# Changes in Sensory Functions after Low-frequency Repetitive Transcranial Magnetic Stimulation over the Motor Cortex

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**Objective: To investigate changes in various sensory functions after low-frequency repetitive transcranial magnetic stimulation (rTMS) in healthy subjects.**
**Methods: A Neurometer® CPT/C was used to measure current perception threshold (CPT) values at frequencies of 2000, 250, and 5 Hz in the left index finger to assess the tactile sense, fast pain, and slow pain, respectively. Somatosensory evoked potentials (SEPs) elicited by left median nerve stimulation at the wrist were used to assess excitability in the primary sensory cortex (S1). These were investigated before and after rTMS (0.9 Hz, 0.9 × resting motor threshold, 500 pulses) or sham rTMS over the right primary motor cortex (M1).**
**Results: All CPT values increased significantly and the P25-N33 of SEP amplitude decreased significantly after real rTMS, but not after sham rTMS; however, no correlations between the changes were observed.**
**Conclusions: Low-frequency rTMS over the M1 provides global anesthetic effects and inhibits excitability in S1. The lack of correlation between these changes suggests that the anesthetic effects may not always relate to the excitability of S1; thus, the mechanisms responsible for the changes remain unclear. Nevertheless, these findings suggest that rTMS may be a useful strategy for treating intractable pain in rehabilitation medicine.**

**Key words: repetitive transcranial magnetic stimulation, current perception threshold, somatosensory evoked potential, therapy, intractable pain**

## INTRODUCTION

Since the 1990s, several studies have reported that repetitive transcranial magnetic stimulation (rTMS) induces long-lasting effects on cortical excitability. The effects of rTMS have been studied mostly over the primary motor cortex (M1): low-frequency rTMS produces a decrease in cortical excitability [1, 2], whereas high-frequency rTMS produces an increase in cortical excitability [3, 4].

It has also been reported that rTMS might provide pain relief [5, 6] and changes in sensory function [7, 8]. Migita *et al*. used rTMS over the M1 to treat two patients with chronic central pain and observed pain relief in one patient but no effect in the other [5]. This was the first reported evidence that rTMS has an analgesic effect. Enomoto *et al*. later observed the suppression of N20-P25 and P25-N33 components of somatosensory evoked potentials (SEPs) after 1-Hz rTMS over the hand motor area. They suggested that the suppression of N20-P25 and P25-N33 components occurred in the primary sensory cortex (S1) [7]. In contrast, Satow *et al*. reported that SEPs were unaffected after 0.9 Hz rTMS, but that tactile threshold was increased [9]. Summers *et al*. also observed that rTMS at both 1 and 20 Hz induced a decrease in the cold detection threshold (i.e., thermohypesthesia), whereas only 20-Hz rTMS significantly lowered the cold pain threshold [10]. Tamura *et al*. showed that 1-Hz rTMS relieved acute pain induced by an intradermal injection of capsaicin compared with sham rTMS [11]. These findings suggest that rTMS may be a useful strategy for treating intractable pain in rehabilitation medicine.

The following issues, however, remain unresolved. First, can different sensory functions (e.g., tactile and pain perception) be affected simultaneously by rTMS? Second, how much does rTMS change these perceptions? Third, do relationships exist between changes in SEPs and tactile and/or pain perception? If the functions of S1 would be affected by rTMS toward suppression, several sensory modalities must be affected simultaneously and equally, with all findings considered from previous reports.

Assessment of quantitative current perception thresholds (CPTs) using a Neurometer® CPT/C (Neurotoron Inc., Baltimore, MD, USA) has been reported to be useful for evaluating sensory function. Sinusoidal electrical currents of 2000, 250, and 5 Hz have been found to stimulate Aβ, Aδ, and C fibers, respectively. According to the neurophysiological theory of Katims, the alternating current wavelengths required to depolarize nerve fibers depend on the diameter of the nerve fibers [12–15]. In other words, CPTs at frequencies of 2000, 250, and 5 Hz are considered to reflect the tactile sense and cutaneous pressure, fast pain and temperature, and slow pain and temperature, respectively [16]. It was also reported that CPT examination is useful not only for evaluating the

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peripheral nervous system [17, 18], but also for evaluating the central nervous system [19, 20]. Therefore, we measured CPTs of the index finger and SEPs of the median nerve before and after 0.9-Hz rTMS over the hand motor area to assess sensory function circumstantially and quantitatively.

## MATERIALS AND METHODS

### Subjects

The subjects were 10 healthy volunteers (five males and five females; mean age: 35.8 ± 5.7 years) with no known neurological disorders or contraindications to TMS, as proposed by Wassermann [21]. The present study was approved by the Clinical Research Review Committee of the Tokai University School of Medicine and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects before the study began.

### Experimental design

The subjects were seated in a comfortable reclining chair so that the whole body, including both arms and hands was at rest. They were instructed to keep their hands and fingers still and as relaxed as possible while remaining awake. The experiment was conducted in a quiet laboratory room at a controlled temperature of 25–27°C. An infrared heater was used to maintain hand and forearm skin temperatures at > 32°C.

All subjects received rTMS over the M1. CPTs and SEPs were measured to evaluate sensory function just before and 5 min after real rTMS or sham rTMS (*see* below). We performed each examination on separate days. Previous studies have shown that the effects of rTMS on M1 last for less than 30 min [1–3]. Therefore, we had to measure CPTs and SEPs after rTMS as quickly as possible. The rTMS sessions were conducted on separate days in a counterbalanced order, and the intervals between two successive sessions were at least 1 week in the same subject.

### rTMS

TMS was delivered using a Maglite® magnetic stimulator (Dantec Medtronic, Skovlunde, Denmark) equipped with a circular magnetic coil with an outside diameter of 140 mm (MMC 140; Medtronic, Minneapolis, MN, USA) with monophasic pulses. Single-pulse TMS was applied around the right motor area. Motor evoked potentials (MEPs) were recorded from the left abductor pollicis brevis muscle by Ag-AgCl surface electrodes using a muscle belly-tendon setup. Next, the position over which the magnetic stimulus elicited the largest and fastest MEPs was determined as the hand motor area (i.e., hot spot). The resting motor threshold (rMT) was defined as the minimal intensity of stimulation capable of inducing MEPs with a peak-to-peak amplitude greater than 50 μV in 5 of 10 consecutive trials [22]. The rMT was measured during complete muscle relaxation while monitoring the electromyography from the abductor pollicis brevis muscle. Thereafter, real rTMS was applied over the M1 at a frequency of 0.9 Hz and an intensity of 0.9 × the rMT. A single train of 250 stimuli was delivered two times (total: 500 stimuli), with an inter-train interval of 30 s.

As a control, we administered sham rTMS, which consisted 0.9 Hz real rTMS through a coil placed 3 cm from the scalp, with seating the lightweight cushion made of polyethylene.

### Measurement of CPTs

We used the Neurometer® CPT/C to measure CPT values. The subjects were stimulated with three different frequencies of sinusoidal electrical current to determine the threshold. A pair of round gold-plated electrodes (1 cm in diameter) for electrical stimuli was fixed on the left index finger distal interphalangeal joint from the inside and the outside.

At first, the intensity alignment mode preprogrammed in the Neurometer® quickly narrowed the range of possible CPT values. Next, we began the Auto Test Cycle, which was also preprogrammed. A double-blind, forced-choice procedure similar to that used in standard auditory tests was used to determine CPT values. Each subject was presented with randomly generated pairs of real and placebo stimuli and was required to choose when the stimulus was identified. The device adjusts the intensity of the stimulus and randomly generates a new testing order for the next pair of stimulus repeatedly, based on the response. After a sufficient number of test results were examined, the CPT value was defined as the lowest current intensity reliably detected by the subject. One CPT value is equivalent to 10 μA, and the CPT value was measured with a resolution of ± 20 μA to a $P$ value < 0.006 [23]. Neither the subjects nor we were aware of the intensity of the stimulus that the device delivered throughout the procedure. Accordingly, to assess the sensory function, the CPT values could be measured exactly in an objective manner.

We measured CPTs independently two times at frequencies of 2000, 250, and 5 Hz, which were averaged and applied to further analyses. The average time required to complete 3 frequency measurements of CPTs was approximately 25 min.

### SEPs

SEPs were recorded from the right hand sensory area after left median nerve stimulation of the wrist. A recording Ag-AgCl surface electrode was placed over the hand sensory area at the C3´ position according to the International 10–20 system (2 cm posterior to C3). A reference electrode was placed over the Fz position. A disposable pre-gelled Ag-AgCl ground electrode was placed around the neck. The median nerve was stimulated (duration: 0.2 ms; stimulus rate: 3.0 Hz) via surface electrodes at the wrist at a level 1.2 times the motor threshold intensity. SEPs were amplified with a band pass of 20–1000 Hz, and at least 300 responses were averaged and obtained three times just before and 5 min after each rTMS. Next, the amplitudes from the onset of N20 to the peak (N20o–p), from the N20 peak to the P25 peak (N20p–P25p) and from P25 to the N33 peak (P25p–N33p) were measured [7], and the average amplitudes of these parameters of SEPs were applied to further analyses. We also recorded antidromic sensory nerve action potentials (SNAPs) using surface electrodes placed on the left index finger to confirm that the intensity of the median nerve

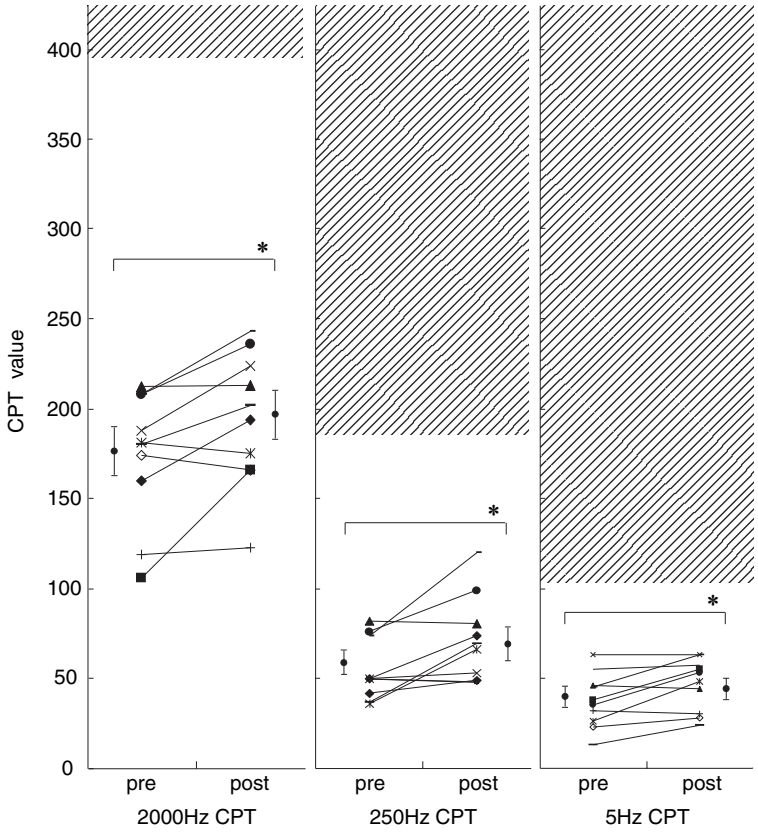


**Fig. 1** Change in CPT values after real rTMS. Current perception threshold (CPT) values increased at frequencies of 2000, 250, and 5 Hz. The results are expressed as means and standard errors ($n$ = 10) * $P < 0.05$ (Wilcoxon's signed-rank test). The shaded areas represent abnormal ranges of CPT values.

stimulus was constant over the SEP recording session. The amplitudes of SNAPs from the onset to peak were measured after several SEP recordings, with an average of 32 responses.

SEPs and SNAPs were recorded using a Signal-Processor® DP1100 (NEC Medical Systems, Tokyo, Japan) and stored for offline analysis after the experiment. Approximately 20–25 min were required to complete the recording of SEPs and SNAPs.

**Data analysis**

CPT values (2000, 250, and 5 Hz), the amplitude of several components of SEPs, and that of SNAPs were compared before and after rTMS by conducting a Wilcoxon's signed-rank test. The percentage changes in CPTs, SEPs, and SNAPs from before to after rTMS were calculated. We conducted a Mann-Whitney $U$ test to assess the percentage change between each rTMS, and used Spearman correlation coefficients to assess the correlations between the percentage change in CPTs and SEPs. Differences were considered significant at a $P$ value < 0.05. The Statistical Packages for Social Sciences (SPSS 13.0J for Windows; SPSS Inc., Chicago, IL, USA) was used to conduct the statistical analysis.

## RESULTS

None of the subjects in this study experienced any side effects from rTMS over the M1. There was hot spot in the same place on each experiment session to examine CPTs or SEPs in all subjects. And no significant difference has been observed between these sessions in the intensity of rMT (50.3 ± 3.6% and 49.8 ± 4.0%, respectively).

We investigated the changes in sensory function from just before to 5 min after rTMS. The individual changes in CPT values at 2000 (left panel), 250 (middle panel), and 5 Hz (right panel) from before to after real rTMS are shown in Fig. 1. Real rTMS induced a significant increase from baseline in all CPT values. The CPT values at 2000, 250, and 5 Hz increased in 7 of 10 subjects (70%) similarly at each frequency: from 173.7 ± 11.5 to 194.2 ± 11.8 ($P < 0.05$, Wilcoxon's signed-rank test), from 54.7 ± 5.3 to 70.8 ± 7.6 ($P < 0.05$), and from 37.6 ± 4.8 to 46.5 ± 4.6 ($P < 0.05$), respectively. However, these values were within normal ranges for CPT determined in healthy adults investigated by Katims JJ *et al.* [12, 14]. There were no significant differences between the CPT values measured before and after sham rTMS.

Percentage changes in CPTs between real and sham rTMS are shown in Fig. 2. Percentage changes in CPTs after real rTMS at 2000, 250, and 5 Hz were 13%, 32%, and 32%, respectively. Percentage changes in CPTs after real rTMS were significantly greater than those after sham rTMS ($P < 0.01$ at 2000 Hz, $P < 0.05$ at 250 Hz, and $P < 0.01$ at 5 Hz CPT).

Typical SEPs in one subject before and after real rTMS over the M1 are shown in Fig. 3. The waveform of SEPs before rTMS is shown in the left panel and that after rTMS is shown in the right panel. A reduction in the amplitude of the P25p–N33p component was observed, whereas N20o–p and N20p–P25p did not change significantly.

The individual changes in several amplitudes of SEP components at N20o–p (left panel), N20p–P25p (middle panel), and P25p–N33p (right panel) from before to after real rTMS are shown in Fig. 4.

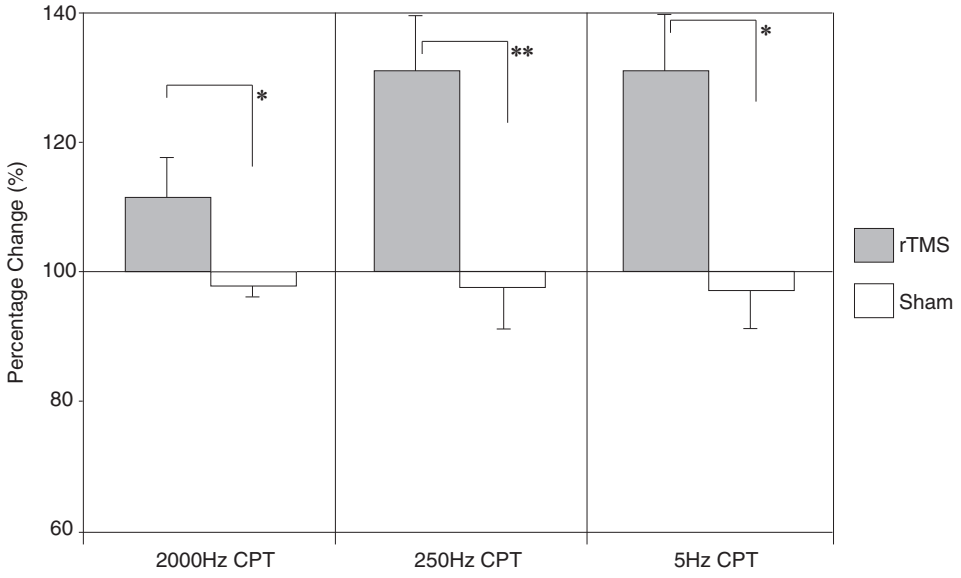


**Fig. 2** Percentage changes in current perception threshold (CPT) values between real rTMS and sham rTMS. Percentage changes were calculated by dividing the values after rTMS by the values before rTMS. The results are expressed as means and standard errors ($n$ = 10). The changes were significantly greater after real rTMS at frequencies of 2000, 250, and 5 Hz: * $P < 0.05$, ** $P < 0.05$ (Mann-Whitney $U$ test).

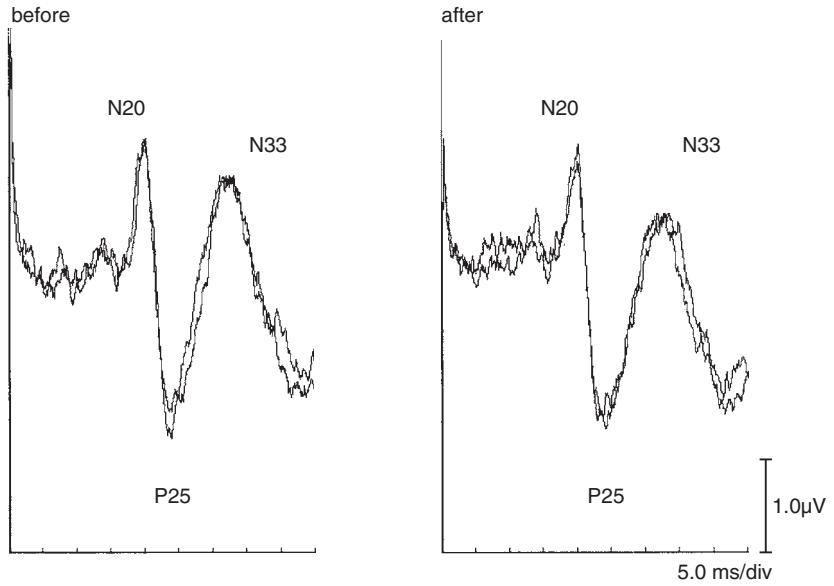


**Fig. 3** SEPs before and after real rTMS over the motor cortex in one subject. A reduction in the amplitude of P25p–N33p was observed.

The amplitudes of N20o–p and N20p–P25p did not change significantly, but the amplitude of P25p–N33p decreased significantly in 8 of 10 subjects (80%): from baseline (1.88 ± 0.32 μV) to 1.51 ± 0.35 μV after real rTMS ($P < 0.05$, Wilcoxon's signed-rank test).

Percentage changes in several SEP components and SNAPs amplitude after real and sham rTMS in all subjects are shown in Fig. 5. There was a significant difference between real and sham rTMS ($P < 0.05$, Mann-Whitney $U$ test), but no significant difference in the change in SNAP amplitude from before to after real rTMS or sham rTMS.

The relationship between the change in CPT at 2000, 250, and 5 Hz and in P25p–N33p amplitude of the SEP component after real rTMS is shown in Fig. 6. There was no significant correlation between each percentage change.

## DISCUSSION

Low-frequency rTMS (1 Hz or less) has been shown to decrease cortical excitability [1–4] and may induce a long-lasting inhibition in interconnected areas. The

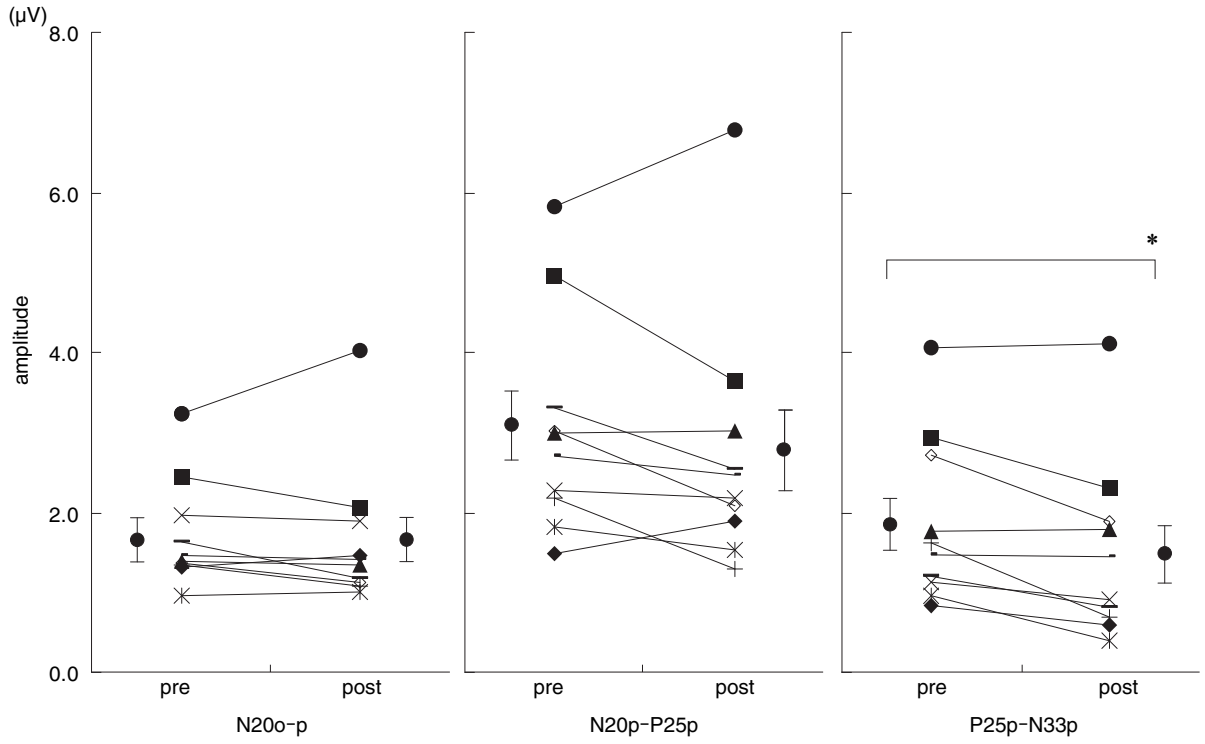


**Fig. 4** Change in amplitudes of SEP components after real rTMS. Amplitude of somatosensory evoked potential reduced at component of P25p–N33p. The results are expressed as means and standard errors ($n = 10$) * $P < 0.05$ (Wilcoxon's signed-rank test).

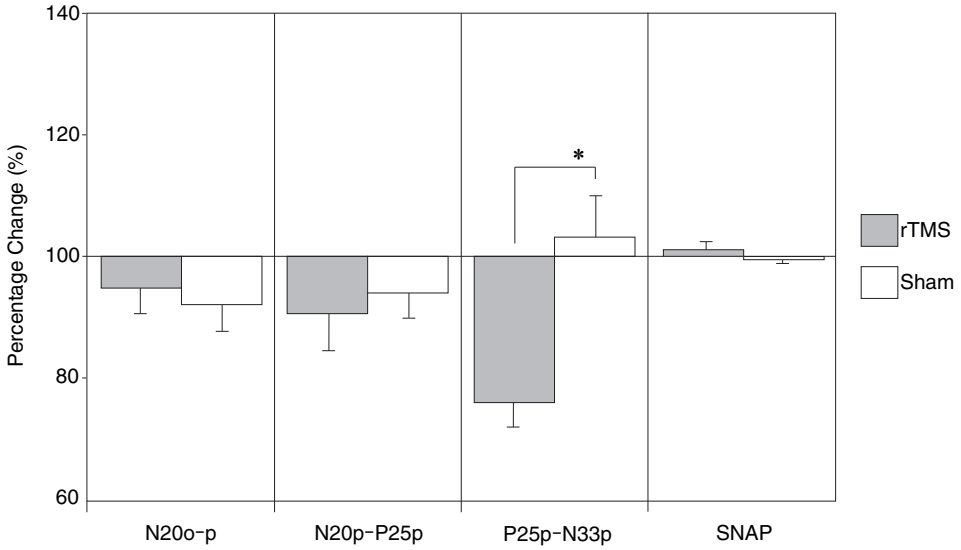


**Fig. 5** Percentage changes in the amplitude of SEP components and SNAPs between real rTMS and sham rTMS. Percentage changes were calculated by dividing the values after rTMS by the values before rTMS. The results are expressed as means and standard errors ($n = 10$). The changes in P25p–N33p were significantly greater after real rTMS: * $P < 0.05$ (Mann-Whitney $U$ test).

neurophysiological mechanisms for the long-lasting effect in the cortex are unclear; however, a previous study has suggested that a reduction in excitability may be related to long-term depression [1]. Furthermore, this inhibition may be related to changes in several sensory thresholds and in pain. Therefore, we investigated the changes in sensory function induced by rTMS as part of basic neurophysiological research of treatment options for intractable pain.

The present study had 3 main findings: a) low-frequency rTMS induced changes in several CPT values simultaneously; b) the observed changes had an anesthetic effect, which did not extend over the abnormal ranges in CPT values in healthy subjects; and c) no relationships were observed between several changes in CPT values and SEP P25p–N33p amplitudes.

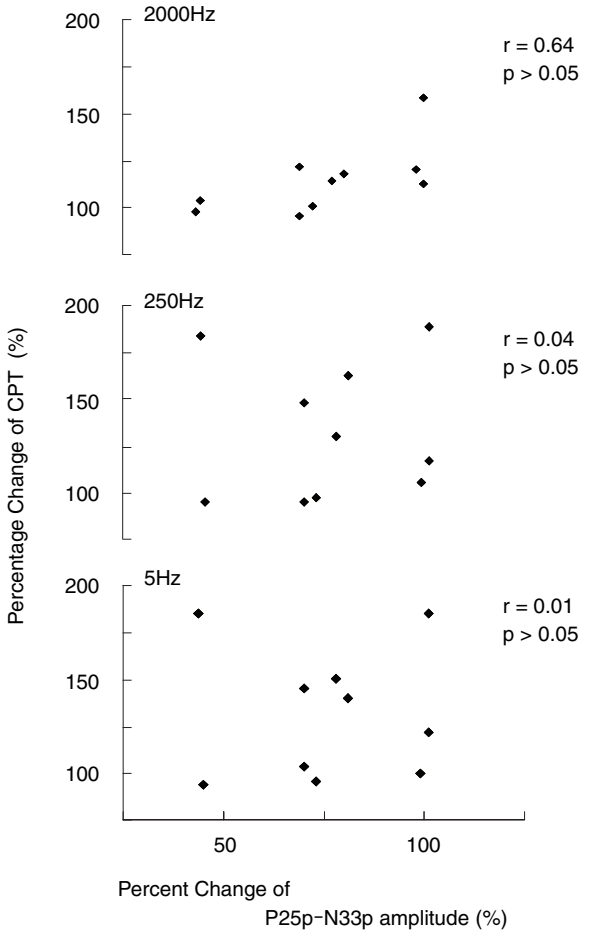


**Fig. 6** Relations between percentage changes in current perception threshold (CPT) at 2000, 250, and 5 Hz and P25p-N33p amplitudes. There was no correlation between the changes in CPT and P25p-N33p amplitudes at each frequency. Spearman correlation coefficients were used for the assessments ($n$ = 10).

Increases in the CPT after real rTMS appeared to be genuine effects, whereas no significant changes in CPT were observed after sham rTMS. We considered that the sham rTMS procedure used in this study did not excite or inhibit the cortex. The magnetic stimulator and coil of the rTMS instrument produce a maximum magnetic field of about 1.8 T and stimulation produces an excitation depth of only 2.0 cm beneath the scalp [24]. Therefore, we lifted the coil and fixed it 3 cm from the scalp for the sham rTMS treatment.

In the present study, we measured CPTs to assess sensory function. In a previous study, several techniques [e.g., two-point discrimination test, Semmes-Weinstein Monofilament Test (SWMT)] were used to evaluate tactile perception [9, 25]; however, these techniques had little reproducibility. Visual analog scales are commonly used to evaluate pain [11, 26, 27]; however, a disadvantage of this method is that it is subjective. In contrast, CPTs can be used to assess sensory function quantitatively and objectively in a double-blind, forced-choice protocol, and its reproducibility is relatively high compared with other techniques [16]. Furthermore, CPT assessment has previously been used in the fields of neuroscience and neurophysiology [28–31]. In studies of patients with demyelinating polyneuropathy, CPT values at 2000 and 250 Hz were above the normal range compared with those at 5 Hz. It was previously suggested that frequencies of 2000 and 250 Hz selectively stimulate myelinated fibers (i.e., Aβ and Aδ fibers), whereas a frequency of 5 Hz selectively stimulates unmyelinated fibers (i.e., C fibers) [32, 33]. Liu *et al.* reported that the intravenous administration of fentanyl increased CPT values at frequencies of 250 and 5 Hz, whereas the epidural administration of fentanyl increased CPT values only at a frequency of 5 Hz [34]. These findings suggest that sensory fiber stimulated by currents of 250 and 5 Hz conduct nociceptive pain (i.e., fast and slow pain). Thus, we conclude that CPTs were useful in the assessment of each sensory modality (i.e., tactile sense, fast pain, and slow pain) in the present study. The observed increases in these sensory thresholds after low-frequency rTMS over the M1 are in agreement with the results of several previous studies [9, 10]. Moreover, it is notable that the thresholds of these three different sensory systems can change simultaneously after a single session of low-frequency rTMS.

The degree of the anesthetic effect induced by rTMS is unclear. In a previous study, Enomoto *et al.* reported transient hypesthesia after rTMS in one healthy subject [7], and Satow *et al.* observed mild sensory symptoms in two subjects during rTMS [9]. The risk of these unexpected side effects is low with therapeutic rTMS. However, we showed in the present study that these perception thresholds remained within normal limit despite changing significantly and that rTMS is safe.

We observed a decrease in SEP amplitude but no change in SNAP amplitude after rTMS, which suggests that electrical stimulation of the median nerve

was the same intensity in recording SEPs at before and after each rTMS. The amplitude of P25p–N33p after rTMS was significantly lower than that before rTMS, and no change in the amplitude of N20o–p was observed. These results are nearly similar to the findings of Enomoto *et al.* [7]. They observed the decrease of the amplitude of N20p–P25p and P25p–N33p, and concluded that these decreases with the lack of change in N20o–p resulted from a suppression of S1 excitability and no change in thalamo-cortical excitability, because N20o–p reflects activation of the S1 by thalamo-cortical fibers. Therefore, they hypothesize that this suppression is produced by cortico-cortical effects from the motor cortex to the sensory cortex. As the evidence, intractable thalamic pain can be alleviated by motor cortical electrical stimulation but not by sensory cortical stimulation [35]. Furthermore, Satow *et al.* [9] compared the change in tactile threshold measured in the SWMT with the change in SEP in the sensorimotor cortex after rTMS. The tactile threshold increased but the SEP remained unchanged immediately after rTMS, as previously described. The rTMS conditions used in the study by Satow *et al.* (i.e., frequency, intensity, and site of stimulation) were the same as those used in our study. The round coil we used usually stimulates a wide area compared with 8 figure coil they used in their study, so that a difference may occur for the changes of SEPs compared with ours. However, the correlations between changes of tactile threshold and SEPs were undetermined in previous report. On the other hand, no correlation between the percentage changes in P25p–N33p and in CPTs was observed in the present study. These findings suggest that a change in threshold might not always relate to the excitability of the S1. Inui *et al.* reported that the senses of pain and tactility were transmitted by Aδ and Aβ fibers, respectively. As a result, the first cortical activity evoked by both stimulations was in the S1 region of the contralateral hemisphere of the stimulated side. Activity was next observed in the bilateral secondary sensory cortex (S2) and subsequently in the insular cortex, cingulate cortex, and anterior medial temporal area of the contralateral side of the stimulated side and in the S1 region of the ipsilateral side of the stimulated side [36]. The cortical processing of pain and tactile information extend widely in this manner. In addition, acute pain induced by an intradermal injection of capsaicin was reduced after low-frequency rTMS. The results of the SPECT study using technetium-99m ethyl cysteinate dimmer suggest that the reduction in pain results from the changes of the regional cerebral blood flow in the medial prefrontal cortex and in the caudal part of the anterior cingulate cortex on ipsilateral side after rTMS [11]; however, the relevance of S1 is negative. Therefore, we suggest that changes in these thresholds may have no relation with S1, and the mechanisms responsible for these changes in sensory threshold may result from broad changes in activity in the cerebral cortex through a network participating in the information processing of the several sensations.

CPTs have been used in studies of the central nervous system. Some studies [19, 20] showed that magnetic resonance imaging at 5 Hz activated several areas of the cerebral cortex (e.g., S1, S2, insula, and cingulate gyrus). These results were similar to those of several neuro-imaging studies that used nociceptive heat stimulation [19], intra-epidermal electrical stimulation [37], and $CO_2$ laser stimulation [38]. We considered that the observed changes in CPT values indicate a change in activity in several areas of the cerebral cortex, as mentioned above. Therefore, we also investigated the SEPs by means of comparison to assess the activity of the sensory cortex.

We found that the observed increases in CPT values and reductions in P25p–N33p lasted for at least 30 minutes after rTMS. These long-lasting effects were also observed in previous studies. The reduction in MEP amplitude continued for approximately 30 minutes after low-frequency rTMS over the M1 [1, 2] and in SEP amplitudes continued for approximately 60 minutes [7]. The results of the previous studies appear to be consistent with those of the present study. However, the change in tactile threshold measured with SWMT was observed only immediately after rTMS [9], possibly because CPTs examination can assess the sensory function in details compared with SWMT.

In summary, low-frequency rTMS over the M1 provides global anesthetic effects in healthy subjects. These anesthetic effects likely result from broad changes in the cerebral cortex, but not from changes in S1 function. However, the mechanism responsible for the reduction in pain remains unclear, and further study is needed to determine whether similar threshold changes can be obtained in patients with intractable pain.

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### REFERENCES

1) Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, Cohen LG. Depression of motor cortical excitability by low-frequency transcranial magnetic stimulation. Neurology 1997; 48: 1398–403.
2) Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clin Neurophysiol 2000; 111: 800–5.
3) Berardelli A, Inghilleri M, Rothwell JC, Romeo S, Currà A, Gilio F, Modugno N, Manfredi M. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Exp Brain Res 1998; 122: 79–84.
4) Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Interindividual variability of the modulatory effects of repetitive transcranial magnetic stimulation on cortical excitability. Exp Brain Res 2000; 133: 425–30.
5) Migita K, Uozumi T, Arita K, Monden S. Transcranial magnetic coil stimulation of motor cortex in patients with central pain. Neurosurg 1995; 36: 1037–40.
6) Lefaucheur JP, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiol Clin 2001; 31: 247–52.
7) Enomoto H, Ugawa Y, Hanajima R, Yuasa K, Mochizuki H, Terao Y, Shiio Y, Furubayashi T, Iwata NK, Kanazawa I. Decreased sensory cortical excitability after 1 Hz rTMS over the ipsilateral primary motor cortex. Clin Neurophysiol 2001; 112: 2154–8.
8) Tsuji T, Rothwell JC. Long lasting effects of rTMS and associated peripheral sensory input on MEPs, SEPs and transcortical reflex excitability in humans. J Physiol 2002; 540: 367–76.

9) Satow T, Mima T, Yamamoto J, Oga T, Begum T, Aso T, Hashimoto N, Rothwell JC, Shibasaki H. Short-lasting impairment of tactile perception by 0.9Hz-rTMS of the sensoriomotor cortex. Neurology 2003; 60: 1045–7.
10) Summers J, Johnson S, Pridmore S, Oberoi G. Changes to cold detection and pain thresholds following low and high frequency transcranial magnetic stimulation of the motor cortex. Neuroscience Letters 2004; 368: 197–200.
11) Tamura Y, Okabe S, Ohnishi T, N Saito D, Arai N, Mochio S, Inoue K, Ugawa Y. Effects of 1-Hz repetitive transcranial magnetic stimulation on acute pain induced by capsaicin. Pain 2004; 107: 107–15.
12) Katims JJ, Naviasky EH, Ng LK, Rendell M, Bleecker ML. New screening device for assessment of peripheral neuropathy. J Occup Med 1986; 28: 1219–21.
13) Katims JJ, Long DM, Ng LK. Transcutaneous nerve stimulation. Frequency and waveform specificity in humans. Appl Neurophysiol 1986; 49: 86–91.
14) Katims JJ, Naviasky EH, Rendell MS, Ng LK, Bleecker ML. Constant current sine wave transcutaneous nerve stimulation for the evaluation of peripheral neuropathy. Arch Phys Med Rehabil. 1987; 68: 210–3.
15) American Association of Electrodiagnostic Medicine Equipment and Computer Committee. Technology review: the Neurometer Current Perception Threshold (CPT). Muscle Nerve. 1999; 22: 523–31.
16) American Association of Electrodiagnostic Medicine. Guidelines in electrodiagnostic medicine. Technology review: the Neurometer Current Perception Threshold (CPT). Muscle Nerve. 1999; 22: S247–59.
17) Nather A, Neo SH, Chionh SB, Liew SC, Sim EY, Chew JL. Assessment of sensory neuropathy in diabetic patients without diabetic foot problems. J Diabetes Complications 2008; 22: 126–31.
18) Kang EK, Lim JY, Shin HI, Gong HS, Oh JH, Paik NJ. Comparison between nerve conduction studies and current perception threshold test in carpal tunnel syndrome. Neurophysiol Clin 2008; 38: 127–31.
19) Bocerra L, Stojanovic M, Chang I, Breiter H, Tracey I, Fishman S, Edwards A, Gonzalez RG, Borsook D. fMRI mapping of CNS activations following noxious heat and electrical stimuli. Fifth Scientific Meeting of the International Society for magnetic Resonance in Medicine in Vancouver, April 1997.
20) Alkire MT, White NS, Hsieh R, Haier RJ. Dissociable brain activation responses to 5-Hz electrical pain stimulation: a high-field functional magnetic resonance imaging study. Anesthesiology. 2004; 100(4): 939–46.
21) Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5–7, 1996. Electroencephalogr Clin Neurophysiol 1998; 108: 1–16.
22) Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijević MR, Hallett M, Katayama Y, Lücking CH, *et al*. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994; 91: 79–92.
23) Neurotron Inc. Neurometer® CPT/C operating manual version 17b, 2002.
24) Daskalakis ZJ, Chen R. The physiology and safety of repetitive transcranial magnetic stimulation. In: Hallett M, Chokroverty S. eds. Magnetic Stimulation in clinical neurophysiology, 2nd ed. Phyladelphia: Elsevier, 2005: 61–81.
25) Nather A, Neo SH, Chionh SB, Liew SC, Sim EY, Chew JL. Assessment of sensory neuropathy in diabetic patients without diabetic foot problems. J Diabetes Complications. 2008; 22: 126–31.
26) Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 2005; 76: 833–8.
27) Mylius V, Reis J, Knaack A, Haag A, Oertel WH, Rosenow F, Schepelmann K. High-frequency rTMS of the motor cortex does not influence the nociceptive flexion reflex but increases the unpleasantness of electrically induced pain. Neurosci Lett. 2007; 415: 49–54.
28) Lerner TH, Goldstein GR, Hittelman E. Quantitative sensory nerve conduction threshold (sNCT) evaluation of the trigeminal nerve at the mental foramen area. J Prosthet Dent 2000; 84: 103–7.
29) Matsutomo R, Takebayashi K, Aso Y. Assessment of peripheral neuropathy using measurement of the current perception threshold with the neurometer in patients with type 2 diabetes mellitus. J Int Med Res 2005; 33: 442–53.
30) Oishi M, Mochizuki Y, Suzuki Y, Ogawa K, Naganuma T, Nishijo Y, Mizutani T. Current perception threshold and sympathetic skin response in diabetic and alcoholic polyneuropathies. Intern Med 2002; 41: 819–22.
31) Shimoda O, Ikuta Y. The current perception thresholds vary between horizontal and 70 degrees tilt–up positions. Anesth Analg 2000; 91: 398–402.
32) Menkes DL, Hood DC, Ballesteros RA, Bodnar P. Quantitative sensory testing distinguishes axonal from demyelinating polyneuropathies. Muscle Nerve 1997; 20: 1056.
33) Berger JS, Brannagan TH, Latov N. Neuropathy with anti–myelinassociated glycoprotein antibodies: quantitative sensory testing and response to intravenous immunoglobulin. Muscle Nerve. 1997; 20: 1056–1057.
34) Liu SS, Gerancher JC, Bainton BG, Kopacz DJ, Carpenter RL. The effects of electrical stimulation at different frequencies on perception and pain in human volunteers: epidural versus intravenous administration of fentanyl. Anesth Analg. 1996; 82(1): 98–102.
35) Tsubokawa T, Katayama Y, Yamamoto T, Hirakawa T, Koyama S. Chronic motor cortex stimulation in patients with thalamic pain. J Neurosurg 1993; 78: 393–401.
36) Inui K, Tran TD, Qiu Y, Wang X, Hoshiyama M, Kakigi R. A comparative magnetoencephalographic study of cortical activations evoked by noxious and innocuous somatosensory stimulations. Neuroscience 2003; 120: 235–48.
37) Inui K, Tran TD, Qiu Y, Wang X, Hoshiyama M, Kakigi R. Pain-related magnetic fields evoked by intra-epidermal electrical stimulation in humans. Clin Neurophysiol 2002; 113: 298–304.
38) Kakigi R, Tran TD, Qiu Y, Wang X, Nguyen TB, Inui K, Watanabe S, Hoshiyama M. Cerebral responses following stimulation of unmyelinated C-fibers in humans: electro- and magneto-encephalographic study. Neurosci Res 2003; 45: 255–75.