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ABSTRACT

In this study, we investigated the effects of repetitive paired-pulse transcranial magnetic stimulation (TMS) on the motor cortex excitability. The interstimulus intervals (ISIs) between the conditioning (first) stimulus and test (second) stimulus were 1,000, 200 and 100 ms. A total of 20 stimuli were delivered to the primary motor cortex using paired-pulse TMS at 10 s intervals, and the intensity of the magnetic stimulus was 110% of the resting motor threshold for each subject. For all ISIs, there was no significant correlation between the number of stimuli and the motor evoked potential (MEP) amplitude. However, there was slight correlation between the number of stimuli and the MEP amplitude in the 200 and 100 ms ISIs (200 and 100 ms ISIs: approximately $r = -0.40$; 1,000 ms ISI: $r = -0.17$). In addition, MEP amplitude increased during the second paired pulse stimulation when an ISI of 200 ms was used, but it decreased dramatically when an ISI of 100 ms was used. In contrast, MEP amplitude did not change significantly when a 1,000 ms ISI was employed. Therefore, 10 consecutive paired-pulse TMS stimuli with a 1,000 ms ISI may not have a cumulative effect on cortical excitability. Previous studies used a long duration (e.g., 6 minutes or longer by 0.1 Hz magnetic stimulation) of magnetic stimulation to evaluate cortical excitability. In evaluating cortical excitability by magnetic stimulation, it is important to shorten the period to reduce the subject's burden and to prevent body movement. Thus, our present findings suggest that repetitive paired-pulse TMS with an ISI of 1,000 ms is suitable for the rapid evaluation of cortical excitability.

I. INTRODUCTION

Transcranial magnetic stimulation (TMS) is a non-invasive method for directly stimulating the human brain. The magnetic field pulse generated by a magnetic coil over the scalp induces eddy currents in the brain.[1] The development of the figure-eight flat coil permits stimulation of brain tissues at 5 mm resolution.[2] These techniques have advanced the treatment of neurological disease and studies of brain function. Using successive magnetic stimulation at supra-motor threshold, magnetic stimulation below 1 Hz suppresses cortical excitability,[3,4] while stimulation above 5 Hz facilitates cortical excitability.[4,5] Previous studies in which successive magnetic stimulation was given to the primary motor cortex suggest that peripheral muscle activity may affect cortical excitability.[6]

Paired-pulse TMS, an alternative to conventional TMS, is considered to not affect the cortex via nerve feedback.[7] In this method, paired TMS stimuli are delivered to the same area (e.g., motor cortex). The intensity of the conditioning (first) stimulus is at sub-motor threshold, while the test (second) stimulus is at supra-motor threshold. Motor evoked potentials (MEP) induced by the second stimulus are considered to be an effect of the first stimulation on the motor cortex, and therefore, the second stimulus can be used to evaluate cortical excitability.[7] In most previous studies of

paired-pulse TMS, the interstimulus interval (ISI) between the two pulses was very short (≤200 ms). In these studies, cortical excitability was suppressed for 1 to 6 ms after the first stimulus, and particularly dramatically between 2 and 3 ms.[8–14] In contrast, cortical excitability was facilitated at 10 and 15 ms,[7–9,11,13] at 25 to 50 ms,[10] and at more than 200 ms,[10] after the first stimulus. Paired-pulse TMS has been used to evaluate cortical excitability, but not when magnetic stimulation intervention is given. Generally, conventional TMS, of 0.1 Hz and 105% resting motor threshold, is given to evaluate the effects of magnetic stimulation intervention.[3,15] However, this method is a burden on the subject, and the 105% motor threshold stimulation intensity may not induce MEPs in rare cases. Previous studies used a long time (6 minutes or longer) before and after the intervention magnetic stimulation to evaluate cortical excitability. If the evaluation time is long, problems of the body movement may occur by the subject's fatigue. The stimulation site may vary by body movement, and it may affect the motor cortex excitability. Shortening the evaluation time of cortical excitability will lead to solving these problems.

Therefore, in this study, we focused on cortical excitability using paired-pulse TMS of a long interstimulus interval (time between the first and second stimuli). Our aim was to assess whether cortical excitability could be rapidly evaluated with repetitive paired-pulse TMS.

II. METHODS

A total of 16 trials were completed. The six enrolled participants were healthy right-handed volunteers, consisting of five men and one woman (age range: 22–65 years; mean age: 36.3 ± 16.0 years), without a history of neurological or psychiatric disease. All subjects gave informed consent for this study.

Fig. 1 shows the experimental paradigm. Magnetic stimulation of the left primary motor cortex (M1) was applied using the Rapid 2 Stimulator (Magstim Co. Ltd., Whitland, UK) and a figure eight-shaped flat coil of 70 mm in diameter. ISIs between the paired TMS stimuli were 1,000, 200 or 100 ms (1 Hz, 5 Hz or 10 Hz frequency), and the stimulation intensity of the first and second stimuli were both at 110% resting motor threshold. The subject's individual resting motor threshold was defined as an MEP amplitude with more than 50 μV peak-to-peak amplitude produced in at least five of 10 successive trials.[16] The average resting motor threshold of the six subjects was 65.0 ± 10.0% of the stimulator output. In the experiment, a total of 10 paired-pulse TMS stimuli were delivered to the M1 at 10 s intervals. The magnetic stimulation of 10 paired-pulse was setup to investigate existence of the cumulative effect. Measurement time was approximately 100 s for the ISI of 1,000 ms, but was shorter for the 200 and 100 ms ISIs.

The MEP induced by the paired-pulse TMS was measured at the right first dorsal interosseous (FDI) muscle using Neuropack S1 (Nihonkohden Co. Ltd., Tokyo, Japan). The amplitude of the MEP was measured to derive the characteristics of each ISI using the peak-to-peak voltage. The recorded data were analyzed using a digital band pass filter of 5 Hz to 3 kHz.

III. RESULTS

A total of six subjects were enrolled for the 1,000 ms ISI (5 men and 1 woman, 36.3 ± 16.0 years of age), and a total of five subjects were enrolled for the 200 and 100 ms ISIs (5 men, 35.2 ± 17.4 years of age). The MEPs were expressed as the ratio of the actual MEP amplitude and mean of the MEP amplitudes of the first four pulse magnetic stimulations for each subject. Fig. 2 shows the correlation between the number of stimuli and the average of all subjects for each ISI. Although there was no correlation at the ISI of 1,000 ms, the 200 and 100 ms ISIs tended to show a weak negative correlation. There was no significant correlation between the number of stimulations and the average MEP amplitude for any ISI (1,000 ms ISI: $r = -0.17$; 200 ms ISI: $r = -0.40$; 100 ms ISI: $r = -0.35$).

Fig. 3 shows the average amplitude of the MEPs induced by the first and second stimuli, and are normalized to the MEP amplitude induced by the first stimulus of each paired-pulse TMS. The amplitude of the MEP induced by the second stimulation at an ISI of 200 ms increased significantly compared with the amplitude of the MEP evoked by the first stimulation ($p < 0.05$, paired t-test), and the rate of increase of the MEP amplitude was approximately 150% compared with the first stimulus (1.47 ± 1.29, mean ± SD). The amplitude of the MEP elicited by the second stimulation at an ISI of 100 ms decreased significantly ($p < 0.01$), and the rate of decrease in MEP amplitude was approximately 60% compared with the first stimulus (0.42 ± 1.33). In contrast, the amplitude of the MEP evoked by the second stimulation slightly increased at an ISI of 1,000 ms, but was not significantly different, and the rate of increase in MEP amplitude was approximately 110% compared with the first stimulus (1.14 ± 0.94).

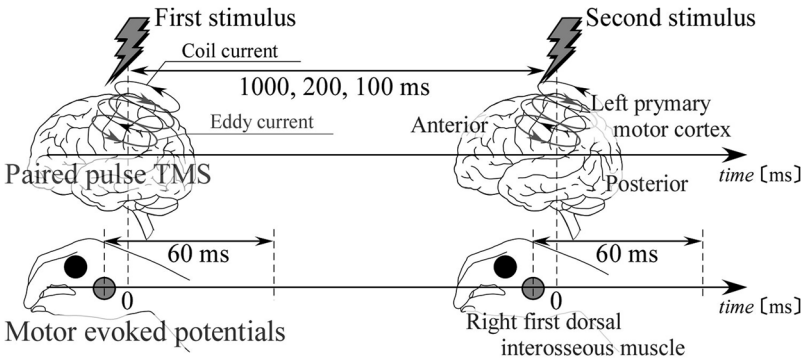

FIG. 1. Experimental paradigm. The Ag/AgCl electrode was used for measurement of motor evoked potentials. EMG (electromyography) from the right first dorsal interosseous (FDI) muscle was recorded for 60 ms in the first and second stimuli with paired-pulse TMS.

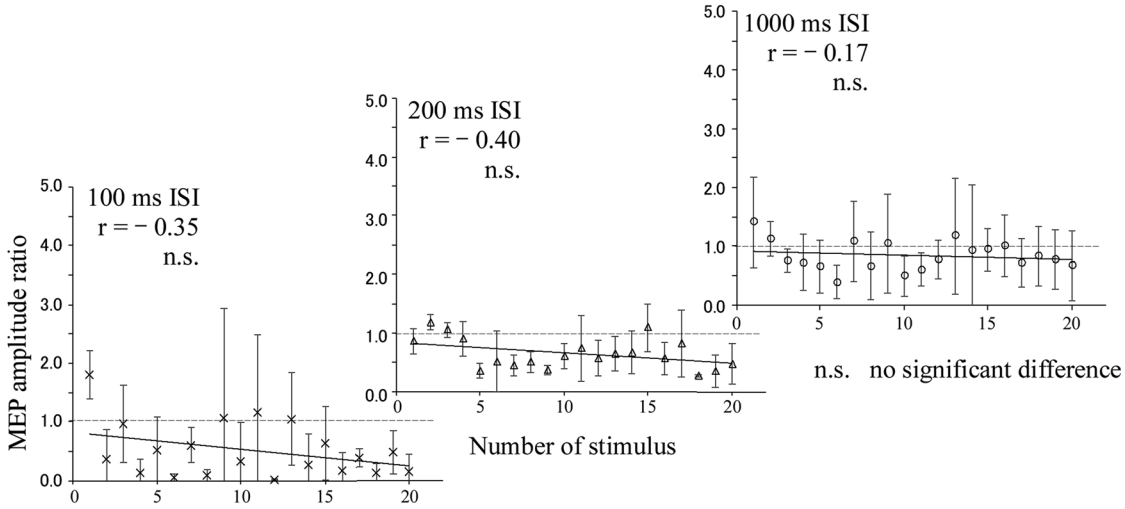

FIG. 2. Relationship between the number of stimulations and the average MEP amplitude (mean ± SD) for each ISI. There were no significant differences for each ISI. The 100 ms (left panel) and 200 ms (center panel) ISIs showed slight negative correlations. In comparison, there was negligible correlation with the 1,000 ms ISI (right panel).

IV. DISCUSSION

Our results show the impact of paired-pulse TMS on cortical excitability. A total of 20 repetitive paired-pulse TMS stimuli were given, revealing no significant difference for each ISI. However, weak negative correlations were observed for 200 and 100 ms ISIs. This tendency towards a decrease in excitability may be a cumulative effect of repetitive paired-pulse TMS on the cortex. In a previous study, the cumulative effect of magnetic stimulation of ≤20 Hz frequency and 100–110% motor threshold intensity was prevented by a 5 s train interval.[17] In the current study with the interval of 10 s between trains with 10 delivers, the 1,000 ms ISI produced no cumulative effect, and the effects of magnetic stimulus with 1,000 ms ISI may have dissipated by 10 s interval, while, in contrast, the 200 and 100 ms ISIs appeared to permit a cumulative effect of the TMS stimulation on cortical excitability. The stimulation interval of 10 s therefore may be insufficient for the 200 and 100 ms ISIs, which may require a longer interval to avoid a cumulative effect. For the 1,000 ms ISI, a cumulative cortical effect may not be produced even by a shorter stimulation interval (e.g., 5 s).

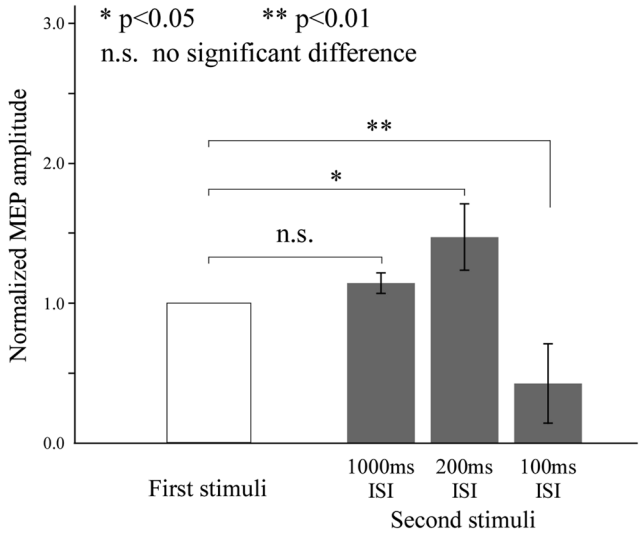

FIG. 3. Comparison of the means (±SEM) of the normalized MEP amplitudes. The normalized white bar is the amplitude of the MEP evoked by the first stimulus, and the normalized gray bars are those elicited by the second stimulus. The normalized amplitude of the MEP induced by the second stimulus decreased significantly with the 100 ms ISI, but it increased significantly with the 200 ms ISI. There was no significant difference with the 1,000 ms ISI.

The amplitude of the MEP induced by the second stimulus was normalized to the amplitude of the MEP induced by the first stimulus. The amplitude of the MEP induced by the paired-pulse TMS of 1,000 ms ISI did not change significantly. Therefore, repetitive paired-pulse TMS may not affect the cortex 1,000 ms from the first stimulation. A previous study suggests that successive stimulation at a frequency of 1 Hz or less inhibits cortical excitability.[3,4] However, in the present study, we applied an extremely small number of stimulations compared with previous studies, and it appears that there is no afferent feedback from muscle activity elicited by the magnetic stimulation.[10] Furthermore, the current study differs from studies that examine the effects of conventional TMS at 1 Hz. The cortical effect of conventional 1 Hz magnetic stimulation may have been negated by afferent feedback.

The amplitude of the MEP induced by the second stimulus increased significantly with the 200 ms ISI and decreased dramatically with the 100 ms ISI, compared with the amplitude of the MEP induced by the first stimulus. This might indicate a facilitating phase for cortical M1 excitability 200 ms after the first stimulation, and an inhibitory phase at 100 ms. However, depending on the subject, the

MEP appeared or disappeared during the second stimulus, suggesting that 100 ms after the first stimulus may be a relative refractory period.

The 100 ms ISI had a strong inhibitory effect. The disappearance of MEPs may be related to the abolishment of I3 waves in corticospinal volleys.[18] The corticospinal volleys induced by TMS were measured by the epidural electrode. Corticospinal volleys consist of D (direct) and I (indirect) waves, and the I3 wave is one of the later I waves.[18–20] In the present study, the disappearance of the I3 wave was produced by the first stimulus, and thus, an MEP did not follow the second stimulus, 100 ms after the first stimulus.

Finally, if the intensity of TMS to be 5% smaller than the previous studies may not appear MEP, in contrast, larger percentage than this study (e.g., 115% or 120% of the resting motor threshold) may not prevent the increase of cumulative effect for cortex by magnetic stimulation. Therefore, the intensity to be 5% larger than previous studies may be the limit to prevent cumulative effects in this study.

V. CONCLUSIONS

In this study, we investigated whether cortical excitability could be evaluated using repetitive paired-pulse TMS of a short duration. Our analyses revealed a cumulative effect of repetitive paired-pulse TMS with ISIs of 200 and 100 ms. In contrast, the 1,000 ms ISI produced no cumulative effect of magnetic stimulation on cortical excitability. Therefore, repetitive paired-pulse TMS with a 1,000 ms ISI may be suitable for evaluating cortical excitability, while TMS with an ISI of 200 or 100 ms might not. Moreover, the intensity of the TMS applied in this study was 5% above that used in previous studies. Thus, our current method and the use of 1,000 ms ISIs may be useful for assessing cortical excitability with paired-pulse TMS.

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