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Jacobs Journal of Physical Rehabilitation Medicine

Research Article

Excitability of the Ipsilateral Motor and Premotor Cortices during Unilateral Finger Movements: A Combined fMRI and TMS Study

Ah-Young Jun[1], Suk Hooh Ohn[2], SeungHo Ahn[2], Kwang-Ik Jung[2], Woo-Kyoung Yoo[2,3*]

[1]*Department of Physical Medicine and Rehabilitation, Dongtan Sacred Heart Hospital, Hallym University College of Medicine*

[2]*Department of Physical Medicine and Rehabilitation, Hallym University Sacred Heart Hospital, Hallym University College of Medicine,*

[3]*Hallym Institute for Translational Genomics & Bioinformatics, Hallym University College of Medicine*

**Corresponding author: Dr. Woo-Kyoung Yoo, Dep. of Physical Medicine and Rehabilitation, 896, Hallym University Sacred Heart Hospital, Pyeoung-chon dong, Dongan-gu, Anyang, Gyeonggi-do 430-070, Republic of Korea, Tel: +82-31-380-3860; Email: mdwooky@gmail.com, wooky@hallym.ac.kr*

Received: 06-01-2015

Accepted: 07-29-2015

Published: 08-05-2015

Abstract

There was a considerable confusion concerning the brain areas that contributes to ipsilateral activity during unilateral finger movement. Limited evidence suggested engagement of the ipsilateral dorsal premotor cortex (PMd) more than the ipsilateral primary motor cortex (M1) only in functional magnetic resonance imaging (fMRI). In this study, we aimed to delineate the physiological changes obtained by transcranial magnetic stimulation (TMS) in the ipsilateral M1 during unilateral hand movement by comparing it with the functional magnetic resonance imaging (fMRI) activity obtained from M1 and PMd within the same set of subjects. The motor evoked potential (MEP) amplitudes changes were well correlated with the relative hemodynamic changes of the ipsilateral PMd, but they were not correlated with those of the ipsilateral M1 on the fMRI. These results support the notion that the activities of the ipsilateral PMd mediate the changes of excitability in the ipsilateral M1 during unilateral finger movements.

Keywords: Excitability; Dorsal Premotor Cortex; Primary Motor Cortex; Transcranial Magnetic Stimulation; Functional Magnetic Resonance Imaging

Introduction

The previous functional imaging studies have demonstrated that ipsilateral motor cortex activation occurred during complex motor tasks [1,2] and upon non-dominant hand movement in healthy volunteers [3,4]. While the functional role of ipsilateral activation is still a matter of debate, [2,3] Verstynen et al [5]. described that the ipsilateral activation is not necessarily related to the execution of complex movements but is rather related to higher level of controls associated with action retrieval, preparation, and/or selection of the ipsilateral motor cortex. This view is in line with the results that were shown in patients with lesions of the central motor systems [6]. A controversial issue that needs to be addressed here is the location of the ipsilateral activity. Many studies demonstrated ipsilateral motor cortex

activation shifted to lateral and ventral area compared to contralateral activation during voluntary finger movements, and suggested the possibility of activation of the ipsilateral dorsal premotor cortex (PMd) rather than ipsilateral primary motor cortex (M1) in functional magnetic resonance imaging (fMRI) [7,8].

On the other hand, cortical excitability that was measured by transcranial magnetic stimulation (TMS) in the ipsilateral hemisphere while performing unilateral finger movements has been discussed mostly based on assumption of changing the excitability in the M1 as TMS stimulate the primary motor cortex [9-12]. It also reported strong facilitation likewise in imaging studies, while performing complex finger movements [13]. Beyond the presumed changes in ipsilateral M1, interhemispheric interaction between bilateral M1 has been generally accepted to be induced by inhibition of contralateral M1 through transcallosal inhibition via corpus callosum [14].

There was another line of studies that showed ipsilateral PMd effects by stimulating contralateral M1 in response selection, which showed causal relationship between ipsilateral PMd and contralateral M1 suggesting the premotor for ipsilateral activity [7,8,15,16]. Nevertheless, it is still unclear whether the location of the ipsilateral activity during voluntary finger movements is related with that of the M1 or the PMd especially when it comes to TMS.

For the purpose of elucidating the ipsilateral activity, we measured the changes in the hemodynamic responses of the ipsilateral M1 and the ipsilateral PMd using fMRI during finger movements with different complexity and dominance and compared the change with motor evoked potential (MEP) amplitude obtained in the M1 using TMS within the same set of individuals.

Materials and Methods

Subjects

Seven healthy right-handed volunteers (five males and two females) between the ages of 19 and 24 (mean age: 21 years) participated in this study. The subjects' handedness was assessed using the Edinburgh Handedness Inventory [17] and all subjects were deemed right-handed. We received the approval of the local ethics committee for the experimental procedures, and a written informed consent was obtained from all subjects.

Apparatus

The subjects were comfortably seated in a reclining armchair with both hands pronated on a pillow, and they were instructed to keep their hand and forearm muscles as relaxed as possible. During stimulation, surface electromyography (EMG) was recorded and monitored continuously on-line (Neuroscreen Plus, Erich Jaeger, Germany) using Ag-AgCl electrodes. Active electrodes were attached to the skin overlying the abductor pollicis brevis (APB) muscle. Reference electrodes were placed over the metacarpophalangeal joint. The EMG signals were filtered (10-2000 Hz), amplified, displayed and stored for off-line analysis.

Procedure

Transcranial magnetic stimulation. A MagStim 200® magnetic stimulator (MagStim Company, UK) with a maximum output intensity of 2.0 T was used for the TMS of the motor cortex, along with a 70-mm figure-of-eight coil. Specifically, the figure of eight coil was positioned tangentially to the scalp at an angle of 45° from the mid-sagittal line such that the electromagnetic current flow perpendicular to the central sulcus. The coil was systematically moved in 1 cm steps at constant supra-threshold stimulus intensity to detect the optimal scalp location ("the hot spot") for eliciting stable MEPs in the APB muscle. Once the hot spot had been identified then marked with a pen to ensure the constant positioning of the coil throughout the experiment. The resting motor threshold (RMT) was determined as the minimum TMS intensity that produced at least five MEPs of ≥50 μV peak-to-peak amplitude out of 10 consecutive trials delivered at a rate of 4-5 s inter-stimulus interval [18]. The test stimulus intensity was determined to be 130% of the resting motor threshold. The subjects were asked to remain silent each time stimulation was delivered to avoid speech-induced modulation of cortical excitability. The subjects were also monitored for drowsiness and asked to keep their eyes open throughout the experiment.

Experimental protocol

Prior to the experimental procedure, all subjects were trained task by using a metronome set at 1 Hz. Three different conditioning tasks were used for the experiment. The subjects kept their hands at rest for the control task (task 1). For the task 2, they performed 1-Hz opposition movements of the 3rd finger to the thumb (the simple movement). The task 3 was composed of alternating thumb opposition movements to the other fingers repeatedly in the following order: 5th, 3rd, 4th and 2nd finger, (the complex movement). The tasks were performed on both hands, and the sequence of which hand was used and the task was randomized and counterbalanced (Figure 1).

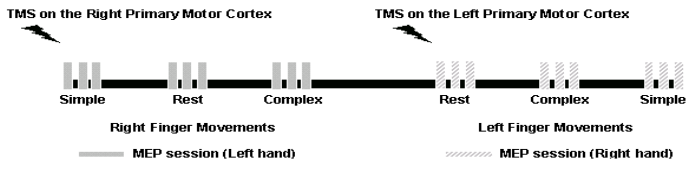

Figure 1. Experimental design for transcranial magnetic stimulation (TMS). Single pulse TMS were applied over the primary motor cortex (M1) that was ipsilateral to the moving hand and the motor evoked potentials (MEPs) were obtained from the Abductor Pollicis Brevis

muscle of the opposite hand.

During each conditioning tasks, fifteen consecutive MEPs were obtained from APB muscle on resting hand. The subjects were instructed to keep their muscles relaxed and if any voluntary muscle activity were detected, the data were not included in analysis.

Functional MRI

A 1.5 T Intera 9.0 Philips MRI system was used for this study. A T1 weighted anatomical scan was acquired from each subject [MPRAGE 3D, TR (repetition time) = 25 ms, TE (echo time) = 4.6 ms, Flip angle = 30°, FOV (field of view) = 230.0 and matrix = 256 x 256]. For the functional scan, the task were presented on the screen using SuperlabPro 2.0 software (Cedrus Co., Phoenix, AZ) and a 5 min echo-planar imaging that consists of alternating 15 sec blocks of rest and movement was performed (20 x 5 mm axial slices, TE = 30 MS, TR = 3000 ms, FOV = 230 and matrix = 128 x 128). The simple or complex movements for the right or the left hand were randomly arranged in the separate blocks.

Image Analysis

The image analysis was performed with using SPM 5 software. For the analysis, all images were realigned to the first volume; motion artifacts were corrected, co-registered with subject's corresponding anatomical (T1-weighted) images, and then normalized into standard stereotaxic space. Images were smoothed using a 5 mm full-width-at-half-maximum. Gaussian kernel and the statistical analysis were performed for each condition using a general linear model. The voxels were defined as being significantly activated for each contrast if they met the requirement of the uncorrected $p < 0.001$. For the group analysis, a random effect analysis was used. Further analysis of the fMRI data was focused on the individually defined volumes of interest (VOIs); the ipsilateral M1 and the ipsilateral PMd. The VOIs were selected within following anatomically defined criteria: [19] the M1 was defined as the volume of the cortex that include the posterior half of the precentral gyrus (including the anterior bank of the central sulcus). The PMd included the anterior bank of the precentral gyrus as well as the anterior bank of the precentral sulcus. The relative hemodynamic changes were obtained from each region by calculating the difference in eigenvariate of all activation and resting conditions of each time series of VOI, within a 2.5 mm radius from the peak coordinates of activation that was noted in each subject's data.

Statistical Analysis

As a first step, the MEP amplitude data for each of the tasks were transformed to a log scale after testing for normality (Kolmogorov--Smirnov tests). To test the statistical significance of the MEP amplitude changes according to the movement complexity and the dominance of the hand, we conducted multivariate analysis (a mixed model), the movement complexity (rest, simple and complex) and the dominance of the hand (dominant and non-dominant) as factors. As a second step, in order to test the relationship between the changes of the MEP amplitude and the relative hemodynamic changes that were noted for each brain area, i.e., the ipsilateral PMd and the ipsilateral M1, we also conducted multivariate analysis applying a mixed model for continuous dependent variables (ie, the changes of the MEP amplitude and the relative hemodynamic changes) by using the complexity of the movements and the dominance of the hand as independent variables. We analyzed this relationship by setting the relative hemodynamic changes of the ipsilateral PMd and the ipsilateral M1 as the independent variables, and the relationship could be expressed as a linear equation.

Results

MEP changes in the TMS study

For all the subjects, the mean baseline cortical excitability threshold was 65 ± 10 (mean ± SD%). The mean baseline MEP amplitude was 1.37 ± 0.55 mV. The average MEP amplitude for the simple movements of the dominant hand was 0.78 ± 0.21 mV, and that of the non-dominant hand was 1.07 ± 0.33 mV. In addition, for the complex finger movements, the MEP amplitude for the dominant hand movement was 1.56 ± 0.79 mV, and that of the non-dominant hand was 1.96 ± 0.95 mV. The MEP amplitude obtained from the ipsilateral hand movements showed bigger changes for the movements of the non-dominant hand than that of the dominant hand ($F(1,6) = 45.41$, $p = 0.0005$), and also for the complex movements than that of the simple movements ($F(2,12) = 89.21$, $p < 0.0001$) (Figure 2).

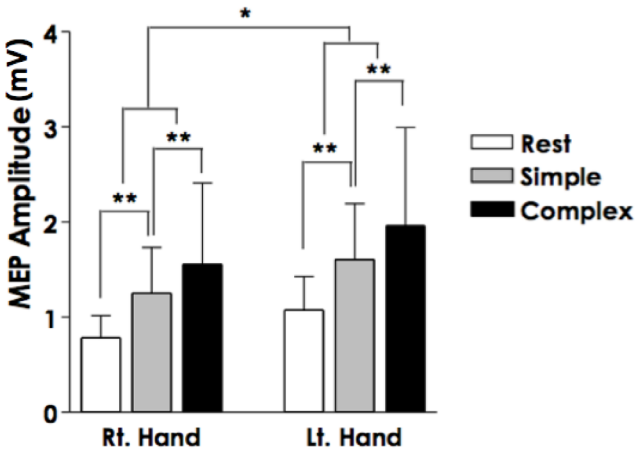

Figure 2. The figure shows the differences in the amplitudes of motor evoked potentials (MEPs) that were obtained by magnetic stimulation of the ipsilateral primary motor cortex (M1) during resting, and simple and complex finger movements of the unilateral hand. Error

bars indicate the standard deviation. *P<0.01, ** P<0.001.

Activation of the ipsilateral PMd and the M1 on the fMRI

The finger opposition tasks significantly activated the ipsilateral PMd when compared with the resting state. The results of the random effect group analysis for the contrasts (Rt. Simple – Rest, Rt. Complex – Rest, Lt. Simple – Rest and Lt. Complex – Rest) are presented in Figure. 3. The group analysis of the individual fMRI data showed that there was greater activation in the ipsilateral PMd for the movements of the non-dominant hand as compared to the dominant hand.

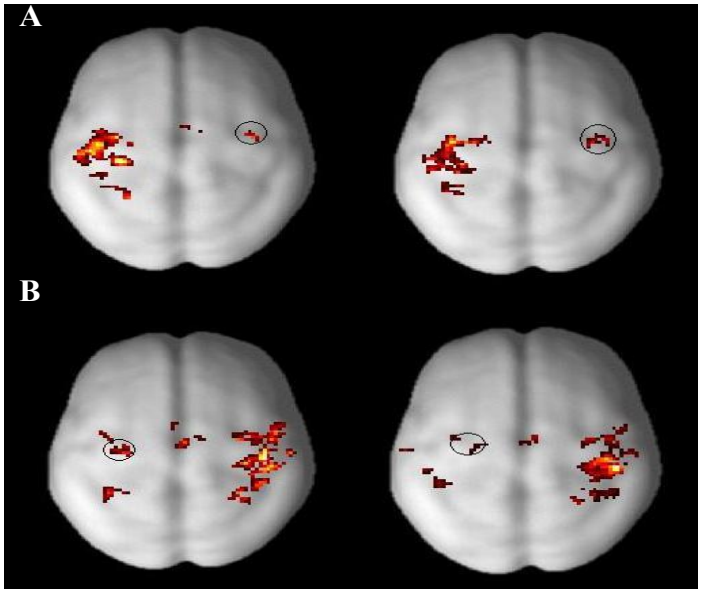

Figure 3. The group activation patterns on functional magnetic resonance imaging (fMRI). (A) The cortical activation pattern during simple finger opposition movements of the dominant (left picture) and non-dominant (right picture) hand (uncorrected p < 0.001). (B) The cortical activation pattern during complex finger opposition movements of the dominant (left picture) and non-dominant (right picture) hand (uncorrected p < 0.001). Open circles indicate the activation of the ipsilateral dorsal premotor cortex (PMd).

The relative hemodynamic change of the ipsilateral PMd for the simple movements of the non-dominant hand was 2.66 ± 0.89 (mean ± SD%), which was significantly greater than that for the dominant hand (1.90 ± 0.85) ($F(1,6) = 66.20$, $p = 0.0002$). In the case of the complex finger movements, the relative hemodynamic change of the non-dominant hand was shown to be 3.18 ± 2.86, while that for the dominant hand movement was 2.26 ± 1.01. When compared to the simple movement, the complex movement was noted to recruit significantly greater activation of the ipsilateral PMd ($F(1,20) = 7.45$, $p = 0.0183$), and this was also significantly different between the dominant and non-dominant hands ($F(1,6) = 45.45$, $p = 0.0005$) (Figure 4A).

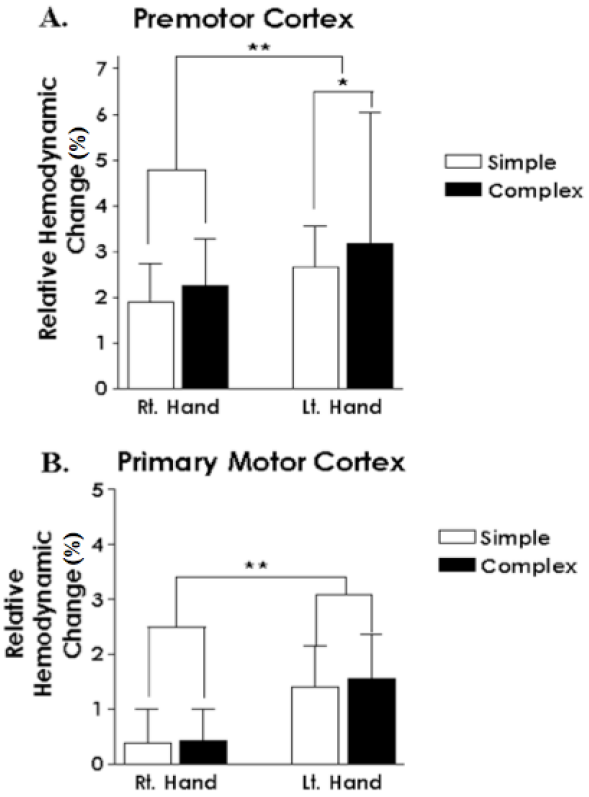

Figure 4. The figure shows the relative hemodynamic changes that were detected by the BOLD (blood-oxygen level dependant) signal changes on the ipsilateral dorsal premotor cortex (PMd) (A) and primary motor cortex (M1) (B) during simple and complex movements of the unilateral hand. Error bars indicate the standard deviation.*P<0.05, ** P<0.001.

The ipsilateral M1 was less activated in contrast to the ipsilateral PMd. The average group data for the relative hemodynamic changes in the M1 for the simple movements of the dominant hand and the non-dominant hand were 0.40 ± 0.61 and 1.42 ± 0.74, respectively, and in the case of the complex finger movements, they were 0.43 ± 0.58 and 1.55 ± 0.83, respectively. The relative changes of the ipsilateral M1 showed no difference between the simple movement and the complex movement ($F(1,20) = 1.46$, $p = 0.2495$), while the difference between the dominant hand and the non-dominant hand was significant ($F(1,6) = 304.89$, $p < 0.0001$) (Figure 4B).

Comparison between the MEP amplitudes and the hemodynamic responses

The results for the hemodynamic changes of the ipsilateral PMd for the finger movements of different complexity and dominance varied across the subjects. However, there was good similarity noted between the pattern of the hemodynamic changes and the MEP amplitudes. The mixed analysis demonstrated that the changes of the MEP amplitude according to the complexity was significantly correlated, in a linear relationship, with the relative hemodynamic changes

in the ipsilateral PMd, when consideration was given for the conditions of task complexity and hand dominance (intercept = 1.5072, p = 0.0003; F(1,16) = 20.41, p < 0.0001), whereas the relative hemodynamic changes in the M1 did not show any significant relationship (F(1,16) = 0.05, p = 0.8285) (Figure 5).

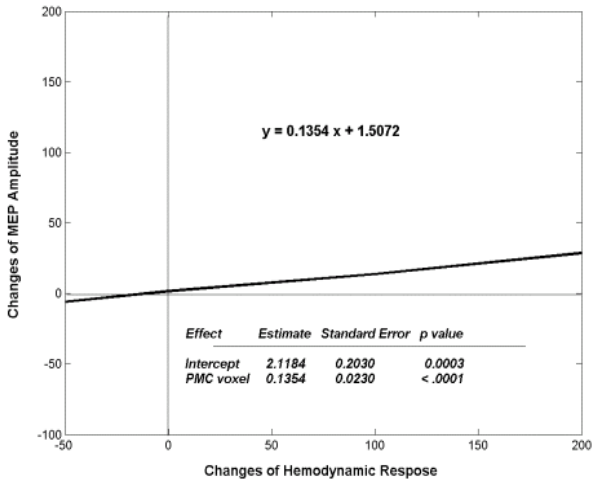

Figure 5. Correlation between the changes on the ipsilateral motor evoked potential (MEP) amplitudes and the hemodynamic changes of the ipsilateral dorsal premotor cortex (PMd) on the functional magnetic resonance imaging (fMRI) during simple and complex finger movements.

Discussion

This study has demonstrated that the changes in the excitability of the ipsilateral M1 as measured by MEP amplitudes during the unilateral finger movements showed significant correlation with the hemodynamic changes of the ipsilateral PMd, but not with that of the ipsilateral M1 on fMRI. The activity of the ipsilateral PMd, which was increased more during the movements of the non-dominant hand and complex movements, might be an important physiological change that modulates the excitability of the ipsilateral M1 during unilateral finger movement via the intracortical facilitation.

Unilateral finger movements are mainly controlled by the contralateral motor cortex, but their performance can be associated with the activation of the ipsilateral motor cortex [5,20,21]. Ipsilateral motor cortex activation has been reported consistently in fMRI studies in normal volunteers and in patients with stroke [1-4,22]. The region activated in the ipsilateral hemisphere upon unilateral finger movements is located more anterior than the location of the contralateral M1[21]. Our results confirm these observations that the locus of ipsilateral activity is centered in the premotor region of the precentral gyrus and not in M1.

The excitability of the ipsilateral M1 is known to increase with increasing contraction strength, [23,24] as well as contributing to the setting of the muscle recruitment timing, most likely through either inhibitory or facilitatory transcallosal influences onto the contralateral M1 [25]. Activity in ipsilateral M1 would therefore contribute to shape precisely the muscular command originating from contralateral M1. In this study, we found that the ipsilateral activity during unilateral hand movement was not significantly correlated with M1 activity in fMRI on either side. This was consistent with the notion that transcallosal inhibition is crucial in suppressing the mirror activation of the ipsilateral motor cortex during intended unilateral hand motor tasks [26,27]. Further support for this inhibitory control hypothesis comes from several previous fMRI [28] and TMS [29] studies of the cortical dynamics during movement. This work has shown a suppression of activity/excitability in M1 during the preparation and execution of an ipsilateral movement. However, when the movements are complex, there is an increase in bilateral activation [5] and correspondingly, the suppression of M1 is attenuated [28].

There are studies suggesting that the PMd is the region that is activated upon ipsilateral distal movements, while there was sparing or even a significant deactivation of the primary sensorimotor cortex in the normal subjects [6,27,30]. The suggested mechanisms for ipsilateral PMd activation upon the unilateral finger movement are related to storing motor sequences for the working memory, [31,32] motor skill learning, [33,34] and post-movement sensation processing [20]. Verestynen et al [5]. also described that the ipsilateral activation is not necessarily related to the execution of complex movements but rather higher-level controls associated with action retrieval, preparation, and/or selection of the ipsilateral motor cortex. They hypothesize that when the spatiotemporal pattern is very complex and when the contralateral hemisphere is not well trained in the production of this task, the ipsilateral motor cortex can help shape the appropriate pattern through both excitatory and inhibitory connections. In the present study, the activation of the ipsilateral PMd became more prominent during the complex finger movement than during the simple finger movement, which is consistent with previous study [5]. Our findings were also congruent with the results of Johansen-Berg et al. [6] they have reported the functional relevance of ipsilateral PMd activation on unilateral hand movement in normal volunteers and in patients with stroke, which further supports the functional recruitment of the ipsilateral PMd might have related to higher-level control of ipsilateral M1 for not only in healthy controls but also in stroke for the adaptive plasticity.

In contrast to the fMRI, TMS activates the descending pathways by primarily exciting the interneurons that target the pyramidal tract neurons via the I-waves, and to a lesser extent, TMS provides for the direct stimulation of the descending pyramidal axons [35]. As a result of this methodological limitation, the previous TMS studies have described the excitability changes in the ipsilateral M1 during ipsilateral

hand movement; [9-12] however, there have been inconsistent results concerning the task complexity. Tinazzi and Zanette [9] have reported increased excitability of the ipsilateral M1 only during the complex finger movements, while other studies have failed to show any differences between the simple and complex task [10]. Our results clearly demonstrated the changes of excitability according to the movement complexity and the hand dominance. The complex finger movements of the non-dominant hand resulted in the greatest MEPs, and these were noted in the group data. In addition, a number of TMS studies have reported the presence of inter-individual variability that was generated in the upper parts of the corticospinal tract and this was caused by the changing degree of cortical excitability [36,37]. Therefore, we applied both of these methods for measuring the neural activities in the same subject to compensate for the individual variability. The results that showed significant correlation between the changes of the hemodynamic response function of the activated voxels in the ipsilateral PMd and the MEP amplitude changes during the finger movements of different complexity and hand dominance implies that the changes in the PMd that were demonstrated on fMRI may have influence on the changes of the amplitude obtained from the M1 on the TMS study. Moreover, there was much greater activity of the ipsilateral PMd than of the ipsilateral M1, and this may additionally support the possibility that the iPMd may have affected the changes of the MEP amplitude in the TMS study as a result of intracortical facilitation [38]. Recent approaches using dual-site TMS giving a suprathreshold test stimulus on M1 followed by a subsequent conditioning stimulus to ipsilateral PMd at 125 ms after presentation of the cue during a two-choice reaction time task facilitated MEP also support it [39].

In addition, interhemispheric interaction between PMd and contralateral M1 has been suggested to have effect through different mechanism compared to interhemispheric interaction between M1; first, the low intensity of conditioning stimuli were effective only in PMd and secondly, tonic voluntary contraction increased only M1 but not PMd interhemispheric suppression and finally, conditioning TMS over right PMd only reduced short-interval intracortical inhibition in the left M1[15]. These differences make clear that interhemispheric interaction of PMd and contralateral M1 is more likely, which might be related in bimanual coordination. Even though this study did not directly compare the activities of M1 and PMd, the activation changes in the ipsilateral PMd that were observed on fMRI can be considered as important basic physiological changes for modulating the excitability of the M1 and corticospinal tract upon unilateral finger movements.

This study has some limitations. First of all, the sample size was too small to generalize into population, though it has statistical significance. It needs to be explored with large number of patients in the future. The second one is that no navigation tool was used for TMS in this study, which was reported to be superior in physiologic and behavioral results in navigated than non-navigated TMS, [40] although the location of M1 in TMS study would be not always necessitate navigation tool as measuring RMT in hotspot by eliciting stable MEPs in the APB muscle is standard method for M1 localization. The third is the fact that the possibility of the spreading of stimulation due to large coil as M1 and PMd are closely located, which warrant to be verified it in the future by using small coil [41]. The fourth one is that the anatomical definition would be suboptimal as it would be clearer if we have used cytoarchitectural maps used in neuroimaging tools. The last limitation would be the fact that we didn't perform TMS and fMRI at the same time, which we can't rule out the possibility of differing baseline status of brain activity.

Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2013R1A1A2012562).

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