



# Exploratory study of optimal parameters of repetitive transcranial magnetic stimulation for neuropathic pain in the lower extremities

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## Abstract

**Introduction:** Pain relief from repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex (M1) is particularly poor in patients with leg pain. The optimal parameters for relieving leg pain remain poorly understood. The purpose of this study was to explore the optimal stimulation parameters of M1-rTMS for patients with leg pain.

**Methods:** Eleven patients with neuropathic pain in the leg randomly underwent 6 conditions of M1-rTMS with different stimulation intensities, sites, and coil directions, including sham stimulation. The 5 active conditions were as follows: 90% or 110% of the resting motor threshold (RMT) on the M1 hand with an anteroposterior coil direction, 90% or 110% RMT on the M1 foot in the anteroposterior direction, and 90% RMT on the M1 foot in the mediolateral direction. Each condition was administered for 3 days. Pain intensity was evaluated using the Visual Analogue Scale and Short-Form McGill Pain Questionnaire 2 at baseline and up to 7 days after each intervention.

**Results:** Visual Analogue Scale scores were significantly reduced after the following active rTMS conditions: 90% RMT on the M1 hand, 90% RMT on the M1 foot with any coil direction, and 110% RMT on the M1 foot. The Short-Form McGill Pain Questionnaire 2 results were similar to those obtained using the Visual Analogue Scale. The analgesic effect of rTMS with stimulus intensity above the RMT was not superior to that below the RMT.

**Conclusion:** We suggest that the optimal stimulation parameters of rTMS for patients with neuropathic pain in the leg may target the M1 foot or M1 hand with an intensity below the RMT.

**Keywords:** Repetitive transcranial magnetic stimulation, Neuropathic pain, Lower extremity, Exploratory study

## 1. Introduction

It has been reported that high-frequency repetitive transcranial magnetic stimulation (rTMS) to the primary motor cortex (M1) has an analgesic effect on patients with neuropathic pain.<sup>4,10,14,16</sup> However, our large rigorous investigator-initiated registration-directed clinical trial failed to show positive primary or secondary outcomes.<sup>8</sup> The lack of sufficient analgesic effect in this clinical trial could have been caused by suboptimal stimulation parameters (5-Hz with 500 pulses/session) and poor efficacy for leg

pain. Recent reviews have recommended multiple sessions at 10 to 20 Hz with 2,000 to 3,000 pulses; we reported that 10-Hz rTMS with 2,000 pulses was more effective than 5-Hz or 10-Hz with 500 pulses.<sup>15</sup> However, the optimal parameters to relieve leg pain remain poorly understood. Regarding the optimal stimulation site, the M1 area somatotopically corresponding to the worst pain was stimulated in some previous studies,<sup>7,8,11,22–24</sup> whereas in others, it was stimulated regardless of the pain location.<sup>1,9,12</sup> The stimulation intensity above the resting motor threshold (RMT) at which stimulation can sufficiently reach the deep M1-foot has

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site ([www.painrpts.com](http://www.painrpts.com)).

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PR9 6 (2021) e964

<http://dx.doi.org/10.1097/PR9.0000000000000964>

rarely been used. Nevertheless, although the TMS coil orientation on the M1 hand was reported to affect pain relief efficacy,<sup>2</sup> it has not been tested for stimulation of the M1 foot. Therefore, in this study, we explored the optimal stimulation parameters of M1 rTMS in patients with neuropathic pain in the lower extremities by examining the pain relief effect with different stimulation parameters.

## 2. Methods

### 2.1. Study design and participants

We performed a randomized, single-blinded, sham-controlled, crossover exploratory study at Osaka University Hospital from August 2018 to March 2019. This study was approved by the Ethics Committee of Osaka University Hospital (approval number: 16309), and written informed consent was obtained from all participants. This trial was registered with the University Hospital Medical Information Network Clinical Trials Registry, number UMIN000025975. We recruited patients with neuropathic pain in the leg (based on the criteria of International Association for the Study of Pain)<sup>5,25</sup> from an outpatient clinic. Patients with contraindications to TMS were excluded from the study.<sup>20,26</sup>

### 2.2. Repetitive transcranial magnetic stimulation protocol

Each patient underwent 6 rTMS conditions (5 different active stimulations and 1 sham stimulation) for 3 consecutive days, with at least two weeks between each session. The order of stimulation conditions was allocated using a computer-generated simple randomization method. The patients and assessors were blinded to the interventions used through. In the rTMS protocol, active rTMS was performed using a stimulator (MagPro X100; MagVenture, Farum, Denmark) with a figure-of-eight coil (MC-B70; MagVenture). The sham stimulation was delivered using a sham coil (MC-P-B70; MagVenture). In the sham condition, electrical stimuli with an intensity of 5-mA were applied to the skin through surface cup electrodes placed over the M1-hand contralateral to the painful leg side.<sup>3</sup>

Before the first session for all conditions, the target stimulation site, motor hot spot, and RMT were determined according to visual detection of muscle twitches.<sup>7,8</sup> In all treatment sessions, rTMS parameters consisted of applying 60 trains of 5 seconds each at 10-Hz (25 seconds intertrain interval), for a total of 3,000 pulses/session. The patients received each of the following 6 types of stimulation: (1) stimulation intensity set at 90% of the RMT, with the coil installed over the M1 hand in an anteroposterior (AP) direction; (2) 90% RMT over the M1 foot in an AP direction; (3) 90% RMT over the M1 foot with coil positioned in a mediolateral (ML) direction; (4) 110% RMT over the M1 hand in an AP direction; (5) 110% RMT over the M1 foot in an AP direction; and (6) sham stimulation. The TMS navigation system (Brainsight, Rogue Research, Inc., Montreal, QC, Canada) was used to monitor the accurate positioning and direction of the coil throughout each session and across sessions.<sup>6,9,15</sup> These rTMS protocols complied with the safety guidelines for rTMS.<sup>20,26</sup>

### 2.3. Clinical assessments

Before the first rTMS session, patient characteristics were assessed. Baseline data, Visual Analogue Scale (VAS) pain intensity, and the Short-Form McGill Pain Questionnaire 2 (SF-MPQ-2) were assessed at baseline (3 days before intervention), immediately after each intervention phase (3 days), and in the

follow-up phase (up to 7 days after intervention). All assessment items were contained in unified forms completed by each patient.

### 2.4. Statistical analyses

The VAS and SF-MPQ-2 were measured for 3 days before the intervention and averaged for baseline values. For the main outcome, we used the Wilcoxon signed rank test to examine the effect of the interventions by comparing the baseline with the mean of the 3 days of intervention and the 7 days of follow-up (mean of 10 days). In addition, we used the Steel test to evaluate the change from the baseline at each time point. To evaluate possible carry-over effects, the Kruskal-Wallis test was applied to the baseline values of each intervention. In all analyses, statistical significance was set at  $P < 0.05$ . JMP Pro version 14 (SAS Institute, Cary, NC) was used for the statistical analyses.

Supplementary information about methods is described in supplementary digital contents 1, available at <http://links.lww.com/PR9/A132>.

## 3. Results

Eleven enrolled patients received the 6 types of stimulation in a randomly assigned order. One patient was unable to perform rTMS over the M1 foot at 110% RMT due to scalp pain; all other patients completed all planned rTMS sessions. **Table 1** presents patients' baseline demographic and clinical characteristics. No serious adverse events were observed during the study (see Table, supplemental digital content 2, available at <http://links.lww.com/PR9/A132>).

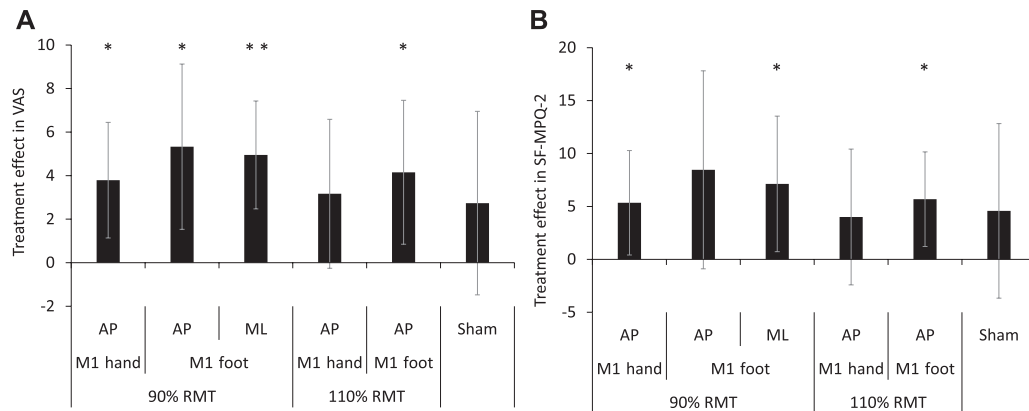
In the comparison between baseline and the mean of 10 days (3 days of intervention and 7 days of follow-up), significant treatment effects in the VAS were observed after 90% RMT on the M1 hand ( $P = 0.01$ ), 90% RMT on the M1 foot with AP ( $P = 0.01$ ), 90% RMT on the M1 foot with ML ( $P = 0.001$ ), and 110% RMT on the M1 foot ( $P = 0.02$ ), but not after 110% RMT on the M1 hand ( $P = 0.07$ ) or sham ( $P = 0.18$ ). Significant treatment effects in the SF-MPQ-2 were observed after 90% RMT on the M1 hand ( $P = 0.04$ ), 90% RMT on the M1 foot with ML ( $P = 0.03$ ), and 100% RMT on the M1 foot ( $P = 0.02$ ), but not after the other conditions (**Fig. 1**; see Tables, supplemental digital content 3 and 4,

**Table 1**  
Patients' characteristics at baseline (N = 11).

Age (y)	62.9 (14.7)
Sex (men/female)	6, 5
Origin of pain	
Central poststroke pain	4
Spinal lesion	4
Complex regional pain syndrome	2
Peripheral nerve injury	1
Treated painful region	
Right, left	8, 3
Duration of pain (mo), median (interquartile range)	111 (51–134)
VAS (0–100 mm)	61.1 (15.0)
SF-MPQ-2 total (0–220)	61.3 (49.2)
Continuous (0–60)	17.3 (16.6)
Intermittent (0–60)	16.5 (14.6)
Neuropathic (0–60)	19.3 (10.5)
Affective (0–40)	8.2 (10.6)
MMSE (0–30)	29.1 (1.3)

Data are expressed as mean (SD).

mo, month; VAS, Visual Analogue Scale; SF-MPQ-2, Short-Form McGill Pain Questionnaire 2; MMSE, Mini-Mental State Examination.



**Figure 1.** Treatment effect in Visual Analogue Scale (VAS) and SF-MPQ-2. Data are expressed as mean difference  $\pm$  95% confidence interval. Significant changes from the baseline are indicated as \* $P < 0.05$ ; \*\* $P < 0.001$ . The mean differences shown in the data were calculated with the following equation: [the baseline—the mean of 10 days (3 days of intervention and 7 days of follow-up)]. AP, anteroposterior; M1, primary motor cortex; hand, hand area; foot, foot area; ML, mediolateral; RMT, resting motor threshold; SF-MPQ-2, Short-Form McGill Pain Questionnaire 2; VAS, Visual Analogue Scale.

available at <http://links.lww.com/PR9/A132>). In the comparison from baseline to each time point, all conditions except sham stimulation produced significant pain relief at some time points compared with the baseline VAS and SF-MPQ-2 scores (see Table, supplemental digital content 5 and 6, available at <http://links.lww.com/PR9/A132>). There was no detectable carry-over effect for VAS or SF-MPQ-2 ( $P = 0.97$  and  $0.99$ , respectively).

#### 4. Discussion

This study explored the optimal stimulation parameters of rTMS in patients with neuropathic pain in the lower extremities by examining the pain relief effect. The findings of this study showed that pain relief was significant according to the VAS following 90% RMT on the M1 hand and M1 foot with any stimulation intensity and coil direction and according to the SF-MPQ-2 following 90% RMT on the M1 hand and M1 foot with ML and 110% RMT on the M1 foot. Thus, the analgesic effect of rTMS with stimulus intensity above the RMT was not superior to that below the RMT. These results suggest that the optimal stimulation parameters of rTMS for patients with neuropathic pain in the leg may target the M1 foot or M1 hand with an intensity below the RMT.

We tested different coil orientations, M1-hand or M1-foot areas, and stronger stimulation to the M1 foot, which was speculated to sufficiently stimulate the deeper brain area. However, compared with conventional 90% RMT, we could not detect a specific optimal parameter that provided more pain relief, indicating that simply increasing the intensity of the stimulus does not improve analgesic effects. Previous studies have reported analgesic effects using deep rTMS with H coils targeting the M1 foot.<sup>17,24</sup> rTMS with an H coil can generate an electric field deeper into the brain than the figure-8 coil can.<sup>21,27</sup> To alleviate pain with rTMS, it may be necessary to properly stimulate the target region, rather than simply increasing the stimulation intensity. In addition, the effects of long-term rTMS treatment for neuropathic pain have been reported.<sup>8,18,19</sup> However, the present protocol only had 3 sessions per condition. It is possible that the insufficient analgesic effect of rTMS is due to the small number of sessions, which could be considered a limitation of this study. It is difficult to identify the specific optimal protocol of rTMS treatment for neuropathic pain because of the enormous number of parameters, such as stimulation intensity, number of pulses or session, number of sessions, frequency, and stimulation site. A practical algorithm for

rTMS in pain treatment has been proposed to manage targeting and the number of rTMS sessions according to pain location and the effect of intervention.<sup>13</sup> In this way, it may be more practical to explore and perform the conditions that are appropriate for each individual. In conclusion, we suggest that the optimal stimulation conditions for patients with neuropathic pain in the leg may target the M1 foot or M1 hand at an intensity below RMT as we found no significant pain relief at an intensity above RMT compared with that below RMT.

#### Disclosures

N. Mori, N. Mori, D. Dong, and Y. Saitoh were members of the Department of Neuromodulation and Neurosurgery, Osaka University Graduate School of Medicine, which was a joint research department established with sponsorship from Teijin Pharma Limited. This department closed on March 31, 2021. The remaining authors have no conflicts of interest to declare.

This study was partly supported by the Japan Agency for Medical Research and Development (AMED) under grant numbers JP17hk0102029, JP19ek0610016, JP19dm0307007, and JP19dm0307008 and the Japan Society for the Promotion of Science KAKENHI under grant numbers JP17K10893, JP18K08993, and JP19K19867.

#### Acknowledgements

The authors thank Editage ([www.editage.com](http://www.editage.com)) for English language editing.

Author contributions: K. Hosomi, N. Mori, and Y. Saitoh contributed to trial design. Y. Saitoh, S. Oshino, and H. Kishima supervised the trials. Experiments and data collection were conducted by N. Mori and K. Hosomi. All authors contributed to the data interpretation. N. Mori drafted the manuscript; K. Hosomi, A. Nishi, A. Matsugi, and Y. Saitoh edited the manuscript, and all other authors reviewed it. N. Mori and K. Hosomi conducted the statistical analyses. All authors approved the final manuscript.

#### Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at <http://links.lww.com/PR9/A132>.

**Article history:**

Received 1 May 2021

Received in revised form 11 August 2021

Accepted 24 August 2021

Available online 12 October 2021

**References**

- [1] Andre-Obadia N, Magnin M, Simon E, Garcia-Larrea L. Somatotopic effects of rTMS in neuropathic pain? A comparison between stimulation over hand and face motor areas. *Eur J Pain* 2018;22:707–15.
- [2] Andre-Obadia N, Mertens P, Gueguen A, Peyron R, Garcia-Larrea L. Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. *Neurology* 2008;71:833–40.
- [3] Arana AB, Borckardt JJ, Ricci R, Anderson B, Li X, Linder KJ, Long J, Sackeim HA, George MS. Focal electrical stimulation as a sham control for repetitive transcranial magnetic stimulation: does it truly mimic the cutaneous sensation and pain of active prefrontal repetitive transcranial magnetic stimulation? *Brain Stimul* 2008;1:44–51.
- [4] Baptista AF, Fernandes A, Sa KN, Okano AH, Brunoni AR, Lara-Solares A, Jreige Iskandar A, Guerrero C, Amescua-Garcia C, Krachete DC, Caparelli-Daquer E, Atencio E, Piedimonte F, Colimon F, Hazime FA, Garcia JBS, Hernandez-Castro JJ, Cantisani JAF, Karina do Monte-Silva K, Lemos Correia LC, Gallegos MS, Marcolin MA, Ricco MA, Cook MB, Bonilla P, Schestatsky P, Galhardoni R, Silva V, Delgado Barrera W, Caumo W, Bouhassira D, Chipchase LS, Lefaucheur JP, Teixeira MJ, de Andrade DC. Latin American and Caribbean consensus on noninvasive central nervous system neuromodulation for chronic pain management (LAC2-NIN-CP). *Pain Rep* 2019;4:e692.
- [5] Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DL, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurmikko T, Raja SN, Rice AS, Serra J, Smith BH, Treede RD, Jensen TS. Neuropathic pain: an updated grading system for research and clinical practice. *PAIN* 2016;157:1599–606.
- [6] Hirayama A, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, Kato A, Yoshimine T. Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. *PAIN* 2006;122:22–7.
- [7] Hosomi K, Shimokawa T, Ikoma K, Nakamura Y, Sugiyama K, Ugawa Y, Uozumi T, Yamamoto T, Saitoh Y. Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: a randomized, multicenter, double-blind, crossover, sham-controlled trial. *PAIN* 2013;154:1065–72.
- [8] Hosomi K, Sugiyama K, Nakamura Y, Shimokawa T, Oshino S, Goto Y, Mano T, Shimizu T, Yanagisawa T, Saitoh Y. A randomized controlled trial of 5 daily sessions and continuous trial of 4 weekly sessions of repetitive transcranial magnetic stimulation for neuropathic pain. *PAIN* 2020;161:351–60.
- [9] Jette F, Cote I, Meziane HB, Mercier C. Effect of single-session repetitive transcranial magnetic stimulation applied over the hand versus leg motor area on pain after spinal cord injury. *Neurorehabil Neural Repair* 2013;27:636–43.
- [10] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, Filipovic SR, Grefkes C, Hasan A, Hummel FC, Jaaskelainen SK, Langguth B, Leocani L, Londero A, Nardone R, Nguyen JP, Nyffeler T, Oliveira-Maia AJ, Oliviero A, Padberg F, Palm U, Paulus W, Poulet E, Quartarone A, Rachid F, Rektorova I, Rossi S, Sahlsten H, Schecklmann M, Szekeley D, Ziemann U. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clin Neurophysiol* 2020;131:474–528.
- [11] Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS in chronic neuropathic pain: pain relief is associated with thermal sensory perception improvement. *J Neurol Neurosurg Psychiatry* 2008;79:1044–9.
- [12] Lefaucheur JP, Hatem S, Nineb A, Menard-Lefaucheur I, Wendling S, Keravel Y, Nguyen JP. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. *Neurology* 2006;67:1998–2004.
- [13] Lefaucheur JP, Nguyen JP. A practical algorithm for using rTMS to treat patients with chronic pain. *Neurophysiol Clin* 2019;49:301–7.
- [14] Leung A, Shirvalkar P, Chen R, Kuluva J, Vaninetti M, Bermudes R, Poree L, Wassermann EM, Kopell B, Levy R. Transcranial magnetic stimulation for pain, headache, and comorbid depression: INS-NANS expert consensus panel review and recommendation. *Neuromodulation* 2020;23:267–90.
- [15] Mori N, Hosomi K, Nishi A, Oshino S, Kishima H, Saitoh Y. Analgesic effects of repetitive transcranial magnetic stimulation at different stimulus parameters for neuropathic pain: a randomized study. *Neuromodulation* 2021. doi: 10.1111/ner.13328 [epub ahead of print].
- [16] O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* 2018;4:CD008208.
- [17] Onesti E, Gabriele M, Cambieri C, Ceccanti M, Raccach R, Di Stefano G, Biasiotta A, Truini A, Zangen A, Inghilleri M. H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. *Eur J Pain* 2013;17:1347–56.
- [18] Pei Q, Wu B, Tang Y, Yang X, Song L, Wang N, Li Y, Sun C, Ma S, Ni J. Repetitive transcranial magnetic stimulation at different frequencies for postherpetic neuralgia: a double-blind, sham-controlled, randomized trial. *Pain Physician* 2019;22:E303–e313.
- [19] Quesada C, Pommier B, Fauchon C, Bradley C, Creac'h C, Murat M, Vassal F, Peyron R. New procedure of high-frequency repetitive transcranial magnetic stimulation for central neuropathic pain: a placebo-controlled randomized crossover study. *PAIN* 2020;161:718–28.
- [20] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMS/CG. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008–39.
- [21] Roth Y, Pell GS, Chistyakov AV, Sinai A, Zangen A, Zaaroor M. Motor cortex activation by H-coil and figure-8 coil at different depths. Combined motor threshold and electric field distribution study. *Clin Neurophysiol* 2014;125:336–43.
- [22] Saitoh Y, Hirayama A, Kishima H, Shimokawa T, Oshino S, Hirata M, Tani N, Kato A, Yoshimine T. Reduction of intractable deafferentation pain due to spinal cord or peripheral lesion by high-frequency repetitive transcranial magnetic stimulation of the primary motor cortex. *J Neurosurg* 2007;107:555–9.
- [23] Saitoh Y, Maruo T, Yokoe M, Matsuzaki T, Sekino M. Electrical or repetitive transcranial magnetic stimulation of primary motor cortex for intractable neuropathic pain. *Conf Proc IEEE Eng Med Biol Soc* 2013;2013:6163–6.
- [24] Shimizu T, Hosomi K, Maruo T, Goto Y, Yokoe M, Kageyama Y, Shimokawa T, Yoshimine T, Saitoh Y. Efficacy of deep rTMS for neuropathic pain in the lower limb: a randomized, double-blind crossover trial of an H-coil and figure-8 coil. *J Neurosurg* 2017;127:1172–80.
- [25] Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, Hansson P, Hughes R, Nurmikko T, Serra J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* 2008;70:1630–5.
- [26] 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.
- [27] Zangen A, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clin Neurophysiol* 2005;116:775–9.