人工的な神経刺激による両側性運動が皮質可塑性に与える影響

The effect of Bilateral Finger Training (BFT) paired with Artificial Neural Stimulation (ANS) on motor cortex plasticity

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2021 Academic Year Doctoral Dissertation Abstract for the Graduate School of Rehabilitation Sciences

The effect of Bilateral Finger Training (BFT) paired with Artificial Neural Stimulation (ANS) on motor cortex plasticity

Neurorehabilitation field

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Introduction:

Upper arm paresis is the most common disability in stroke. The quality of life (QOL) of stroke survivors is associated with the level of ability to perform ADL. Bilateral motor training is a useful method to modify the excitability of the primary motor cortex (M1). Severe upper arm paresis limits voluntary bilateral training. Therefore, it is important to investigate rehabilitation protocols which can move severely paralysed arm artificially. The effects of artificial bilateral movement on M1 excitability through functional electrical stimulation or transcranial magnetic stimulation (TMS) have not been compared with voluntary bilateral training. Therefore, we compared motor-evoked potentials (MEPs) following TMS over the M1 of voluntary movements after voluntary bilateral motor training and repetitive artificial bilateral movements generated through peripheral nerve stimulation and TMS.

Methods:

Surface electromyograms of the abductor pollicis brevis (APB) muscles were recorded bilaterally in 12 healthy participants. Three sessions with different interventions were conducted: (1) bilateral finger training (BFT) involving bilateral thumb abduction, (2) right APB-triggered TMS of the ipsilateral M1 (i-TMS), and (3) right APB-triggered contralateral median nerve stimulation (c-MNS). Each protocol consisted of 360 trials for ~30 min. Resting motor threshold (RMT), MEPs

induced by single-pulse TMS, short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) induced by paired-pulse TMS were assessed as outcome measures at baseline and at 0, 20, 40, and 60 min after intervention.

Results:

RMT showed no significant change with time course when compared to the baseline. The MEP amplitude significantly increased at the post-intervention periods in comparison to the baseline in all three protocols. The MEP amplitude was significantly increased in BFT and in APB-triggered i-TMS protocols, at post 0, 20 and 40 minutes and in APB triggered c-MNS at post 20, 40 minutes. No significant effect of intervention on baseline MEP. SICI was significantly decreased at 0 min post-intervention in the BFT and APB-triggered i-TMS. ICF was significantly increased at 0 min post-intervention in the BFT and at 20 min post-intervention in the APB-triggered c-MNS.

Discussion:

The main finding of the present study was the long-lasting increase in MEP amplitude in all three bilateral movement protocols.

Conclusion:

Thus, whether voluntarily or artificially caused, repetitive bilateral movements enhance corticospinal excitability.

Keywords

bilateral training, transcranial magnetic stimulation, functional electrical stimulation, neuroplasticity

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List of Abbreviations

APB – Abductor pollicis brevis muscle

BFT – Bilateral finger training

BMT – Bilateral motor training

EMG - Electromyographic

FES – Functional electrical stimulation

ICF – Intracortical facilitation

M1 – Primary motor cortex

MEP – Motor evoked potential

MNS – Median nerve stimulation

RMT – Resting motor threshold

rTMS – repetitive transcranial magnetic stimulation

SICI – Short- interval intracortical inhibition

TMS - Transcranial magnetic stimulation

1. Introduction

1.1 Definition and classification of stroke

'Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral haemorrhage (ICH), and subarachnoid haemorrhage (SAH)'[1]. According to World Health Organization (WHO) definition, 'stroke is a clinical syndrome, of presumed vascular origin, typified by rapidly developing signs of focal or global disturbance of cerebral functions lasting more than 24 hours or leading to death' [2].

There are two main types of strokes; ischemic and haemorrhagic strokes. Ischemic strokes are far more common than haemorrhagic strokes. The brain has a blood supply which is fairly consistent between individuals. Ischemic strokes can be due to large vessel atherosclerosis, small vessel occlusion, other determined causes, and undetermined causes. Haemorrhagic strokes are most often due to hypertension but may be caused by specific blood vessel abnormalities and other medical problems.

The clinical impact of a stroke is depended largely on the stroke's location in the brain, whether it is ischemic or haemorrhagic, and the size/severity of the stroke itself [3]. According to Oxfordshire classification of stroke, patients with stroke were allocated into one of four groups according to presenting symptoms and signs [4].These subtypes are Total Anterior Circulation stroke (TACS), Partial Anterior Circulation stroke (PACS), Posterior Circulation Syndrome (POCS) and lacunar syndrome (LACS) [5].

1.2 Global burden of stroke

Ischaemic heart disease and stroke are the top two diseases, accounting for a combined 15.2 million deaths in 2016. Stroke is the second leading cause of death globally [6]. Stroke is a non-communicable disease (NCD) which causes high mortality and morbidity rates. It is the second leading cause of mortality and third leading cause of disability worldwide [7]. Furthermore, in 2013, 25.7 million stroke survivors were identified globally and 6.5 million deaths occurred due to stroke. It had been estimated that in 2001, 86% of deaths related to stroke occurred in developing countries [8].

The Disability Adjusted Life Years (DALYs) is a method used to quantify the burden of a disease from mortality and morbidity. The DALYs for a disease are calculated as the sum of the years of life lost due to disability or consequences of a disease. Since 1990 the DALYs due to stroke showed a steady increase. In the year 2019, the total number of DALYs due to stroke reached up to 143 million and caused 6.55 million deaths globally [8]. A systematic review on trends in global stroke incidence has shown that there is a 42% decrease in stroke incidence in developed countries while there is 100% increase in developing countries over the past four decades [9]. These findings pointed out the incidences of stroke have been increased in developing countries than in developed countries.

Age is the strongest non-modifiable risk factor for stroke. When the elderly population is increasing the burden of stroke is also expected to increase. Five major modifiable risk factors for stroke were identified; hypertension, current smoking, abdominal obesity, diet, and lack of physical activity. These factors were accounted for more than 80% of the global risk for stroke [10].

1.3 Stroke related disabilities ADL and the QOL of stroke survivors

Disabilities that occurred due to stroke depend on the area of the brain damage and the intensity of damage. Therefore, it is difficult to differentiate how the stroke and related disabilities affect each individual. Stroke can cause five types of disabilities. Those are paralysis or problems controlling movement (motor impairment), sensory disturbances including pain, problems using or understanding language, problems with thinking and memory, and emotional disturbances [11, 12].

Paresis of the contralateral upper arm is the most common disability in stroke (about 80%-acute stage, 40%-chronic) [13]. Upper arm paresis limits activities of daily living (ADL) such as eating, dressing, bathing, toileting and etc [14]. It has been found that about 75% of stroke survivors experience difficulties in performing ADL [15]. The quality of life (QOL) of stroke survivors is associated with the level of ability to perform ADL according to the previous literature [16, 17, 18].

Kim et al (2014) showed that there is a high correlation between functional independence and QOL [18]. Moreover, these impairments can cause emotional and economic hardships for both patients and their families [19]. Proper rehabilitation therapies help to recover and return to their normal life

style and also minimize the complications that occurred due to stroke while enhancing the wellbeing of the patient [16].

Rather than using traditional rehabilitation therapies such as training of paretic arm and using range of motion exercise to improve the arm functions novel rehabilitation therapies using neurophysiological therapies such as non invasive brain stimulation showed advantages according to previous literature.

1.4 The concept of neuroplasticity

"Neuroplasticity is the ability of neurons to change their function, chemical profile (quantities and types of neurotransmitters produced) or structure" [20].

This ability of the brain is essential for recovery from damage to the central nervous system [21]. Change of the balance in cortical and intracortical excitability is one of the most important underlying neurophysiological mechanisms which play a major role in motor recovery from brain lesions such as a stroke [22]. In fact, it is important that motor recovery therapies facilitate neural plasticity to compensate for functional loss. Traditional neurorehabilitation techniques only aimed at restoring function of weakened limbs which only provides a modest benefit [23]. Novel stroke rehabilitation techniques for motor recovery have been developed based on basic evidence based studies of neural plasticity [22].

1.5 Activity dependent plasticity

Activity dependent plasticity is a complex process which involves with long-lasting changes in the strength of synapses between neurons and neuronal networks. It is considered as a necessary mechanism of recovery subsequent to a brain injury [24]. Rather than short-term reversible effects, this complex process can cause long lasting changes in the neurons. Several mechanisms underlie the activity dependent plasticity and the best-known mechanism is long-term potentiation (LTP) and long-term depression (LTD) of excitatory synapses [25]. Activity is the main force of adaptive changes in the nervous system. When there is persistent changes in the activity level it may lead to re-adjust the neuronal and synaptic components of the nervous system which cause haemostatic changes [24].

New rehabilitation interventions focused on neuroplasticity should include meaningful, repetitive, intensive, and task-specific movement training to promote neural plasticity and motor recovery [26]. New brain stimulation techniques have been discovered by researchers to enhance the neural plasticity in the motor cortex. Repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and epiduralcortical stimulation (ECS), artificial neural stimulation (ANS) are few techniques out of them [27]. Changes in the plasticity mainly occur in connections between motor cortical neurons firing naturally during generation of muscle contraction and those activated artificially by the brain stimulation. Activity-dependent brain stimulation is an alternative to stroke rehabilitation that can be designed to create more focused neural plasticity [28].

1.6 Bilateral motor training (BMT)

Upper limb paresis is one of the major consequences of a stroke which can affect the activities of daily living [14]. Bilateral training is important because we perform tasks involving both arms in day to day life. Moreover, the older adults who are at the higher risk of developing stroke usually use both hands in their day to day activities than others. In stroke, traditional rehabilitation therapies such as range of motion exercises are mainly focused on the paretic limb to reduce the functional impairment. But, when the patient cannot move the paretic limb completely the intact limb is used to do the activities. Hence, bimanual tasks that they do can be affected as a consequence of upper limb paresis. In order to improve upper extremity paresis of patients with stroke, the effect of bilateral arm training has been studied by researchers. Upper extremity disabilities due to stroke could severely limit the motor capabilities and minimize the activities of daily living (ADL) [14]. There is a balanced Interhemispheric inhibition (IHI) between two hemispheres in healthy people [29]. But, in stroke, there is a disproportionate amount of inhibition from the contralesional hemisphere towards the ipsilesional hemisphere. Contralesional M1 inhibits the ipsilesional M1 via an abnormal transcallosal inhibition (TCI) [29]. Bilateral motor training (BMT) is a neurophysiological intervention which helps to control abnormal IHI among stroke survivors.

Therefore, researchers and therapists in the field of rehabilitation and stroke are searching for more effective upper extremity rehabilitation techniques to improve the voluntary motor control [30].

The effectiveness of BMT for recovery of arm function after stroke had been investigated [31, 32]. BMT induces the plasticity of the primary motor cortex (M1) [32]. Mirror symmetric bilateral movements may have the ability to activate similar neural networks in both hemispheres [32]. According to Mc Combe Waller et al (2008), after short term bilateral training there is an increased intracortical facilitation and decreased intracortical inhibition in each hemisphere among healthy adults [28].

According to Sinear and Byblow (2004), rhythmic bilateral movement training modulates the M1 excitability and improves upper limb motor functions. The motricity score of the upper limb which was measured using the Fugl-Meyer motor rating was significantly increased after intervention [33]. However, when the patients have severe upper arm paresis with difficulties in moving the arm voluntarily and severe weakness of the muscles they are unable to move the paretic hand voluntarily. Therefore, the effectiveness of BMT is limited when the patients have severe upper arm paresis [32]. For these patients, several technologies producing artificial movement of the paretic limb may complement difficulties in performing BMT.

1.7 Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a method that uses magnetic fields to stimulate the brain. In TMS the changes occur in the magnetic field deliver electric stimuli through the scalp in conscious humans. TMS is used to explore the brain function and also therapeutically. Usually, single-pulse and paired-pulse TMS is used to explore brain functioning, while repetitive TMS (rTMS) is used therapeutically to induce changes in brain activity. Delivering TMS over the motor cortex leads to a twitch in the target muscle evoking motor-evoked potential (MEP) on electromyography [34]. Simplified mechanism of action of TMS of the motor cortex is shown in figure 1.

TMS is a non invasive brain stimulation technique which can be used to cause an artificial movement. The excitability which occurs due to rTMS depends on the frequency. In healthy adults, low frequency TMS (< 1Hz) decreases the M1 excitability, whereas frequency more than 1Hz causes facilitation [35, 36]. As a therapeutic stroke rehabilitation intervention, repetitive transcranial magnetic stimulation (rTMS) on the contralesional (intact) motor cortex helps to adaptively compensate the stroke related dysfunctions [37, 38, 39]. Ipsilesional M1 also plays a major role in post

stroke motor recovery by cortical reorganization and a recent review suggested that rTMS to the lesioned hemisphere is safe and could be a powerful approach for modulating brain function in persons who have had a stroke [40]. Low frequency (1Hz) rTMS on contralesional M1 of stroke patients showed a reduced MEP showing decreased M1 excitability. Moreover, they found that it improves hand function. [41].

1.8 Functional Electrical Stimulation (FES)

The electrical stimulation of peripheral nerves innervating muscles is a method for easily producing an artificial movement. According to a review on electrical stimulation (ES) for rehabilitation of patients with stroke concluded that enhanced plasticity through ES is important to improve the motor function. Among reviewed articles, majority used stimulation intensity which is sufficient to induce motor response such as causing muscle twitch/contraction. When there is a sufficient intensity to cause muscle contraction it showed significant increase in the corticomotor excitability. These studies used muscles in the upper arm for stimulation including APB, abductor digiti minimi, radial and ulnar nerve at wrist [42]. According to another review typical frequency range is 20-60 Hz while intensity is above motor threshold which is able to activate both sensory and motor axons to assist in arm function [43]. In stroke patients with upper arm paresis, contralaterally controlled functional electrical stimulation (CCFES) which was conducted as two 55- minutes sessions daily for 12 weeks. The intervention showed an improvement in arm functions as measured by Fugl- Mayer scale [44]. Cunningham et al (2019), investigated the effect of Bilateral CCFES in patients with stroke. The target muscles were extensor digitorum communis (EDC) and extensor pollicis longus muscles. The frequency and amplitude of current pulses were 35 Hz and 40 mA respectively [45]. Their results showed the IHI from contralesional to ipsilesional M1 was decreased. Moreover, bilateral CCFES showed differences related to neurophysiological mechanisms when compared to unilateral cyclical neuromuscular stimulation.

1.9 Paired Associative Stimulation (PAS)

Stefan et al (2000) investigated the Paired Associative Stimulation (PAS) technique in humans. The original experiment was conducted using single pulse TMS over the left M1 area correspond to right APB muscle. Peripheral nerve stimulation (PNS) was delivered to the median nerve before TMS at an interstimulus interval (ISI) of 25 ms. This ISI was set estimating the synchronous arrival of both stimuli to the M1 to cause long lasting induced plasticity. Their findings revealed two

independent stimuli from different routes which arrive synchronously on the M1 have the capability to induce the cortical excitability [46]. The PAS can be used to investigate principles of synaptic plasticity as well as therapeutically in stroke rehabilitation. It is well known that PAS can cause LTP (Long Term Potentiation) like effects via hemispheres [47]. However, a review article concluded PAS protocols using upper arm muscles showed either LTP or long term depression (LTD) depending on the ISI [47]. A preliminary PAS protocol which was conducted using PNS and TMS among patients with chronic stroke showed improved corticomotor excitability which was measure using MEP [48]. PAS protocols usually use relatively low intensity and low frequency PNS and TMS for stimulation. Arrival of two independent stimuli to primary M1 make rapid changes in the corticomortor excitability. However, the corticomotor excitability depends on the ISI. There is an increase in excitability of the targeted corticospinal pathway when the peripheral afferent stimulus arrives in the M1 in synchronously or just before the TMS stimulus (facilitatory PAS); There is a corticomotor inhibition if the peripheral afferent stimulus arrives after the TMS stimulus (inhibitory PAS) [49]. Thabit and colleagues used the movement-triggered PAS method to induce movement-specific M1 plasticity, compare with only use rTMS or tDCS [50]. Additionally, If this method adapts to contralateral movement, we may use it for the patients with stroke who has severe paralysis.

In our study we planned to investigate unilateral voluntary movement of APB muscle and APB-triggered TMS over ipsilateral M1 and APB-triggered MNS. Our protocol is different from PAS protocol as we can not control the interstimulus interval as we used APB triggered TMS. But we assume that the effect of two stimuli will reach the M1 together (synchronously) and increase M1 excitability.

1.10 Justification

The most common disability of stroke is paresis of the contralateral upper arm. About 80% has arm paresis at the acute stage whereas, 40% remains with chronic arm paresis [13]. HRQOL of stroke survivors is associated with the level of ability to perform activities of daily living which is assessed using the Barthel index. Higher scores for the Barthel index indicate good ability to perform ADL [16]. HRQOL is significantly correlated with the Barthel index score [16]. Improving upper arm function of stroke survivors by proper rehabilitation is important to perform ADL. Improving the ADL performance will be helpful for better HRQOL.

Traditional rehabilitation therapies including physical therapy and range of motion exercises and novel rehabilitation therapies including neurophysiological interventions using non invasive brain stimulation are commonly used rehabilitation therapies for patients with stroke. Unilateral training of paretic hand such as constrained induced movement therapy is one of the best ways to induce neuroplasticity [20]. But it has limitations for patients with severe upper arm paralysis because these protocols need movement of the paretic arm. ADL training using non-paretic hand including changing hand dominance is a common way to recover activity limitation. But, there is a possibility that use of non-paretic hand delay recovery of paresis. It is known as abnormal interhemispheric inhibition (IHI) which causes strong inhibition of cortical excitability of lesion side [29]. One of the hypothetical mechanisms of recovery is normalization of abnormal IHI with BMT [28]. BMT enhance recovery of arm function after stroke [31]. However, BMT is not effective for patients with severe hemiplegia because they can't move the paretic hand voluntarily.

Artificial movement of the paretic upper arm is an alternative method to create bilateral motor training artificially. Functional electrical stimulation is a method to produce artificial movement of paretic arm easily. Previous studies used electric stimulation paired with voluntary contraction of the paretic arm [43, 44]. A review article on EMG-triggered FES among patients with stroke concluded that EMG-triggered FES recover the function in hand muscles including releasing, grasping and pinching [51]. But, the studies mentioned in the review mainly focused on functional outcomes based on muscle movement rather than neurophysiological measures. Therefore, it is not clear that the bilateral movement caused artificially using EMG-triggered FES has the potential of changing cortical excitability of the resting hemisphere or not. Therefore, in this study we evaluate the effects of EMG-triggered FES on the excitability of the M1.

Another way to create artificial movements is TMS over the primary motor cortex [52, 53]. A review regarding unilateral rTMS on lesioned hemisphere showed an improvement in function of the paretic arm among patients with stroke [52]. However, it has not been reported the effects on the cortical excitability of the artificial bilateral movement by TMS. In a previous study by Edwardson et al (2015) used EMG-triggered TMS protocol with the participation of ten healthy subjects [23]. The MEP was significantly increased followed by 40 minutes training. However, this protocol caused unilateral movement and the contralateral primary M1 used to assess the excitability. To the best of our knowledge, artificial bilateral movement using TMS is not investigated so far using

EMG-triggered TMS protocol up to now. When the EMG- triggered TMS applied over the ipsilateral M1 which is correspond to the APB muscle of the paretic arm there is an artificial movement. This basic protocol was investigated in our study with the participation of healthy subjects. We investigated the effect of conventional BMT and artificial bilateral training using FES and TMS on the M1 excitability which is triggered by voluntary muscle activity of the opposite hand. Moreover, in the present study, we compared the cortical excitability on the ipsilateral side of voluntary movements with the conventional BMT, and the artificial bilateral movements, which generated by FES and TMS in healthy individuals.

As the main outcome measurement we assessed the motor evoked potential (MEP). MEP usually use to assess the cortical excitability. MEP indicates the level of excitability of the primary motor cortex. When the MEP increased that means there is an increase in excitability of the motor cortex. Several neurophysiological mechanisms may take part in the brain to make changes in the MEP which ultimately cause changes in the M1 excitability. Intracortical communication including cortical facilitation and intracortical inhibition may also contribute to the changes that can be occurred in the M1 excitability. Therefore, in this study we test MEP and other physiological outcome measurements including intracortical inhibition (ICI) and intracortical facilitation (ICF).

1.11 Aims of the study

1. To determine the effect of voluntary muscle activity-triggered transcranial magnetic stimulation and median nerve stimulation on motor cortical plasticity

2. To compare the effect of voluntary bilateral training and artificial bilateral training by TMS and FES on motor cortex plasticity

2. Methods

2.1 Participants

Experiments were performed with the participation of 12 right-handed healthy adults [8 men and 4 women; age, 20–50 (mean 26.8 ± 8) years] without any neurological diseases after obtaining the written informed consent. Sample size was calculated using G*power software using F test and ANOVA. Based on that needed minimal sample size is 12, 6 and 6 for intervention, time and intervention*interaction respectively.

The ethical approval was obtained from the ethics review committee, School of Rehabilitation Sciences, Health Sciences University of Hokkaido (approval number: 18R057066). Participants were seated on a chair comfortably and the forearms and wrists on both sides were fixed on a table in a neutral position during the experiments.

2.2 General experimental protocol

The general experimental conditions and time course in the present study are illustrated in Figure 1. The present study was performed with counterbalanced crossover design, which consisted of three experimental sessions with different intervention; (1) bilateral finger movement training (BFT) involving bilateral thumb abduction, (2) electromyographic (EMG) activity of the right abductor pollicis brevis (APB) triggered transcranial magnetic stimulation (TMS) of the ipsilateral M1 (APB-triggered i-TMS), (3) EMG activity of the right APB triggered contralateral median nerve stimulation (APB-triggered c-MNS) (Figure 2A). The intervention consisted of two same blocks lasting for 15 min each (see below for details). A break period for 5 min was interposed between blocks. Outcome measurements were performed before (baseline), immediately after (post 0), 20, 40 and 60 min after the intervention (Figure 2B). Each session took for ~2 hours and was performed in a separate day at least one week apart between sessions.

2.2.1 EMG recording

Surface EMGs were recorded from the APB bilaterally. A pair of Ag/AgCl disc electrodes (NE-101; Nihon Kohden, Tokyo, Japan) was placed with the active electrode over the muscle belly and the reference electrode over the metacarpophalangeal joint of the thumb. The EMG signals were amplified (× 1,000) and bandpass filtered (5–3,000 Hz) with a bioamplifier (BIOTOP 6R12; NEC San-ei Instruments, Tokyo, Japan). The analogue EMG signals were digitized at 6 kHz and stored on a computer using an A/D converter (Power1401-3; Cambridge Electronic Design, Cambridge, UK) and data acquisition software (Spike2 version 7; Cambridge Electronic Design).

2.2.2 TMS

A monophasic single-pulse TMS was given using a magnetic stimulator (Magstim 200^2; Magstim, Whitland, UK) and a figure-of-eight coil (D70 Alpha B.I.; Magstim). For paired-pulse TMS protocol, a set of two magnetic stimulator units through a bistim connecting module (Magstim BiStim^2; Magstim) was used. The coil was held over the right scalp so that induced current flowed in posterior-anterior direction in the brain [54, 55]. Optimal coil position for producing a large MEP in the left APB was determined at rest and was marked on the scalp prior to data collection. The resting motor threshold (RMT) was defined as the minimum intensity that produced an MEP of > 50 μV in the left APB in at least 5 of consecutive 10 TMS pulses at 0.2 Hz while participants kept at rest. The RMT was determined by increasing or decreasing the stimulus intensity in steps of 1% of the maximum stimulator output.

2.2.3 Median nerve stimulation (MNS)

A single rectangular electrical pulse (1-ms duration) was given with an electrical stimulator (SEN-8203; Nihon Kohden) connected with a constant-voltage isolator unit (SS-104J; Nihon Kohden). The left median nerve at the wrist was stimulated using a pair of surface electrodes (NE-101; Nihon Kohden) with a bipolar montage (2 cm apart, cathode on the proximal). The optimal electrode positions for eliciting a large motor (M-) wave in the left APB were determined and the electrodes were fixed with elastic surgical tape.

2.3 Interventions

Three interventional protocols are described in Figure 2A. As mentioned above, each intervention included 2 blocks of 180 trials (360 trials in total). In the BFT protocol, participants were requested to perform ballistic voluntary abduction movements of the both thumbs simultaneously with the maximum effort in responding to an auditory imperative cue (tone burst, 2 kHz, 100 ms duration). A warning cue (tone burst, 1 kHz, 100 ms duration) was presented at 0.8–1.5 s prior to the imperative cue to keep arousal. The set of warning and imperative cues was presented every 5 s. A visual feedback of the rectified and smoothed EMG signals was given on a monitor in front of participants to maintain the EMG activity during movements. In the APB-triggered i-TMS and APB-triggered c-MNS protocols, participants were asked to perform a ballistic voluntary abduction movement of the right thumb alone and to keep the left APB relaxed during the intervention. In these protocols, a specific EMG waveform of the right APB was discriminated in real time by a template-matching algorism of a spike detector (Alpha Spike Detector; Alpha-

Omega Engineering, Nazareth, Israel) and converted into a transistor-transistor logic (TTL) pulse event. Only a single pulse event was generated per each movement to prevent unnecessary high frequency stimulation which would cause muscle fatigue or other undesired effects. Then, the generated TTL pulse triggered TMS over the right M1 in the APB-triggered i-TMS and electrical stimulation of the left median nerve in the APB-triggered c-MNS. In both APB-triggered i-TMS and APB-triggered c-MNS protocols, there is an artificial movement of left thumb which is caused by voluntary right thumb abduction triggered TMS and MNS. Stimulus intensity of TMS was set at 120% of the RMT. Stimulus intensity of median nerve stimulation was set at 120% of the stimulator output that was required to elicit the maximum M-wave.

2.4 Outcome measurements

Four different outcomes were measured; Resting motor threshold (RMT), Motor evoked potential (MEP) amplitudes, short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF). All measurements were performed at rest. For measurement of MEP amplitude, ten MEPs were evoked by a train of single TMS pulses at 0.17–0.25 Hz. The TMS intensity that elicited an MEP of 0.5–1 mV was determined at baseline and the intensity was kept constant across time periods. TMS is used to activate intracortical circuits in the hand muscle representations. The SICI and ICF can be investigated using paired pulse TMS paradigm. Paired pulse TMS is delivered using a sub threshold conditioning stimulus followed by supra threshold test stimulus. Kujirai et al (1993) described the basics of SICI and ICF [56].

SICI

When the interstimulus interval between test and conditioning stimuli is short (1-4 ms) the test responses are inhibited (SICI).

ICF

When the interstimulus interval between test and conditioning stimuli are longer (8-15 ms) the test responses are facilitated (ICF).

Conceptual figure of SICI and ICF is shown in figure 3.

Ten test MEPs and ten conditioned MEPs were elicited by randomly altered single (for test MEPs) and paired (for conditioned MEPs) TMS pulses at 0.17–0.25 Hz. The stimulus intensity of the test TMS pulse was set at an intensity that evoked MEP of 1 mV and adjusted at each time period if necessary. The stimulus intensity of the conditioning TMS pulse was set at 0.8 times the RMT [55].

Inter-stimulus intervals between test and conditioning pulses were set at 2 ms for SICI and 10 ms for ICF.

In the offline analysis, the peak-to-peak amplitude of the MEP was measured in individual unrectified EMG sweeps. The mean value of the peak-to-peak amplitude across ten sweeps was then calculated. The MEP amplitude for the single-pulse TMS was normalized by the baseline value. For SICI and ICF, the amplitude of the conditioned MEP was normalized by that of the test MEP. The normalization of data was done using STANDARDIZE function in Microsoft Excel.

2.5 Statistics

All statistical tests were performed with SPSS software (SPSS Statistics version 25; IBM, Chicago, IL). A two-way repeated measures ANOVA (intervention × time) was performed on each dependent variable. If the reported F value was statistically significant, post hoc test was performed with Tukey's test to reveal difference from the baseline values. A p value < 0.05 was taken as statistically significant. Group data are shown as mean ± standard error of the mean.

Results

3.1 RMT and MEP amplitude

Averaged data of the RMT values are shown in Figure 4A. Two-way ANOVA that subjected RMT showed no significant effect of intervention [F (2, 22) = 2.79, p = 0.08] and time [F (4, 44) = 0.94, p = 0.45] and interaction [F (8, 88) = 0.84, p = 0.57]. Changes in the mean value of the MEP amplitude are represented in Figure 4B. Two-way ANOVA showed significant effect of time [F (4, 44) = 17.39, $p < 0.01$] but no effect of intervention [F (2, 22) = 1.09, p = 0.35) and

interaction [F (8, 88) = 1.69, p = 0.11]. Post hoc analysis with Tukey's test indicated that the MEP amplitude significantly increased at post 0, 20 and 40 minutes in BFT ($p < 0.05$), at post 0, 20, and 40 in APB-triggered i-TMS ($p < 0.05$) and at post 20 and 40 in APB-triggered c-MNS ($p < 0.05$) in comparison to the baseline. For the MEP amplitude at the baseline, separate one-way ANOVA revealed no effect of intervention [F (2, 22) = 3.28, p = 0.06].

3.2 SICI

Group data of SICI are shown in Figure 5A. Two-way ANOVA yielded significant effect of time [F (4, 44) = 3.84, p =0.009] but no effect of intervention [F (2, 22) = 0.03, p = 0.98] and interaction [F (8, 88) = 1.82, p = 0.08]. Results of post hoc test showed that SICI was significantly decreased at Post 0 in BFT (p =0.01) and APB-triggered i-TMS protocols (p = 0.01) when compared to the baseline values. There was no significant difference of SICI in different time periods in the APB-triggered c-MNS protocol (p = 0.61).

3.3 ICF

Changes in ICF are displayed in Figure 5B. Two-way ANOVA revealed significant effect of time [F (4, 44) = 6.13, p = 0.01] but no effect of intervention [F (2, 22) = 0.66, p = 0.57] and interaction [F (8, 88) = 1.06, p = 0.09]. Post hoc test results showed that ICF was significantly increased at post 0 min in the BFT (p = 0.02) and at 20 min after intervention in the APB-triggered c-MNS protocol (p = 0.001). In the APB-triggered i-TMS protocol there was no significant difference of ICF in different time periods when compared to the baseline values (p = 0.09).

Mean and standard error of mean of all variables are shown in Table 1.

4. Discussion

4.1 Changes in MEP

In this study, we found that the MEP amplitude increased after all tested protocols using repetitive bilateral movements; BFT is considered as the normal protocol, the APB-triggered c-MNS protocol uses the MNS, and the APB-triggered i-TMS protocol uses TMS. Our results suggest that despite being voluntarily or artificially caused, repetitive bilateral movements induce short-term modification of the motor cortical and corticospinal excitabilities.

In the present study, the increase in MEP amplitude lasted up to 40 min in each intervention. Short-term changes in the MEP have been induced by neuromodulation protocols such as repetitive TMS (rTMS), transcranial direct current stimulation (tDCS), and paired associative stimulation (PAS) [57,58,59]. For instance, low-frequency rTMS (<1Hz) caused cortical depression, and high-frequency rTMS (>1 Hz) promoted cortical activity over time [35]. These changes are similar to the cell-level experiments that revealed long term depression (LTD) and long-term potentiation (LTP) [60]. The tDCS technique generates a small amount of continuously flowing direct current over the scalp, which induces plasticity. The tDCS protocols showed increased cortical excitability, which lasted for about 30 min after stimulation [59]. PAS, which uses low-frequency nerve stimulation and TMS over the optimal cranial site to stimulate the target muscle, is a technique that causes LTP-like plasticity. The PAS protocol increased the MEP amplitude by about 150% and lasted over 30 min [61]. Likewise, the long-lasting increase in MEP could be induced by the present protocols, but the duration of the effects may long compared with that of the previous neuromodulation protocols. Therefore, voluntary movement paired with FES or TMS showed increased M1 excitability. Moreover, increase MEP could be induced by the present protocols, but the duration of the effects seems to be relatively long compared with that of the previous neuromodulation protocols.

4.2 Comparison of APB triggered cMNS with previous peripheral nerve stimulation protocols

It is known that cortical excitability changes can occur with electrical stimulation of the peripheral nerves and rTMS alone. Previous studies have demonstrated that cortical plasticity can be induced by electric stimulation of peripheral nerves [44, 45]. However, most of the previous studies using electrical stimulation used high-frequency stimulation or train pulse stimulation. According to a review by Carson and Buick, the typical frequency of neuromuscular electrical stimulation to activate sensory and motor axons should be 1–100 Hz [62]. Upon comparison with these studies, it was considered that frequency used in our protocol was too low to cause an impact on the brain.

4.3 Comparison of APB triggered iTMS with previous rTMS protocols

As mentioned previously, it is widely known that rTMS causes brain plasticity. In particular, low-frequency rTMS (<1Hz) causes depression of cortical activity [35]. Our data at 0.2 Hz of stimulation frequency increased MEP, which might not be only due to rTMS. Since the MEP should be decreased at the stimulation frequency, we speculate that a synergistic effect was observed.

When combining the input by interhemispheric communication from the contralateral motor cortex with the input via the sensory cortex by peripheral electrical stimulation or direct cortical stimulation by TMS there is an increased excitability in M1. The increase in MEP amplitude may occur because of the interactions in the motor cortex or subcortical structures [29]. The MEP may be increased because of primary mechanisms that increase the facilitatory circuits and/or decrease the inhibitory circuits in the M1.

4.4 Changes in RMT

The RMT is one of the factors that change MEP, which reflects the stimulus intensity needed to activate the most excitable corticospinal neurons and motoneurons [60]. In our study, RMT did not change throughout the experimental protocols. Hence, the influences of these elements are likely small.

4.5 Changes in ICF and SICI

In our BFT protocol, the ICF was significantly increased, and the SICI was decreased. According to Waller and others, bilateral movement caused increased ICF and reduced ICI in both hemispheres [28]. These results are consistent with those of our study, and the voluntary bilateral movement was thought to induce enhancement of the facilitation circuit and attenuation of the inhibitory circuit. In the APB-triggered c-MNS protocol, ICF significantly increased, but SICI did not show a significant change. Conversely, the APB-triggered i-TMS protocol did not show a significant change in ICF, but SICI significantly decreased.

Based on this, it is considered that the function of reducing the inhibitory circuit in APB-triggered i-TMS and enhancing the facilitatory circuits in the APB-triggered c-MNS protocol contributed to the increase in MEP. There are no robust effects such as in the BFT, but changes in the cortical circuits may have occurred in both protocols. The long lasting increase of cortical excitability has been thought to be evidence of LTP-like plasticity. Especially, the PAS protocol has been discussed the mechanics of plastic changes as the spike-timing-dependent plasticity (STDP) [61]. There are some similarities to our protocols that use inputs from multiple paths for a specific neuron.

4.6 Limitations

However, as our protocol used template matching techniques for detecting muscle activity, we could not precisely control the interstimulus interval (spike shapes that detect in this technique do

not always appear at the onset of muscle activity). Therefore, we are unable to discuss the time locked effect on our results as in the PAS protocol.

On the other hand, some studies investigate non-time dependent plasticity with multi source inputs which include voluntary movement. Bisio and others used paired stimulation protocols using voluntary finger movement and action observation with FES also showed that spontaneous movement tempo rate was significantly increased 30 minutes after the conditioning protocol [63]. A study which used paired corticospinal motoneuronal stimulation by Bunday and others showed increase in MEP 30min after intervention using TMS and FES (PNS) with voluntary movement [64]. These results suggest that inputs from multiple sources, including voluntary movements, may cause non-time dependent changes.

The dose of stimulation is also related to the plastic change, but the amount of muscle activity evoked by the three protocols was different from each other. Therefore, with our results we can not discuss the effect of dose. Further, we did not use unilateral control for each protocol independently. Hence, it is difficult to investigate the effect of artificial bilateral movement directly. These issues need to further investigate.

5. Conclusion

Artificially created arm movements (by APB-triggered i-TMS and the APB-triggered c-MNS) and voluntary BFT, increase the excitability of the M1. Though, voluntarily or artificially caused, bilateral training enhance the excitability of the M1. However, the changes in the SICI and ICF differed depending on the protocol. These differences may need to be taken into account when applying these protocols to rehabilitation.

6. Recommendations and future perspectives

The use of artificial bilateral training for patients with upper arm impairment is a technique that can be used those who can not move the impaired arm voluntarily.

The new protocols that have been tested in our study can be further investigated with the participation of patients with stroke in future. Moreover, we can assess the effect of artificial bilateral training in order to improve the ability to perform ADL and QOL of stroke survivors.

7. Acknowledgement

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Figures

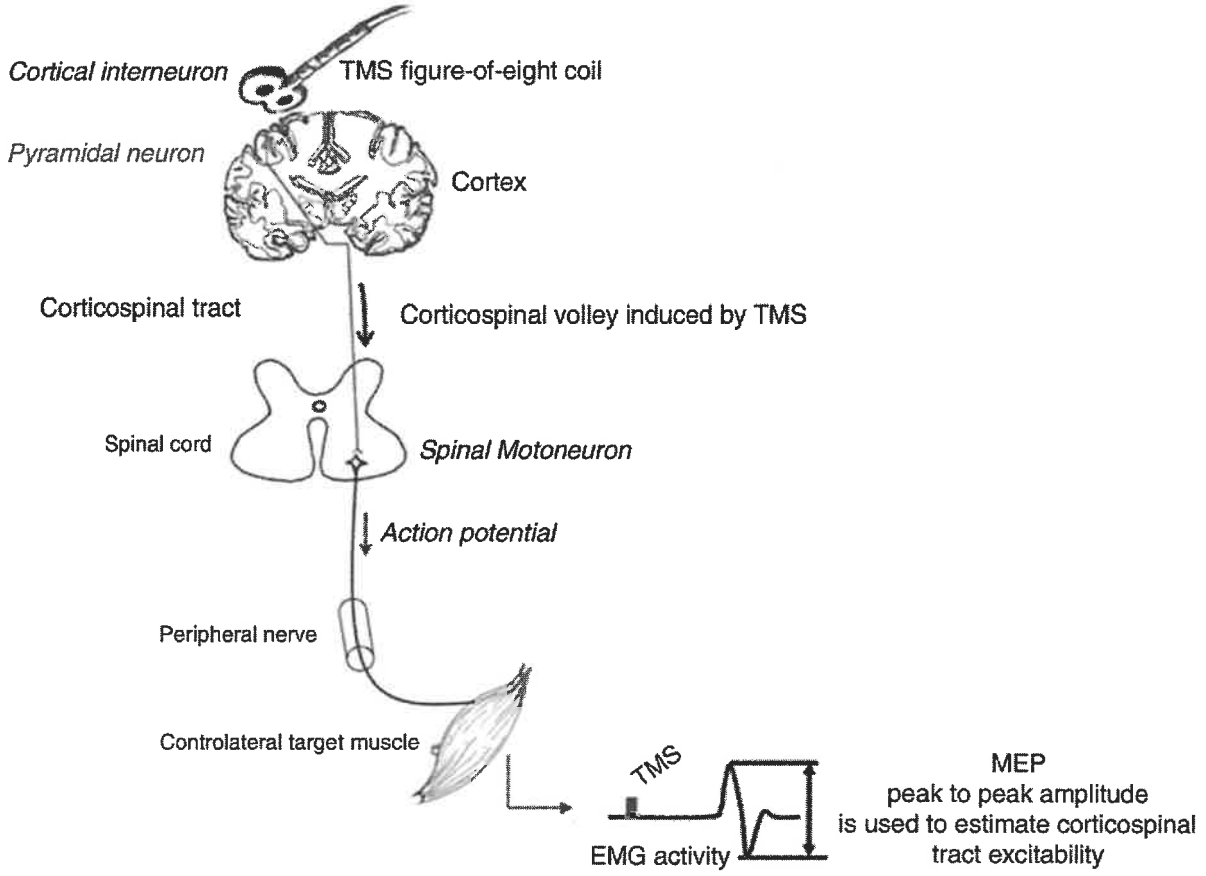
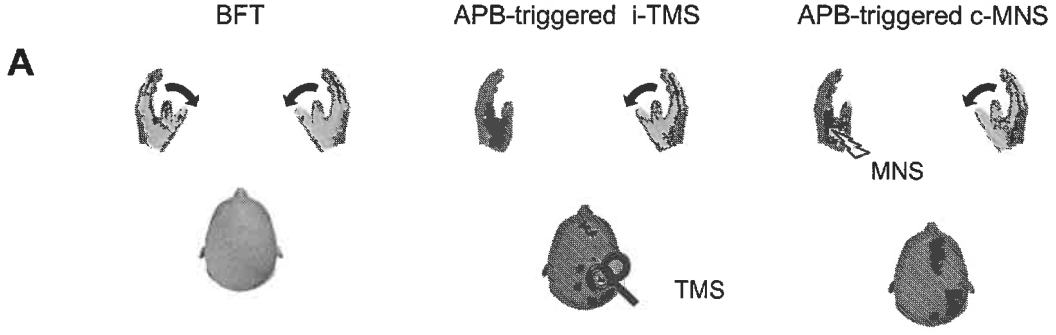


Figure 1. Simplified mechanism of action of TMS of the motor cortex

Note. This image was created from the research article "Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS)" authored by Wanalee Klomjai, Rose Katz, Alexandra Lackmy-Valle´



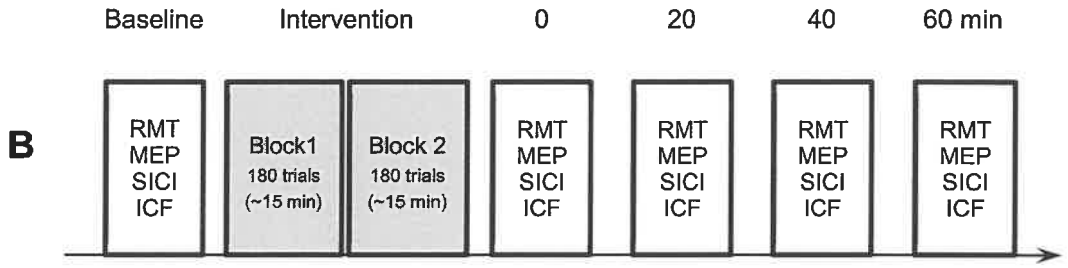


Figure 2. Protocol of the experiment

A: Schematic illustration of the intervention protocols in the present study. Left panel: In the bilateral finger training session (BFT), bilateral thumb abduction. Middle panel: In theAPB-triggered ipsilateral transcranial magnetic stimulation session (APB-triggered i-TMS), participants exerted unilateral thumb abduction and TMS over the motor cortex was triggered by EMG activity of the ipsilateral APB.

Right panel: APB-triggered contralateral median nerve stimulation session (APB-triggered c-MNS), participants exerted unilateral thumb abduction and contralateral MNS was triggered by EMG activity of the ipsilateral abductor pollicis brevis (APB) muscle.

B: Time course of each experiment session. Four types of outcome measurements [i.e., resting motor threshold (RMT), motor-evoked potential (MEP), short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF)] were performed before (baseline), immediately after (0), 20, 40 and 60 min after the intervention. The intervention period consisted of two blocks (180 trials over ~15 min each).

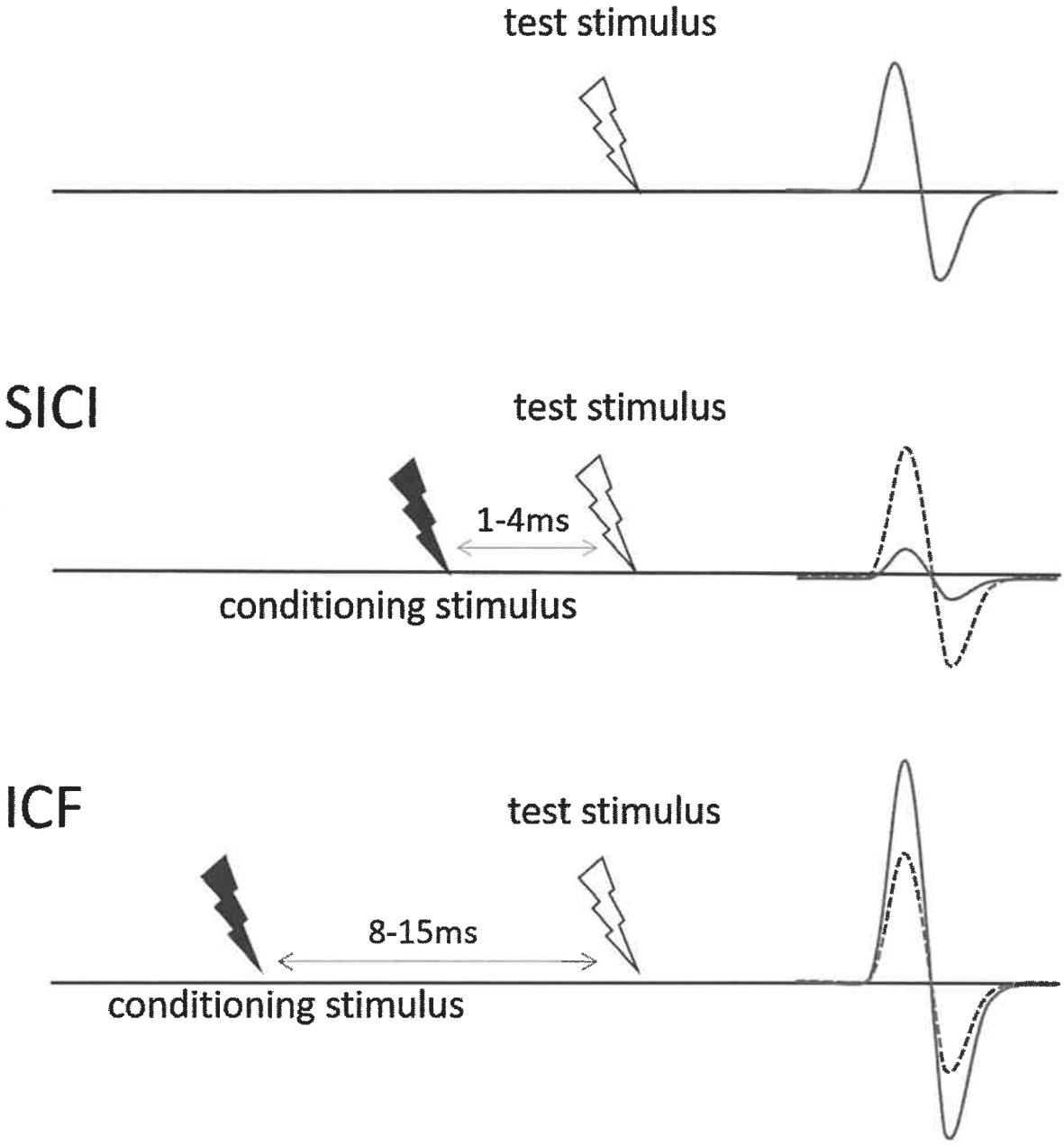


Figure3. Conceptual figure of short interval intracortical inhibition (SICI) and Intracortical facilitation (ICF)

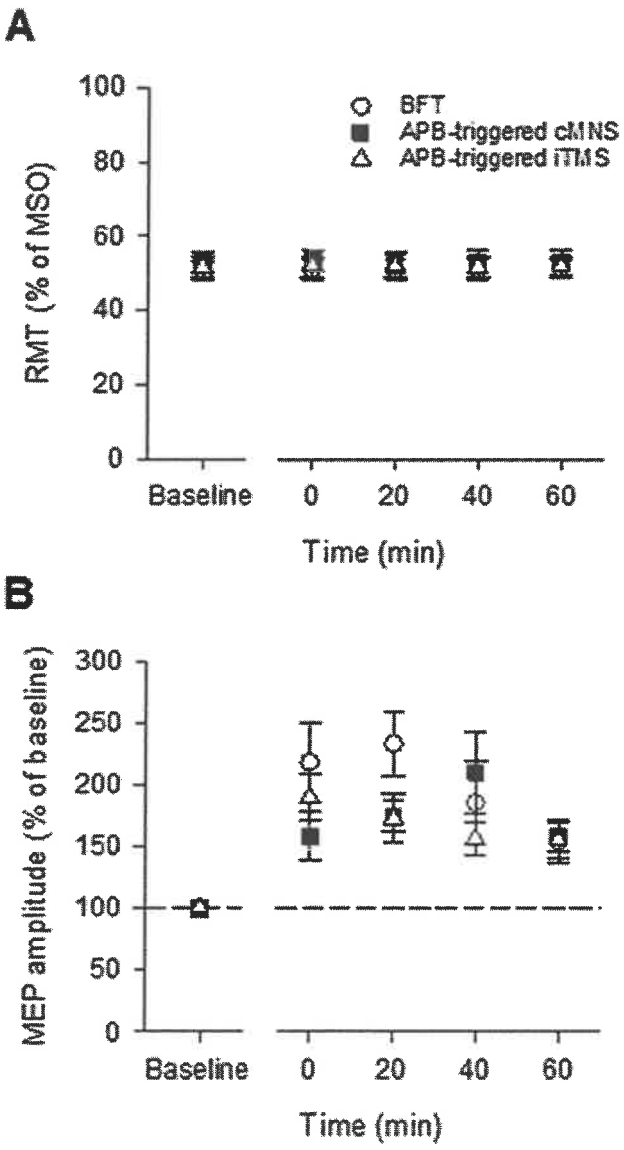


Figure 4. Averaged data of resting motor threshold (RMT) (A) and amplitude of the motor-evoked potential (MEP) (B) in all participants.

RMT is expressed as % of the maximum stimulator output (MSO). The MEP amplitude is expressed as % of the baseline value. Each plot and error bar represents mean and standard error of the mean, respectively.

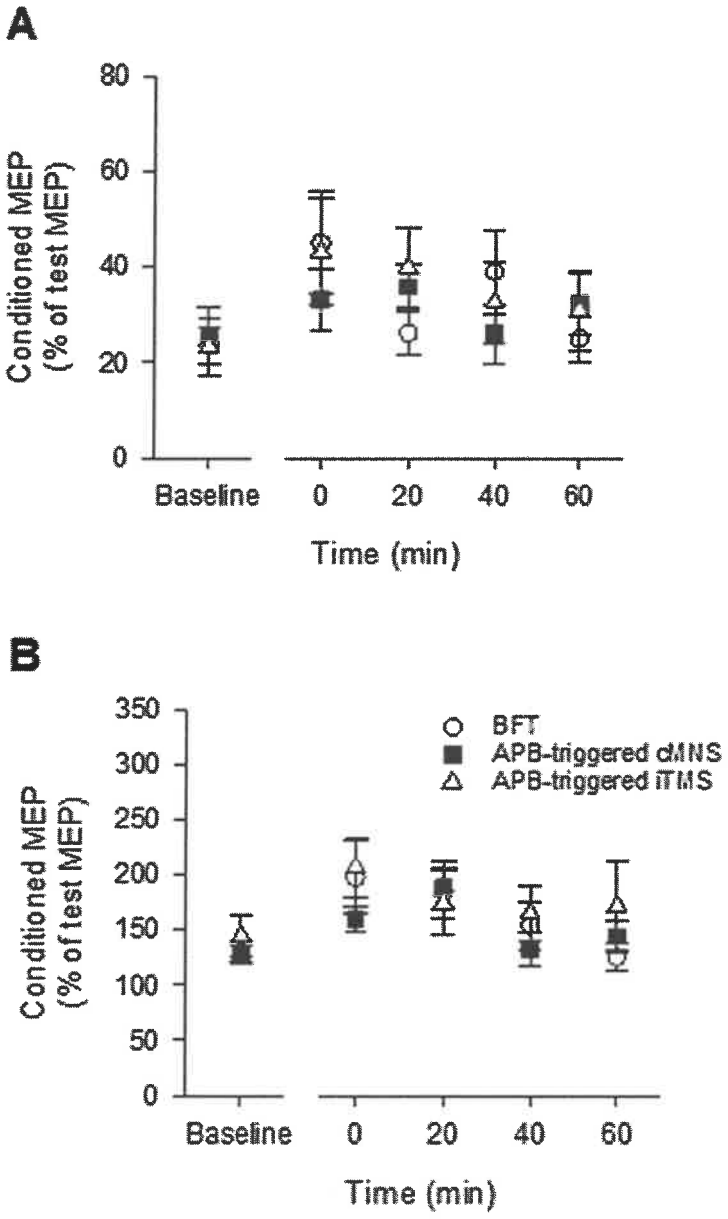


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Figure 5. Population data of short-interval intracortical inhibition (SICI) (A) and intracortical facilitation (ICF) (B) in all participants.

The conditioned MEP amplitude is expressed as % of the unconditioned MEP amplitude. Each plot and error bar represents mean and standard error of the mean, respectively.

Table 1. Mean and Standard error of the mean(SE) of all the participants (n=12)

Intervention	Outcome measure	Time course				
		Baseline	Post0	Post20	Post40	Post60
		Mean(SE)	Mean(SE)	Mean(SE)	Mean(SE)	Mean(SE)
BFT Intervention	RMT	50.83 (2.49)	51.08 (2.48)	51.08 (2.44)	51.08 (2.47)	51.50 (2.44)
	MEP	100.00(0.00)	217.92(32.12)	232.94(26.29	185.39(33.91)	154.16(16.70)
	SICI	23.50(3.86)	45.02(10.69)	26.09(4.39)	39.02(8.74)	25.01(4.76)
	ICF	130.72(10.17)	198.04(33.18)	186.29(26.12)	154.51(22.02)	125.67(12.07)
EMG triggered cMNS intervention	RMT	51.58(2.78)	51.83(2.74)	51.83(2.84)	51.67(2.68)	51.83(2.74)
	MEP	100.00(0.00)	189.67(18.56)	172.34(19.77)	156.32(12.97)	50.86(14.68)
	SICI	23.30(5.78)	43.23(11.05)	39.858.35)	32.60(8.63)	30.96(8.36)
	ICF	144.50(19.43)	206.50(26.49)	174.92(29.34)	164.88(24.72)	172.08(40.38)
EMG triggered i-TMS intervention	RMT	52.83(2.92	53.42(2.92)	52.83(2.93)	53.00(3.01)	52.83(3.03)
	MEP	100.00(0.00)	158.11(19.42)	174.31(12.31)	210.17(32.84)	158.51(12.51)
	SICI	25.74(5.81)	33.17(6.58	35.84(4.84)	25.98(6.26)	32.24(6.35)
	ICF	127.38(9.02)	159.25(11.85)	188.28(18.16)	132.70(15.53)	144.30(14.14)