

## Suprathreshold 0.2 Hz Repetitive Transcranial Magnetic Stimulation (rTMS) Over The Prefrontal Area

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**Objective:** This study was designed to evaluate the effects of suprathreshold 0.2 Hz repetitive transcranial magnetic stimulation (rTMS) to the prefrontal area and motor cortex on the cerebral cortex excitability.

**Methods:** The study involved 15 healthy volunteers. With a concave circular coil, rTMS to Fz (bilateral dorsolateral prefrontal areas) was carried out for 100 sessions at a frequency of 0.2 Hz and an intensity 1.2 times the resting motor threshold. In addition, rTMS to M1 (primary motor cortex) (Lt motor hand area) was performed in a similar manner. Before and after rTMS, resting motor threshold, motor evoked potential, cortical silent period (CSP) and F wave were recorded, and their changes after rTMS as compared to the pre-rTMS were analyzed.

**Results:** Neither Fz stimulation nor M1 stimulation caused any significant change in the resting motor threshold, motor evoked potential latency, amplitude or area as compared to the values measured before rTMS. No significant changes were seen in the amplitude and persistence of the F wave. However, while Fz stimulation produced significant prolongation of the CSP duration ( $p < 0.01$ ), M1 stimulation produced no such prolongation. The sham stimulation (control) showed no significant prolongation of the CSP duration following either M1 or Fz stimulation.

**Conclusion:** These results suggest that suprathreshold 0.2 Hz rTMS of Fz induces a significant suppression of excitability in the primary motor cortex.

**Key words:** repetitive transcranial magnetic stimulation, bilateral dorsolateral prefrontal areas, cortical silent period

### INTRODUCTION

Transcranial magnetic stimulation (TMS) [1] allows non-invasive stimulation of the human cerebrum and has been used in studies designed to evaluate the mechanism of excitation and suppression of the cerebral cortex. Excitation within the cerebral cortex has usually been evaluated through analysis of the resting motor threshold (RMT) and the motor evoked potential (MEP) (latency, amplitude and area), while suppression within the cerebral cortex has been evaluated through analysis of the cortical silent period (CSP) duration or by the paired-pulse TMS method.

CSP is considered to result from suppression of the motor cortex pyramidal neurons due to stimulation of the inhibitory intercalated neurons within the cerebral cortex following single-pulse TMS. The duration of CSP has been suggested to be associated with the inhibitory mechanism involving the receptors of the transmitter GABA<sub>B</sub> within the cortex [2-5].

Repetitive TMS (rTMS) has recently been used as a means of altering excitation or suppression within the cerebral cortex. In studies involving rTMS of M1 (primary motor cortex), there has been reported about the analysis of the changes in the RMT, MEP, CSP duration, intracortical inhibition (ICI), intracortical facilitation (ICF), etc., as well as changes in these parameters in the hemisphere contralateral to the simulated hemisphere [6-7].

Generally speaking, high-frequency rTMS has been

reported to elevate the excitability within the cortex, while low frequency ( $\leq 1$  Hz) rTMS has been shown to suppress it. [8]. However, these effects of rTMS seem to vary depending on the intensity, site and frequency of the stimulation, and the properties of the coil used for the stimulation.

Low-frequency rTMS has been used clinically as a method for non-invasive therapeutic stimulation of the cerebral cortex. Owing to its effect of suppressing cortical excitability, this method has been applied for stroke, epilepsy, dystonia and major depression disorder [9-12]. In Parkinson's disease, low-frequency rTMS applied to the motor cortex (MC), prefrontal cortex (PFC) using a 0.2 Hz to 1Hz circular or 8-shaped coil has been shown to be useful for improving the motor function or alleviating depression [13-15]. We also applied suprathreshold 0.2 Hz rTMS with a circular concave coil to the Fz (the bilateral dorsolateral prefrontal areas) of Parkinson's disease and found improvement in the cognitive and motor functions [16].

Furthermore, there are several published reports demonstrating improvement of motor function accompanied by changes in various parameters (CSP duration, MEP amplitude, etc.) following rTMS. It has additionally been suggested that rTMS of brain sites associated with the motor area, even those that are distant from the motor area, affects the continuous excitability of the motor cortex [17-18].

Within the framework of our series of studies aimed at exploring the mechanism underlying the efficacy

of rTMS in Parkinson's disease, we were prompted to assess the influence of rTMS on the excitability of the cerebral cortex at brain sites distant from the motor area in healthy individuals.

The present study was undertaken to examine the effects of suprathreshold 0.2 Hz rTMS applied to the brain sites Fz (bilateral dorsolateral prefrontal areas) and M1 on parameters such as the duration of CSP, RMT, MEP, the amplitude and persistence of F wave, and to analyze the differences in the effects between Fz stimulation and M1 stimulation.

## MATERIALS AND METHODS

### 1. Subjects

The study involved 15 healthy volunteers (9 males and 6 females; age, 24-42 years; mean age, 28.7 years). All the subjects gave their informed consent to participate in this research project, which was approved by the Ethics Committee of Tokai University School of Medicine.

### 2. Methods

#### (1) Magnetic stimulation

TMS and rTMS were applied with the MagLite™ (Dantec, Skovlunde, Denmark) combined with a concave circular coil (MMC-140, Dantec). The coil had a diameter of 140 mm and was designed to produce the maximum percent change of the magnetic flux at the center of the tissue facing the coil and to produce the maximum induced current in the area within a 2-cm radius. Because this coil assumes a concave circular form, it is easy to fit it to the head shape and can be fixed easily at the site for stimulation.

The head area Fz and M1 (Lt motor hand area) were selected as the sites for rTMS.

The subjects participated in the experiment of the Fz stimulation, the M1 stimulation, and the control. Ten subjects were allocated for the Fz stimulation and M1 stimulation, and 7 subjects for the control group. Therefore two subjects participated in the all of the stimulations. Stimulation of different sites was carried out with an interval of at least one week for each subject.

In the Fz stimulation, the center of the coil was set at the head point Fz, and 100 sessions of stimulations were applied at a frequency of 0.2 Hz and an intensity 1.2 times RMT. In the M1 stimulation, the center of the coil was set at the optimal stimulation site for the right abductor pollicis brevis (APB) muscle on the left side of the head, and 100 sessions of stimulations were applied at a frequency of 0.2 Hz and an intensity 1.2 times RMT. In the control group, sham stimulation was applied with the stimulation coil kept 15 cm or more away from the scalp.

#### (2) Electromyography

Electromyography was recorded with a disc-shaped surface electrode on the right APB muscle according to the belly-tendon method, using a Neuropack Micro (MEB-9104, Nihon Kohden Corporation) with a frequency range of 5 to 1.5 KHz.

#### (3) Experimental procedure

Each subject sat on a chair equipped with a back-

rest and an elbow rest. While sitting on the chair, each subject kept the hip and knee bent at an angle of 90 degrees. The right arm was placed at the forearm-intermediate position, with the shoulder bent at 15 degrees, the elbow bent at 60 degrees, the fingers placed on the elbow rest. The left forearm was kept pronated. Each subject thus took a resting position on the chair. The head positions Cz and Fz were determined according to the international 10-20 system.

The optimal stimulation site was determined by moving the coil around the left side of the Cz on a scalp until a maximum MEP was recorded. The RMT was determined as the minimal stimulation intensity resulting in 4 or more records of MEP over 50  $\mu$ V among the 8 sessions of stimulation at the optimal stimulation site at rest.

Then, the subject's MVC of the right APB muscle was determined with an electromyography biofeedback device (KR-1 Myometer, Ematsu). Before recording CSP, each subject practiced 2-3 exercises (isometric tonic 15% MVC contraction during thumb abduction) while watching the indicator of the biofeedback device.

Changes in each parameter after rTMS, as compared with the pre-rTMS level, were recorded.

Before stimulation, the RMT was determined. TMS was applied at 1.2 times RMT to record the MEP during rest. Then, the subject was instructed to maintain voluntary contraction at 15% MVC and 3-5 seconds later TMS at a intensity of 1.2 times RMT was applied to record the CSP. The F waves at rest were then recorded at rest.

rTMS was applied for 100 sessions each at a frequency of 0.2 Hz and an intensity 1.2 times RMT. MEPs during rTMS were monitored. Immediately after rTMS, the RMT, F waves and CSP were recorded again. Eight waves of MEP were recorded. The F wave was recorded after 32 sessions of stimulation, and the CSP was recorded 10 times. CSP duration was defined as the length of time from the initial rise of the MEP to disappearance of muscular activity and resumption of muscular activity potential through voluntary contraction (Fig 1).

#### (4) Statistical analysis

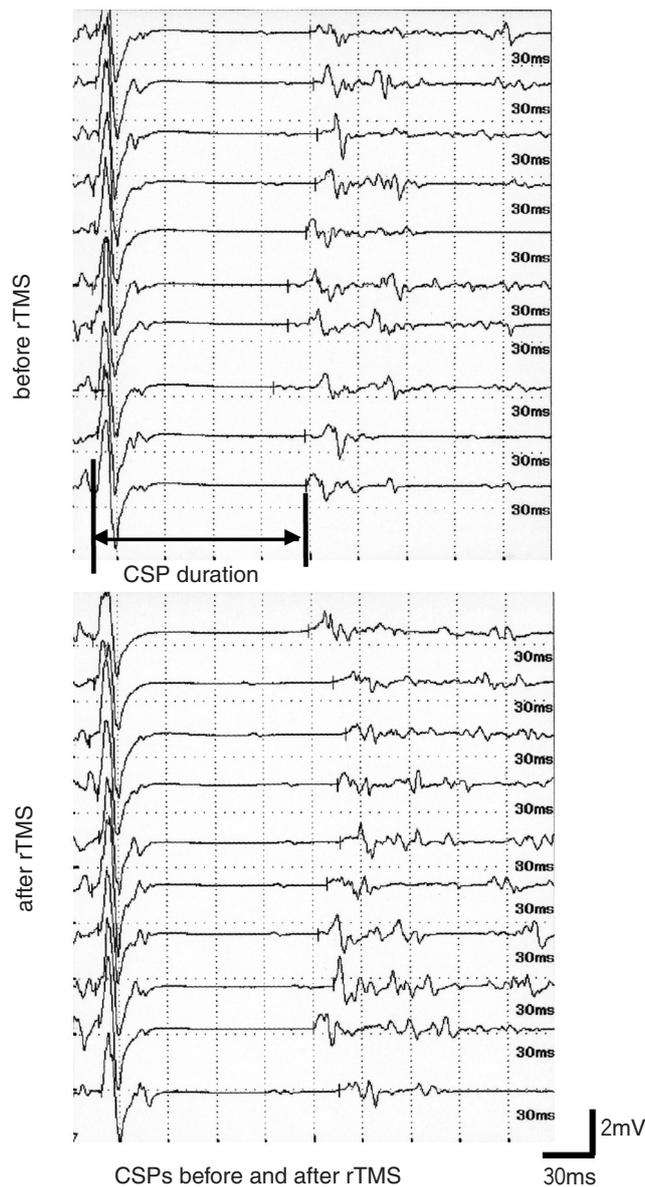
Between pre-rTMS and post-rTMS, the averages of the RMT, MEP latency, amplitude and area, CSP duration, and F wave amplitude and persistence, were compared among the three groups.

Data were analyzed statistically by Wilcoxon's signed rank test, using the computer software program, SPSS.  $P < 0.05$  was regarded as denoting statistical significance.

## RESULTS

There were no significant differences in the amplitude and persistence of the F wave. There were no significant differences between the pre-rTMS and post-rTMS about RMT, MEP latency, MEP amplitude or MEP area in either the M1 stimulation or the Fz stimulation and control (Table 1).

The M1 stimulation induced no significant prolongation of the CSP duration following stimulation, while the Fz stimulation resulted in significant prolongation of the CSP duration following rTMS (Table 1).



**Fig. 1** Changes in waveforms after rTMS of Fz, as compared with the pre-rTMS waveforms. CSP duration is defined as the length of time from the onset of MEP to the start of the electromyographic potentials.

The MEP, recorded during rTMS of Fz, was less than  $50 \mu\text{V}$  in all subjects.

The control stimulation produced no significant prolongation of the CSP duration as compared to the M1 or the Fz stimulation (Table 1).

### DISCUSSION

In this study, rTMS was applied to Fz and M1 over 100 sessions at a frequency of 0.2 Hz and intensity of 1.2 RMT, using a concave circular coil, and the changes in the parameters of the excitability of the motor cortex were analyzed. Stimulation of Fz resulted in prolongation of the CSP duration, while stimulation of M1 caused no such prolongation of the duration of CSP.

Since CSP is affected not only by intercalated neurons within the motor cortex but also by the excitability of the spinal cord. We recorded the F wave to evaluate the excitability of the anterior horn cell in the spinal cord in this study. No significant change in either the amplitude or the persistence of the F wave was

observed, suggesting that the excitability of the spinal motor neurons did not change after rTMS. Thus CSP is primarily due to the inhibitory mechanisms at the level of the motor cortex.

No significant differences were observed between pre-rTMS and post-rTMS about the RMT, MEP amplitude or MEP area in either the M1 stimulation or the Fz stimulation. No change in the CSP duration was noted in the M1 stimulation. Prior to the present study, numerous reports have been published concerning low-frequency (1 Hz) stimulation of M1 in healthy adults [6-7, 11, 17, 19-21]. In regard to the influence of suprathreshold 1 Hz rTMS on M1, suppression within the motor cortex, accompanied by reduced MEP amplitude was often observed. On the other hand, conflicting results have also been reported. For example, 115% RMT rTMS at a frequency of 1 Hz over 900 sessions caused only an immediate reduction of the MEP and no change of the RMT, short interval ICI and ICF [7]. According to one report, rTMS over 900 sessions at a frequency of 1 Hz and intensity of

**Table 1** Comparison of pre-rTMS and post-rTMS averages of the CSP duration, RMT, MEP latency, amplitude and area, and the amplitude and persistence of the F wave.

	M1			Fz			Control		
	Before	After	<i>P</i> value	Before	After	<i>P</i> value	Before	After	<i>P</i> value
CSP duration (ms)	140.7 ± 49.1	143.9 ± 47.1	n.s.	144.4 ± 50.5	162.0 ± 54.1	0.005*	161.3 ± 36.7	164.4 ± 34.6	n.s.
RMT (%)	46.8 ± 3.1	46.0 ± 5.8	n.s.	45.8 ± 3.1	44 ± 4.3	n.s.	41.0 ± 6.1	40.0 ± 6.1	n.s.
MEP latency (ms)	22.4 ± 1.5	22.6 ± 1.1	n.s.	22.0 ± 1.3	22.3 ± 1.1	n.s.	22.4 ± 0.9	22.7 ± 1.1	n.s.
MEP amplitude (µV)	674.6 ± 553.6	502.2 ± 325.4	n.s.	784.2 ± 568.0	630.8 ± 463.5	n.s.	1288.2 ± 1021.4	1362.7 ± 1286.7	n.s.
MEP area (µV ms)	2570.0 ± 2004.6	2008.1 ± 1337.7	n.s.	2669.2 ± 1663.4	2167.0 ± 1637.4	n.s.	4742.9 ± 4466.0	5301.8 ± 6021.4	n.s.
F wave amplitude (µV)	219.5 ± 153.1	159.2 ± 105.6	n.s.	224.9 ± 87.4	199.6 ± 92.0	n.s.	206.8 ± 89.1	135.3 ± 42.8	n.s.
F wave persistence (%)	58.1 ± 21.5	48.9 ± 24.2	n.s.	60.6 ± 23.5	51.9 ± 24.4	n.s.	38.1 ± 13.4	36.0 ± 12.2	n.s.

\* *P* value indicates the results of Wilcoxon's signed-rank test (*n* = 10). Values represent means ± SD. n.s., not significant.

120% RMT with an 8-shaped coil caused no change in the MEP or CSP duration [6]. The method in that study resembled the present study in that M1 was subjected to low-frequency suprathreshold stimulation. Regarding the effects of rTMS at frequencies lower than 1 Hz, Cincotta *et al.* [22] reported prolongation of the CSP duration without accompanying changes in the RMT and MEP amplitude following 540 sessions of suprathreshold 0.3 Hz rTMS with an 8-shaped coil applied to the motor cortex. The difference in the results despite the similarity in the method employed between that study and the present study is probably attributable to differences in the intensity and number of sessions of low-frequency stimulation, the properties of the coil and the direction of stimulation [6, 23].

The prolongation of the CSP duration following Fz stimulation suggests that stimulation under this setting acted on the suppression mechanism more powerfully than stimulation of motor cortex. This seems to reflect the effects of regulation mediated by intercalated neurons, i.e., effects of indirect suppression of the motor cortex mediated by the neurons of the premotor area or the supplementary motor area, suppression mediated by direct neurons in the prefrontal cortex through motor cortex, or regulation mediated by the neurotransmitter GABA<sub>B</sub> receptor [5, 24].

In the present study, the MEP amplitude remained 50 µV or lower during rTMS of Fz. That is, the intensity of this stimulation was below the threshold level in the motor cortex. For this reason, 0.2 Hz 120% RMT rTMS of the Fz is interpreted to have resulted in subthreshold stimulation of the motor cortex. Daskalakis *et al.* [25] reported that after 900 sessions of subthreshold 1 Hz rTMS of M1 with an 8-shaped coil, while no change was noted in the RMT or MEP amplitude, prolongation of CSP duration was observed, resembling the results of our present study in terms of the magnitude of the subthreshold low frequency stimulation of M1.

Gerschlagler *et al.* [17], on the other hand, reported a study in which subthreshold 1 Hz rTMS with an

8-shaped coil was applied over a total of 1500 sessions of to each of the prefrontal cortex, PMC, motor cortex and parietal cortex, and suppression of the motor cortex depending on the site of stimulation was evaluated through analysis of the reduction in MEP amplitude. Their study revealed significant suppression of the motor cortex following weak subthreshold stimulation of the premotor area. Rollnik *et al.* [18] applied subthreshold 5 Hz rTMS to the prefrontal and occipital areas for a period of 12 seconds, and observed reduction of the MEP area 8 seconds after the start of the prefrontal rTMS alone. These reports demonstrate that rTMS of brain areas other than the motor cortex can suppress the motor cortex, strongly supporting the findings of the present study.

To date, few reports have been published concerning stimulation of the frontal cortex of healthy individuals. Among the few published reports, some have demonstrated that high-frequency subthreshold (5 Hz, 90% RMT) prefrontal stimulation reduced the MEP amplitude and that high-frequency subthreshold (10 Hz, 90% RMT) stimulation of the dorsolateral prefrontal cortex elevated the MEP amplitude [18, 26]. However, no report has been published previously about low-frequency suprathreshold (0.2 Hz, 1.2 Mth) rTMS of Fz with a concave circular coil as in the present study. The finding of prolongation of the CSP duration in this study indicates that low-frequency suprathreshold rTMS of the prefrontal area can significantly suppress excitability of the motor cortex.

For extensive clinical application of this procedure, it would seem necessary to carry out further studies as to the conditions of the rTMS (frequency, intensity, location, etc., of the stimulation) and evaluation of two consecutive applications of magnetic stimulation, including evaluation of the ICI and ICF.

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