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Response of Motor Evoked Potential by Paired Pulse Stimulation with Supra-Motor Threshold

by

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1. INTRODUCTION

Transcranial magnetic stimulation (TMS) is a noninvasive technique to stimulate the brain directly. The figure-eight coil used for TMS has a magnetic stimulation resolution of less than 5 mm [1]. Accordingly, magnetic stimulation using the figure-eight coil is useful for the study of brain function. However, many previous studies have used repetitive stimulation, ranging from 100 to 1,000 pulses. The direct effect of magnetic stimulation for the brain is difficult to fully understand with the use of repetitive magnetic pulses [2-4]. For example, the peripheral muscle activity induced by magnetic stimulation to the motor cortex may affect the motor cortex through the feedback nerve [5]. The clinical application of TMS has already begun with treatment of diseases including Parkinson's disease and depression. However, the effects vary between patients, which appears to stem from a lack of fundamental research on the technique. Therefore, this study is aimed to clarify the effects of magnetic stimulation with one pulse. TMS was used to survey the effects of magnetic stimulation of the motor area. The effects of magnetic stimulation using TMS for motor cortex were evaluated by analyzing the amplitude of the motor evoked potential (MEP). Thus, this study applied paired-pulse TMS over the motor cortex. Conventionally, the first pulse of paired-pulse TMS is set at the sub-motor threshold (conditioning stimulus), then second pulse is a supra-motor threshold (test stimulus) [6]. This study focused on the effects of single-pulse magnetic stimulation with supra-motor threshold to the primary motor cortex (M1) in humans. MEP amplitude induced by the second pulse of magnetic stimulation with supra-motor threshold over M1 may be affected by the first pulse of magnetic stimulation. Those effects are estimated to be dependent on the stimulus frequency (interstimulus interval, ISI).

2. METHODS

A total of 5 healthy, right-handed volunteers were enrolled in this study, ranging 22 to 45 years old (4 men and 1 woman; mean age 30.6±10.6 years old). None of the participants had history of neurological or psychiatric disease.

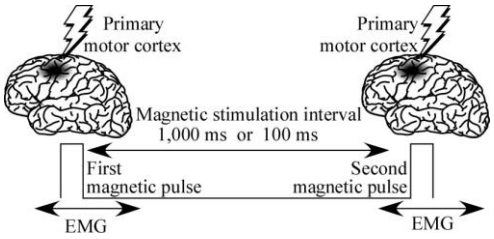

Fig. 1 Experimental paradigm. *The electrode used to measure motor evoked potential (MEP) was Ag/AgCl. EMG, electromyogram.*

All subjects gave informed consent for this study. In the experiment, all subjects were instructed to sit on a comfortable chair. TMS (Super Rapid stimulator, Magstim Co. Ltd, Whitland, Carmarthenshire, UK) with a figure eight-shaped flat coil (70 mm diameter) was applied over M1 of the left hemisphere. The magnetic stimulation by Super Rapid stimulator was biphasic magnetic stimulation. The MEP induced by TMS over M1 was measured at the right first dorsal interosseous (FDI) muscle using the Neuropack S1 (Nihonkohden Co. Ltd, Tokyo, Japan). The recorded data were analyzed using a digital band pass filter of 5 Hz to 3 kHz. The participant's individual resting motor threshold (rMT) was defined as an MEP with more than 50 μV peak-to-peak amplitude produced in at least five of 10 successive trials [3]. Fig. 1 shows the experimental paradigm. In both the first pulse and second pulse with paired-pulse TMS, magnetic stimulation intensity was 110% rMT. ***Experiment 1***: ISI of 1,000ms (1 Hz stimulus frequency). Four subjects (4 men, mean age 28±10.0 years old) participated in this study. ***Experiment 2***: ISI of 100 ms (10 Hz stimulus frequency). Four subjects (3 men and 1 woman, mean age 28±10.0 years old) participated in this study.

3. RESULTS

Paired-pulse TMS with an ISI of 1,000 ms had little effect on the induced MEP amplitude (Fig. 2). MEP amplitude with the second pulse decreased in subject A, and MEP amplitude with the second pulse increased in subject B. The average MEP amplitude with the ISI of 1,000 ms was increased by approximately 12% at the second pulse compared with MEP amplitude of the first pulse (Fig. 3). The MEP amplitude induced by the second pulse over M1 was not significantly different than that of the first pulse. In contrast, MEP amplitude induced by the second pulse with an ISI of 100 ms was decreased (Fig. 2). The average MEP amplitude was dramatically decreased by approximately 55% at the second pulse. The average MEP amplitude induced by the second pulse over M1 was significantly decreased compared with that of the first pulse ($p < 0.05$; Fig. 3).

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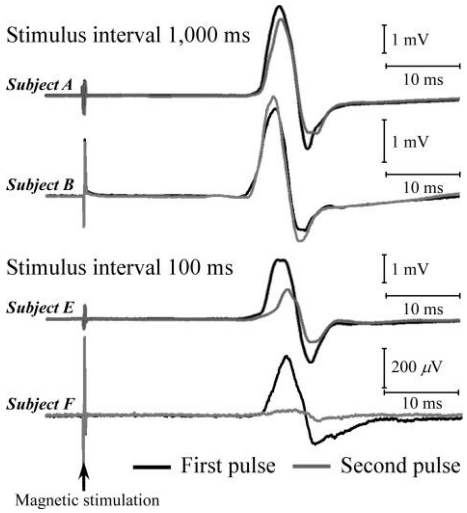

Fig. 2 MEP measured at the first dorsal interosseous (representative subjects). *The black line and gray line represent the MEP induced by the first and second pulse, respectively.*

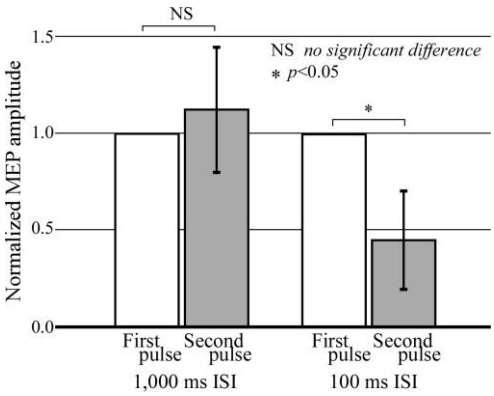

Fig. 3 Comparison of MEP amplitude induced by first and second pulses for the primary motor cortex (all subjects). *The measure data for each subject was normalized by the MEP amplitude which was induced by first pulse.*

4. DISCUSSION

In studies of repetitive TMS, magnetic stimulation inhibits neuronal activity with the low frequency of 1 Hz, and facilitates neuronal activity with the high frequency of 10 Hz [7]. This suggests that the change of neuronal activity may be affected by the ISI of paired-pulse TMS. However, the results of this study differ with previous studies using repetitive magnetic stimulation. In this study, the MEP induced by the second pulse with an ISI of 1,000 ms was not affected by the first pulse. However, the MEP induced by the second pulse was affected when the ISI was 100 ms, showing an inhibition of neural activity. A previous study has shown that with an ISI of 5 ms or less, the electromyogram (EMG) response by the second pulse with supra-motor threshold is inhibited by the first pulse with sub-motor threshold; in contrast, ISIs of 10 and 15 ms facilitate the EMG response [6]. In another study, with ISIs of 25–50 ms, the MEP amplitude by the second pulse is facilitated, and with ISIs of 60–200 ms, the MEP amplitude by the second pulse is inhibited [8]. The stimulus intensity in this previous study was 120–150% rMT for both the first and second pulses. However, in this previous study, motor threshold was defined as the intensity to induce an MEP of at least 20 μV by half of the stimuli in a series of 10, recording with the subject at rest. Therefore, the stimulus intensity was lower than 120–150% rMT in this study. Moreover, in another previous study, the MEP amplitude induced by the second pulse was reduced with ISIs of 50–200 ms, and the stimulus intensity was about 130% rMT [9]. In previous studies and this study, MEP amplitude induced by the second pulse of paired-pulse TMS with an ISI of 100 ms tended to be reduced with stimulus intensity of 110% to 150% rMT. These studies suggest that the change of MEP amplitude may be dependent on the stimulus interval. In particular, the MEP amplitude induced by the second pulse was drastically reduced with an ISI of 100 ms. MEP disappearance may relate to abolished I3 wave in corticospinal volleys and may not relate to afferent feedback from active muscles [9]. The corticospinal volleys induced by TMS were measured at the epidural electrode. Corticospinal volleys consist of D (direct) and I (indirect) waves, and the I3 wave is one of the later I waves [9, 10]. A previous study has shown that magnetic stimulation intensities of 1.4 and 2.0 T dramatically reduce the later I waves in corticospinal volleys, suggesting that the later I waves are reduced by magnetic stimulation of stronger intensity[10]. The result of the current study was consistent with previous reports. In this study, the MEP induced by the second pulse disappeared or was drastically reduced in all subjects. The absence period of later I waves are due to magnetic stimulation intensity, and there are individual differences in the absence period. The individual differences may affect the appearance of MEP. In summary, this study indicates that the absolute refractory period with individual differences exists with an ISI of 100 ms.

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