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Effects of Sub-Motor-Threshold Transcranial Magnetic Stimulation on Event-Related Potentials and Motor-Evoked Potentials

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Abstract

The purpose of this study was to investigate the effects of low-frequency (1-Hz or 0.5-Hz) sub-motor-threshold repetitive transcranial magnetic stimulation (rTMS) on cognitive and motor function. rTMS was delivered to the supramarginal gyrus (SMG) or primary motor cortex (M1) of the left hemisphere, followed by a sub-threshold 100-pulse stimulus intervention. Effects of the intervention on cognitive function were evaluated by measuring the event-related potential (ERP) P300 before, and after the intervention using an auditory oddball task. Following the intervention, P300 latency was reduced by a mean of around 20 ms at 1-Hz stimulation, and increased by a mean of around 15 ms at 0.5-Hz stimulation. Effects on motor function were evaluated by measuring the amplitude of motor-evoked potentials (MEPs) evoked by 10 supra-threshold rTMS pulses at 0.1-Hz before and after low-frequency sub-threshold rTMS. The MEP amplitude was increased by 150% with 1-Hz rTMS, and decreased by 40% with 0.5-Hz rTMS. Thus, 1-Hz sub-threshold rTMS induced the facilitation of SMG and M1 excitability. Conversely, 0.5-Hz rTMS induced the depression of SMG and M1 excitability. This study demonstrates that modulation of ERP P300 latency and MEP amplitude by low-frequency rTMS is dependent upon the frequency of the stimulus and that sub-motor-threshold rTMS can facilitate cortical excitability.

Key Words: Repetitive Transcranial Magnetic Stimulation (rTMS), Sub-Motor-Threshold, Event-Related Potential (ERP), P300 latency, Motor-Evoked Potential (MEP)

1. INTRODUCTION

Transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS) were developed in the 1980s following studies of brain function [1, 2], and are used in psychiatry as diagnostic tools. TMS is an important technique that enables noninvasive, direct stimulation of the brain without attenuation of the stimulus owing to the high impedance of the scalp, skull and hair [3, 4]. Compared with transcranial electrical stimulation (TES), which has been used clinically since 1980, TMS or rTMS has fewer adverse effects on the deeper cerebrum, and the coil can easily be moved to different areas of the skull, thus changing the region of stimulation [1, 2, 5, 6]. TMS devices enable the generation of a magnetic field by rapidly discharging an electrical current pulse along the TMS coil (the magnetic coil wire). The coil, which is placed on the scalp, then produces a magnetic field, which is oriented orthogonally to the plane of the coil. This magnetic field generates a non-uniform ‘eddy’ current in the brain, owing to the irregular shape of the brain. The eddy current is able to modulate cortical excitability [4, 7, 8], thus providing direct noninvasive stimulation of the brain. The resolution of TMS was improved by the development of the figure-of-eight-shaped coil [9, 10]. Studies investigating cortical function, including the role of cortical function in visual perception, memory and muscle control typically use high-resolution TMS [11-13].

Motor-evoked potentials (MEPs) can be induced by TMS or rTMS [1-4]. In many previous studies, the effects of magnetic stimulation of the primary motor cortex (M1) were investigated using TMS or rTMS [14-16]. A frequency range of 5–20 Hz has been used for high-frequency rTMS, and a frequency of 1-Hz has been used for low-frequency rTMS [3, 4, 7, 17, 18]. Data from many previous studies using rTMS at supra-threshold stimuli (120% of the motor threshold) suggest that the effect of rTMS on cortical excitability is dependent on the frequency of rTMS used. High-frequency rTMS promotes cortical excitability, and low-frequency rTMS produces suppression of cortical excitability [19-21]. Furthermore, the effects of low-frequency rTMS might vary by intensity of magnetic stimulation: the effects of rTMS on the M1 region have been shown to depend on the stimulus intensity [22]. However, the exact effects of sub-motor-threshold magnetic stimulation on the M1 region are unknown.

The effects of magnetic stimulation on cognitive function have been investigated by researchers since the year 2000. These effects are typically monitored using

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electroencephalography [23, 24]. In many previous studies, the effects of stimulation of the left hemisphere were compared with those of stimulation of the right hemisphere. Cognitive function (as indicated by event-related potentials: ERPs) was found to be altered by stimulation of the left hemisphere. By contrast, stimulation of the right hemisphere had no effect on the cortical excitability [25-29].

The aim of this study was to clarify the effects of low-frequency, sub-threshold rTMS over the supramarginal gyrus (SMG) and M1 of the left hemisphere.

2. METHODS

2.1 Determination of Motor Threshold

The intensity of rTMS used in this study was set at 80% of the motor threshold of each participant. The motor threshold of each participant was determined as the intensity of stimulation required to generate a motor-evoked potential (MEP) in the primary cortex with a peak-to-peak amplitude of greater than 50 μV in at least six of 10 successive trials. The motor threshold was measured by the presence of stimulation-induced contractions of the right abductor pollicis brevis (APB) muscle.

2.2 Delivery and Measurement of Event-Related Potentials

A total of 20 trials (1-Hz rTMS in 10 participants with a mean age of 30.4 ± 9.9 years: six males and four females, 0.5-Hz rTMS in 10 participants with a mean age of 30.8 ± 10.1 years: six males and four females), were conducted in healthy volunteers with no prior diagnosis of psychosis or neuropathy. The latency of the ERP component observed approximately 300 ms after the onset of the stimulus (P300) was used to evaluate the effects of magnetic stimulation on cognitive function. The experimental procedure consisted of three phases. During the first phase, P300 was measured using an auditory oddball task. Next, during the second phase, rTMS was delivered to the SMG, which is thought to be the area of origin of the P300. In the last phase, an auditory oddball task was performed again immediately after the second phase, followed by measurement of the latency of the P300 induced by the second auditory oddball task.

The auditory oddball task generated in the first and third phases was conducted using a STIM2 stimulus presentation and experimental design system (Compumedics Neuroscan USA Ltd, Charlotte, North Carolina, USA). The auditory oddball task protocol used two tone-burst sounds, at frequencies of 1 kHz (standard, 80% of trials) and 2 kHz (deviate, 20% of trials). Tone-burst sounds (a total of 100 sounds) of a 50 ms duration were randomly generated at intervals of approximately 2.5 s and an intensity of 60 dB.

ERPs generated by the auditory oddball task in the first and third phases of the protocol were measured using electrodes placed in the Fz, Cz and Pz positions, according to the international 10/20 electrode system. The impedance of each electrode was less than 5 kΩ. Data were sampled at 1000 Hz with a synchronized sum of 20 times. All data were analyzed using a 0.5–30 Hz band-pass filter.

The rTMS delivered during the second phase was conducted using a Super Rapid Stimulator (Magstim Co. Ltd, Whitland, Carmarthenshire, UK) with a figure-of-eight-shaped flat coil of 70 mm in diameter. The magnetic stimulator was positioned over the left SMG, and 100 pulses with a width of 250 μs and a frequency of 1 Hz or 0.5-Hz were applied. All participants were instructed to relax and remain seated during the experiment.

2.3 Delivery and Measurement of Motor-Evoked Potentials

A total of 14 trials (1-Hz rTMS in seven participants with a mean age of 26.4 ± 4.3 years: five males and two females, 0.5-Hz rTMS in seven participants with a mean age of 25.0 ± 1.8 years: five males and two females) were conducted in healthy volunteers with no prior diagnosis of psychosis or neuropathy. All participants were instructed to maintain a state of muscle relaxation throughout the experimental procedure. MEP amplitude was used to evaluate the effects of rTMS on motor function. The experimental procedure consisted of three phases. During the first phase, 10 pulses of 0.1-Hz rTMS were delivered at an intensity of 105% of the motor threshold. In the second phase, 100 pulses of 1-Hz or 0.5-Hz rTMS were delivered to the left M1 at an intensity of 80% of the motor threshold. In the third phase, rTMS with 10 pulses of 0.1-Hz stimulation at intensity of 105% of the motor threshold was delivered immediately after intervention. The pulse width used for the magnetic stimulation was 250 μs in all phases.

The rTMS delivered during each phase was conducted using a Super Rapid Stimulator with a figure-of-eight-shaped flat coil of 70 mm in diameter. The MEPs induced by rTMS during the first and third phases were measured at the right APB muscle using a Neuropack X1 EMG/EP measuring system (Nihonkohden, Tokyo, Japan). Data were sampled at 10 kHz, and all data were filtered using a 3–5 kHz band-pass filter.

3. RESULTS

3.1 Event-related Potentials

In this study, P300 latency was determined approximately 250–400 ms after target sounds stimulation of the oddball task. Fig. 1 shows ERP recordings at the Fz electrode before and after rTMS of the left SMG. In the top waves shown in Fig. 1, 1-Hz rTMS resulted in a shorter P300 latency compared with the control (P300 prior to sub-threshold stimulation). This latency was shortened by a mean of 19.4 ms at the Fz electrode, 19.7 ms at the Cz electrode and 20.8 ms at the Pz electrode. In the bottom waves in Fig. 1, 0.5-Hz rTMS expanded the mean P300 latency relative to that of the control by 14.3 ms at the Fz electrode, by 16.8 ms at the Cz electrode and by 14.8 ms at the Pz electrode. Considerable inter-individual variations in P300 latencies were observed. Therefore, latency was normalized to the P300 latency of the same individual under control conditions.

Fig. 2 shows normalized P300 latencies before and after rTMS, as measured at the Fz, Cz, and Pz electrodes. P300 latency was significantly shorter following 1-Hz magnetic stimulation than under control conditions (p <0.01, for latencies measured at Fz, Cz, and Pz). P300 latency was significantly longer following 0.5-Hz magnetic stimulation than under control conditions (p <0.01 for latencies measured at Fz, Cz, and Pz).

3.2 Motor-evoked potentials

The left panel in Fig. 3 shows MEPs before and after magnetic stimulation of the M1. With 1-Hz rTMS, MEP amplitude increased following sub-threshold magnetic stimulation compared with 1-Hz rTMS under control conditions. By contrast, MEP amplitude decreased with 0.5-Hz rTMS following sub-threshold magnetic stimulation compared with 0.5-Hz rTMS under control conditions. Considerable inter-individual variations in MEP amplitudes were observed. Therefore, the MEP amplitude was normalized to the MEP amplitude of the same individual under control conditions.

The right panel in Fig. 3 shows normalized MEP amplitude under control conditions. MEP amplitude increased significantly (by 166% relative to controls, p <0.01) with 1-Hz rTMS following sub-threshold magnetic stimulation, and MEP amplitude decreased significantly (by 36% relative to controls, p <0.01) with 0.5-Hz rTMS following sub-threshold magnetic stimulation.

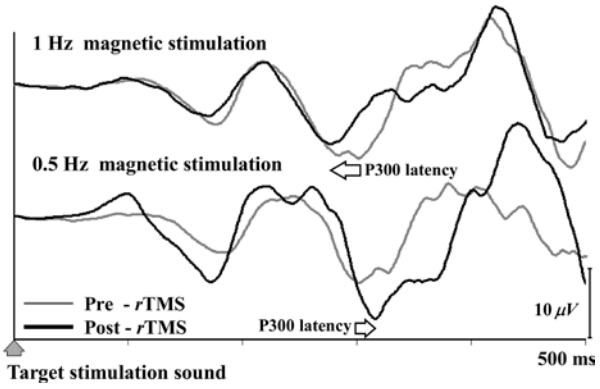

Fig. 1. ERPs measured at the Fz electrode before (grey) and after (black) sub-threshold rTMS of the left SMG. The rTMS frequency used was 1-Hz in the top panel and 0.5-Hz in the bottom panel.

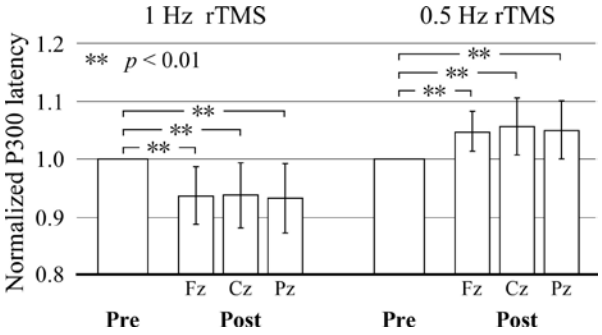

Fig. 2. Normalized P300 latency at the Fz, Cz, and Pz electrodes before and after sub-threshold rTMS of the left SMG. The left panel shows normalized P300 latency following 1-Hz rTMS, and the right panel shows normalized P300 latency following 0.5-Hz rTMS.

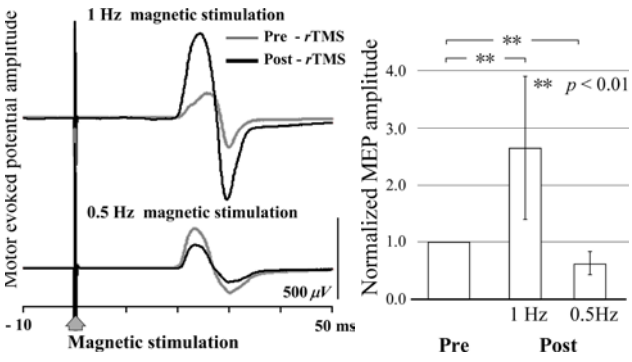

Fig. 3. MEPs measured before (grey) and after (black) sub-threshold rTMS of the left M1 (left panel). Normalized MEP amplitude at the APB before and after sub-threshold rTMS of the left M1 (right panel).

4. DISCUSSION

In previous studies, modulation of cortical excitability was obtained using both high-frequency and low-frequency supra-motor-threshold rTMS. Moreover, cortical excitability was inhibited by 1-Hz supra-threshold rTMS, while cortical excitability was facilitated by TMS of supra-threshold more than 5Hz [14, 17, 19]. However, the results of this study differ from those of previous studies. In this study, cortical excitability was increased by 1-Hz sub-threshold rTMS, and was inhibited by 0.5-Hz sub-threshold rTMS. This result suggests that the effects of low-intensity rTMS are frequency dependent.

In previous studies, it was reported that 0.1-Hz magnetic stimulation with supra-threshold induced the transitory facilitation of cortical excitability, then the cortex excitability indicated an inhibitory tendency [15]. 1-Hz magnetic stimulation with sub-threshold induced the facilitation of cortical excitability [30], whereas 1-Hz magnetic stimulation with supra-threshold induced the inhibition of cortical excitability [30, 31]. Therefore, the inhibition of cortical excitability may be inverted from the facilitation by the action of suppression function, which is dependent to intensity of magnetic stimulation. While, these results suggested that the facilitation of the cortical excitability was maintained by intensity of sub-threshold magnetic stimulation.

Similarly, in this study, 1-Hz magnetic stimulation with sub-threshold induced the facilitation of cortical excitability. 1-Hz rTMS with sub-threshold did not induce the action of the suppression function. The cortical excitability was inhibited by 1-Hz supra-threshold magnetic stimulation; although, facilitation of cortical excitability was induced by 1-Hz sub-threshold magnetic stimulation. Accordingly, the effects of 1-Hz rTMS appear to depend upon the intensity of the stimulus.

In this study, 0.5-Hz rTMS with sub-threshold induced the action of suppression function. However, this suppression function may be induced by the interval of magnetic stimulation [32]. Therefore, it is considered that 0.5-Hz rTMS induced the inhibition regardless of the intensity of magnetic stimulation, after the transitory facilitation of cortical excitability by the magnetic stimulation.

Therefore, the effect of the magnetic stimulation is complicated, because inhibition or facilitation of cortical excitability is induced by many parameters of magnetic stimulation [33].

Finally, in this study, the effect of magnetic stimulation was evaluated by the ERP P300 latency and MEP amplitude. And, the effects of magnetic stimulation on SMG and M1 were not different. Accordingly, this study indicated that the magnetic stimulation effect is not dependent upon the stimulation region.

5. CONCLUSIONS

The purpose of this study was to clarify the effects of low-frequency sub-threshold rTMS of the left SMG and left M1 regions of the brain. The effects were evaluated by measuring alterations in ERP P300 latency and MEP amplitude. 1-Hz magnetic stimulation resulted in facilitation of cortical excitability, and 0.5-Hz magnetic stimulation resulted in inhibition. The results of previous studies suggest that the effects of sub-motor-threshold rTMS are frequency dependent. The findings of many previous studies and this study indicate that the effects of 1-Hz rTMS are also dependent on the strength of the stimulation.

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