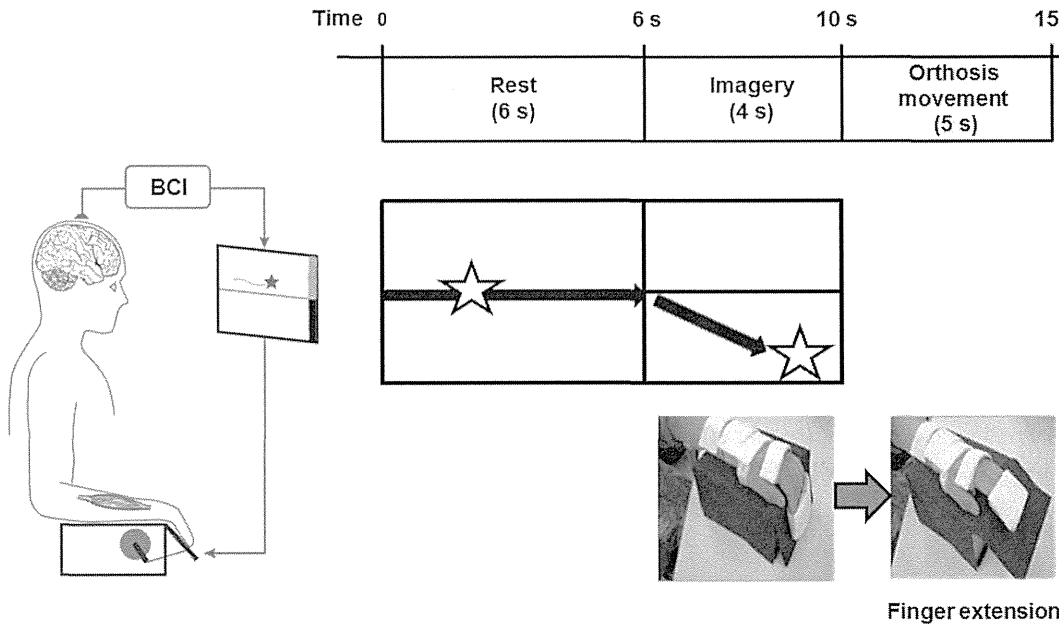

Fig. 1. Brain–computer interface (BCI) system. The participant is seated in front of a screen that displays the task and visual feedback. The paretic hand is placed on the motor-driven orthosis, which extends the paretic fingers. The task cue shows "Rest" for 6 s and "Imagine" for 4 s. The imagery task indicates that the participant should imagine extension of the paretic fingers. The star-shaped cursor moves from left to right on the screen. When event-related desynchronization is detected with electroencephalography, the star-shaped cursor moves downward on the screen, and then the motor-driven orthosis extends the paretic fingers for 2 s and returns them to the rest position for 3 s.

was placed over the M1 of the affected hemisphere, and the cathode was placed over the contralateral supraorbital area. tDCS was applied for 10 min with a current intensity of 1 mA. Participants were awake and sat in an upright position in a comfortable armchair during stimulation.

The positions of EEG electrodes were established before tDCS. For placing the stimulation electrodes, the EEG electrodes over the stimulus sites were removed after marking the scalp. After the tDCS stimulation, the EEG electrodes were placed in the same position as before, and this procedure took less than 1 min.

Outcome measures

The following clinical assessments and the measurement of mu ERD were conducted 1 day before (before) and after the intervention (post-), as described below. The accuracy rate of BCI training was also calculated on each day. To determine the long-term effects, the clinical evaluations were also assessed 3 months after the intervention (3 months) (Fig. 2).

Clinical assessments

UE motor function was assessed with the Fugl-Meyer Assessment UE motor score (FM-U) (66 points, total score) (21). The FM-U includes 33 items and consists of test A (shoulder/elbow/forearm: 36 points, A score), test B (wrist: 10 points, B score), test C (hand/finger: 14 points, C score) and test D (coordination: 6 points, D score). The D score was excluded because all patients in this study could not touch their noses with their index finger fully extended and had no remaining finger extension. The FM-U was assessed according to the scoring manual (22), and the validity and reliability of this method has been previously confirmed (23). Spasticity was measured with the Modified Ashworth Scale (MAS) (24) for finger, wrist and elbow flexors.

The FM-U and the MAS were scored by an independent assessor who was blinded to the allocation of the participants. This assessor scored all patients with stroke who were admitted to the department during the study period, including patients not recruited for this study.

The brain lesions were assessed with MRI or CT. The volumes of haemorrhage were calculated by the ABC/2 method, where A is the greatest haemorrhage diameter by MRI, B is the diameter 90° to A, and C is the approximate number of slices with haemorrhage multiplied by the slice thickness (25).

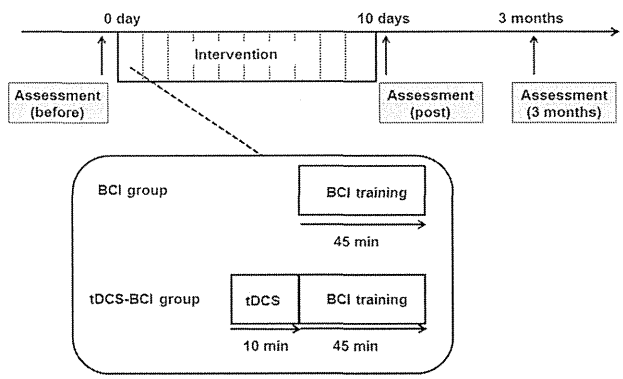

Fig. 2. Experimental design. All participants received the intervention of 10 days of training, which consisted of 1 × 45-min brain–computer interface (BCI) training session per day. The participants in the transcranial direct current stimulation (tDCS)-BCI group received anodal tDCS (1 mA, 10 min) over the affected motor cortex immediately prior to every BCI training session. Clinical examinations were performed 1 day before (before), 1 day after (post), and 3 months after the intervention (3 months).

Assessment of mu event-related desynchronization

The values of mu ERD during motor imagery of extension of the affected fingers were assessed 1 day before and 1 day after the 10-day intervention. The detail method was described previously (14) and is summarized in Appendix S1[1].

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-1925

Table I. *Clinical characteristics of participants*

	tDCS-BCI group (n=11)	BCI group (n=7)	p-value
Age, years, mean (SD)	53.5 (12.4)	48.0 (9.7)	0.441
TFO, months, mean (SD)	46.2 (20.2)	56.4 (36.4)	0.389
Gender, M/F, n*	9/2	4/3	0.225
Type of stroke*			0.629
Ischaemic, n	6 (1 lacunar)	3 (1 lacunar)	
Haemorrhagic, n	5	4	
Volume of lesion* (mm^3), mean (SD)	8,000 (7,282)	34,083 (29,795)	0.268
Paretic side, right/left, n*	6/5	5/2	0.417
Lesion, n*			
Putamen	4	3	0.398
Corona radiata	0	1	
Putamen-corona radiata	6	3	
Thalamus	1	0	
FM-U	27.6 (11.2)	23.4 (13.8)	0.487
MAS, median (min-max)**			
Finger flexors	1+ (1, 2)	2 (1+, 3)	0.038
Wrist flexors	2 (1, 3)	2 (1, 3)	0.845
Elbow flexors	1+ (1, 2)	1+ (1, 2)	0.316

p-values were calculated with Student's t-test, χ^2 tests* or Mann-Whitney U test**. TFO: time from onset of stroke; FM-U: Fugl-Meyer Assessment upper extremity motor score; MAS: Modified Ashworth scale; tDCS: transcranial direct current stimulation; BCI: brain–computer interface; M: male; F: female.

Accuracy rate of brain–computer interface training

The numbers of successful performances (i.e. moving the orthosis after imagery cues and not moving after the resting cues) were counted, and the accuracy rate was calculated as the number of successful performances divided by the number of trials. The mean accuracy rates on the first day and the last day of BCI training were compared.

Data analysis

Student's t-test was used to compare the baseline data of age, time from stroke onset and FM-U total score/subscores of the 2 groups. The Mann–Whitney U test was used to compare the baseline data of volumes of haemorrhage and MAS scores. The normality of the distribution of these variables was confirmed with the Kolmogorov–Smirnov test. A χ^2 test was used to compare categorical variables (gender, type of stroke, paretic side and lesion) of the 2 groups. Differences were considered significant if $p<0.05$.

A 2-factor mixed factorial analysis of variance (ANOVA) was used to compare the FM-U and MAS scores with the between-subjects factor of Intervention (BCI and tDCS-BCI groups) and the within-subjects factor of Time (before, post- and 3 months). The mu ERD and accuracy rate were also analysed using a 2-factor mixed factorial ANOVA with the between-subjects factor of Intervention (BCI and tDCS-BCI groups) and the within-subjects factor of Time (before and post for the mu ERD; the first and last trials for the accuracy rate). If the difference within the subjects was significant, *post-hoc* analysis was performed with a paired t-test in the FM-U, mu ERD and accuracy rate, and the Wilcoxon signed-rank test in the MAS. All statistical analyses were performed with SSPS version 18.0J (SPSS Japan, Japan).

RESULTS

All participants finished the intervention without experiencing any adverse effects. Table I shows the clinical characteristics of the participants. There were no significant differences between the 2 groups in any of the clinical evaluation items (age, time from onset of stroke, gender, type of stroke, paretic side, lesion and FM-U) before the intervention, except for the MAS of the finger flexors (Table I).

In the clinical assessment, 2 participants were not assessed at 3 months. One in the BCI group received different treatment after the intervention, and 1 in the tDCS-BCI group did not show up. The changes of the FM-U and MAS are shown in Table II. The 2-factor mixed factorial ANOVA showed no significant interaction effect between Intervention and Time in the total FM-U score ($F(2,28)=2.43$, $p=0.107$), the A score ($F(2,28)=2.96$, $p=0.068$), the B score ($F(2,28)=0.18$, $p=0.833$) and the C score ($F(2,28)=1.56$, $p=0.228$). It showed a significant main effect of Time in the total FM-U score ($F(2,28)=17.42$, $p<0.001$), the A score ($F(2,28)=8.19$, $p=0.002$) and the C score ($F(2,28)=10.94$, $p<0.001$), but not in the B score ($F(2,28)=3.02$, $p=0.065$). A *post-hoc* paired t-test showed significant differences in the total, A and C scores between before and post- ($p<0.001$, $p=0.004$ and $p=0.011$,

Table II. *Clinical assessment scores*

	tDCS-BCI group			BCI group			Interaction	Main effect of time
	Before (n=11)	Post (n=11)	3 months (n=10)	Before (n=7)	Post (n=7)	3 months (n=6)	p	p
FM-U, mean (SD)								
A	21.64 (7.32)	23.91 (7.20)**	26.10 (6.49)**	18.29 (8.98)	22.00 (8.19)	21.17 (9.56)	0.068	0.002
B	1.55 (1.86)	2.73 (2.61)	2.40 (1.58)	1.43 (2.51)	2.29 (2.75)	2.67 (2.42)	0.833	0.65
C	4.45 (2.54)	7.00 (2.76)*	7.90 (2.23)**	3.71 (2.75)	5.71 (2.98)*	5.67 (1.51)	0.228	<0.001
Total	27.64 (11.17)	33.64 (10.91)**	36.40 (8.72)**	23.43 (13.79)	30.00 (12.48)*	29.50 (12.23)	0.107	<0.001
MAS, median (min–max)								
Finger	1+(1, 2)	1 (0, 2)*	1 (0, 1+)**	2 (1+, 3)	1+ (1, 3)*	1 (1, 2)*	0.663	<0.001
Wrist	2 (1, 3)	1+ (0, 3)	1 (0, 2)*	2 (1, 3)	1+ (1, 3)	1~1+ (1, 1+)	0.230	<0.001
Elbow	1+ (1, 2)	1 (1, 1+)*	1 (0, 1+)*	1+ (1, 3)	1+ (1, 2)	1 (0, 1+)	0.608	<0.001

*$p<0.05$, **$p<0.01$ compared with the score of before; post-hoc paired t-test for the FM-U, Wilcoxon signed-rank test for the MAS. tDCS: transcranial direct current stimulation; BCI: brain–computer interface; FM-U: Fugl-Meyer Assessment upper extremity motor score; A: shoulder/elbow/forearm, 36 points; B, wrist, 10 points; C: hand/finger, 14 points; MAS: Modified Ashworth scale; finger: finger flexors; wrist: wrist flexors; elbow: elbow flexors; SD: standard deviation.

respectively), and between before and 3 months ($p=0.001$ for all) in the tDCS-BCI group. In contrast, in the BCI group, there were significance differences between before and post- in the total and C scores ($p=0.027$, $p=0.038$, respectively), and a not significant but slight improvement in the A score ($p=0.056$). There was no significant difference in all of the scores between before and 3 months (total score: $p=0.093$, A score: $p=0.376$, C score: $p=0.139$).

The 2-factor mixed factorial ANOVA showed no significant interaction between Intervention and Time ($p>0.05$), and a significant main effect of Time ($p<0.001$) in the MAS of the finger, wrist and elbow flexors. The Wilcoxon signed-rank test showed a significant decrease in the MAS of the finger flexors in both groups between before and post- (tDCS-BCI group: $p=0.011$, BCI group:$p=0.038$) and between before and 3 months ($p=0.004$, 0.024, respectively). There were also tendencies toward decrease in the MAS of the elbow and wrist flexors in both groups between before and post- (tDCS-BCI group: $p=0.025$ and 0.059, BCI group: $p=0.102$ and 0.102, respectively) and between before and 3 months ($p=0.016$ and 0.010, $p=0.059$ and 0.102, respectively).

The changes in the mu ERD values are shown in Fig. 3. The 2-factor mixed factorial ANOVA showed a significant interaction between Intervention and Time ($F(1,16)=6.94$, $p=0.018$), and a significant main effect of Time ($F(1,16)=14.68$, $p=0.001$). The *post-hoc* paired *t*-test showed a significant increase in the mu ERD values between before and post- in the tDCS-BCI group ($p<0.001$), but not in the BCI group ($p=0.483$).

The mean accuracy rate in the tDCS-BCI group increased from 49.91 ± 7.92% to 58.68% (SD 8.62), whereas it increased in the BCI group from 52.10% (SD 9.39) to 55.76% (SD 4.42). The 2-factor mixed factorial ANOVA showed no significant interaction between Intervention and Time ($F(1,16)=2.34$, $p=0.145$), and a significant main effect of Time ($F(1,16)=14.12$, $p=0.002$). The *post-hoc* paired *t*-test showed a significant improvement between the first and last trials in the tDCS-BCI group, but not in the BCI group (tDCS-BCI group: $p=0.001$, BCI group: $p=0.220$).

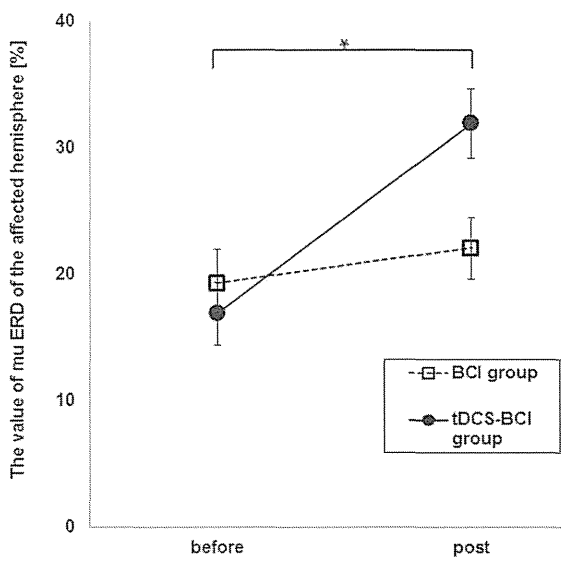

Fig. 3. The change in mu event-related desynchronization (ERD). The means of the mu ERD values of the transcranial direct current stimulation (tDCS)-brain–computer interface (BCI) group (square) and the BCI group (round) are plotted before and one day after the intervention (post). Error bars indicate standard error. Asterisks indicate significant differences from the baseline value with the *post-hoc* Student's *t*-test (*$p<0.01$).

DISCUSSION

The present study demonstrated that a 10-day BCI training improved motor function in patients with chronic severe hemiparetic stroke. Although there was a significant increase in ERD only in the tDCS-BCI group, no significant difference was found in improvement in motor function between the 2 groups. The tDCS-BCI group, however, showed a slightly longer-lasting improvement in motor function compared with the BCI group.

BCI training may produce an increase in appropriate brain activity and lead to the restoration of function through neuroplasticity (12). Shindo et al. (8) showed that BCI training increased the motor cortex excitability of the affected hemisphere, as confirmed with TMS. Functional MRI showed that BCI training increased ipsilesional motor cortex and premotor cortex activities (9). The combination of a coincident movement of the paretic fingers and the volitional brain signals by BCI training may induce sensorimotor integration and increase the recruitment of descending corticospinal fibres. These increments of excitability of motor pools may induce neural plasticity or neural compensation, leading to improvement in motor function.

Anodal tDCS increases cortical excitability (15) because of the increase in spontaneous neurone firing (26, 27) and the modulation of resting membrane potential (26, 28). Anodal tDCS is known to facilitate immediate production of mu ERD in healthy subjects and stroke patients (14, 19). Anodal tDCS could help to improve decoding of brain signals during BCI training by immediately increasing mu ERD, which might lead to an additional increase in mu ERD even after the BCI training was completed. It has been reported that ERD was correlated with M1 excitability (29) and blood-oxygen-level-dependent (BOLD) response (30). An increase in mu ERD in the tDCS-BCI group may be related to neural excitation in the affected hemisphere. Although tDCS could lead to an increase in ERD, we could not find a clear difference in motor improvement between the tDCS-BCI and BCI groups in this study. There was no interaction effect between Intervention and Time. It is possible that anodal tDCS improves motor function (31), but the effect may be limited only to patients with milder paresis (32). There was no substantial difference in the accuracy rate in this study. This could mean that the number of doses offered in successful trials of BCI training was not high enough to improve motor function. However, a more extensive change in brain signals (i.e. ERD) could result in a more significant long-term effect.

We found a reduction in spasticity in both groups. This may be due to the increase in awareness and learning of relaxation that comes through BCI training. It is difficult for patients with severe motor impairment to recognize their affected hand. BCI training can help patients concentrate on their affected hand, resulting in increases in awareness and use of the affected UE in their activities of daily living (8). In addition, the sequential training between relax and imagery may enable patients to learn how to decrease involuntary muscle activity (8). These effects of BCI training could have an impact on the whole UE, leading to improvements in proximal, as well as distal, portions. All participants received occupational therapy for 40 min per day in addition to the intervention. Occupational therapy may also contribute to the improvement. However, the change in the FM-U from baseline to post-intervention was 6.6±6.0 points in our BCI group. This improvement was better than the changes in the FM-U only by conventional therapy for severe chronic patients with stroke in previous studies, showing that conventional therapies for 6–8 weeks resulted in 1.2–2.2 point improvements in the FM-U (5, 33, 34).

Study limitations

Several limitations must be considered regarding this study. First, the method of group allocation could have given rise to bias. The allocation of participants to the tDCS-BCI and BCI groups was controlled, but not randomized, with different group sizes among small samples. We excluded subjects who had undergone brain surgery or who were at risk for seizures from the tDCS-BCI group, while including them in the BCI group. There was no sham stimulation in the BCI group. The clinical features in the 2 groups, such as the gender, size of stroke, lesion side and motor function, were not significantly different except for finger spasticity. These discriminations, however, may have introduced a further variable. Secondly, anodal tDCS was applied for only 10 min immediately before the BCI training. The effect of 10 min of anodal tDCS with an intensity of 1 mA on TMS-evoked MEPs was shown to be maintained for less than 40 min in a previous study (35). In this study, the BCI training was performed for 45 min. The effect of the tDCS may have been lost by the end of the training. Thirdly, the position of M1 of the affected hemisphere was determined by using the symmetrical opposite side as a marker, that is, M1 of the unaffected hemisphere. This is not the exact position as identified by MEP of the affected EDC through directly stimulating the affected hemisphere. Finally, there is a possibility that some participants did not imagine well, which is very difficult to assess. The development of more effective BCI systems for stroke patients in terms of feedback accuracy, delay and modality is needed.

Conclusion

Anodal tDCS can be used as a conditioning tool for BCI training to increase ERD for the trigger of BCI. However, further randomized controlled trials are needed to ascertain the real effect of BCI training and the adjunctive effect of anodal tDCS for BCI training in more homogenous stroke populations.

ACKNOWLEDGEMENTS

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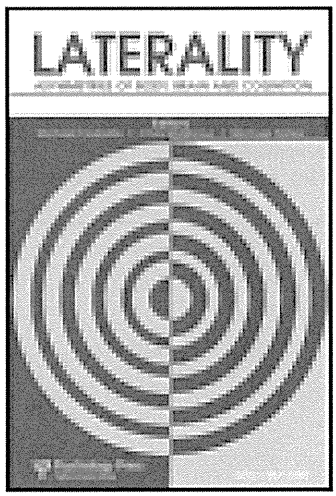
Supplementary material to article by Y. Kasashima-Shindo et al. "Brain–computer interface training combined with transcranial direct current stimulation in patients with chronic severe hemiparesis: proof of concept study"

APPENDIX SI. Assessment of mu event-related desynchronization (ERD)

Electroencephalography (EEG) signals were recorded with 22 Ag–AgCl disc electrodes with binaural references according to the International 10–20 system of electrode placement with the average of bilateral earlobe references. Impedance for all channels was maintained below 10 kΩ throughout the experiment. Electromyograms were simultaneously recorded from the bilateral EDC with surface Ag–AgCl disc electrodes to monitor electromyographic (EMG) activities during the imagery task to avoid unexpected muscle contraction. EEG and EMG signals were amplified, digitized with a sampling frequency of 1000 Hz and bandpass filtered (EEG 0.53–100 Hz, EMG 20–1 kHz) using a commercially available bio-signal recorder (Neurofax EEG-9100, Nihon Kohden Corporation, Japan).

The participants sat in an upright position in an armchair. Their eyes were open, and they were facing the computer monitor that displayed the task. The monitor was placed approximately 50 cm in front of the subject at eye level. One trial started with a 10-s period of relaxation during which the word "Rest" was shown on the monitor. After that, the word "Image" was presented for 5 s, and the participants were asked to imagine extension of their affected fingers. The trial ended when the word "Rest" reappeared. After that, the next trial began. To avoid a learning effect, they were given no feedback regarding EEG changes. One session consisted of 20 trials, and the 2 sessions were performed with approximately 5-min rest periods between each session.

The values of mu ERD on the affected motor area (C3 and FC3, or C4 and FC4) were calculated. The same electrodes used in the BCI training were chosen. Event-related trials lasting 5 s during motor imagery were selected for off-line data processing. All trials were visually assessed. The trials with artefacts resulting from eye movement and the trials with increased EMG activity were excluded. All trials were segmented into successive 1-s windows with 900 overlapping samples, and the Fourier transform with the Hanning window was applied to each segment. The power spectral density of each segment was estimated over the trials using Welch's averaged periodogram method (36). All off-line analysis of EEG data was performed using MATLAB (The MathWorks, Inc., USA).



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Transcranial direct current stimulation enhances mu rhythm desynchronization during motor imagery that depends on handedness

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Transcranial direct current stimulation enhances mu rhythm desynchronization during motor imagery that depends on handedness

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Transcranial direct current stimulation (tDCS) can modulate the amplitude of event-related desynchronization (ERD) that appears on the electroencephalogram (EEG) during motor imagery. To study the effect of handedness on the modulating effect of tDCS, we compared the difference in tDCS-boosted ERD during dominant and non-dominant hand motor imagery. EEGs were recorded over the left sensorimotor cortex of seven healthy right-handed volunteers, and we measured ERD induced either by dominant or non-dominant hand motor imagery. Ten minutes of anodal tDCS was then used to increase the cortical excitability of the contralateral primary motor cortex (M1), and ERD was measured again. With anodal tDCS, we observed only a small increase in ERD during non-dominant hand motor imagery, whereas the same stimulation induced a prominent increase in ERD during dominant hand motor imagery. This trend was most obvious in the participants who used their dominant hand more frequently. Although our study is preliminary because of a small sample size, these results suggest that the increase in ERD by applying anodal tDCS was stronger on the dominant side than on the non-dominant side. The background excitability of M1 may determine the strength of the effect of anodal tDCS on ERD by hand motor imagery.

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Keywords: Transcranial direct current stimulation; Electroencephalogram; Event-related desynchronization; Handedness; Motor cortex.

The mu rhythm is a spontaneous characteristic feature of the electroencephalogram (EEG)/magnetoencephalogram pattern. It consists of 8–13 Hz activities that appear maximally over the central rolandic or sensorimotor areas during a relaxed state (Pfurtscheller, Neuper, Andrew, & Edlinger, 1997; Pfurtscheller, Stancak, & Neuper, 1996). The mu rhythm is attenuated by tactile stimulation, movement execution and motor imagery, a process referred to as event-related desynchronization (ERD; Arroyo et al., 1993; Kozelka & Pedley, 1990; Kuhlman, 1978). Such ERD of the mu rhythm, named mu ERD in this study, is interpreted as the desynchronized activities of the activated neurons based on externally or internally paced events (Pfurtscheller & Lopes da Silva, 1999).

Recent studies infer that mu ERD when preparing for contralateral extremity movement is somehow related to cortical activity. For instance, increased excitability of the contralateral corticospinal tract (Facchini, Muellbacher, Battaglia, Boroojerdi, & Hallett, 2002; Kasai, Kawai, Kawanishi, & Yahagi, 1997) has been observed during motor imagery of hand muscles, which is a task known to induce mu ERD. Also during motor imagery and movement, the contralateral decrease of alpha/beta EEG (i.e., mu ERD was presumably present) co-localized with an increase of the blood-oxygen-level dependent signal in the primary sensorimotor cortex in functional magnetic resonance imaging (Yuan et al., 2010). More recently, association of mu ERD of contralateral corticospinal tract excitability and GABAergic interneuronal disinhibition in the primary motor cortex (M1) was reported (Takemi, Masakado, Liu, & Ushiba, 2013). Based on these findings, neurofeedback or Brain–Computer Interface (BCI), an EEG operant-conditioning training technique with mu ERD, may offer a new strategy to train the voluntary regulation of corticospinal excitability for functional recovery in people with severe motor disabilities following stroke (Ang et al., 2011; Birbaumer & Cohen, 2007; Broetz et al., 2010; Buch et al., 2008; Caria et al., 2011; Daly & Wolpaw, 2008; Mukaino et al., 2014; Prasad, Herman, Coyle, McDonough, & Crosbie, 2009; Ramos-Murguialday et al., 2013; Shindo et al., 2011). More recently, combining mu ERD-based BCI rehabilitation with active physical therapy or with functional electrical stimulation may improve the motor abilities of chronic stroke patients (Broetz et al., 2010), revealing the potential therapeutic utility of mu ERD-based BCI rehabilitation.

Transcranial direct current stimulation (tDCS), which involves applying a weak direct current through the scalp, is another candidate for increasing cortical excitability. Anodal tDCS is known to induce long-lasting facilitatory effects (Nitsche & Paulus, 2001), confirmed by changes in the motor evoked potential (MEP; Nitsche & Paulus, 2000, 2001), blood oxygenation level (Baudewig, Nitsche, Paulus, & Frahm, 2001) and regional cerebral blood flow

(Kwon et al., 2008; Lang et al., 2005; Merzagora et al., 2010). These effects of tDCS may have the potential to facilitate the efficacy of mu ERD-based BCI rehabilitation. Matsumoto et al. (2010) actually found that mu ERD by hand motor imagery increased significantly after anodal stimulation. However, the effect of hand dominance on ERD remains unknown. The mechanisms of motor control and learning are different between the dominant and non-dominant hand (Duff & Sainburg, 2007; Schabowsky, Hidler, & Lum, 2007; Yokoi, Hirashima, & Nozaki, 2014). For example, Duff and Sainburg (2007) found that interlimb differences in motor control produce different patterns of adaptation to novel dynamics. Recently, Yokoi et al. (2014) showed interlimb differences in how adaptation to novel dynamics in one arm is influenced by the kinematics of the opposite arm. Thus, the effect of anodal tDCS on the improvement of mu ERD by hand motor imagery might be different between the dominant and the non-dominant hand.

To assess this issue, we asked participants to perform either dominant or non-dominant hand motor imagery before and after anodal tDCS to the corresponding hemisphere and investigated its effect on changes in mu ERD.

METHODS

Participants

This study involved seven right-handed healthy participants (6 males, 1 female; mean age, 25 ± 4 years; age range, 22–31 years). Participants were informed about all aspects of the experiments and all gave informed consent. No participant had a history of neurological disease or was receiving any acute or chronic medication affecting the central nervous system. Handedness was tested using the Edinburgh Handedness Inventory (Oldfield, 1971). Laterality Quotient (LQ), which ranges from −1.0 to +1.0 (+, right-handed; −, left-handed; near 0, ambidextrous), was obtained from each participant. All participants were judged as right-handed, with an LQ range of 0.5–1.0. This study was carried out in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Data recording

EEG signals were recorded from 15 Ag/AgCl disc electrodes (1 cm in diameter) according to the international 10–20 system of electrode placement (FC3, FC1, FCz, FC2, FC4, C3, C1, Cz, C2, C4, CP3, CP1, CPz, CP2, CP4) with the average of left and right earlobe references to cover the motor areas of both hands and occipital area. Using the belly-tendon method, an electromyogram (EMG) was simultaneously recorded from the left and right first dorsal interosseous (FDI) muscles with surface Ag/AgCl disc electrodes (1 cm in

diameter) to confirm EMG activity during imagery tasks and to avoid unexpected muscle contraction. EEGs and EMGs were amplified and digitized (1000 Hz sampling frequency) using a commercially available biosignal recorder (Neurofax EEG-9100, Nihon Kohden Corporation, Japan). Impedance was kept below 10 kΩ during the whole experiment.

Experimental paradigm

The experimental design of the present study was previously established elsewhere (Matsumoto et al., 2010) and also described below.

Experiments took place on four different days, each separated from the preceding one by more than one week for the same participant. On each experimental day, the following paradigm was examined with either left- or right-hand motor imagery, and either anodal or sham stimulation prior to the task. The hand for motor imagery and type of stimulation were randomly chosen for each individual.

Participants sat in an armchair with their eyes open facing a computer monitor placed approximately 0.9 m in front of them at eye level. A trial started with an 8-s resting-state period during which the word "Rest" was shown at the centre of the monitor. After that was a 2-s period during which the word "Ready" was shown. Then, the word "Start" was presented for 5 s, and participants were asked to imagine their hand grasping. The trial ended when the word "Rest" reappeared, and the next trial began after a break of 8 s (Figure 1a). Participants were given no feedback about EEG changes to avoid a learning effect. One session consisted of 20 trials, and four sessions were conducted before and after

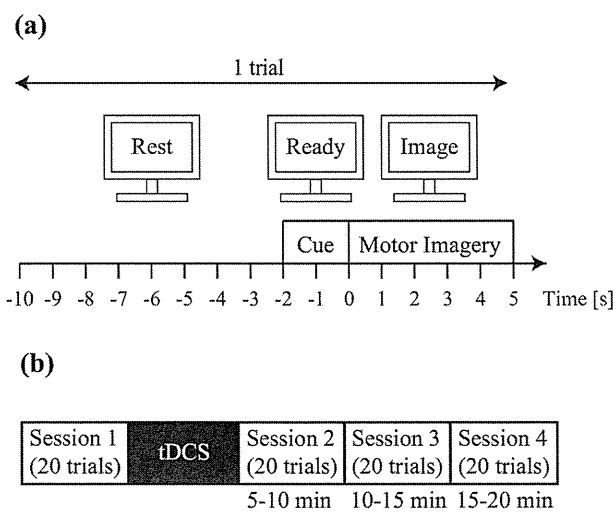

Figure 1. The experimental paradigm used in this study (Redrawn from Matsumoto et al., 2010).

tDCS (Figure 1b). There were breaks for about 5 min between sessions. All four sessions were completed within 30 min.

Transcranial direct current stimulation

Bipolar stimulation was delivered by a battery-driven stimulator (CX-6650, Rolf Schneider Electronics, Gleichen, Germany) through a pair of rectangular water-soaked sponge electrodes (50×70 mm^2). The current intensity was set at 1 mA and the ramp time was set at 5 s, and the stimulation was administered for 10 min. The position of M1 was confirmed through the induction of the largest MEPs in the right FDI muscle with constant stimulus intensity using transcranial magnetic stimulation (TMS) with a figure-eight stimulation coil connected to a Magstim 200 magnetic stimulator (Magstim, Whitland, UK). One electrode was placed over the M1 contralateral to the hand of imagery, and the other was placed over the right supraorbital area.

The stimulation protocol described below was previously established (Matsumoto et al., 2010; Nitsche et al., 2008) and also used in this study. For the sham stimulation, the current was applied for only 10 s to mimic the transient skin sensation at the beginning of actual tDCS without producing any conditioning effects on the brain. Participants were blinded to stimulation condition. For placing the stimulation electrode, three to four EEG electrodes over the stimulus site were removed after marking the scalp. After the tDCS stimulation, the EEG electrodes were set in the same position as before. Impedance was confirmed to be 10 kΩ, similar to the situation prior to tDCS. It took less than 3 min for electrode replacement, and thus the effect of elapsed time after tDCS on ERD measurement was limited.

Quantification of ERD and statistical analysis

Event-related trials 5 s in duration during motor imagery were selected for offline data processing. All trials were visually assessed, and trials with artefacts (resulting from eye movement) as well as trials with increased EMG activity of the right FDI were excluded. All trials were segmented into successive 1-s windows with 900 overlapping samples, and the Fourier spectrum density in each segment was calculated with a Hamming window. The mu ERD was expressed as the percentage power decrease in relation to a 2-s reference interval before the "Ready" instruction. The ERD was calculated for each time point (resolution of 0.1 s) and frequency according to Equation (1):

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

where A is the power spectrum density of the EEG at a certain frequency f [Hz], time t [s] is the duration from the start of the imagery task and R is the power spectrum at the same frequency f [Hz] of the baseline period (a 1-s interval before the "Ready" instruction was displayed). A large positive value indicates a large power decrease during motor imagery compared with that at rest. ERD was calculated in each trial and then averaged over 60 times for pre- and post-tDCS sessions. Only in cases where the ERD time course was assessed after tDCS, ERD was calculated with 20 averages each, and a total of 3 epochs (5–10 min, 10–15 min and 15–20 min after tDCS) were obtained (Figure 1b). The strongest power decrease during motor imagery was selected as the value of mu ERD. Before tDCS application, the values of mu ERD were compared in all adjacent pairs of bipolar derivations of EEG, and then we determined the electrode pair showing the strongest value of mu ERD for each individual. Then, the values of mu ERD in two stimulation conditions (anodal and sham stimulation) were calculated from the same bipolar derivation of EEG. All offline analyses of EEG data were performed using MATLAB (The Mathworks Inc., USA).

A two-way repeated measures analysis of variance (ANOVA; time × hand) was used to compare (1) the mu ERD during imagery with main factors of time (before and 5–10 min, 10–15 min and 15–20 min after tDCS) and side of motor imagery (right and left) and (2) the mu ERD during imagery with main factors of time (before and after sham stimulation) and side of motor imagery (right and left). We could not directly compare (1) with (2) because the number of time points was different between conditions. Therefore, we performed a three-way repeated measures ANOVA (time × hand × condition) using the data before anodal tDCS and data from the average of three time periods after the anodal tDCS, and the data before and after sham stimulation. If statistical analysis yielded a significant F value ($P < 0.05$), a post hoc Bonferroni test was carried out.

RESULTS

None of the participants reported any adverse effects of tDCS during or after the experiments. All participants showed mu ERD over the sensorimotor cortex contralateral to the hand of motor imagery during motor imagery before tDCS. The electrode pairs that showed the strongest mu ERD varied between individuals. Further analysis was performed with the electrode pairs that in each participant showed the strongest mu ERD to assess the effect of anodal stimulation on mu ERD by motor imagery.

Typical examples of the effect of anodal tDCS on EEG power spectrum densities are shown in Figure 2a and b. Averaged EEG power spectrum densities are shown in Figure 2c and d. Mu EEG power increased in both rest and motor imagery periods. The increase was significant in the left hemisphere

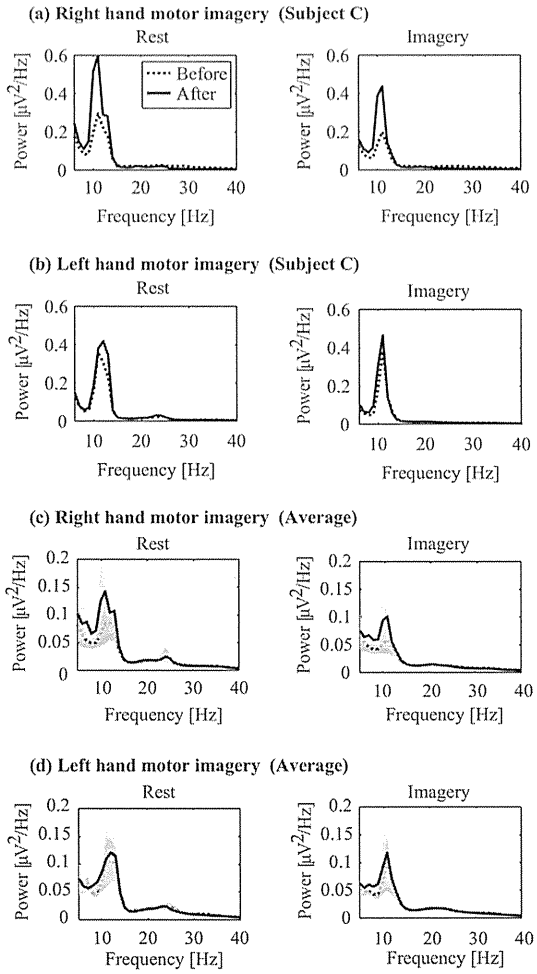

Figure 2. EEG power spectrum densities before and after tDCS during rest or motor imagery periods. (a) Typical examples of EEG power spectrum densities during rest or right-hand motor imagery periods (participant C). The mu EEG power component was increased after tDCS in both rest and motor imagery periods. Dotted lines indicate data before stimulation and solid lines indicate data after stimulation. (b) Typical examples of EEG power spectrum densities during rest or left-hand motor imagery periods (participant C). The mu EEG power component was increased after tDCS in rest periods but was almost unchanged in motor imagery periods. Dotted lines indicate data before stimulation and solid lines indicate data after stimulation. (c) Averaged EEG power spectrum densities during rest or right-hand motor imagery periods across all participants. Dotted lines indicate data before stimulation and solid lines indicate data after stimulation. Shaded areas indicate standard error. (d) Averaged EEG power spectrum densities during rest or left-hand motor imagery periods across all participants. Dotted lines indicate data before stimulation and solid lines indicate data after stimulation. Shaded areas indicate standard error.

during right-hand (dominant) motor imagery (Figure 3). The mean (standard deviation, s.d.) increase of mu EEG was 230.6% (293.2%) in the rest period and 177.1% (196.4%) in the motor imagery period. During left-hand (non-dominant) motor imagery, mu ERD power also increased in both rest and imagery periods in some participants, but their increase in amplitudes were limited. For this reason, the mean (s.d.) of the change of mu EEG among the participants remained almost unchanged: 108% (30.3%) in the rest period and 115.9% (47.1%) in the motor imagery period.

Mu ERD is calculated from the EEG power of the alpha band in the motor imagery period divided by the power during the rest period. To compare the change in Mu ERD before and after stimulation between hands (i.e., right and left) and conditions (i.e., sham and anodal; Figure 4), we performed a three-way repeated measures ANOVA. There was a significant effect of time, $F(1, 48) = 4.98$, $p < 0.05$, and condition, $F(1, 48) = 4.09$, $p < 0.05$. The effect of hand was not significant, $F(1, 48) = 0.39$, $p = 0.53$ (Table 1). A post hoc test indicated that there was a significant difference between conditions in the dominant hand after stimulation ($p < 0.01$; Bonferroni corrected), and a significant difference between before and after tDCS in the anodal stimulation condition in the dominant hand ($p < 0.05$; Bonferroni corrected; Figure 4a). The difference in condition for mu ERD before stimulation was not significant (dominant hand, $p = 0.84$; non-dominant hand, $p = 0.65$; Bonferroni corrected).

Enhancement of mu ERD by anodal tDCS during right-hand (dominant) motor imagery in which the data from three time periods after the tDCS were averaged is shown in Figure 5. Mu ERD following motor imagery was enhanced in all participants. The mean (s.d.) mu ERD value before anodal stimulation was 41.6% (27.5%) and was 58.4% (23.2%) after anodal stimulation. A paired t-test confirmed a significant difference, $t(7) = 3.3$, $p < 0.05$. In the case of left-hand (non-dominant) motor imagery, tDCS also enhanced mu ERD following motor imagery, but the effect was smaller than during dominant hand motor imagery as only 4 of 7 participants showed an increase in ERD. The mean (s.d.) mu ERD value before anodal stimulation was 46.8% (28.3%) and was 49.4% (24.4%) after anodal stimulation; this change was not statistically significant, $t(7) = 0.32$, $p = 0.76$.

When we investigated temporal changes in mu ERD after the stimulation, mu ERD was strongest during right-hand (dominant) motor imagery not immediately, but 15–20 min after anodal stimulation (Figure 5a), and it slowly decayed. A two-way repeated measures ANOVA detected a significant main effect of time, $F(3, 45) = 3.1$, $p < 0.05$, and an interaction effect, $F(3, 45) = 4.8$, $p < 0.01$. There was no effect of hand, $F(1, 45) = 1.9$, $p = 0.18$ (Table 1). A post hoc test showed that there was a significant increase in mu ERD between before and 15–20 min after the stimulation ($p < 0.01$, Bonferroni corrected). Conversely, during left-hand (non-dominant) motor imagery, the time course of mu ERD after tDCS

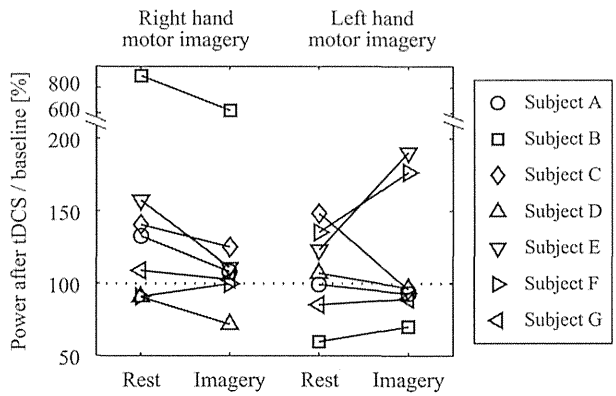

Figure 3. Pooled data of increase in mu EEG by anodal tDCS. A similar increase to that shown in a single case (Figure 2a and b) was also seen.

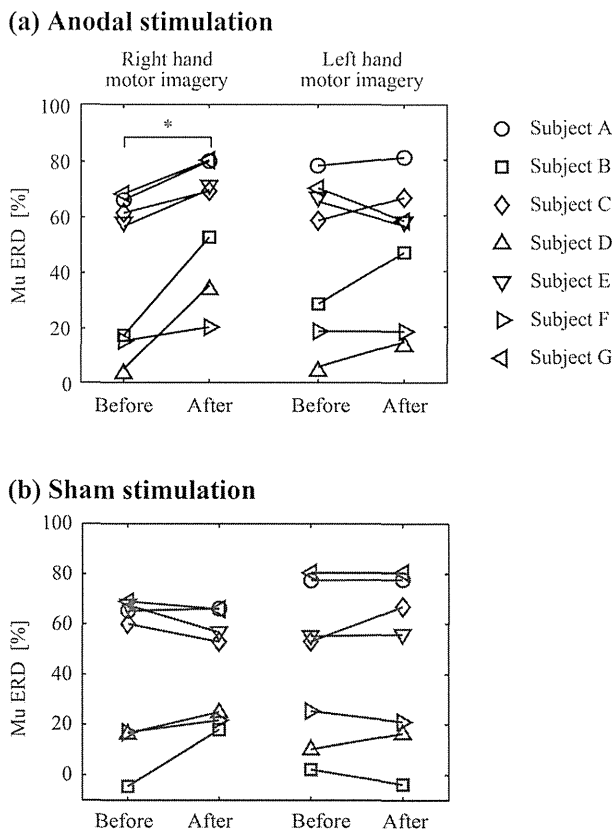

Figure 4. Mu ERD before and after anodal/sham tDCS during right- and left-hand motor imagery. (a) Mu ERD before and after anodal stimulation. (b) Mu ERD before and after sham stimulation. $*p < 0.05$.

TABLE 1
ANOVA

Source of variance	*Sum of squares*	*Degrees of freedom*	*Mean squares*	F	P
A three-way repeated measures ANOVA for two conditions					
Time	408.6327	1	408.6327	4.9799	0.0310
Hand	32.3053	1	32.3053	0.3937	0.5338
Condition	335.3060	1	335.3060	4.0863	0.0496
Time × hand	61.3339	1	61.3339	0.7475	0.3922
Hand × condition	165.4012	1	165.4012	2.0157	0.1631
Time × condition	258.7495	1	258.7495	3.1533	0.0830
Time × hand × condition	506.6890	1	354.1075	4.3154	0.0439
Error	3446.3959	48	82.0570		
Total	5214.8135	55			
A two-way repeated measures ANOVA for anodal stimulation condition when sessions after the stimulation were separately analyzed					
Time	1077.0017	3	359.0006	3.1311	0.0364
Hand	214.1468	1	214.1468	1.8677	0.1796
Time × hand	1644.4477	3	548.1492	4.7808	0.0062
Error	4471.6119	45	114.6567		
Total	7407.2082	52			

varied among the participants, and no common pattern was observed (Figure 5b). The time at which mu ERD peaked was different in each participant.

As mentioned above, anodal tDCS promoted a large mu ERD during right-hand (dominant) motor imagery, but a small mu ERD was observed during left-hand (non-dominant) motor imagery. To account for this, we hypothesized that participants who almost always use their dominant hand in daily life may show this trend the strongest. Therefore, we examined the relationship between degree of handedness (rated using LQ in the Edinburgh Handedness Inventory) and the laterality of ERD (ERD during right-hand (dominant) motor imagery after tDCS *minus* ERD during left-hand (non-dominant) motor imagery after tDCS). Figure 6 shows a positive correlation between LQ and the laterality of tDCS-boosted ERD, $r = 0.72$, $p < 0.05$.

DISCUSSION

Cortical activation can result in phasic changes in the synchrony of cell populations because of externally or internally paced events and produce characteristic EEG patterns. Mu ERD is thought to arise from a decrease in the synchrony of the underlying neuronal population at the frequency of interest (Pfurtscheller & Lopes da Silva, 1999). Consistent with our previous study (Matsumoto et al., 2010), the present study shows that anodal tDCS on M1 increased mu ERD. This might be because of the increase of cortical excitability by anodal stimulation, such as

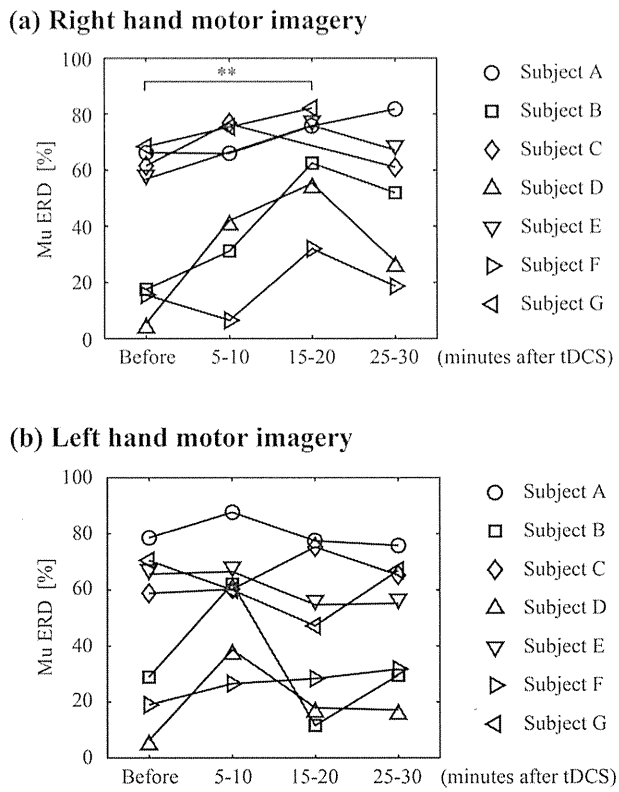

Figure 5. Time course of mu ERD after anodal tDCS. (a) Time course of mu ERD after anodal simulation during right-hand motor imagery. Mu ERD was significantly stronger around 15–20 min after tDCS compared with that before stimulation.**$p < 0.01$. (b) Time course of mu ERD after anodal simulation during left-hand motor imagery. Mu ERD was enhanced immediately after stimulation and rapidly decayed.

modifications of membrane depolarization (Bindman, Lippold, & Redfearn, 1964; Nitsche, Fricke, et al., 2003; Nitsche & Paulus, 2000, 2001; Purpura & McMurtry, 1965; Terzuolo & Bullock, 1956), increases in spontaneous firing rate (Bindman et al., 1964; Purpura & McMurtry, 1965) and other synaptic mechanisms (Nitsche, Nitsche, et al., 2003, Nitsche et al., 2005). These mechanisms may cause changes in the oscillatory activity of cortical neurons according to input signals in response to motor imagery and thus increase mu ERD.

The present study first showed that anodal tDCS promoted a large mu ERD during right-hand (dominant) motor imagery, but not during left-hand (non-dominant) motor imagery. This difference between the dominant and the non-dominant hand in motor control and learning reported in previous studies (Duff & Sainburg, 2007; Schabowsky et al., 2007) is similar to that during motor imagery. Moreover, this trend of the effect of tDCS was more prominent in participants who use their right hand the most in daily life.

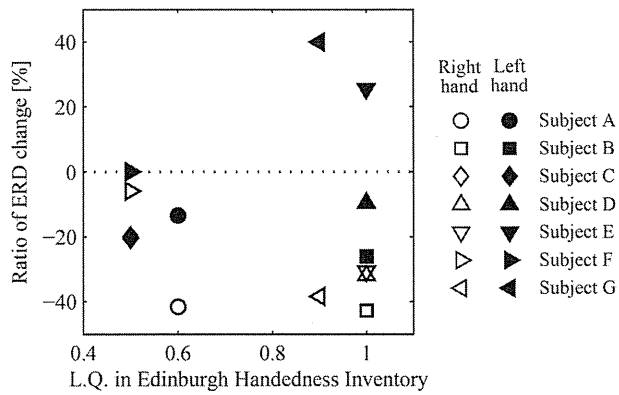

Figure 6. Ratio of change of mu ERD during right- and left-hand motor imagery. Ratio of ERD changes in participants who had low LQ scores was almost the same between right- and left-hand motor imagery. However, ERD ratio changes were different in participants who had high LQ scores.

These findings support our hypothesis that these diminished effects of tDCS on the non-dominant hand are due to lower cortical activity during non-dominant hand motor imagery. Voluntary movement is preceded by increased activity of corticospinal neurons in animal recordings (Evarts, 1966). A comparison between mu ERD and corticospinal excitability measured by TMS in reaction time paradigms demonstrates that mu ERD may be associated with contralateral corticospinal facilitation and ipsilateral corticospinal inhibition (Leocani, Toro, Zhuang, Gerloff, & Hallett, 2001). Thus, the varying degree of mu ERD change could conceivably reflect differences in the density, excitability or synaptic efficacy of these corticospinal efferents. In right-handed people, the threshold for activation of muscles in the right arm was lower than that of corresponding muscles in the left arm (Triggs, Calvanio, Macdonell, Cros, & Chiappa, 1994), and in particular, consistency of hand preference is associated with lateralized differences in the excitability of motor system projections activated by TMS (Macdonell et al., 1991; Triggs et al., 1994). Moreover, the upstream brain regions of the primary sensorimotor cortex, associated with motor planning, also shows hemispheric asymmetry (Sabaté, González, & Rodríguez, 2004). Therefore, the difference in the tDCS effect might be associated with asymmetries of excitability in the corticospinal tract. A smaller increase in the excitability of the corticospinal tract descending to the left-hand (non-dominant) muscle might be induced by tDCS during left-hand (non-dominant) imagery, because motor imagery may fail to activate a large number of neurons with high motor thresholds. However, because we did not check cortical excitability in this experiment, using TMS for example, we cannot strongly conclude this. Considering evidence that there are hemispheric differences in sensitivity to tDCS (Schade, Moliadze, Paulus, & Antal, 2012), it is also possible that the hand