Title: Neurofeedback control of the human GABAergic system using non-invasive brain stimulation

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Abbreviation:

aMT: active motor threshold, APB: abductor pollicis brevis, cRT: choice reaction time, EEG: electroencephalography, EMG: electromyography, FDI: first dorsal interosseous, fNIRS: functional near-infrared spectroscopy, ISI: interstimulus interval, M1: primary motor cortex, MEP: motor evoked potential, SICI: short intracortical inhibition, TMS: transcranial magnetic stimulation

Abstract

Neurofeedback has been a powerful method for self-regulating brain activities to elicit potential ability of human mind. GABA is a major inhibitory neurotransmitter in the central nervous system. Transcranial magnetic stimulation (TMS) is a tool that can evaluate the GABAergic system within the primary motor cortex (M1) using paired-pulse stimuli, short intracortical inhibition (SICI). Herein we investigated whether neurofeedback learning using SICI enabled us to control the GABAergic system within the M1 area. Forty-five healthy subjects were randomly divided into two groups: those receiving SICI neurofeedback learning or those receiving no neurofeedback (control) learning. During both learning periods, subjects made attempts to change the size of a circle, which was altered according to the degree of SICI in the SICI neurofeedback learning group, and which was altered independent of the degree of SICI in the control learning group. Results demonstrated that the SICI neurofeedback learning group showed a significant enhancement in SICI. Moreover, this group showed a significant reduction in choice reaction time compared to the control group. Our findings indicate that humans can intrinsically control the intracortical GABAergic system within M1 and can thus improve motor behaviors by SICI neurofeedback learning. SICI neurofeedback learning is a novel and promising approach to control our neural system and potentially represents a new therapy for patients with abnormal motor symptoms caused by CNS disorders.

Keywords: Learning, neurofeedback, GABAergic neuron, intracortical inhibition, transcranial magnetic stimulation

Introduction

The brain functions on the balance between excitatory and inhibitory activities. Due to inhibitory neurotransmittesr, such as GABA, neuronal hyper-excitation is prevented and neuronal networks are therefore stabilized in the central nervous system (Cardinali and Golombek, 1998; Hines et al., 2012; Zemankovics et al., 2013).

The intracortical inhibitory system in human primary motor cortex (M1) can be evaluated by short intracortical inhibition (SICI) using paired-pulse transcranial magnetic stimulation (TMS) which a subthreshold conditioning stimulus is followed by a suprathreshold test stimulus at an interstimulus interval of 1–6 ms (Kujirai et al., 1993; Ziemann et al., 1996a; Ilic et al., 2002). The SICI represents post-synaptic inhibition mediated by $GABA_A$ receptors (Ziemann et al., 1996b; Di Lazzaro et al., 2007). Inhibitory neuronal systems in M1 play an important role in temporally and spatially accurate motor executions and inhibitions (Liepert et al., 1998; Schneider et al., 2002; Sohn et al., 2002; Sohn et al., 2003; Stinear and Byblow, 2003b, a; Buccolieri et al., 2004; Sugawara et al., 2012; Capaday et al., 2013). Volitional suppression of finger movements during the No go task accompanied the globally enhanced SICI (Sohn et al., 2002). Increased SICI enabled a clear temporal resolution of specific activity by suppressing undesirable activities of muscles at the appropriate timing during voluntary finger movements (Stinear and Byblow, 2003b). Imagery of motion suppression also modulates corticospinal excitability and membrane excitability (Sohn et al., 2003; Stinear and Byblow, 2003a). In a process of skill learning, inhibitory networks are also modulated. Repetitive task of the finger movements with specific muscle activation induced an enhancement of SICI of the non-targeted muscle in M1

(Liepert et al., 1998; Sugawara et al., 2012). While those previous studies showed SICI modulation related to motor task, it has not been clarified whether a SICI enhancement could be induced by mental strategy independent on motor task and it could improve our motor behavior.

Recently, neurofeedback has served as a powerful method for self-regulating brain activities. Subjects can learn to regulate a targeted brain activity based on real-time information provided by electroencephalography (EEG) recordings (Tan et al., 2009; Arani et al., 2010; Arnold et al., 2013; Ogrim and Hestad, 2013; Sreedharan et al., 2013; Zotev et al., 2014), fMRI (Weiskopf, 2012; Stoeckel et al., 2014; Zotev et al., 2014), and functional Near-infrared Spectroscopy (fNIRS) (Naseer and Hong, 2015; Thibault et al., 2015). The neural mechanism of neurofeedback has been proposed to involve operant conditioning and reinforcement learning (Gruzelier and Egner, 2005; Levesque et al., 2006; Ros et al., 2013). This can result in the ability to alter related behavior and cognitive function to a targeted brain activity (Keizer et al., 2010; Zoefel et al., 2011; Ros et al., 2013; Stoeckel et al., 2014).

As far as we know, there is only one report of neurofeedback method using TMS (Majid et al., 2015). They reported that the subjects could establish an effective mental strategy to reduce MEP amplitudes of a specific finger muscle by a neurofeedback using TMS, suggesting that the mental strategies acquired in the neurofeedback may help inhibitory control to suppress movement (Majid et al., 2015). We considered that it may also be an effective method to enhance inhibitory motor control if mental strategies to enhance SICI could be established by neurofeedback.

Deficits in the GABAergic system are associated with various motor and cognitive disorders such as Huntington disease (Pinborg et al., 2001), primary dystonia (Garibotto et al., 2011), ischemic stroke (Heiss et al., 2004), vascular parkinsonism (Ihara et al., 2007), epilepsy (Galanopoulou, 2010), schizophrenia (Lewis et al., 2005), autism (Fatemi et al., 2009) and major depressive disorder (Luscher and Shen, 2011; Luscher et al., 2011a). However, pharmacological therapies to extrinsically enhance or reduce the GABAergic system are not always sufficient in ameliorating symptoms (Doggett, 2004; Kalia et al., 2013; Frank, 2014; Pilleri and Antonini, 2015; Walker et al., 2015). Approaches that target GABAergic neurons still have therapeutic potential (Rudolph and Mohler, 2014; Braat and Kooy, 2015).

Herein we investigated whether intrinsic learning could be used to self-regulate a GABAergic system within M1 by neurofeedback learning based on SICI in healthy subjects. We hypothesized that neurofeedback learning to enhance SICI would be possible by an effective mental strategy and that it would enable us to improve our motor performance to require selective activation and inhibition of finger muscles. The main outcome measure was the degrees of SICI, and the secondary measures were corticospinal excitability, and basic motor behaviors such as choice reaction time and pinch force.

Experimental Procedures

Subjects

Forty-six healthy subjects were recruited in the study using the Web advertisement of Kyoto University (URL: http://www.s-coop.net/service/arbeit/). Inclusion criteria was no history of chronic or acute neurological, psychiatric, or medical diseases; no family history of epilepsy; no present pregnancy; no cardiac pacemaker; no previous surgery involving implants (aneurysm clips and brain or spinal electrodes), and absence of acute or chronic medication or drug intake according to safety guidelines of TMS (Wassermann, 1998; Rossi et al., 2009). Based on the consideration of inclusion criteria, one volunteer was excluded and only 45 healthy individuals (fifteen women and 30 men) aged 20–40 years [mean ± standard deviation (SD), 24.2 ± 4.9 years] participated in the study. The sample size was determined for detecting the effect of neurofeedback learning according to the previous reports (Ogrim and Hestad, 2013, n = 32, effect size, d = 1.1; Sokhadze et al., 2014, n = 42, *partial eta squared* = 0.11). All subjects were right-handed in accordance with the Edinburgh Handedness Inventory (Oldfield, 1971). The study protocol was accepted by the Committee of Medical Ethics of the Graduate School of Medicine, Kyoto University, Japan (No. 267). Written informed consent was obtained from all participants.

Preparation

Electromyographic (EMG) data were collected from the left first dorsal interosseous (FDI) and the left abductor pollicis brevis (APB) muscles via a pair of 12 mm diameter silver electrodes. EMG signals were amplified, bandpass-filtered at 5–1000 Hz, and sampled at a rate of 10 kHz by the Map1496 system and software (Nihon-

Santeku Co., Osaka, Japan). We selected the right M1 hand area of the non-dominant hemisphere as a target site of neurofeedback learning. Due to dexterity, it is expected that the non-dominant hand might have room for motor learning and functional enhancement (Waldron and Anton, 1995). There are functional differences between both hemispheres in motor control. The motor processing of the right hemisphere is rather mediated by sensory information representing an external environment, whereas that of the left hemisphere is guided by internal motor representations (Serrien et al., 2006). We considered that the right M1 might be more easily modulated by the external feedback signal.

Subjects were comfortably seated in an armchair. TMS was given using a flat and figure-of-eight magnetic coil (outer diameter of each wing, 9 cm). Magstim 200 magnetic stimulator (maximum output intensity 2.0 T; Magstim, Whitland, Dyfed, UK) was used to stimulate M1. The coil was held tangentially to the scalp with the handle pointing backwards and at 45° lateral away from the midline for the induced current to flow in a posterior to anterior direction. The optimal scalp positions for the induction of the motor response for the left FDI muscle were determined for each subject.

Active motor threshold (aMT) was defined as the minimal stimulus intensity required to produce motor evoked potentials (MEPs) with a peak-to-peak amplitude of >150 μV in 5 of 10 consecutive trials in tonically contracting muscles at approximately 20% of the maximum voluntary contraction by using online EMG monitoring (Rossini et al., 1994; Rossini et al., 2015).

To assess corticospinal excitability, amplitudes of MEPs were measured with a fixed intensity to elicit approximately 1 mV of peak-to-peak amplitudes (stimulus

intensity, SI_{1mV}) from both the left FDI and APB muscles during rest. The peak-to-peak amplitudes of MEPs were measured and averaged for each subject.

The M1 intracortical inhibitory system was assessed by MEP amplitudes from the left FDI muscle evoked by paired-pulse TMS. The paired-pulse TMS comprised of a conditioning stimulus with an intensity of 70% aMT followed by a test stimulus with SI_{1mV} with ISI of 3 ms (SICI3). The extent of intracortical inhibition was determined by the ratio of the amplitudes of paired test stimuli with conditioned stimuli to the amplitudes of unpaired test stimuli (SICI ratios) (Chen, 2004). SICI ratios decrease in a correlation with increase of the conditioning stimulus intensity within a certain range and reach the plateau (Kujirai et al., 1993; Fisher et al., 2002; Rossini et al., 2015). Then, we chose 70% aMT as a conditioning stimulus intensity, which produced weak inhibition (approximately 0.8 SICI ratio) so that we could detect any enhancement of inhibitory activities by avoiding the flooring effect according to the previous study (Stinear and Byblow, 2003b).

We performed continuous monitoring whether muscles were completely relaxed by visual feedback of the EMG recordings.

Interventional protocols: Neurofeedback of SICI3

Twenty-three subjects participated in the neurofeedback sessions (Neurofeedback-SICI). The remaining twenty-two participated in the control sessions (control).

The paired-pulse TMS were each given with an interval of 5–7 s. A circle was displayed on a 20-inch monitor placed 70 cm (40° horizontal and vertical visual angles) in front of the subject. In Neurofeedback-SICI, the size of the circle was changed according to the ratio of a current conditioned MEP amplitude to the average of

consecutive 5 conditioned MEP amplitudes including a current one (a conditioned MEP amplitude = an MEP amplitude produced by test stimulus 3 ms following conditioned stimulus, Neurofeedback-SICI; Figure 1) using a Visual Basic program (Microsoft Visual Basic.NET). The conditioned MEP amplitude was measured from the left FDI muscle. For the first 5 paired stimuli, the size of the circle was fixed with 800 pixels of the initial diameter (D_5). After sixth paired stimuli were given, the size of the circle was changed following the rule described below.

$$m_k = \frac{1}{5}\sum_{i=k-4}^{k} x_i$$

$$D_k = D_{k-1} \times x_k / m_k \ \ (\mathrm{k} \geq 6)\ ,\ D_5 = 800 \text{ (pixel)}$$

, where x_k is the MEP amplitude produced by the *k* th paired pulse stimuli, m_k is the average of a series of 5 MEP amplitudes ($x_{k-4}, x_{k-3}, \ldots, x_k$) and D_k is the diameter of the circle seen on the monitor after the *k* th paired pulse stimuli are given. If the background raw EMG activity had exceeded 20 μV at any point within 50 msec before paired-pulse stimuli, the MEP amplitude was excluded from the above calculation (the size of the circle was not changed) and subjects were asked to be relaxed because SICI was reduced during muscle activation (Zoghi et al., 2003). In control, the size of the circle was changed according to the surrogate data in Neurofeedback-SICI session previously performed by a different subject. Delay of the feedback was within 40 ms after the paired-pulse stimuli occurred. Neurofeedback-SICI or control lasted for 10 min and was repeated twice with a 10-min intermission. We did not measure non-conditioned test MEPs during both of the Neurofeedback-SICI and the control interventions due to a limitation of the program to produce a circle on the monitor.

During the intervention, the subjects were instructed to attempt to decrease the size of the circle on the monitor. They were not informed about the meaning of the size of the circle to avoid them from trying to respond to particular expectations of the experimenter.

Experimental paradigm

To investigate whether subjects could regulate the GABAergic system within M1, we evaluated the averaged 10 SICI ratios of the left FDI muscle in the following two conditions: intentional and non-intentional states. In the intentional state, a subject was asked to recall the intervention and attempt to decrease the size of the circle without seeing any circle on the monitor. In the non-intentional state, a subject was asked to rest without any efforts. For evaluating other electrophysiological parameters, we measured amplitudes of 10 MEPs with SI_{1mV} of the left FDI and APB muscles in the non-intentional state. In addition, to test whether the possible effects of neurofeedback may be generalized to other body parts, we measured the averaged 10 SICI ratios of the right FDI muscle and 10 MEPs with SI_{1mV} of the left FDI and APB muscles in the intentional state in 27 of the 45 subjects (Neurofeedback-SICI group: n=14, control group: n=13).

To evaluate basic motor behavior, we measured choice reaction times (cRTs) as a selective motor task and pinch force. For cRTs, subjects had to select one of two button and press it by using their right or left index finger according to the right and left arrows as promptly and accurately as they could. Subsequent to practice trials, data from 32 trials were gathered from each subject. The mean cRTs of the left and right fingers were calculated. Incorrect responses were excluded. The pinch force of the left

hand was assessed via a force transducer (range, 0–20 kg; diameter of contact surface area, 2 cm).

We performed the evaluation before, immediately after, and 30 min after either Neurofeedback-SICI or control (designated as the pre, post0, and post1 conditions, respectively), which took approximately 15 min. Each measurement was conducted in a random order (Figure 2).

Statistical analysis

The SICI ratios and the MEP amplitudes were subjected to a two-way repeated-measures ANOVA with Time (pre, post0 and post1) × Intervention (Neurofeedback-SICI and control) as factors in the intentional and non-intentional states.

The cRT and pinch force data were subjected to repeated-measures ANOVA with Time (pre, post0 and post1) × Intervention (Neurofeedback-SICI and control) as a factor.

To investigate whether there was a correlation between changes of SICI and cRT, correlation coefficients were calculated in the post0 and the post1 conditions.

The Greenhouse–Geisser correction was used to fit for sphericity by changing the degrees of freedom using the correction coefficient epsilon if it is appropriate. The *post hoc* t-test was performed with Bonferroni correction for multiple comparisons. A significance level of $p < 0.05$ was adopted for all comparisons. All data are represented as the mean ± SD unless otherwise indicated.

Results

None of the subjects experienced side effects while participating in the experiments. AMTs, other TMS parameters and the baseline data for the Neurofeedback-SICI and control groups were represented in Table. There were no significant differences between the Neurofeedback-SICI and control groups. Recording of cRT was stopped in the middle of the experiment because of the program error in four subjects. We analyzed the cRT data of the 41 subjects (Neurofeedback-SICI, n = 21; control, n = 20).

Effects of Neurofeedback-SICI on the GABAergic system within M1

Figure 3 presented the change ratio of the circle size to the initial circle size during the Neurofeedback-SICI learning in one subject. The presented size was fluctuating but gradually reduced in the learning process.

The SICI ratios from the Neurofeedback-SICI group were significantly decreased in the intentional state compared to those from the control group. Repeated-measures ANOVA showed significant differences in the SICI ratios for the left FDI muscle in the intentional state ('Time', $F_{2, 86} = 3.75$, $p = 0.027$, eta-squared 0.063, 'Intervention', $F_{1, 43} = 11.41$, $p = 0.0016$, eta-squared 0.095, 'Time' × 'Intervention' interaction, $F_{2, 86} = 7.59$, $p = 0.0009$, eta-squared 0.126). The *post hoc* t-test revealed a significant decrease of SICI ratios immediately and 30 min after Neurofeedback-SICI compared to control (Neurofeedback-SICI vs. control; *post hoc* t-test, post0, $p = 0.0033$, $t = -3.00$, $d = 0.74$ and post1, $p < 0.0001$, $t = -4.40$, $d = 1.35$; Figure 4a). No significant differences were found in the non-intentional state ('Time', $F_{2, 86} = 1.53$, $p = 0.223$, eta-squared 0.033, 'Intervention', $F_{1, 43} = 0.80$, $p = 0.375$, eta-squared 0.009, 'Time' × 'Intervention' interaction, $F_{2, 86} = 1{,}12$, $p = 0.332$, eta-squared 0.024; Figure 4b).

No significant differences in the SICI ratios of the right FDI muscles and in the MEP amplitudes with SI_{1mV} of the left FDI and APB muscles were observed between the Neurofeedback-SICI and control groups in both of the non-intentional and the intentional states (the SICI ratios of the right FDI muscles, non-intentional, 'Time', $F_{2, 50} = 0.669$, $p = 0.517$, eta-squared 0.023, 'Intervention', $F_{1, 25} = 3.83$, $p = 0.062$, eta-squared 0.066, 'Time × Intervention interaction', $F_{2, 50} = 1.41$ $p = 0.254$, eta-squared 0.049; intentional, 'Time', $F_{2, 50} = 0.241$, $p = 0.786$, eta-squared 0.009, 'Intervention', $F_{1, 25} = 0.219$, $p = 0.644$, eta-squared 0.004, 'Time' × 'Intervention' interaction, $F_{2, 50} = 0.673$, $p = 0.515$, eta-squared 0.026; the MEP amplitudes with SI_{1mV} of the left FDI muscles, non-intentional, 'Time', $F_{2, 86} = 0.604$, $p = 0.549$, eta-squared 0.014, 'Intervention', $F_{1, 43} = 0.081$, $p = 0.777$, eta-squared 0.0009, 'Time' × 'Intervention' interaction, $F_{2, 86} = 0.052$, $p = 0.950$, eta-squared 0.001; intentional, 'Time', $F_{2, 50} = 0.912$, $p = 0.408$, eta-squared 0.035, 'Intervention', $F_{1, 25} = 0.407$, $p = 0.529$, eta-squared 0.008, 'Time' × 'Intervention' interaction, $F_{2, 50} = 0.036$, $p = 0.965$, eta-squared 0.001; the left APB muscles, non-intentional, 'Time', $F_{2, 86} = 0.148$, $p = 0.863$, eta-squared 0.003, 'Intervention', $F_{1, 43} = 1.370$, $p = 0.248$, eta-squared 0.015, 'Time' × 'Intervention' interaction, $F_{2, 86} = 0.970$, $p = 0.383$, eta-squared 0.022; intentional, 'Time', $F_{2, 50} = 2.97$, $p = 0.061$, eta-squared 0.106, 'Intervention', $F_{1, 25} = 0.074$, $p = 0.788$, eta-squared 0.001, 'Time' × 'Intervention' interaction, $F_{2, 50} = 0.020$, $p = 0.980$, eta-squared 0.0007).

Effects of Neurofeedback-SICI on basic motor behavior

Selective motor behavior of the left hand, as measured by the cRT task, was improved in the Neurofeedback-SICI group compared to that in the control group.

Repeated-measures ANOVA with 'Time' × 'Intervention' interaction showed that the intervention type had a significant effect on cRTs in the left hand, with *post hoc* analyses revealing that cRTs were significantly shorter 30 min after Neurofeedback-SICI compared with those after control ($F_{2, 78} = 6.24$, $p = 0.0031$, eta-squared 0.136, *post hoc* t-test, post0, $p = 0.324$, $t = -0.996$, $d = 0.31$ and post1, $p = 0.039$, $t = -2.12$, $d = 0.68$; Figure 5a). There were no significant effects of both of 'Time' and 'Intervention ('Time', $F_{2, 78} = 0.224$, $p = 0.800$, eta-squared 0.005, 'Intervention', $F_{1, 39} = 1.02$, $p = 0.320$, eta-squared 0.011). No significant difference was observed in cRTs of the right hand between the Neurofeedback-SICI and control groups ('Time', $F_{2, 78} = 0.265$, $p = 0.768$, eta-squared 0.012, 'Intervention', $F_{1, 39} = 0.016$, $p = 0.900$, eta-squared 0.0004, 'Time' × 'Intervention' interaction, $F_{2, 78} = 1.56$, $p = 0.216$, eta-squared 0.073). In the pinch forces, there were no significant differences ('Time', $F_{2, 86} = 0.130$, $p = 0.878$, eta-squared 0.003, 'Intervention', $F_{1, 43} = 0.137$, $p = 0.713$, eta-squared 0.002, 'Time' × 'Intervention' interaction, $F_{2, 86} = 0.582$, $p = 0.561$, eta-squared 0.013; Figure 5b).

The changes of SICIs were not significantly correlated with those of cRT after Neurofeedback-SICI (post0, $r = 0.068$, $p = 0.770$; post1, $r = 0.137$, $p = 0.549$).

Discussion

We found that the neurofeedback of SICI enabled subjects to intentionally control SICI-related neural circuits within the M1 area. After Neurofeedback-SICI, the subjects could decrease SICI ratios when they intended to. Since previous studies suggested that SICI was mediated by post-synaptic $GABA_A$ receptors based on the time-course of inhibition (McCormick, 1989; Davies et al., 1990; Kujirai et al., 1993; Kang et al., 1994; Hanajima et al., 1998; Deisz, 1999) and pharmacological interventions (Ziemann et al., 1996b, c), it is likely that the GABAergic system within M1 was self-regulated by learning with Neurofeedback-SICI. Furthermore, cRT was shortened in the left hand targeted by the neurofeedback learning, not in the non-targeted right hand, after Neurofeedback-SICI compared with that after control. It supported the modulation of inhibition-related basic motor behavior as well as physiological parameters, such as SICI.

As far as we know, there is only one report of the TMS neurofeedback study showing that it was possible to establish mental strategies to reduce corticospinal excitability of a specific finger muscle (Majid et al., 2015). While they suggested that those mental strategies might be useful in a situation to demand selective motor inhibition, they did not investigate thier effects on selective motor behavior (Majid et al., 2015). In the present study, we have shown that mental strategies to enhance SICI by the Neurofeedback-SICI enabled the subjects to improve selection movements in the cRT task.

Inhibitory neuronal systems represented by SICI play an important role in shaping M1 output function such as movement inhibition and specific finger movements with inactivation of unrelated finger muscles (Liepert et al., 1998;

Schneider et al., 2002; Sohn et al., 2002; Sohn et al., 2003; Stinear and Byblow, 2003b, a; Buccolieri et al., 2004; Marneweck et al., 2011; Sugawara et al., 2012; Capaday et al., 2013). The SICI was modulated in the motor selection, inhibition and learning (Liepert et al., 1998; Sohn et al., 2002; Stinear and Byblow, 2003b; Sugawara et al., 2012). While the previous studies reported SICI modulation during specific movements or inhibition, the present study showed that increased SICI could improve movement selection by a mental strategy without actual action of movements nor inhibition. Since the change degree of SICIs did not linearly correlated with that of cRTs, the SICI and motion selectivity might not be directly connected.

We measured the aMTs of the right FDI muscle in 27 of the 45 subjects. Although they seemed to have relatively high aMTs of the right FDI muscles, we found no significant difference of aMTs between the right and left FDI muscles in those 27 subjects. We confirmed that their results (n = 27) were similar to the main results (n = 45).

The proposed mechanisms of neurofeedback effects may be reward-based learning through cortical-basal ganglia brain networks (Birbaumer et al., 2013; Thibault et al., 2015). The previous reports that dopaminergic neurons encode a prediction error in a process of instrumental conditioning which is learning a relationship between a stimulus, an action and a reinforcer determining the action (Romo and Schultz, 1990; Ljungberg et al., 1992; Schultz, 2000). An unpredicted reward following a certain action activates dopaminergic neurons and induced plasticity to enhance a neuronal network involved in the action which brought a reward (Schultz, 2000). Learning is established by induction of plasticity to strength neuronal circuits due to concurrent pre- and post-synaptic activation and a release of dopamine (Ashby et al., 2010; Sitaram et

al., 2017). Metanalysis of fMRI neurofeedback studies showed several cortices including PFC and basal ganglia were activated during the learning process (Emmert et al., 2016). In animal studies, cortico-striatal neuroplasticity was essential for the feedback learning (Koralek et al., 2012). In the present study, the feedback of SICI ratios might have functioned as an instrumental conditioning, where obtaining a smaller size circle was recognized as a reward. Striatal dopaminergic activities with a success trial might have induced neural plasticity specific for the GABAergic inhibitory system within M1 and the successful mental strategy might have been strengthened to produce a smaller size circle.

We found that cRTs improved in the left hand following Neurofeedback-SICI. The behavior of choice has been found to be produced through attenuating inhibitory inputs to activated output neurons and exerting the surround inhibition of non-related neuronal activities in M1 (Reynolds and Ashby, 1999; Meynier et al., 2009; Razak and Fuzessery, 2009; van den Wildenberg et al., 2010). Shortening motor response time was due to two functionally opposing mechanisms, increase of both corticospinal excitability to prepare fast responses and intracortical inhibition of M1 to prevent premature responses (Cohen et al., 2010; Fujiyama et al., 2012). In this regard, the shortening of cRTs may be related to the enhanced GABAergic activities within the right M1 area. Furthermore, Neurofeedback-SICI for the left hand had an effect on the selective behavior specific for the left hand, not generalized to the right hand. The specificity might have some advantage if it is applied to treatment of focal motor deficits limited to one side of the body.

Meanwhile, the improvement in cRT was not correlated with the degree of increase in SICI in the present study. A previous report showed the positive correlation

between SICI ratios during a preparatory period and shortening reaction time of the Go task in older subjects, not in younger subjects who had shown the elevated level of corticospinal excitability all the timepoints (Fujiyama et al., 2012). In the present study, SICI modulation seemed state-dependent. The SICI changes might have been correlated during a preparatory period of the cRT task although we did not measure it. Furthermore, subjects in the present study were in relatively young-age and it might have made it more difficult to find a correlation. Neurofeedback learning was not always associated with behavioral modification (Fetz, 2007; Sitaram et al., 2017). It might have exerted independent effects on the inhibitory neuronal activity and selective movements in which they get engaged. A further investigation would be needed about whether post-SICI was changed during a motor selection task after the Neurofeedback-SICI learning.

The inner-thought situations are important in demonstrating the effects of Neurofeedback-SICI. The subjects were only able to enhance GABAergic function when they intended to, with no significant changes observed in a mere rest when they did not intend to. Similarly, during the cRT task, they were able to improve their performance likely due to enhancing the GABAergic inhibitory system. Neural plasticity based on neurofeedback learning has been shown to be both selective and specific (Sur and Rubenstein, 2005). In specific situations that demand activation of inhibitory neurons, subjects might have enhanced their GABAergic inhibitory neurons in M1. State-dependency was reported in artificially induced changes of brain activity, which could be potentiation or depression according to activity of the target brain area (Silvanto and Pascual-Leone, 2008; Dayan et al., 2013). The effect of the SICI feedback learning might be determined not only by individual mental strategies but

also by underlying M1 activity in the state to demand inhibitory neuronal networks or not. Therefore, the Neurofeedback-SICI might have enabled a state-dependent control of GABAergic function.

Dysfunction of the $GABA_A$ receptor in the motor cortical areas has been found in patients with primary dystonia, suggesting that the disinhibition of neurons produces dystonic movements (Garibotto et al., 2011). In vascular Parkinsonism, the reduction of GABAergic receptors in the striatum is associated with gait disturbance (Ihara et al., 2007), whereas in Huntington's disease, the reduction of GABAergic receptors is also observed in the striatum and inversely correlated with clinical state (Pinborg et al., 2001). A mutation of GABA receptors is related to epileptogenesis and seizure occurrence due to hyperexcitation (Galanopoulou, 2010). Pathological alterations in GABAergic tonic inhibition following stroke are related to functional recovery (Heiss et al., 2004; Hines et al., 2012). During a development period, $GABA_A$ receptor-mediated transmission has been linked to some neurodevelopmental disorders such as autism (Fatemi et al., 2009). Adult-onset psychiatric diseases, including schizophrenia and depression, are also caused by the improper formation of GABAergic neuronal circuits (Lewis et al., 2005; Luscher and Shen, 2011; Luscher et al., 2011a; Marin, 2012). GABAergic transmission regulates neuronal plasticity by setting the inhibitory–excitatory balance in neuronal networks (Marsden et al., 2007; Luscher et al., 2011b). The Neurofeedback-SICI method would therefore represent a possible treatment method for the above-mentioned neurological and psychiatric disorders.

The neurofeedback using TMS has some advantages, compared with those of other neuroimaging techniques such as EEG, MEG, fMRI and fNIRS. It has relatively high spatial and temporal resolutions and needs just a simple and inexpensive setting

without complicated calculation of recorded data. The spatial resolution of TMS with a figure-eight coil can be around a few millimeters (Bolognini and Ro, 2010), while those of EEG, MEG and fNIRS are lower, around 5 cm^2 (Nunez et al., 1994), 10 mm^2 (Hari et al., 1988) and 1 cm^2 (Quaresima et al., 2012), respectively. Then, it could accurately reflect the right M1 activity without mixed activities of other cortices. The temporal resolution of a single-pulse TMS is around a few milliseconds (Bolognini and Ro, 2010), while those of fMRI and fNIRS are lower, around 5 seconds (Shmuel et al., 2007) and 0.1 – 1 second (Quaresima et al., 2012), respectively. Then, the online targeted activity could be immediately represented to the subjects in the Neurofeedback-SICI. Neurofeedback using other neuroimaging techniques needs complicated experimental settings for real-time analysis, decoding data and representing the feedback signal. The EEG and MEG data need transformation into frequency domain, decomposition into a specific frequency and feature extraction such as coherence and power spectral density (Sitaram et al., 2017). Meanwhile, the Neurofeedback-SICI needs a simple calculation of peak-to-peak amplitudes and transformation to size of a circle on the monitor. This neurofeedback technique might be easier to apply to a clinical practice. The disadvantages of the Neurofeedback-SICI are high intra-subject variability (Rossini et al., 2015) and inability to control network activities in broad and distant brain areas unlike other neuroimaging techniques (Sitaram et al., 2017). It needs a rather complicated preparation to determine stimulation parameters such as relatively weak intensity of conditioned stimulus and a number of stimuli to reduce variability. In order to monitor a network activity, other neuroimaging technique would be still necessary.

Previous neurofeedback studies were difficult to prove the physiological link between the regulation of neurofeedback signal and brain neurophysiological activities (Thibault et al., 2015). In our study however, the signal from Neurofeedback-SICI was based on physiological activities of inhibitory networks in M1, particularly related to $GABA_A$ function. Furthermore, if the state-dependent control of the GABAergic system would be possible by neurofeedback learning, it would represent a more feasible approach in patients than a pharmacological approach. Neurofeedback-SICI would therefore be clinically applicable and serve as an alternative or additional treatment.

To our knowledge, this is the first report where a new neurofeedback method targeting the GABAergic system within M1 has been developed. It represents a promising method for ameliorating abnormal positive symptoms caused by the dysfunction of inhibitory neural networks in both neurological and psychiatric patients.

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References

Arani FD, Rostami R, Nostratabadi M (2010) Effectiveness of neurofeedback training as a treatment for opioid-dependent patients. Clin EEG Neurosci 41:170-177.

Arnold LE, Lofthouse N, Hersch S, Pan X, Hurt E, Bates B, Kassouf K, Moone S, Grantier C (2013) EEG Neurofeedback for ADHD: Double-Blind Sham-Controlled Randomized Pilot Feasibility Trial. Journal of Attention Disorders 17:410-419.

Ashby FG, Turner BO, Horvitz JC (2010) Cortical and basal ganglia contributions to habit learning and automaticity. Trends in cognitive sciences 14:208-215.

Birbaumer N, Ruiz S, Sitaram R (2013) Learned regulation of brain metabolism. Trends Cogn Sci 17:295-302.

Bolognini N, Ro T (2010) Transcranial Magnetic Stimulation: Disrupting Neural Activity to Alter and Assess Brain Function. The Journal of Neuroscience 30:9647-9650.

Braat S, Kooy RF (2015) The GABAA Receptor as a Therapeutic Target for Neurodevelopmental Disorders. Neuron 86:1119-1130.

Buccolieri A, Abbruzzese G, Rothwell JC (2004) Relaxation from a voluntary contraction is preceded by increased excitability of motor cortical inhibitory circuits. J Physiol 558:685-695. doi: 610.1113/jphysiol.2004.064774. Epub 062004 Jun 064774.

Capaday C, Ethier C, Darling w, Van Vreeswijk C (2013) On the functional organization and operational principles of the motor cortex. Frontiers in Neural Circuits 7.

Cardinali DP, Golombek DA (1998) The rhythmic GABAergic system. Neurochem Res 23:607-614.

Chen R (2004) Interactions between inhibitory and excitatory circuits in the human motor cortex. Exp Brain Res 154:1-10.

Cohen O, Sherman E, Zinger N, Perlmutter S, Prut Y (2010) Getting ready to move: transmitted information in the corticospinal pathway during preparation for movement. Curr Opin Neurobiol 20:696-703.

Davies CH, Davies SN, Collingridge GL (1990) Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. J Physiol 424:513-531.

Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG (2013) Noninvasive brain stimulation: from physiology to network dynamics and back. Nature Neuroscience 16:838.

Deisz RA (1999) GABA(B) receptor-mediated effects in human and rat neocortical neurones in vitro. Neuropharmacology 38:1755-1766.

Di Lazzaro V, Pilato F, Dileone M, Profice P, Ranieri F, Ricci V, Bria P, Tonali PA, Ziemann U (2007) Segregating two inhibitory circuits in human motor cortex at the level of GABAA receptor subtypes: A TMS study. Clinical Neurophysiology 118:2207-2214.

Doggett AM (2004) ADHD and drug therapy: is it still a valid treatment? J Child Health Care 8:69-81.

Emmert K, Kopel R, Sulzer J, Bruhl AB, Berman BD, Linden DEJ, Horovitz SG, Breimhorst M, Caria A, Frank S, Johnston S, Long Z, Paret C, Robineau F, Veit R, Bartsch A, Beckmann CF, Van De Ville D, Haller S (2016) Meta-analysis of real-time fMRI neurofeedback studies using individual participant data: How is brain regulation mediated? Neuroimage 124:806-812.

Fatemi SH, Reutiman TJ, Folsom TD, Thuras PD (2009) GABA(A) receptor downregulation in brains of subjects with autism. J Autism Dev Disord 39:223-230.

Fetz EE (2007) Volitional control of neural activity: implications for brain-computer interfaces. J Physiol 579:571-579.

Fisher RJ, Nakamura Y, Bestmann S, Rothwell JC, Bostock H (2002) Two phases of intracortical inhibition revealed by transcranial magnetic threshold tracking. Exp Brain Res 143:240-248.

Frank S (2014) Treatment of Huntington's disease. Neurotherapeutics 11:153-160.

Fujiyama H, Hinder MR, Schmidt MW, Tandonnet C, Garry MI, Summers JJ (2012) Age-related Differences in Corticomotor Excitability and Inhibitory Processes during a Visuomotor RT Task. Journal of Cognitive Neuroscience 24:1253-1263.

Galanopoulou AS (2010) Mutations affecting GABAergic signaling in seizures and epilepsy. Pflugers Arch 460:505-523.

Garibotto V, Romito LM, Elia AE, Soliveri P, Panzacchi A, Carpinelli A, Tinazzi M, Albanese A, Perani D (2011) In vivo evidence for GABA(A) receptor changes in the sensorimotor system in primary dystonia. Mov Disord 26:852-857.

Gruzelier J, Egner T (2005) Critical validation studies of neurofeedback. Child Adolesc Psychiatr Clin N Am 14:83-104, vi.

Hanajima R, Ugawa Y, Terao Y, Sakai K, Furubayashi T, Machii K, Kanazawa I (1998) Paired-pulse magnetic stimulation of the human motor cortex: differences among I waves. J Physiol 509 (Pt 2):607-618.

Hari R, Joutsiniemi SL, Sarvas J (1988) Spatial resolution of neuromagnetic records: theoretical calculations in a spherical model. Electroencephalogr Clin Neurophysiol 71:64-72.

Heiss WD, Sobesky J, Smekal U, Kracht LW, Lehnhardt FG, Thiel A, Jacobs AH, Lackner K (2004) Probability of cortical infarction predicted by flumazenil binding and

diffusion-weighted imaging signal intensity: a comparative positron emission tomography/magnetic resonance imaging study in early ischemic stroke. Stroke 35:1892-1898.

Hines RM, Davies PA, Moss SJ, Maguire J (2012) Functional regulation of GABAA receptors in nervous system pathologies. Curr Opin Neurobiol 22:552-558.

Ihara M, Tomimoto H, Ishizu K, Yoshida H, Sawamoto N, Hashikawa K, Fukuyama H (2007) Association of vascular parkinsonism with impaired neuronal integrity in the striatum. J Neural Transm (Vienna) 114:577-584.

Ilic TV, Meintzschel F, Cleff U, Ruge D, Kessler KR, Ziemann U (2002) Short-interval paired-pulse inhibition and facilitation of human motor cortex: the dimension of stimulus intensity. J Physiol 545:153-167.

Kalia LV, Brotchie JM, Fox SH (2013) Novel nondopaminergic targets for motor features of Parkinson's disease: review of recent trials. Mov Disord 28:131-144.

Kang Y, Kaneko T, Ohishi H, Endo K, Araki T (1994) Spatiotemporally differential inhibition of pyramidal cells in the cat motor cortex. J Neurophysiol 71:280-293.

Keizer AW, Verment RS, Hommel B (2010) Enhancing cognitive control through neurofeedback: A role of gamma-band activity in managing episodic retrieval. NeuroImage 49:3404-3413.

Koralek AC, Jin X, Long JD, 2nd, Costa RM, Carmena JM (2012) Corticostriatal plasticity is necessary for learning intentional neuroprosthetic skills. Nature 483:331-335.

Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD (1993) Corticocortical inhibition in human motor cortex. J Physiol 471:501-519.

Levesque J, Beauregard M, Mensour B (2006) Effect of neurofeedback training on the neural substrates of selective attention in children with attention-deficit/hyperactivity disorder: a functional magnetic resonance imaging study. Neurosci Lett 394:216-221.

Lewis DA, Hashimoto T, Volk DW (2005) Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 6:312-324.

Liepert J, Classen J, Cohen LG, Hallett M (1998) Task-dependent changes of intracortical inhibition. Exp Brain Res 118:421-426.

Ljungberg T, Apicella P, Schultz W (1992) Responses of monkey dopamine neurons during learning of behavioral reactions. J Neurophysiol 67:145-163.

Luscher B, Shen Q (2011) Gamma-aminobutyric acidergic deficits cause melancholic depression: a reply to Markou and Geyer. Biol Psychiatry 69:e13-14; author reply e15-16.

Luscher B, Shen Q, Sahir N (2011a) The GABAergic deficit hypothesis of major depressive disorder. Mol Psychiatry 16:383-406.

Luscher B, Fuchs T, Kilpatrick CL (2011b) GABAA receptor trafficking-mediated plasticity of inhibitory synapses. Neuron 70:385-409.

Majid DSA, Lewis C, Aron AR (2015) Training voluntary motor suppression with real-time feedback of motor evoked potentials. Journal of Neurophysiology 113:3446-3452.

Marin O (2012) Brain development: The neuron family tree remodelled. Nature 490:185-186.

Marneweck M, Loftus A, Hammond G (2011) Short-interval intracortical inhibition and manual dexterity in healthy aging. Neurosci Res 70:408-414. doi: 410.1016/j.neures.2011.1004.1004. Epub 2011 Apr 1023.

Marsden KC, Beattie JB, Friedenthal J, Carroll RC (2007) NMDA receptor activation potentiates inhibitory transmission through GABA receptor-associated protein-dependent exocytosis of GABA(A) receptors. J Neurosci 27:14326-14337.

McCormick DA (1989) GABA as an inhibitory neurotransmitter in human cerebral cortex. Journal of Neurophysiology 62:1018-1027.

Meynier C, Burle B, Possamai CA, Vidal F, Hasbroucq T (2009) Neural inhibition and interhemispheric connections in two-choice reaction time: a Laplacian ERP study. Psychophysiology 46:726-730.

Naseer N, Hong KS (2015) fNIRS-based brain-computer interfaces: a review. Front Hum Neurosci 9:3.

Nunez PL, Silberstein RB, Cadusch PJ, Wijesinghe RS, Westdorp AF, Srinivasan R (1994) A theoretical and experimental study of high resolution EEG based on surface Laplacians and cortical imaging. Electroencephalogr Clin Neurophysiol 90:40-57.

Ogrim G, Hestad KA (2013) Effects of neurofeedback versus stimulant medication in attention-deficit/hyperactivity disorder: a randomized pilot study. J Child Adolesc Psychopharmacol 23:448-457. doi: 410.1089/cap.2012.0090. Epub 2013 Jun 1029.

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97-113.

Pilleri M, Antonini A (2015) Therapeutic strategies to prevent and manage dyskinesias in Parkinson's disease. Expert Opin Drug Saf 14:281-294.

Pinborg LH, Videbaek C, Hasselbalch SG, Sorensen SA, Wagner A, Paulson OB, Knudsen GM (2001) Benzodiazepine receptor quantification in Huntington's disease with [(123)I]omazenil and SPECT. J Neurol Neurosurg Psychiatry 70:657-661.

Quaresima V, Bisconti S, Ferrari M (2012) A brief review on the use of functional near-infrared spectroscopy (fNIRS) for language imaging studies in human newborns

and adults. Brain Lang 121:79-89. doi: 10.1016/j.bandl.2011.1003.1009. Epub 2011 Apr 1019.

Razak KA, Fuzessery ZM (2009) GABA shapes selectivity for the rate and direction of frequency-modulated sweeps in the auditory cortex. J Neurophysiol 102:1366-1378.

Reynolds C, Ashby P (1999) Inhibition in the human motor cortex is reduced just before a voluntary contraction. Neurology 53:730-735.

Romo R, Schultz W (1990) Dopamine neurons of the monkey midbrain: contingencies of responses to active touch during self-initiated arm movements. J Neurophysiol 63:592-606.

Ros T, Munneke MA, Parkinson LA, Gruzelier JH (2013) Neurofeedback facilitation of implicit motor learning. Biol Psychol 95:54-58.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology 120:2008-2039.

Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lucking CH, et al. (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 91:79-92.

Rossini PM et al. (2015) Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 126:1071-1107.

Rudolph U, Mohler H (2014) GABAA receptor subtypes: Therapeutic potential in Down syndrome, affective disorders, schizophrenia, and autism. Annu Rev Pharmacol Toxicol 54:483-507.

Schneider C, Devanne H, Lavoie BA, Capaday C (2002) Neural mechanisms involved in the functional linking of motor cortical points. Exp Brain Res 146:86-94.

Schultz W (2000) Multiple reward signals in the brain. Nat Rev Neurosci 1:199-207.

Serrien DJ, Ivry RB, Swinnen SP (2006) Dynamics of hemispheric specialization and integration in the context of motor control. Nature Reviews Neuroscience 7:160.

Shmuel A, Yacoub E, Chaimow D, Logothetis NK, Ugurbil K (2007) Spatio-temporal point-spread function of fMRI signal in human gray matter at 7 Tesla. Neuroimage 35:539-552.

Silvanto J, Pascual-Leone A (2008) State-Dependency of Transcranial Magnetic Stimulation. Brain Topography 21:1.

Sitaram R, Ros T, Stoeckel L, Haller S, Scharnowski F, Lewis-Peacock J, Weiskopf N, Blefari ML, Rana M, Oblak E, Birbaumer N, Sulzer J (2017) Closed-loop brain training: the science of neurofeedback. Nat Rev Neurosci 18:86-100. doi: 110.1038/nrn.2016.1164. Epub 2016 Dec 1022.

Sohn YH, Wiltz K, Hallett M (2002) Effect of volitional inhibition on cortical inhibitory mechanisms. J Neurophysiol 88:333-338.

Sohn YH, Dang N, Hallett M (2003) Suppression of corticospinal excitability during negative motor imagery. J Neurophysiol 90:2303-2309.

Sreedharan S, Sitaram R, Paul JS, Kesavadas C (2013) Brain-computer interfaces for neurorehabilitation. Crit Rev Biomed Eng 41:269-279.

Stinear CM, Byblow WD (2003a) Motor imagery of phasic thumb abduction temporally and spatially modulates corticospinal excitability. Clin Neurophysiol 114:909-914.

Stinear CM, Byblow WD (2003b) Role of intracortical inhibition in selective hand muscle activation. J Neurophysiol 89:2014-2020.

Stoeckel LE et al. (2014) Optimizing real time fMRI neurofeedback for therapeutic discovery and development. Neuroimage Clin 5:245-255.

Sugawara K, Tanabe S, Higashi T, Suzuki T, Tsurumi T, Kasai T (2012) Functional plasticity of surround inhibition in the motor cortex during single finger contraction training. Neuroreport 23:663-667. doi: 610.1097/WNR.1090b1013e3283556522.

Sur M, Rubenstein JL (2005) Patterning and plasticity of the cerebral cortex. Science 310:805-810.

Tan G, Thornby J, Hammond DC, Strehl U, Canady B, Arnemann K, Kaiser DA (2009) Meta-Analysis of EEG Biofeedback in Treating Epilepsy. Clinical EEG and Neuroscience 40:173-179.

Thibault RT, Lifshitz M, Raz A (2015) The self-regulating brain and neurofeedback: Experimental science and clinical promise. Cortex 74:247-261.

van den Wildenberg WP, Burle B, Vidal F, van der Molen MW, Ridderinkhof KR, Hasbroucq T (2010) Mechanisms and dynamics of cortical motor inhibition in the stop-signal paradigm: a TMS study. J Cogn Neurosci 22:225-239.

Waldron EM, Jr., Anton BS (1995) Effects of exercise on dexterity. Percept Mot Skills 80:883-889. doi: 810.2466/pms.1995.2480.2463.2883.

Walker LE, Mirza N, Yip VL, Marson AG, Pirmohamed M (2015) Personalized medicine approaches in epilepsy. J Intern Med 277:218-234.

Wassermann EM (1998) Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of

Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalogr Clin Neurophysiol 108:1-16.

Weiskopf N (2012) Real-time fMRI and its application to neurofeedback. Neuroimage 62:682-692.

Zemankovics R, Veres JM, Oren I, Hajos N (2013) Feedforward inhibition underlies the propagation of cholinergically induced gamma oscillations from hippocampal CA3 to CA1. J Neurosci 33:12337-12351.

Ziemann U, Rothwell JC, Ridding MC (1996a) Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol 496 (Pt 3):873-881.

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996b) Effects of antiepileptic drugs on motor cortex excitability in humans: a transcranial magnetic stimulation study. Ann Neurol 40:367-378.

Ziemann U, Lonnecker S, Steinhoff BJ, Paulus W (1996c) The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res 109:127-135.

Zoefel B, Huster RJ, Herrmann CS (2011) Neurofeedback training of the upper alpha frequency band in EEG improves cognitive performance. NeuroImage 54:1427-1431.

Zoghi M, Pearce SL, Nordstrom MA (2003) Differential modulation of intracortical inhibition in human motor cortex during selective activation of an intrinsic hand muscle. J Physiol 550:933-946.

Zotev V, Phillips R, Yuan H, Misaki M, Bodurka J (2014) Self-regulation of human brain activity using simultaneous real-time fMRI and EEG neurofeedback. NeuroImage 85, Part 3:985-995.

Table TMS parameters and baseline data

TMS parameters

	Neurofeedback-SICI		control	
aMT (% of the maximum stimulator output)				
left FDI muscles	42.8 ± 8.8	(n=23)	44.7 ± 9.2	(n=22)
right FDI muscles	48.3 ± 10.5	(n=14)	49.7 ± 12.6	(n=13)
Intensities for SI1mV (% of the maximum stimulator output)				
left FDI muscles	76.7 ± 13.7	(n=23)	75.8 ± 14.3	(n=22)
left APB muscles	78.1 ± 13.8	(n=23)	79.5 ± 13.3	(n=22)
right FDI muscles	76.2 ± 15.4	(n=23)	72.6 ± 4.2	(n=22)

Baseline data

	Neurofeedback-SICI		control	
SICI ratio				
left FDI muscles	0.81 ± 0.12	(n=23)	0.80 ± 0.11	(n=22)
right FDI muscles	0.77 ± 0.08	(n=14)	0.81 ± 0.11	(n=13)

MEP amplitudes with SI1mV				
(mV)				
left FDI muscle	1.00 ± 0.43	(n=23)	1.13 ± 0.64	(n=22)
left APB muscles	1.16 ± 0.45	(n=23)	1.20 ± 0.60	(n=22)
Choice reaction time (cRT) (msec)	341.4 ± 35.9	(n=21)	337.7 ± 33.3	(n=20)
Pinch force (kg)	2.85 ± 1.06	(n=23)	2.94 ± 1.20	(n=22)

Figure legends

Figure 1. *Interventional protocol*

In the Neurofeedback-SICI intervention, the paired-pulse TMS were given with an interval of 5–7 s. A circle was displayed on a 20-inch monitor in front of the subject. The size of the circle was changed according to the average of 5 MEP amplitudes from the left FDI muscle by test stimuli 3 ms following conditioned stimuli of TMS.

Figure 2. *Experimental paradigms*

The TMS evaluations were performed before, immediately after, and 30 min after the Neurofeedback-SICI or control intervention (designated as the pre, post0, and post1 conditions, respectively). Behavioral evaluations including cRT and pinch force were performed before and 30 min after the Neurofeedback-SICI or control intervention. During the intervention, the Neurofeedback-SICI or control session lasted for 10 min and was repeated twice with a 10-mi intermission.

Figure 3. *Change ratio of the circle size during the Neurofeedback-SICI learning*

The change ratio of the circle size to the initial circle size (= the present circle size / the initial circle size) presented during the Neurofeedback-SICI learning in one subject. The presented size was fluctuating but gradually reduced in the learning process.

Figure 4. *SICI ratio in intentional and non-intentional states*

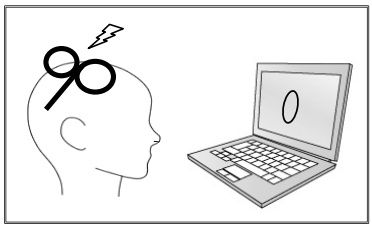
A significant decrease in SICI ratio occurred in the post1 condition in the intentional state in the Neurofeedback-SICI group compared with that in the control group (*$p <$

0.05). No significant differences were observed between the Neurofeedback-SICI and control groups in the non-intentional state. Error bars show SEM.

Figure 5. *cRTs and pinch force*

(A) cRT was significantly decreased in the Neurofeedback-SICI group compared with those in the control group (*$p < 0.05$). (B) There were no significant differences in the pinch force between the Neurofeedback-SICI and the control group. Error bars show SEM.

Figure 1



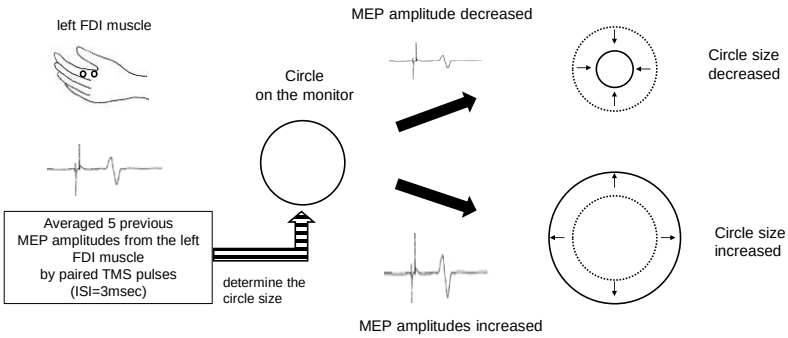


Figure 2

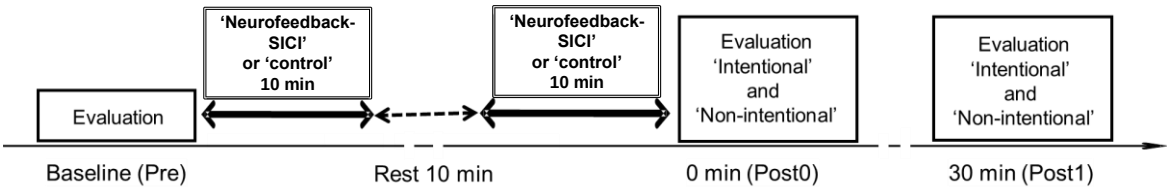


Figure 3

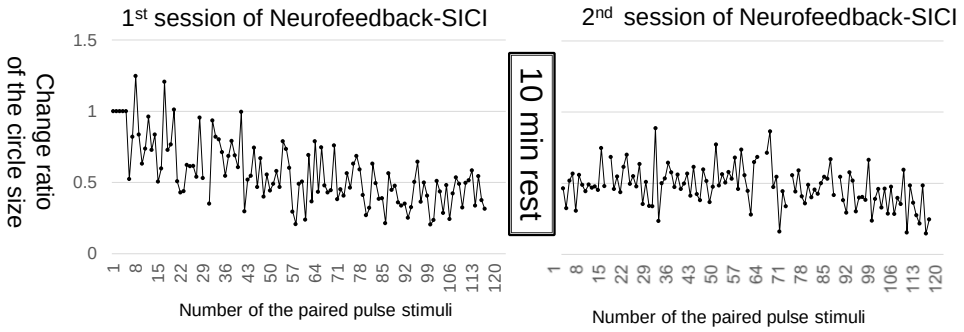
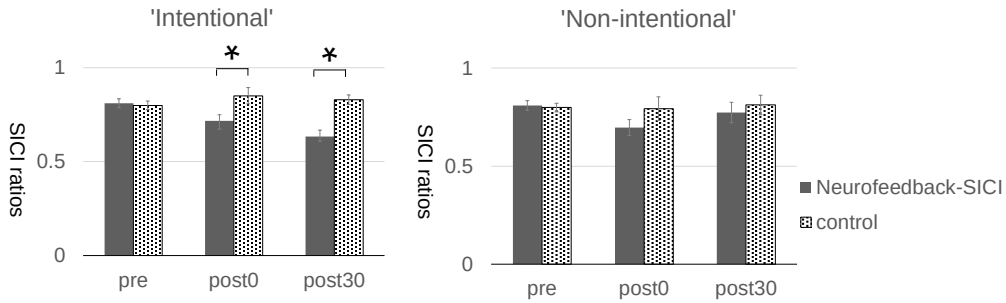
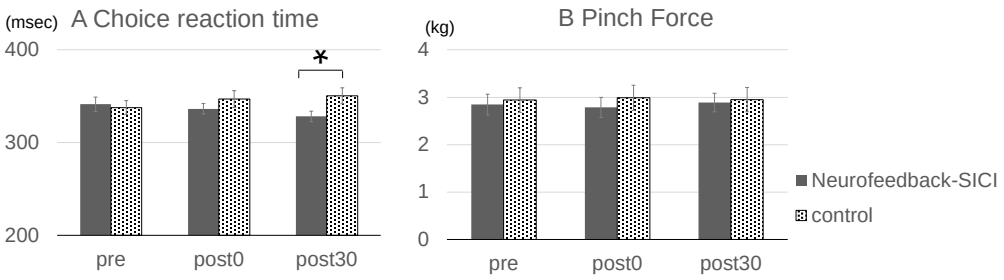


Figure 4



(*p<0.05)
Error bar: SEM

Figure 5



(*p<0.05)
Error bar: SEM