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Is event-related desynchronization a biomarker representing corticospinal excitability?

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***Abstract*—Brain computer interfaces (BCIs) using event-related desynchronization (ERD) of the electroencephalogram (EEG), which is believed to represent increased activation of the sensorimotor cortex, have attracted attention as tools for rehabilitation of upper limb motor functions in hemiplegic stroke patients. However, it remains unclear whether the corticospinal excitability is actually correlated with ERD. The purpose of this study was to assess the association between the ERD magnitude and the excitability of primary motor cortex (M1) and spinal motoneurons. M1 excitability was tested by motor evoked potentials (MEPs), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) using transcranial magnetic stimulation, and spinal motoneuronal excitability was tested by F-waves using peripheral nerve stimulation. Results showed that large ERD during motor imagery was associated with significantly increased F-wave persistence and reduced SICI, but no significant changes in ICF and the response average of F-wave amplitudes. Our findings suggest that ERD magnitude during motor imagery represents the instantaneous excitability of both M1 and spinal motoneurons. This study provides electrophysiological evidence that ERD-based BCI with motor imagery task increases corticospinal excitability as changes accompanying actual movements.**

I. Introduction

There is an increasing interest in electroencephalogram (EEG)-based brain-computer interface (BCI) as a possible tool for rehabilitation of upper limb motor functions in hemiplegic stroke patients [1]-[6]. This type of BCI often exploits the oscillations in the EEG occurring in the mu and beta bands recorded over the sensorimotor areas (SM1). Their amplitude typically decreases during movement and similarly during motor intention or motor imagery [7]-[9], and has been referred to as event-related desynchronization (ERD). Some studies revealed that movement or motor imagery-induced ERD and blood-oxygen-level-dependent (BOLD) signal in functional MRI changes co-localize at the SM1, and that the magnitude of ERD and BOLD co-vary [8][9]. Therefore ERD following motor imagery is believed to represent increased activation of the SM1.

However, it remains unclear whether the excitabilities at the cortical and spinal level in the motor system are actually correlated with ERD over duration ranging from several hundred milliseconds to seconds. The BOLD signal used in numerous studies [8][9] is inferior in time resolution (2–3 s) compared to mu and beta bands in EEG (of the order of 100 ms). Further, BOLD signal indicates hemodynamic cortical activity, but not necessarily electric corticospinal excitability. Identification of a relationship between instantaneous ERD magnitude and corticospinal excitability could provide a physiological basis for BCI-based neurorehabilitation to promote motor recovery.

The purpose of this study was to assess the association of the magnitude of ERD with the excitability of primary motor cortex (M1) and spinal motor neurons during hand motor imagery. We sought to identify such a relationship using simultaneous acquisition of ERD magnitude, which was calculated from EEG online, and transcranial magnetic stimulation (TMS) or peripheral nerve stimulation (PNS), which was contingent on the instantaneous ERD magnitude. Motor evoked potential (MEP) induced by single pulse TMS and short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) induced by paired-pulse TMS are widely accepted as measures for assessing cortical excitability non-invasively [10][11]. F-wave induced by peripheral nerve stimulation is used for assessing spinal motoneuronal excitability non-invasively [12].

II. Methods

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.

A. Experiment 1: ERD and M1 excitability

Ten healthy participants were recruited. Single-pulse TMS adjusted to 120% of the individual resting motor threshold was applied to the left hemisphere over the optimal position for eliciting a response in the right extensor carpi radialis (ECR) muscle. The resulting MEP recorded from the ECR muscle was evaluated by its peak-to-peak amplitude. This index reflects the corticospinal excitability. Paired-pulse TMS was used to investigate SICI and ICF. A subthreshold conditioning stimulus adjusted to 80% of the resting motor threshold 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 resting motor threshold. SICI and ICF, which were expressed as the mean conditioned MEP divided by the mean unconditioned MEP in percent, reflect the activity of excitatory and inhibitory interneurons in M1, respectively. Each participant participated in a series of three experimental conditions. In the first condition, we applied single and

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paired-pulse TMS during the rest, and collected 50 MEPs. In the second condition, participants performed 7 s of rest followed by 5 s of motor imagery of right wrist extension, and received real-time visual feedback of the ERD magnitude of the right hand SM1 while they performed a motor imagery task. We applied either single or paired-pulse TMS immediately after the ERD exceeded 5% during motor imagery. We collected 30 MEPs. The online algorithm to calculate ERD is described below (*II-C. BCI experimental system*). The third experimental condition was the same conditions as the second except that TMS was applied immediately after ERD exceeded 15% during motor imagery.

B. Experiment 2: ERD and spinal motoneuronal excitability

Ten healthy participants were recruited. F-waves, which is not not only the most sensitive measure of diffuse nerve disease also used to demonstrate increased excitability of spinal motoneurons were recorded from the right abductor pollicis brevis muscle. To elicit F-waves, we firstly determined the maximal stimulus by delivering 0.2 ms square-wave pulses of increasing intensity to elicit the largest compound muscle action potentials (CMAPs). Supramaximal shocks, adjusted up to the value of 20% higher than the maximal stimulus, were applied to the right median nerve at the wrist level. Each participant participated in a series of three experimental conditions. In the first condition, we applied PNS during rest and collected 50 CMAPs. In the following conditions, we used the same BCI experimental system as Experiment 1. The participants performed 7 s of rest followed by 5 s of motor imagery of right thumb abduction. We applied PNS immediately after the ERD exceeded 5% or 15% during motor imagery, and collected 50 CMAPs in both conditions. The trials produced F-wave were defined as a deflection of at least 50 μV occurring from 24 ms to 36 ms after PNS with baseline subtraction. F-wave measurements consisted of persistence, which is the number ofdefinable F-waves per 50 stimuli, and response average, which is averaged peak amplitude in counting only those trials with detectable responses.

C. BCI experimental system

EEG signals were recorded over right hand SM1 (C3 and its four neighbors) with Ag/AgCl electrodes (φ= 10 mm) sampled at 512 Hz using an EEG amplifier (Guger Technologies, Graz, Austria). The signal from C3 was re-referenced using a four neighbors Laplacian spatial filter [13]. The EEG data was segmented into successive 512-point (1,000 ms) windows with 480-point overlapping, and a fast Fourier transformation was applied in each segment. ERD was defined as the decrease in spectral power relative to 3 s reference intervals during the resting period in each trial. ERD was calculated at each segment (time resolution of 62.5 ms) with a frequency resolution of 1 Hz, according to the following calculations:

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

where A is the power spectrum density of the EEG at time t [s] with the onset of motor imagery and frequency f [Hz], and R is the mean power spectrum [μV^2/Hz] of the reference intervals. Feedback was provided as the length of a bar displayed on a screen placed 60 cm in front of the participant's eyes and was continuously moving in accordance with the ERD magnitudes while the participant performed the motor imagery task. TMS or PNS was triggered online by the BCI experimental system (Fig. 1) when ERD magnitude reached the predetermined threshold during the motor imagery task.

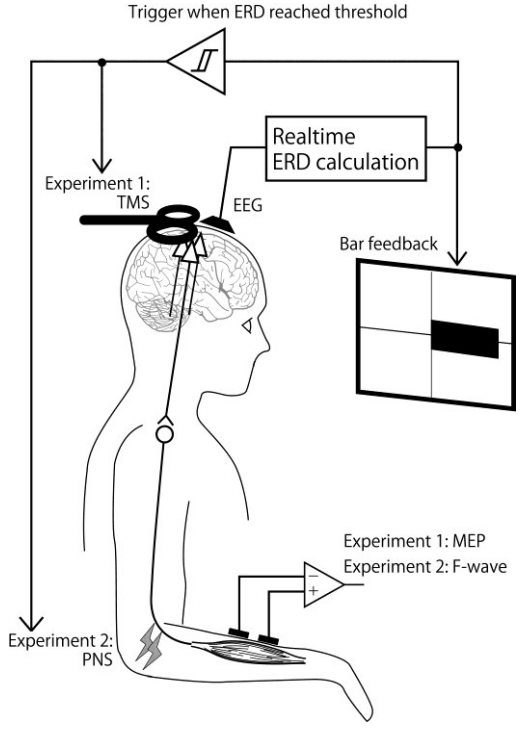

Figure 1. BCI experimental system

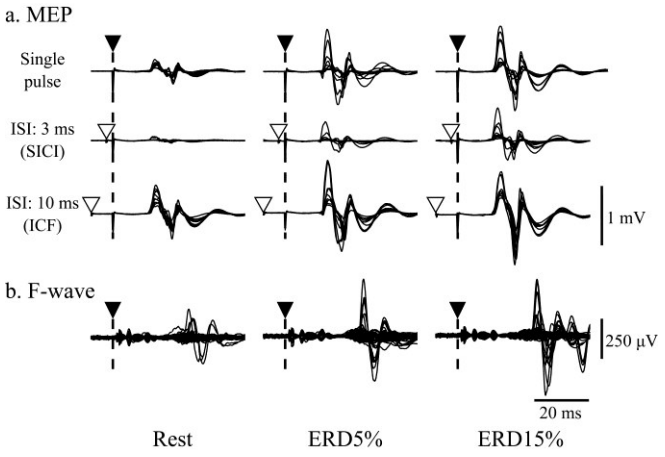

Figure 2. Ten overlaid MEP traces from right ECR muscle (a) and fifty overlaid F-waves traces with baseline subtraction from right abductor pollicis brevis muscle (b) during the resting condition, motor imagery at ERD 5% and ERD 15% (N=1). MEP analysis of 10 traces showed 0.55 mV, 1.03mV and 1.42 mV in single pulse induced MEP amplitude, 16.1%, 36.7% and 59.9% in SICI and 231%, 185% and 158% in ICF at the resting condition, ERD 5% and ERD 15%, respectively. F-wave analysis of 50 traces showed 14%, 26% and 46% in persistence and 161 μV, 288 μV and 238 μV in response average of amplitude at the resting condition, ERD 5% and ERD 15%, respectively. Filled and open trialgles indicate onset of suprathereshold and conditioning stimuli, respectively.

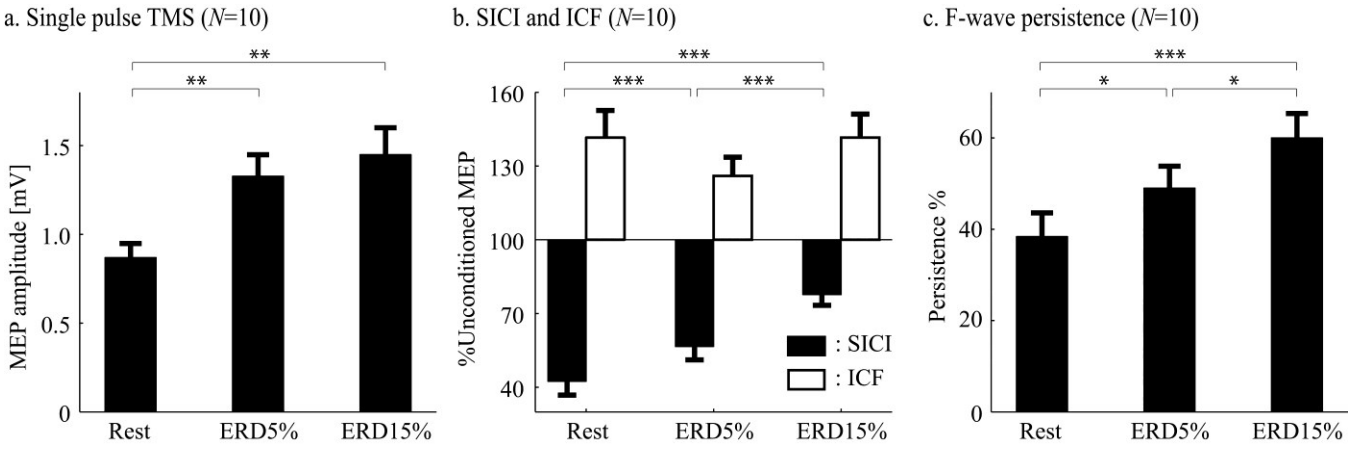

Figure 3. Mean value of MEP amplitudes induced by the single pulse TMS (a) as well as SICI, ICF (b) and F-wave persistence (c) in 10 healthy participants. Error bar indicates that standard error of the mean. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

III. Results

A. Experiment 1: ERD and M1 excitability

Figure 2a shows MEP responses of the ECR muscle during the resting condition and motor imagery at ERD 5% and 15% from a single participant. During motor imagery, MEP amplitudes evoked by the single pulse TMS were dramatically facilitated, and SICI and ICF were dramatically reduced. The increase of MEP amplitudes induced by the single pulse TMS and SICI were related to ERD magnitude. Figure 3 represents MEP amplitudes induced by the single pulse TMS (Fig. 3a), SICI and ICF (Fig. 3b) from the ECR muscle during the resting condition, motor imagery at ERD 5% and 15%. MEP amplitudes induced by single pulse TMS (mean ± S.E.) increased from 0.87 ± 0.08 mV in the resting condition to 1.33 ± 0.12 mV at the ERD 5% and 1.45 ± 0.15 mV at the ERD 15%. SICI reduced from 42.4 ± 5.6% in the resting condition to 56.6 ± 5.4% at the ERD 5% and 77.7 ± 4.4% at the ERD 15%. SICI monotonically reduced in accordance with the ERD magnitude in 9 out of 10 participants. However, ICF unchanged from the resting condition (141.6 ± 11.0%) to the condition of ERD 5% (126.0 ± 7.6%) and the condition of ERD 15% (141.6 ± 9.6%). One-way repeated measures ANOVA showed that the effect of ERD Condition for MEP amplitudes ($F = 10.6$, $P < .001$) and SICI ($F = 61.5$, $P < .001$) were statistically significant, but not for ICF ($F = 1.69$, $P = .21$). Post-hoc analysis revealed that MEP amplitudes were significantly larger at ERD 5% ($P < .01$) and ERD 15% ($P < .01$) compared to the resting condition. SICI at ERD 15% was significantly smaller than at ERD 5% ($P < .001$) and at rest ($P < .001$) and SICI at ERD 5% was significantly smaller than at rest ($P < .001$).

B. Experiment 2: ERD and spinal motoneuronal excitability

Figure 2b shows typical example of F-wave changes in all experimental conditions from a single participant. Figure 3c represents the results of F-wave persistence during the resting condition, motor imagery at ERD 5% and 15% from 10 healthy participants. F-wave persistence (mean ± S.E.) increased from 38.4 ± 5.2% in the resting condition to 49.0 ± 4.8% at the ERD 5% and 60.0 ± 5.3% at the ERD 15%. F-wave persistence monotonically increased in accordance with the ERD magnitude in 7 out of 10 participants. However, response average of F-wave amplitudes unchanged from 145.0 ± 46.6 μV in the resting condition to 204.4 ± 99.4 μV at the ERD 5% and 189.7 ± 85.3 μV at the ERD 15%. One-way repeated measures ANOVA showed that the effect of ERD Condition for F-wave persistence ($F = 15.9$, $P < .001$) was statistically significant, but not for response average of F-wave amplitudes ($F = 3.30$, $P = .06$). Post-hoc analysis revealed that F-wave persistence at ERD 15% was greater than at ERD 5% ($P < .05$) and at rest ($P < .001$) and F-wave persistence at ERD 5% was greater than at rest ($P < .05$).

IV. Discussion

Numerous studies have examined the changes of corticospinal excitability during motor imagery by using single pulse TMS [14]-[17], and have reported that motor imagery significantly increases corticospinal excitability. Furthermore, Pattuzo et al. (2003) showed that SICI was significantly reduced during hand motor imagery, but not ICF [14]. Our results are in agreement with those studies. We showed single-pulse MEP size was larger during motor imagery. In addition, and most importantly, we found that the reduction of SICI was 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 [11]. As it was reported that $GABA_A$ agonists enhance SICI [18] and *N*-methyl-D-aspartate antagonists abolish ICF [19], 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 also found that the magnitude of ERD during motor imagery was associated with a significant increase in F-wave persistence compared to rest, but no significant change was found in response average of F-wave amplitude. Rivner (2008) reported that the increase in response average of

F-wave amplitudes, disregarding absent responses, would indicate a shift in the motor neurons recruited from smaller ones to larger ones [20]. In contrast, persistence or the number of F-wave per 50 stimuli is probably best measure of an increase in spinal motoneuronal excitability [20]. Based on the previous findings, our results indicate that the magnitude of ERD during motor imagery has an effect on the general excitability of the motoneuron pool, but not on the type of motoneuron excited. The result of Rossini et al. (1999), that motor imagery increased the excitabilities of both M1 and spinal motoneuron pool [14], has a close resemblance to the present result. In contrast, some papers reported that motor imagery significantly increased MEP amplitudes, but not F-wave persistence [16][17]. These inconsistencies may result from two reasons. First, since a recent study showed that more than 50 stimuli are needed to adequately measure F-wave persistence [21], the previous studies, which used fewer than 50 stimuli, may not properly evaluate the excitability of spinal motoneuron pool [16][17]. The second reason is the difficulties associated with motor imagery performance due to fatigue and lapse of concentration. In the present study, since we collected fifty F-waves and monitored the state of motor imagery by ERD, these problems have been resolved. Therefore, our finding clearly suggests that subliminal central drives (i.e., ERD by hand motor imagery) play an important role in increasing the excitability of the spinal motoneurons.

Our data indicate that ERD during motor imagery increases M1 excitability by decreasing the activity of GABAergic inhibitory interneurons. In addition, we found that ERD magnitude during hand motor imagery represents the excitabilities of both the contralateral M1 and ipsilateral spinal motoneuron pool. This study provides electrophysiological evidence that ERD-based BCI, which is a promising new intervention for neurorehabilitation in stroke, may be useful as a tool to allow users to voluntarily increase or decrease corticospinal excitability based on their intention. Through this BCI framework, stroke patients may learn to increase corticospinal excitability by repeated use of the BCI, resulting in use-dependent functional recovery.

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