International Journal of Physical Medicine & Rehabilitation

Watanabe et al., Int J Phys Med Rehabil 2015, 3:6
DOI: 10.4172/2329-9096.1000310

Research Article Open Access

# Optimum Stimulation Frequency of High-Frequency Repetitive Transcranial Magnetic Stimulation for Upper-Limb Function in Healthy Subjects

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**Received date**: 25 September, 2015; **Accepted date:** 26 October, 2015; **Published date:** 30 October, 2015



## Abstract

**Objective:** Because rTMS requires the subject's head to be immobilized and the subject to maintain the same posture throughout stimulation, stimulation of long duration may induce discomfort. If changing the stimulation parameters can allow the duration of rTMS to be shortened, physical discomfort may decrease. The purpose of this study was to identify the most beneficial stimulation parameters for high-frequency rTMS in terms of the effect on upper-limb function in healthy subjects.

**Materials and Methods:** Forty right-handed healthy volunteers were divided into four groups: three real rTMS groups (5, 10, and 20 Hz rTMS) and one sham group. In the real rTMS groups, 600 impulses were applied at a frequency of 5, 10, or 20 Hz and an intensity of 90% of resting motor threshold. Performance on a peg-board task, tapping task, and grip strength were measured before stimulation, immediately after stimulation, and 20 min after stimulation.

**Results:** All real rTMS groups showed a significant increase in performance on the peg-board task and tapping task after rTMS. There was no significant increase in grip strength in any group.

**Conclusions:** 10-Hz rTMS may improve upper-limb function with a shorter duration of stimulation than rTMS at 5 or 20 Hz. 10-Hz rTMS had the shortest stimulation time, and is recommended as beneficial setting to use with a little discomfort. These results can be used when deciding rTMS stimulation frequency.

**Keywords:** Repetitive transcranial magnetic stimulation; High frequency; Optimum setting

## Introduction

Transcranial magnetic stimulation (TMS) is a technique to stimulate the brain using a coil placed beside the cranium [1]. Single or paired stimulation has primarily been used for functional investigation or physiological investigation. Repetitive TMS (rTMS) is a continuous stimulation method of three or more stimuli.

There are various rTMS paradigms that vary in terms of stimulation frequency, intensity of stimulation, and stimulation time [2]. Stimulation frequency in particular influences the excitability of the stimulated brain area. It has been shown that low-frequency rTMS (<1 Hz) suppresses local neural activity, whereas high-frequency rTMS (>5 Hz) increases local neural activity [3-6]. Using this principle, rTMS has been applied to treat various disorders including stroke, pain, psychiatric disorders, and neuromuscular disease [7-9]. A beneficial effect of rTMS combined with functional therapy has been reported in many diseases [10,11]. It has been reported that high-frequency rTMS has a more beneficial effect on hemiplegia than low-frequency rTMS [12]. In combined therapy, it is necessary to elicit a carry-over effect from rTMS that lasts into the functional therapy. It has not been reported whether a carry-over effect occurs at all high-frequency stimulation. It is difficult to determine whether any effect is due to combined therapy or the independent effect of either modality.

The duration of the stimulation train and the inter-train interval at each stimulation frequency are decided according to safety standards [12,13]. By contrast, stimulation frequency is decided by the examiner. rTMS requires the subject to be immobilized and in a sitting or lying position during treatment, and head immobilization is also required. Therefore, treatment for a long duration may induce discomfort. If a change in the stimulation parameters can reduce the stimulation time of rTMS, physical discomfort may decrease.

The purpose of this study was to consider the most beneficial stimulation settings for high-frequency rTMS in terms of the influence on upper-limb function in healthy subjects.

## Materials and Methods

### Subjects

Forty right-handed healthy male volunteers (age range, 21-30 years; mean age, 25 years) provided informed consent to participate in this study, which was approved by our Institutional Review Board. Study patients were randomly assigned to one of three real rTMS groups (5-Hz rTMS (n=10), 10-Hz rTMS (n=10), or 20-Hz rTMS (n=10)) or a sham stimulation group (n=10). Those who had common

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contraindications of rTMS (e.g., past history of seizure, metallic substance in the brain like aneurysm clip or cardiac pacemaker) were excluded.

## Intervention

A 70-mm figure-of-eight coil and a MagPro R100 (MagVenture A/S, Farum, Denmark) was used for real rTMS and sham stimulation. In the real rTMS groups, the intensity of rTMS was 90% of resting motor threshold in the right primary motor area (Figure 1). The duration of stimulation at each frequency was determined according to a previous study, and set as the maximum possible duration [2,13]. For subjects in the 5-Hz rTMS group, stimulation was applied to the primary motor area of the right hemisphere in 10-s trains with 20 s between trains for a total of 340 s (total 600 pulses). For subjects in the 10-Hz rTMS group, stimulation was applied in 5-s trains with 20 s between trains for a total of 280 s (total 600 pulses). For subjects in the 20-Hz rTMS group, stimulation was applied in 2-s trains with 20 s between trains for a total of 310 s (total 600 pulses). Sham stimulation was performed with the coil held at an angle of 90° to the scalp to reproduce the noise of 5-Hz stimulation for duration of 340 s.

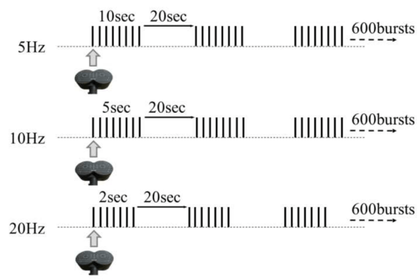


**Figure 1:** rTMS stimulation paradigm.

## Outcome measures

Performance of a peg-board task was quantified as the time taken to turn all 16 pegs of the peg-board (SAKAI Medical Co. Ltd., Tokyo, Japan, SOT-2102) upside-down (Figure 2a). Performance of a tapping task was quantified as the number of times the thumb pushed with maximum effort in 10 s (Figure 2b), and was counted using a Tally counter (KOKUYO S&T Co. Ltd., Osaka, Japan, CL-201). Subjects were instructed not to remove their forearm from the table by pronation.

Grip strength was measured twice using a hand dynamometer (Takei Scientific Instruments Co. Ltd., Niigata, Japan, T.K.K.5001), and the maximum value was taken as grip strength (Figure 2c). All tasks were performed with the non-dominant hand and subjects were allowed several practice trials in consideration of the effect of motor learning. These evaluations were performed before stimulation, immediately after stimulation and 20 min after stimulation.

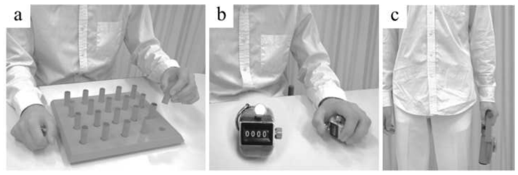


**Figure 2:** Outcome measures. a) Peg-board task b) Tapping task c) Grip strength.

## Statistical analysis

Baseline characteristics and baseline performance measures were compared among the four groups using a one-way analysis of variance. For each of the four groups, outcome measures were compared across the three time points (before stimulation, immediately after stimulation, and 20 min after stimulation). Tukey's post hoc tests were used to investigate significant main effects. $p<0.05$ was considered statistically significant. SPSS 22.0 version was used for the statistical analysis.

# Results

## Baseline characteristics and performance measures

There were no significant differences in baseline characteristics or baseline motor function (peg-board performance time, number of thumb presses, and grip strength) across the four groups (Table 1).

| | Age(Y) | Peg board task (sec) | Tapping task (time) | Grip strength (Kg) | Statistics |
|---|---|---|---|---|---|
| 5Hz | 24 ± 1 | 25.6 ± 2.0 | 57 ± 3 | 42.3 ± 5.8 | NS |
| 10Hz | 23 ± 2 | 27.7 ± 1.7 | 52 ± 3 | 38.2 ± 4.3 | NS |
| 20Hz | 24 ± 2 | 26.3 ± 1.5 | 56 ± 3 | 46.1 ± 3.2 | NS |
| Sham | 24 ± 2 | 25.6 ± 1.7 | 58 ± 4 | 41.0 ± 4.2 | NS |

**Table 1:** Baseline characteristics. There was no significant difference in the baseline characteristics or baseline performance measures (time taken to complete a peg-board task, number of thumb presses in the tapping task and grip strength) across groups.

## Peg-board task

The peg-board task results are shown in Figure 3. In the 5-Hz rTMS group, the time taken to complete the peg-board task was 25.6 ± 2.0 (mean ± SD) s before stimulation, 22.6 ± 2.5 s immediately after stimulation, and 22.1 ± 1.9 s 20 min after stimulation. Performance was significantly faster both immediately after and 20 min after stimulation compared to before stimulation ($p<0.05$). There was no significant difference in performance time immediately after and 20 min after stimulation, indicating that improved performance was maintained for 20 min after stimulation.

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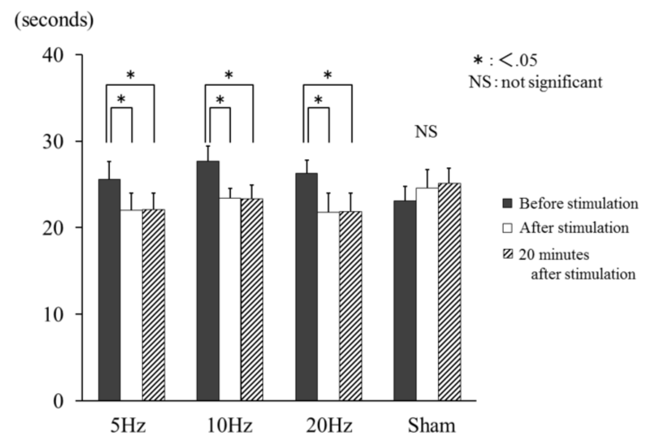


**Figure 3:** Time taken to complete the peg-board task. In all real rTMS groups there was a significant increase in performance immediately and 20 min after rTMS (P<0.05) there was no significant increase in performance in the sham group.

In the 10-Hz rTMS group, the time taken to complete the peg-board task was 27.7 ± 1.7 s before stimulation, 23.4 ± 1.1 s immediately after stimulation, and 23.3 ± 1.6 s 20 min after stimulation. Performance was significantly faster both immediately after and 20 min after stimulation compared to before stimulation (p<0.05). There was no significant difference in performance time immediately after and 20 min after stimulation, indicating that improved performance was maintained for 20 min after stimulation.

In the 20-Hz rTMS group, the time taken to complete the peg-board task was 26.3 ± 1.5 s before stimulation, 21.8 ± 2.2 s immediately after stimulation, and 21.9 ± 2.1 s 20 min after stimulation. Performance was significantly faster both immediately after and 20 min after stimulation compared to before stimulation (p<0.05). There was no significant difference in performance time immediately after and 20 min after stimulation, indicating that improved performance was maintained for 20 min after stimulation.

In the sham stimulation group, the time taken to complete the peg-board task was 25.6 ± 1.7 s before stimulation, 25.1 ± 2.1 s immediately after stimulation, and 25.2 ± 1.8 s 20 min after stimulation. There were no significant differences across time points.

## Tapping task

The tapping task results are shown in Figure 4. In the 5-Hz rTMS group, the number of thumb presses was 57 ± 3 (mean ± SD) before stimulation, 63 ± 3 immediately after stimulation, and 63 ± 3, 20 min after stimulation. The numbers of thumb presses was significantly greater both immediately after and 20 min after stimulation compared to before stimulation (p<0.05). There was no significant difference in the number of thumb presses immediately after and 20 min after stimulation, indicating that improved performance was maintained for 20 min after stimulation.

In the 10-Hz rTMS group, the number of thumb presses was 52 ± 3 before stimulation, 57 ± 2 immediately after stimulation, and 58 ± 3, 20 min after stimulation. The number of thumb presses was significantly greater both immediately after and 20 min after stimulation compared to before stimulation (p<0.05). There was no significant difference in the number of thumb presses immediately after and 20 min after stimulation, indicating that improved performance was maintained for 20 min after stimulation.

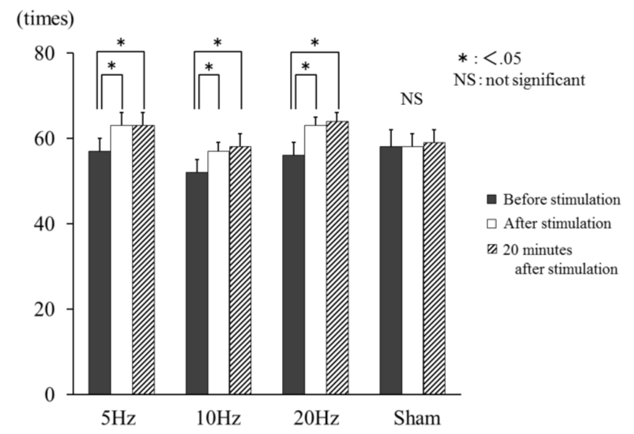


**Figure 4:** Tapping task. In all real rTMS groups there was a significant increase in the number of maximal thumb presses performed in 10 s immediately and 20 min after rTMS (p<0.05). There was no significant increase in the number of maximal thumb presses performed in 10 s in the sham group.

In the 20-Hz rTMS group, the number of thumb presses was 56 ± 3 before stimulation, 62 ± 2 immediately after stimulation, and 63 ± 2, 20 min after stimulation. The number of thumb presses was significantly greater both immediately after and 20 min after stimulation compared to before stimulation (p<0.05). There was no significant difference in the number of thumb presses immediately after and 20 min after stimulation, indicating that improved performance was maintained for 20 min after stimulation.

In the sham stimulation group, the number of thumb presses was 58 ± 4 before stimulation, 58 ± 3, immediately after stimulation, and 59 ± 3, 20 min after stimulation. There were no significant differences across time points.

## Grip strength

The grip strength results are shown in Figure 5. In the 5-Hz rTMS group, grip strength was 42.3 ± 5.8 (mean ± SD) kg before stimulation, 43.1 ± 4.7 kg immediately after stimulation, and 42.6 ± 5.1 kg 20 min after stimulation. There were no significant differences across time points.In the 10-Hz rTMS group, grip strength was 38.2 ± 4.3 kg before stimulation, 38.6 ± 2.9 kg immediately after stimulation, and 37.9 ± 4.5 kg 20 min after stimulation. There were no significant differences across time points. In the 20-Hz rTMS group, grip strength was 46.1 ± 3.2 kg before stimulation, 45.7 ± 4.8 kg immediately after stimulation, and 46.3 ± 5.2 kg 20 min after stimulation. There were no significant differences across time points. In the sham stimulation group, grip strength was 41.0 ± 4.2 kg before stimulation, 41.4 ± 4.3 kg immediately after stimulation, and 40.7 ± 6.2 kg 20 min after stimulation. There were no significant differences across time points.

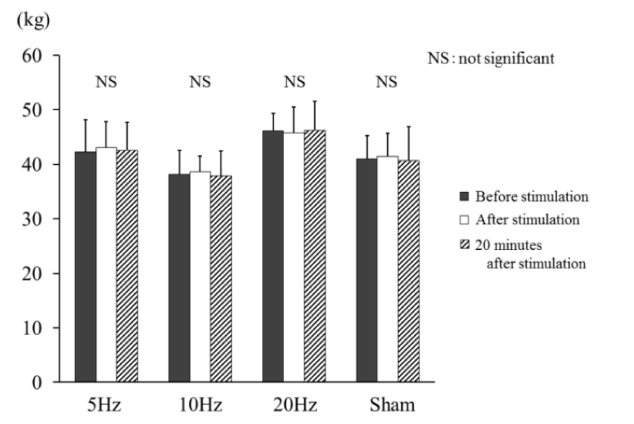


**Figure 5:** Grip strength there was no significant increase in grip strength in any group.

## Discussion

In this study, we considered the most beneficial settings of high-frequency rTMS. The time taken to complete a peg-board task and the number of maximal thumb presses in 10 s indicated that upper limb function improved immediately after stimulation in all real rTMS groups. In addition, a carry-over effect was observed 20 min after stimulation in all real rTMS groups. On the other hand, grip strength was not changed by stimulation in any group.

Previous studies of high-frequency rTMS have shown that brain activity at the site of the stimulus increases (evaluated using functional magnetic resonance imaging) and the stimulation facilitates motor evoked potentials [14,15]. In this study, upper limb function was improved in all real rTMS groups. In all real rTMS groups, excitation of the ipsilateral cerebral cortex was increased by rTMS. Grip strength did not change, and this may be because the study was performed on healthy persons. A previous study has reported that grip strength improved after rTMS in patients with motor-neuron disorder [12,16]. Therefore, although rTMS improved motor performance, it did not influence muscle strength.

The duration of the stimulation in this study was 340 s for the 5-Hz rTMS group, 280 s for the 10-Hz rTMS group, and 310 s for the 20-Hz rTMS group. Our results suggest that 10-Hz rTMS may improve upper-limb function with a shorter duration of stimulation than other rTMS stimulation frequencies. During rTMS, the stimulation coil has to be held over a specific region of the cranium. This requires head immobilization and requires the subject to maintain the same posture throughout stimulation; therefore, stimulation of long duration may induce discomfort. Therefore, 10-Hz rTMS, which had the shortest stimulation time, is recommended to minimize subject discomfort.

It is known that high-frequency rTMS will suppress spasms, not only in hemiplegia but also in multiple sclerosis, Parkinson's disease, and spinal cord injury [11,17-19]. Our results indicating the optimal stimulation frequency for rTMS will be helpful to scientists and clinicians performing rTMS in these populations.

Recently, it has been reported that combined treatment with rTMS and a functional therapy cause a long-term carry-over effect [10]. However, there are various rTMS stimulation paradigms, which vary not only according to stimulation frequency, but also according to stimulation time and inter-train interval [12]. In recent years, theta-burst stimulation has been reported and stimulation paradigms are further complicated [20,21]. Therefore, it is necessary to clarify the paradigms that involve minimal discomfort, and not to rely on rule of thumb when determining stimulation parameters.

## Study Limitations

The number of patients in this study was relatively small, and our findings should be confirmed in a larger number of patients. Moreover, subjects in this study were healthy, and it is necessary to determine whether the same results are obtained in patient populations.

## Conclusions

We investigated the most beneficial frequency of high-frequency rTMS for upper-limb function in healthy subjects. Immediately and 20 min after stimulation, we observed a significant decrease in the time taken to complete a peg-board task and increase in the number of maximal thumb presses performed in 10 s in all real rTMS groups. Stimulation time was shortest in the 10-Hz rTMS group, and 10-Hz rTMS is recommended, as the short duration will minimize subject discomfort. Until now, stimulation frequency has always been decided using the examiner's rule of thumb, and our results will be helpful for determining the stimulation frequency of rTMS.

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