学位（博士）論文　要旨

リズミックな一側手指筋収縮中の同側大脳皮質一次運動野興奮性変化について
― 経頭蓋磁気刺激法を用いた神経生理学的研究 ―

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EXCITABILITY CHANGE IN THE IPSILATERAL PRIMARY MOTOR CORTEX DURING A UNILATERAL RHYTHMIC CONTRACTION OF FINGER MUSCLES
: A NEUROPHYSIOLOGICAL STUDY USING TRANSCRANIAL MAGNETIC STIMULATION

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Chapter 1: General introduction

Recent transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) studies in human demonstrated that while performing a unilateral movement, activity of primary motor cortex (M1) ipsilateral to the movement side contributes to motor performance. (Muellbacher et al., 2000; Kobayashi et al., 2003; Sohn et al., 2003; Carson et al., 2004). And it has been well known that the modulations of ipsilateral M1 (ipsi-M1) excitability are dependent on type of motor task and difference in muscle force output level. Although the modulations of ipsi-M1 excitability depend on these task properties, little is known about the effect of rhythmic movement on modulations of ipsi-M1 excitability. In the recent stroke rehabilitation, it has been also reported that rhythmic movement training with affected limb in response to auditory cues is able to induce improvement of motor function and to produce re-organization in damaged hemisphere (Stinear et al., 2004; Waller et al., 2008). Hence, revealing effects of a unilateral rhythmic movement with auditory cues on modulations of ipsi-M1 excitability is important to enhance an understanding of human motor control. The main goal of the present study is to reveal effects of unilateral rhythmic contractions with isochronal auditory cues at three different frequencies on changes in ipsi-M1 excitability in healthy subjects by measuring motor evoked potential (MEP) induced in response to TMS. In general introduction, author explained background of the present study and relationships between rhythmic movement and brain activity form a perspective of neurophysiology and *neural-based rehabilitation*. In addition, the author provided reviews of anatomical or physiological M1 structures and principle of TMS using relative literatures.

The doctoral thesis is consisted of four experiments, which are shown as follows;

1. Experiment 1 (Chapter 2):
Excitability changes in the ipsilateral primary motor cortex during unilateral rhythmic contraction

2. Experiment 2 (Chapter 3):
Phase-independent change in the ipsi-M1 during unilateral rhythmic contraction

3. Experiment 3 (Chapter 4):
Neural mechanisms underlying the changes in ipsilateral primary motor cortex excitability during unilateral rhythmic muscle contraction

4. Experiment 4 (Chapter 5):
Changes in the ipsilateral motor cortex excitability induced by different frequencies of afferent inputs

Chapter 2: Excitability changes in the ipsilateral primary motor cortex during rhythmic contraction of finger muscles

Purpose: To investigate the effects of unilateral rhythmic muscle contraction with auditory cue at different frequency on modulations of ipsi-M1 and spinal motoneuron excitability by measuring MEP and F-wave induced in response to TMS and electrical nerve stimulation.

Methods: Eight healthy right-handed subjects participated in experiment 1. The subjects were instructed to perform the repetitive isometric abductions of their left index-finger at 10% of maximum voluntary contraction (MVC) according to a beep sound delivered at frequencies of 1, 2, and 3Hz. During each rhythmic contraction, TMS was delivered to left M1 for assessing the modulations of ipsi-M1 excitability. MEPs, which reflect the ipsi-M1 excitability, were recorded from right first dorsal interosseous muscle (FDI). In addition, the author recorded F-wave induced in the right FDI to assess the spinal motoneuron activity during these contractions.

Result and conclusion: Experiment 1 showed that modulations of ipsi-M1 excitability induced during unilateral rhythmic muscle contraction with auditory cues depended on frequency of rhythm itself. In particular, it was revealed that the ipsi-M1 was facilitated at 1 and 3Hz conditions and inhibited at 2Hz condition without any spinal motoneuron activity. Hence, this phenomenon is occurred at cortical rather than spinal level.

Chapter 3: Change in the ipsilateral motor cortex excitability is independent from a muscle contraction phase during unilateral repetitive isometric contractions.

Purpose: To confirm a feasible methodological approach to recording MEP in the opposing hand to the primary mover during unilateral rhythmic muscle contractions. In experiment 1, the author used randomized TMS trigger for evoking MEP in the right FDI to assess modulations of ipsi-M1 excitability. The advantage of such randomized TMS trigger is to assess ipsi-M1 excitability across all muscle contraction phase. However, validity of this trigger system had never been reported. Preliminary experimental results showed that MEP recorded from the opposing homologous muscle to the primary mover muscle appeared to be independent from the muscle contraction phase in the primary mover. According to this result, the author predicted that TMS can deliver to M1 ipsilateral to the primary mover muscle side regardless of the muscle contraction phase in the primary mover. In order to verify this hypothesis, experiment 2 was designed from two different perspectives. The author hypothesized that if phase-dependent changes in the ipsi-M1 excitability are not observed, the randomized TMS trigger can be revealed as appropriate method.

Methods: Ten healthy right-handed subjects participated in experiment 2. We instructed the subjects to perform repetitive isometric contractions of left index finger abduction at 10% of MVC according to a beep sound delivered at 1Hz. During performance of muscle contractions, TMS was automatically delivered to one M1 at one of eight intervals after EMG onset (0, 20, 40, 60, 80, 100, 300, and 500ms). MEPs were recorded from right and left FDI.

Result and conclusion: Ipsi-M1 excitability was enhanced throughout the muscle contraction phase. However, the enhanced ipsi-M1 excitability induced by unilateral repetitive isometric contractions of index finger abduction was hardly affected by the muscle contraction phases. Result of experiment 2 suggested that the randomized TMS trigger is revealed as appropriate method for assessing ipsi-M1 excitability induced during rhythmic unilateral muscle contractions.

Chapter 4: Neural mechanisms underlying the changes in ipsilateral primary motor cortex excitability during unilateral rhythmic muscle contraction.

Purpose: Experiment 1 demonstrated that ipsi-M1 excitability was modulated by unilateral rhythmic contractions, and these modulations depended on frequency of rhythm itself. However, little is known regarding detailed neural mechanisms to produce these phenomena. The purpose of the experiment 3 was to reveal the detailed neural mechanisms for modulations of ipsi-M1 excitability by using paired-pulse TMS paradigms.

Methods: Twenty-eight healthy right-handed subjects participated in experiment 3. The subjects were asked to perform repetitive left index finger abductions at 10% of MVC in response to isochronic auditory cues at three different frequencies (1, 2, and 3Hz). While performing those contractions, cortical inhibition/facilitation within ipsi-M1, interhemispheric inhibition from contra- to ipsi-M1 and dorsal premotor cortex (PMd)-M1 connectivity from contra- to ipsi-hemisphere were examined by using paired-pulse TMS techniques. The reason for choosing PMd-M1 connectivity is that PMd has been reported to be one of the main centers for auditory-motor interaction (Chen et al., 2006).

Result and conclusion: Significant modulations of long intracortical inhibition (LICI) within ipsi-M1 and PMd-M1 connectivity were detected and these modulations depended on the rhythm frequency that was in agreement with modulations of ipsi-M1 excitability. PMd is responsible for rhythmic movement with auditory cue (Chen et al., 2006), which is coincident with the result of experiment 3. In addition, LICI circuit has been reported to reflect activity of cerebellum and subcortical area including basal ganglia and thalamus (Daskalakis et al., 2004). There is good evidence that rhythmic movement specifically activates cerebellum and subcortical area (witt et al., 2008). Hence, there is a possibility that the modulations of LICI within ipsi-M1 induced during the unilateral rhythmic muscle contractions reflect activity of subcortical area.

Chapter 5: Changes in the ipsilateral motor cortex excitability induced by different frequencies of afferent inputs

Purpose: The purpose of experiment 4 was to investigate effects of unilateral muscle afferent inputs from the peripheral nerve induced by mimicking the rhythmic contractions on modulations of ipsi-M1 excitability.

Methods: Sixteen healthy right-handed subjects participated in experiment 4. While electrical stimulation (ES) was applied to the left ulnar nerve at three different frequencies (1, 2 and 3Hz) to produce artificial muscle afferent inputs, TMS was then delivered to the left M1 to elicit MEP in the right FDI.

Result and conclusion: Modulations of ipsi-M1 excitability provoked by the muscle afferent inputs with different frequencies were in good agreement with those induced by rhythmic muscle contraction tasks in experiment 1. Thus, Ipsi-M1 excitability was enhanced at 1 and 3Hz ES conditions, and reduced at 2Hz ES condition. Result of experiment 4 suggests that frequency-dependent afferent input from the periphery is also one of the important roles to modulate ipsi-M1 excitability.

Chapter 6: General discussion

The novel findings of the present study show that the unilateral rhythmic contractions or muscle afferent inputs alone at different frequencies had an effect on modulations of ipsi-M1 excitability that depended on rhythm frequency. In addition, it was suggested that PMd and the subcortical area or cerebellum activities may be involved in modulations of ipsi-M1 excitability induced during rhythmic contractions. As for the clinical implications, the novel findings of the present study are applicable to movement-based stroke rehabilitation in the near future and could be the first step in the direction of "*neural-based rehabilitation*".