, the TCR cells, the
I-wave generating neurons and the cortical pyramidal neurons. A = GABA_A receptors; ○ =
excitatory synapse; ● = inhibitory synapse; TCR = thalamo-cortical relay neurons; TRN =
thalamic reticular nucleus neurons; I = group of I-wave generating neurons; SICI and ICF =
neurons generating SICI and ICF, respectively; up and down arrows = increase and decrease
in its excitability, respectively.
Table 1. The most reactive frequency band and bipolar channels displaying ERD during right wrist motor imagery in the screening session.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Imagery task</th>
<th>Channel</th>
<th>Frequency [Hz]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>wrist extension</td>
<td>C3-C3m</td>
<td>9-11</td>
</tr>
<tr>
<td>B</td>
<td>wrist extension</td>
<td>C3-C3m</td>
<td>8-10</td>
</tr>
<tr>
<td>C</td>
<td>wrist flexion</td>
<td>C3-C3l</td>
<td>13-15</td>
</tr>
<tr>
<td>D</td>
<td>wrist flexion</td>
<td>C3-C3a</td>
<td>10-12</td>
</tr>
<tr>
<td>E</td>
<td>wrist extension</td>
<td>C3-C3a</td>
<td>16-18</td>
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<tr>
<td>F</td>
<td>wrist extension</td>
<td>C3-C3l</td>
<td>10-12</td>
</tr>
<tr>
<td>G</td>
<td>wrist extension</td>
<td>C3-C3a</td>
<td>8-10</td>
</tr>
<tr>
<td>H</td>
<td>wrist flexion</td>
<td>C3-C3p</td>
<td>10-12</td>
</tr>
<tr>
<td>I</td>
<td>wrist extension</td>
<td>C3-C3m</td>
<td>12-14</td>
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<tr>
<td>J</td>
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<td>C3-C3p</td>
<td>10-12</td>
</tr>
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<td>K</td>
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<td>17-20</td>
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<td>8-10</td>
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<td>7-9</td>
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<tr>
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<td>9-11</td>
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<td>20-22</td>
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<tr>
<td>Q</td>
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<tr>
<td>R</td>
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<td>C3-C3p</td>
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<td>wrist extension</td>
<td>C3-C3p</td>
<td>8-10</td>
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<tr>
<td>T</td>
<td>wrist flexion</td>
<td>C3-C3p</td>
<td>10-12</td>
</tr>
</tbody>
</table>
Fig. 1

a

b

Rest

Ready

Image

Rest

0  6  7  12

s

Trigger when ERD reached threshold

Realtime
ERD calculation

Bar feedback

MEP

TMS

EEG

GND

Ref.

F3 Fz F4

C3 Cz C4

T3 T4

P8 P4 Pz P3 P7

Fp1 Fp2

O2 O1

F8 F7

Ref.

GND

C3p C3m C3a

C3

F.3 FBMUJNF &3% DBMDVMBUJPO

5SJHHFSXIFO &3% SFBDIFEUISFTIPME

#BSGFFECBDL

5.4 &&(1

Rest ImageReady

Rest

Ready

Image

Rest

0  6  7  12

s
Fig. 2

a

b

c

ERD%
Fig. 3

- Single-pulse
- Paired-pulse: SICI (ISI: 3 ms)
- Paired-pulse: ICF (ISI: 10 ms)

Graph showing latency in ms and voltage in mV.
Fig. 4

a

Single pulse MEP

SICI

ICF

MEP amplitude [mv]

% Unconditioned MEP

% Unconditioned MEP

b

Single pulse MEP

SICI

ICF

MEP amplitude [mv]

% Unconditioned MEP

% Unconditioned MEP
Fig. 5

a) Rest

b) ERD during wrist motor imagery