

## 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

Takeshi Shimizu, MD,<sup>1,2,7</sup> Koichi Hosomi, MD, PhD,<sup>1,2,7</sup> Tomoyuki Maruo, MD, PhD,<sup>1–3</sup>  
Yuko Goto, MD, PhD,<sup>1,2</sup> Masaru Yokoe, MD, PhD,<sup>1,4</sup> Yu Kageyama, MD, PhD,<sup>2,5</sup>  
Toshio Shimokawa, PhD,<sup>6</sup> Toshiki Yoshimine, MD, PhD,<sup>2,7</sup> and Youichi Saitoh, MD, PhD<sup>1,2,7</sup>

Departments of <sup>1</sup>Neuromodulation and Neurosurgery, <sup>2</sup>Neurosurgery, and <sup>4</sup>Neurology, Osaka University Graduate School of Medicine; <sup>7</sup>Center for Pain Management, Osaka University Hospital, Suita; <sup>3</sup>Department of Neurosurgery, Otemae Hospital, Osaka; <sup>5</sup>Department of Neurosurgery, Saitama Children's Medical Center, Saitama; and <sup>6</sup>Clinical Research Center, Wakayama Medical University, Wakayama, Japan

**OBJECTIVE** Electrical motor cortex stimulation can relieve neuropathic pain (NP), but its use requires patients to undergo an invasive procedure. Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) using a figure-8 coil can relieve NP noninvasively, but its ability to relieve lower limb pain is still limited. Deep rTMS using an H-coil can effectively stimulate deep brain regions and has been widely used for the treatment of various neurological diseases; however, there have been no clinical studies comparing the effectiveness of figure-8 coils and H-coils. This study assessed the clinical effectiveness of 5 once-daily stimulations with H-coils and figure-8 coils in patients with NP.

**METHODS** This randomized, double-blind, 3-way crossover trial examined 18 patients with NP who sequentially received 3 types of stimulations in the M1 for 5 consecutive days; each 5-day stimulation period was followed by a 17-day follow-up period before crossing over to the next type of stimulation. During each rTMS session, patients received a 5-Hz rTMS to the M1 region corresponding to the painful lower limb. The visual analog scale (VAS) and the Japanese version of the short-form McGill Pain Questionnaire 2 (SF-MPQ2-J) were used to measure pain intensity. The primary outcome was VAS score reduction immediately after and 1 hour after intervention.

**RESULTS** Both the VAS and SF-MPQ2-J showed significant pain improvement immediately after deep rTMS with an H-coil as compared with the sham group ( $p < 0.001$  and  $p = 0.049$ , respectively). However, neither outcome measure showed significant pain improvement when using a figure-8 coil. The VAS also showed significant pain improvement 1 hour after deep rTMS with an H-coil ( $p = 0.004$ ) but not 1 hour after rTMS using a figure-8 coil. None of the patients exhibited any serious adverse events.

**CONCLUSIONS** The current findings suggest that the use of deep rTMS with an H-coil in the lower limb region of the M1 in patients with NP was tolerable and could provide significant short-term pain relief.

Clinical trial registration no.: UMIN000010536 (<http://www.umin.ac.jp/ctr/>)

<https://thejns.org/doi/abs/10.3171/2016.9.JNS16815>

**KEY WORDS** repetitive transcranial magnetic stimulation; neuropathic pain; deep rTMS; H-coil; lower limb pain; figure-8 coil

**S**TIMULATION of the motor cortex is a technique developed by Tsubokawa et al. for the treatment of patients with thalamic pain syndrome after stroke.<sup>23</sup> A previous study by our group showed that electrical motor

cortex stimulation (EMCS) targeting the primary motor cortex (M1) achieved good pain relief in half of the tested patients with refractory neuropathic pain (NP).<sup>20</sup> However, EMCS requires invasive implantation of intracranial

**ABBREVIATIONS** ANOVA = analysis of variance; BDI = Beck Depression Inventory; CPSP = central poststroke pain; EMCS = electrical motor cortex stimulation; FBSS = failed-back surgery syndrome; H-coil = Heschl coil; M1 = primary motor cortex; NP = neuropathic pain; PGIC = patient global impression of change; RMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; SF-MPQ2-J = short-form McGill Pain Questionnaire 2, Japanese version; SCD = subacute combined degeneration; SCI = spinal cord injury; TCS = tethered spinal cord syndrome; TMS = transcranial magnetic stimulation; VAS = visual analog scale.

**SUBMITTED** April 2, 2016. **ACCEPTED** September 15, 2016.

**INCLUDE WHEN CITING** Published online February 3, 2017; DOI: 10.3171/2016.9.JNS16815.

electrodes and a pulse generator. In addition, targeting the lower-limb region of the M1 often requires a complicated procedure and tends to provide insufficient relief of lower-limb pain.

Transcranial magnetic stimulation (TMS) is a noninvasive method that can be used to safely stimulate cortical neurons,<sup>22</sup> and high-frequency repetitive TMS (rTMS) over the M1 has shown clinical effectiveness in treating patients with NP.<sup>1,6,8,11,14,19</sup> In a previous randomized crossover trial by our group, we demonstrated that rTMS using a figure-8 coil over the M1, as compared with sham stimulation, provided significant pain relief in patients with NP.<sup>8</sup> In that trial, the efficacy rate for alleviation of lower-limb pain tended to be lower than that for upper-limb pain.<sup>8</sup> Given those results, we speculated that the difference in pain relief between upper- and lower-limb pain was attributable to differences in the distance from the coil to the targeted M1 region. The lower-limb M1 locates in a deep brain region, while the figure-8 coil only permits stimulation of the superficial cortex of the brain. Therefore, using a figure-8 coil for rTMS targeting the lower-limb M1 requires high-intensity stimulation that can cause scalp pain and increase the risk of seizure.

A newly developed variant of TMS uses a Heschl coil (H-coil) and is referred to as “deep TMS.” This technique can achieve an improved deeper penetration and a slower decay of the electric field as a function of distance than the figure-8 coils.<sup>16,18</sup> Lefaucheur et al. examined the depth of TMS in healthy volunteers; they found that rTMS using an H-coil could stimulate the hand area of M1 even at a distance of 5.5 cm from the scalp, while rTMS using a standard figure-8 coil stimulated M1 at a distance of 2.0 cm from the scalp.<sup>11</sup> Several studies using head models revealed that the H-coil makes it possible to stimulate deep brain regions effectively without inducing an unbearable field in the cortical regions.<sup>17,18,24</sup> Deep rTMS using an H-coil has been reported to be an effective treatment for a variety of neurological and psychopathological disorders that require targeting of deep brain regions.<sup>5,9,15,21</sup> Based on the results of these previous studies, the H-coil will be increasingly used to treat several neurological disorders. The need now arises for a clinical evaluation comparing the efficacy of deep rTMS using an H-coil versus rTMS using a figure-8 coil for patients with NP; however, there has been no such comparative study thus far.

The purpose of the present study was to assess the efficacy of deep rTMS using an H-coil versus rTMS using a figure-8 coil in patients with NP in their lower limbs. We postulated that deep rTMS using an H-coil would relieve pain as well as rTMS using a figure-8 coil and that the H-coil would provide this relief because it would stimulate deep brain regions more effectively.

## Methods

### Patients

A total of 18 patients (12 men and 6 women) with intractable NP in the lower limb were included in this study. Each patient experienced NP that was refractory to ordinary medical, surgical, or pharmaceutical treatments and

had lasted for more than 6 months. We determined the sample size by referring to our previous study.<sup>6</sup> All patients were recruited through the outpatient clinic at the Osaka University Hospital from April 2013 to December 2014 and diagnosed based on the grading system for NP.<sup>22</sup> Underlying diseases consisted of central poststroke pain (CPSP), failed-back surgery syndrome (FBSS), diabetic neuropathy, subacute combined degeneration (SCD) of the spinal cord, tethered spinal cord syndrome (TCS), and spinal cord injury (SCI). Patients consented to maintaining their current drug regimen and not using opioid rescue medication before completing the trial. Exclusion criteria included implanted devices, history of seizures, any metal implanted in the head, dementia (Mini-Mental State Examination score < 24), higher brain dysfunction, and major depression. Written informed consent was obtained from all patients before inclusion in the study. The protocol was reviewed and approved by the institutional ethics review board at Osaka University Hospital. We registered the protocol with the University hospital Medical Information Network (UMIN) Clinical Trials Registry (<http://www.umin.ac.jp/ctr>), and its registration no. is UMIN000010536.

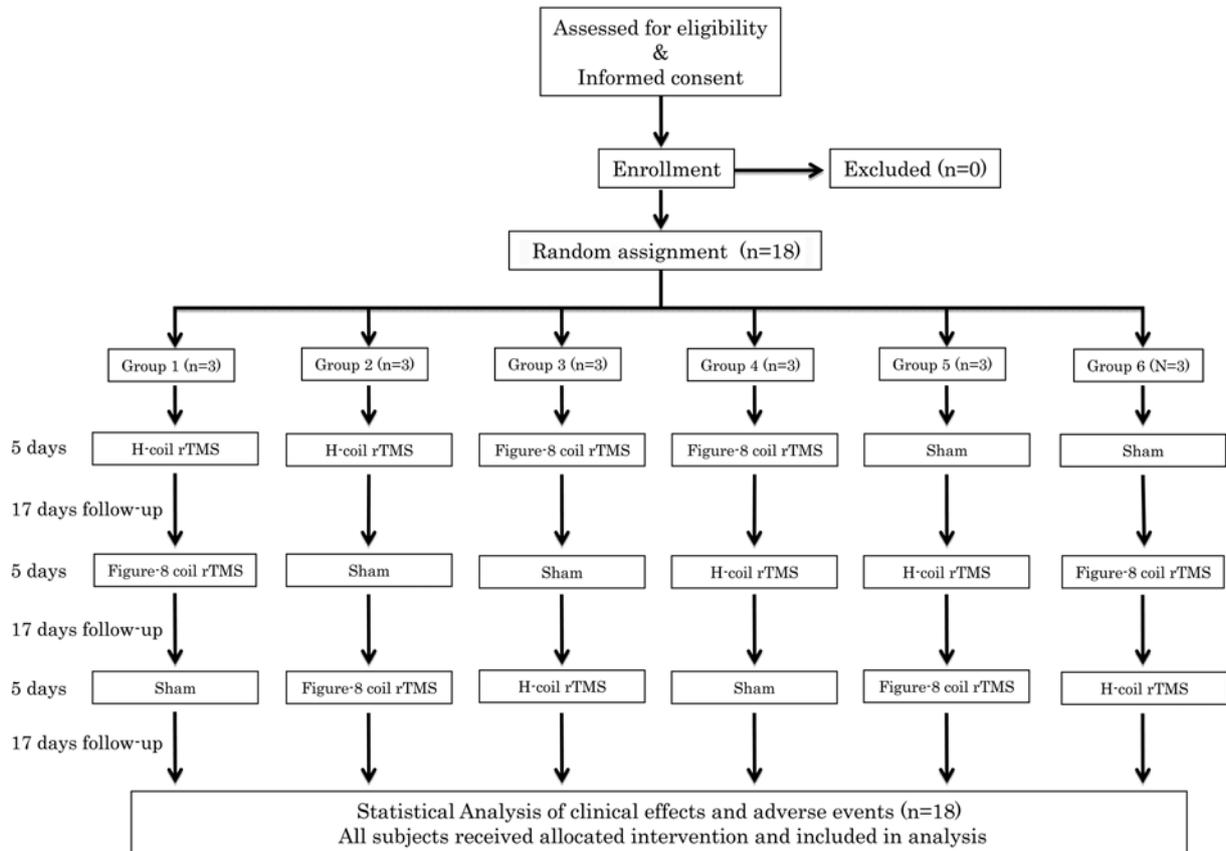
### Randomization and Masking

We conducted a randomized, double-blind crossover trial that consisted of 3 different stimulations: deep rTMS using an H-coil, rTMS using a figure-8 coil, and sham stimulation. Patients sequentially crossed over to these 3 types of stimulation, and the independent data center determined the order of stimulation for each patient. According to the permuted-block randomization method, patients were randomly assigned to 1 of 6 groups (Fig. 1). Patients and assessors were blinded to the assignment until after study completion.

### Procedures

Patients received 5-Hz rTMS (500 pulses/session) using a figure-8 coil, H-coil, or sham stimulation in their lower-limb M1 for 5 consecutive days (Days 1–5), followed by a 17-day follow-up period. Each stimulation period was separated by a minimum 17-day follow-up period starting on Day 6. This treatment interval was derived from the results of a previous study with the same stimulation parameters, which reported that 17 days was enough time for the rTMS effects to be washed out.<sup>8</sup> Figure 2 presents the time schedule of the present study.

To evaluate the effect of rTMS on pain relief in the lower limb during the stimulation period, the visual analog scale (VAS) and the Japanese version of the short-form McGill Pain Questionnaire 2 (SF-MPQ2-J) were used immediately before, immediately after, and 1 hour after the intervention.<sup>2,13</sup> During the follow-up period (Days 6–22), the patients recorded their VAS and SF-MPQ2-J scores daily at the same time as the intervention. On Day 5, we also obtained the Patient Global Impression of Change (PGIC) score.<sup>3</sup> The Beck Depression Inventory (BDI) was obtained at baseline (before stimulation) and on Days 5 (after stimulation) and 22 to assess the severity of depression symptoms. The BDI consists of 21 questions about



**FIG. 1.** Trial profile. A flowchart shows the organizational structure of the study, with numbers of patients initially enrolled ( $n = 18$ ). There were no dropouts during the study. The number of patients in each stimulation group is indicated.

how the patient has been feeling in the past week. All of the evaluation scores were written by patients and assessed by blinded assessors who observed the incidence of adverse events. The primary outcome was the short-term change in the VAS score, while the secondary outcomes were the short-term and long-term changes in the SF-MPQ2-J score, the long-term changes in the VAS score, the PGIC score, and the changes in the BDI. Short-term effect means that the pain relief was observed immediately after intervention and 1 hour later. Long-term effect means that the pain relief was observed during the follow-up period as compared with Day 1 before the intervention.

#### Deep rTMS, or H-Coil rTMS

We performed deep TMS using an H-coil (H10, HMMC) connected to a Magstim Rapid<sup>2</sup> stimulator (Magstim Company). The H-coil was designed for effective activation of neuronal structures within the motor cortex, including the deeper structures of the lower limb region of the M1 with hemispheric symmetry. The H-coil and sham coil were installed within the system. The mode of operation was switched by unlabeled magnetic cards to ensure that the patients and assessors remained blinded to which stimulation would be administered, real or sham.

To determine the coil position, we first placed the center of the helmet to install the H-coil at a point 1 cm lateral and 1 cm posterior from Cz. Next, we identified the location and angle of the helmet by identifying the minimum

stimulator intensity needed to cause a motor response in the targeted lower limb. We kept the front surface of the helmet facing forward to ensure that the coil orientation was the same. The resting motor threshold (RMT) was defined as the minimum stimulator intensity needed to evoke at least 1 visible muscle twitch in the extensor hallucis brevis muscle while maintaining a relaxed position.<sup>4</sup> The H-coil was then tightly fixed into the same position with a belt during the stimulation. The position of the coil was recorded based on nasal point and external earhole position on Day 1 to ensure that we could conduct the stimulation at the same position on Days 2 through 5. Each daily session consisted of 10 trains of 5 Hz at 90% intensity of RMT. Each train consisted of a 50-second intertrain interval. A total of 500 pulses were applied in each session.

#### Figure-8 Coil rTMS

A MagPro R60 (Magventure) was used with a figure-8 coil (MC-B70, Magventure) for the TMS. The coil position was determined during each daily session by evoking visible muscle twitches with the Brainsight TMS navigation system (Rogue Research Inc.) to ensure the optimal positioning needed to stimulate the M1 of the lower limbs. We placed the coil in such a way that the induced current ran in an anteroposterior direction. All patients underwent rTMS with a figure-8 coil using the same parameters as the deep rTMS. In cases in which coil positioning failed to evoke the twitch response, patients underwent rTMS

Day	Stimulation period					Following-up period	
	1	2	3	4	5	6 - 21	22
VAS						<input type="checkbox"/>	<input type="checkbox"/>
SF-MPQ 2						<input type="checkbox"/>	<input type="checkbox"/>
PGIC					<input type="checkbox"/>		<input type="checkbox"/>
BDI	<input type="checkbox"/>				<input type="checkbox"/>		<input type="checkbox"/>

**FIG. 2.** Evaluation time schedule. Current pain intensity of the patient was evaluated using the VAS and the SF-MPQ2-J. On each stimulation day, pain intensity was examined at 3 time points: immediately before, immediately after, and 1 hour after the intervention. The Patient Global Impression of Change (PGIC) was obtained on Days 5 and 22. The severity of depression symptoms was measured by the BDI on Day 1 (before stimulation), Day 5 (after stimulation), and Day 22.

with the maximum intensity that they could bear (i.e., scalp pain caused by the stimulation). In such sessions, we set the stimulation intensity to 100 A/ $\mu$ sec, which was the same as in the previous study.<sup>6</sup> The stimulation using MagPro at 100 A/ $\mu$ sec was almost equivalent to the stimulation produced using Magstim (Whitland) at the maximum output.<sup>10</sup>

#### Sham Stimulation

Sham stimulation was delivered using a sham coil that was placed in the same helmet that encased the active deep TMS coil (Brainsway). Activation of the sham coil produced scalp sensations, acoustic artifacts, and facial muscle activation similar to the active coil. In the sham mode, the electric current was delivered in opposite directions in each of the double wires. Hence, the induced electric field in the sham mode was negligible, while reproducing the auditory and visual sensations of the real TMS mode.<sup>12</sup> In addition, the nontangential orientation relative to the scalp and the elements canceling the electric field ensured that there was a rapid reduction of the field as a function of distance.<sup>9</sup> The method for determining sham coil orientation was the same as for the real stimulation using an H-coil, as described above.

#### Statistical Analysis

Statistical analyses of short-term VAS and SF-MPQ2-J outcomes were performed using the pain scores calculated immediately before the stimulation on each day and the reduced values observed after stimulation. The reduced pain values after deep rTMS using both an H-coil and a figure-8 coil were compared with those from the sham stimulation by using a linear mixed-effects model analysis (random effect: patient, fixed effect: type of stimulation [dummy variables were applied for rTMS using an H-coil and figure-8 coil, and the sham stimulation was baseline] and day [Day 1–5]). A 2-sample t-test was performed to compare the clinical effectiveness of rTMS in 12 patients with CPSP and 6 patients with noncerebral lesions. To evaluate carry-over effect, a paired t-test was applied to the values at Day 1 for each period. To evaluate the long-term effect of each type of stimulation, we used repeated measures analysis of variance (ANOVA) with the VAS and SF-MPQ2-J scores as the dependent variable and the Day 1 value or each day

during the follow-up period (Days 6–21) as the independent variable. We also performed paired t-tests with the Bonferroni correction between Day 1 and each day of the follow-up period to assess when the pain that was offset during treatment returned. Paired t-tests were performed to evaluate the BDI change induced by each stimulation, and Wilcoxon signed-rank tests were performed to compare the PGIC score between each stimulation. In all analyses, p values less than 0.05 were considered statistically significant. Data were analyzed with R version 3.1.1 (R Foundation for Statistical Computing).

## Results

We enrolled 18 patients with intractable NP in their lower limbs. Although 4 of the 12 patients with CPSP had upper-limb pain in addition to lower-limb pain, they were asked to report only lower-limb pain that was the most painful.

The 18 enrolled patients received the 3 types of stimulations in a randomly assigned order. We asked patients if they could distinguish between the various stimulations, but none was able to confidently detect the sham stimulation. TMS with the H-coil induced the twitch response in all patients during all sessions, but TMS with the figure-8 coil failed to induce the twitch response in 2 patients through all 5 sessions and in 1 patient in 1 session. Table 1 presents the baseline clinical characteristics of the patients. Four patients did not take any drugs because no drug could relieve the pain to any degree. There was no detectable carry-over effect for either the VAS or the SF-MPQ2-J scores.

#### Short-Term Effects of rTMS on VAS Changes (Primary Outcome)

Deep rTMS using an H-coil resulted in the best pain improvement among all 3 types of stimulation immediately after and 1 hour after stimulation. The mean VAS reductions (standard error of the mean) immediately after stimulation were 5.36 (1.03) for deep rTMS using an H-coil, 3.36 (0.78) for rTMS using a figure-8 coil, and 1.71 (0.59) for the sham stimulation. The mean VAS reductions at 1 hour after stimulation were 3.14 (0.77) for deep rTMS using the H-coil, 2.25 (0.51) for rTMS using the figure-8 coil, and 0.97 (0.80) for the sham stimulation (Fig.

**TABLE 1. Baseline patient characteristics**

Case No.	Sex	Age (yrs)	Painful Side	Underlying Disease	Location of Lesion	Pain Duration (mos)	VAS Score	SF-MPQ2-J Score	BDI	Op	Daily Medication
1	M	64	Lt	FBSS	Lumbar vertebra	36	89	127	50	SCS	Pregabalin 600 mg, tandospirone 15 mg, sodium valproate 300 mg, tramadol hydrochloride 8T
2	M	57	Rt	CPSP	Putamen	12	72	67	5		None
3	M	53	Rt	FBSS	Lumbar vertebra	63	62	81	31	SCS, block	Pregabalin 600 mg, clonazepam 1.5 mg, amitriptyline 30 mg
4	M	50	Rt	CPSP	Putamen	28	68	165	16	SCS trial	Tramadol hydrochloride 3T
5	F	66	Lt	CPSP	Thalamus	42	82	49	7		None
6	M	62	Lt	CPSP	Thalamus	96	97	68	16		Clonazepam 0.5 mg, imipramine 25 mg
7	M	69	Lt	CPSP	Subcortical	36	46	83	13	SCS trial	Pregabalin 150 mg, duloxetine
8	M	70	Rt	DN	Peripheral nerve	132	60	140	8	SCS	Pregabalin 150 mg, amitriptyline 20 mg, codeine phosphate 120 mg
9	M	66	Rt	CPSP	Putamen	84	62	41	11	SCS trial	Gabapentin 1200 mg, duloxetine
10	M	75	Lt	CPSP	Putamen	180	75	85	10	SCS trial	Pregabalin 75 mg, clonazepam 1.5 mg
11	F	75	Lt	CPSP	Putamen	15	84	125	5		Pregabalin 300 mg
12	M	53	Rt	CPSP	Putamen	9	78	110	12		Gabapentin 300 mg
13	F	62	Rt	CPSP	Putamen	14	34	18	8	SCS	Pregabalin 150 mg, amitriptyline 10 mg
14	M	61	Lt	CPSP	Thalamus	24	72	86	3	SCS trial	None
15	F	76	Rt	TCS	Spinal cord	144	65	63	24		Pregabalin 100 mg, tramadol hydrochloride 4T, diazepam 4 mg
16	F	56	Lt	SCD	Spinal cord	96	56	82	30	SCS trial	Gabapentin 1800 mg, carbamazepine 500 mg, duloxetine
17	F	73	Rt	CPSP	Putamen	180	60	108	6	SCS	Clonazepam 0.5 mg, gabapentin 1200 mg
18	M	23	Lt	SCI	Spinal cord	60	52	41	2		None
Mean (SD)		61.7 (12.2)				69.5 (55.5)	67.4 (15.2)	85.5 (37.1)	14.3 (12.0)		

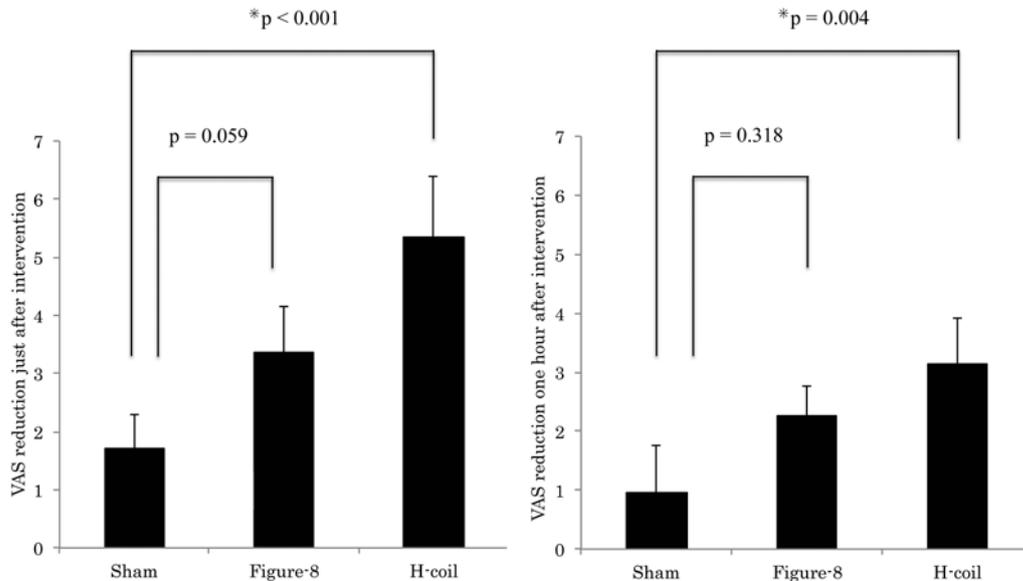
DN = diabetic neuropathy; SCS = spinal cord stimulation.

3). Analysis of the linear mixed-effects model revealed a significant effect of the H-coil immediately after ( $p < 0.001$ ) and 1 hour after ( $p = 0.004$ ) stimulation compared with sham stimulation. There were no significant changes to the VAS score with rTMS using a figure-8 coil (Table 2). There were also no significant variations in VAS scores among the stimulation days. The mean VAS reduction values following deep rTMS in 12 patients with CPSP were 4.62 (1.23) just after stimulation and 2.24 (0.87) at 1 hour after stimulation. The mean VAS reduction values in 6 patients with noncerebral lesions were 6.83 (1.53) just after

stimulation and 4.93 (1.19) at 1 hour after stimulation. A 2-sample t-test showed no significant difference in pain relief between patients with CPSP and those with noncerebral lesions immediately after and 1 hour after deep rTMS ( $p = 0.108$  and  $0.340$ , respectively).

**Short-Term Effects of rTMS on SF-MPQ2-J Changes**

Similar to the changes seen in VAS scores, deep rTMS with an H-coil resulted in the best pain improvement among the 3 types of stimulation immediately after and 1 hour after stimulation. The mean SF-MPQ2-J reductions



**FIG. 3.** The mean VAS reduction in the short term (primary outcome). The mean VAS reduction just after stimulation was 5.36 (SEM 1.03) using rTMS with an H-coil, 3.36 (3.33) using rTMS with a figure-8 coil, and 1.71 (2.50) for sham stimulation. The mean VAS reduction 1 hour after stimulation was 3.14 (0.77) with the H-coil, 2.25 (0.51) with the figure-8 coil, and 0.97 (0.80) with sham stimulation.

immediately after stimulation were 8.43 (2.13) for the deep rTMS using an H-coil, 6.05 (1.60) for the rTMS using a figure-8 coil, and 5.95 (1.65) for the sham stimulation. The mean SF-MPQ2-J reductions at 1 hour after stimulation were 5.10 (1.43) for the H-coil, 3.68 (1.18) for the figure-8 coil, and 3.71 (1.68) for the sham stimulation. Analysis of the SF-MPQ2-J reduction using the linear mixed-effects model revealed a significant effect for the H-coil ( $p = 0.049$ ) but not for the figure-8 coil (Table 3). There was statistically significant interday variation in SM-MPQ2-J changes at 1 hour after stimulation.

#### Long-Term Effects of 5 Consecutive Days of rTMS

Repeated-measures ANOVA revealed no significant long-term effects on VAS scores ( $F = 1.3$ ,  $p = 0.21$  using H-coil;  $F = 1.1$ ,  $p = 0.36$  using figure-8 coil;  $F = 1.3$ ,  $p = 0.19$  sham) or SF-MPQ2-J scores ( $F = 1.7$ ,  $p = 0.051$  using H-coil;  $F = 1.3$ ,  $p = 0.18$  using figure-8 coil;  $F = 1.5$ ,  $p = 0.10$  sham) for all types of stimulation. There was no significant difference between Day 1 and each day of the follow-up period.

#### Changes in PGIC and BDI Scores

Neither the H-coil nor the figure-8 coil resulted in significantly better PGIC scores compared with those obtained following sham stimulation, even during the stimulation period (H-coil,  $p = 0.346$ ; figure-8 coil,  $p = 0.346$ ). In addition, none of the 3 types of stimulation caused any significant changes in BDI scores during the stimulation period (H-coil,  $p = 0.543$ ; figure-8 coil,  $p = 0.621$ ; sham,  $p = 0.647$ ).

#### Safety Measurements

Table 4 presents the adverse events observed during the study. Of the adverse events reported, neither the number

of patients nor the number of sessions was higher when using the H-coil versus the figure-8 coil. No patient was eliminated from the study because of adverse events related to the stimulation. One patient slipped and broke the phalanges in her foot during the follow-up period, but she could assess the intensity of targeted pain separately from the pain caused by the fracture. Another patient suffered from painless contact dermatitis during sham stimulation. We thought that these events did not strongly affect pain scoring. These events did not have any relevance to the stimulation.

#### Discussion

This is the first double-blind crossover trial to assess the efficacy of rTMS over the lower limb region of the M1 using an H-coil and a figure-8 coil in patients with NP in their lower limbs. We demonstrated that deep rTMS using an H-coil was effective for treating intractable NP, even in the lower limbs, while rTMS using a figure-8 coil resulted in no significant pain relief. The present study also showed that rTMS using an H-coil relieved pain without any serious adverse events. Results of the present study were compatible with findings of a previous study that assessed the clinical effect of deep rTMS in patients with painful diabetic neuropathy in their lower limbs, and the clinical effect of the H-coil was not compared with that of the figure-8 coil in that study.<sup>15</sup> In the present study, we assessed the clinical effects of deep rTMS with an H-coil and rTMS using a figure-8 coil in patients with FBSS, SCD, SCI, and CPSP; we report that deep rTMS provides pain relief to these patients both immediately after and 1 hour after stimulation. Our study also indicates that deep rTMS tends to relieve pain better in patients with noncerebral lesions than in those with CPSP. These results are compatible with those in our previous study in which patients with a nonce-

**TABLE 2. Short-term results of VAS reduction (primary outcome)**

Period	Stimulation (compared w/ sham)		
	Figure-8 Coil	H-Coil	Day
Immediately after stimulation	1.569 (p = 0.059)	3.503 (p < 0.001*)	-0.218 (p = 0.363)
1 hr after stimulation	1.199 (p = 0.318)	3.443 (p = 0.004*)	-0.339 (p = 0.328)

Random effect: patient, fixed effect: day and type of stimulation.  
\* p < 0.05 statistically significant.

**TABLE 3. Short-term results of SF-MPQ2 reduction**

Period	Stimulation (compared w/ sham)		
	Figure-8 Coil	H-Coil	Day
Immediately after stimulation	1.574 (p = 0.639)	6.578 (p = 0.049*)	-1.095 (p = 0.257)
1 hr after stimulation	0.072 (p = 0.967)	1.152 (p = 0.517)	-2.082 (p < 0.001*)

Random effect: patient, fixed effect: day and type of stimulation.  
\* p < 0.05 statistically significant.

rebral lesion were found to be more suitable candidates for high-frequency rTMS to M1.<sup>19</sup>

We believe the clinical advantage of the H-coil is largely attributable to its ability to deliver stimulation to a deeper cortical region than the figure-8 coil, thus creating a greater physiological effect. A previous head model simulation study has shown that deep TMS using the H-coil results in a significantly improved depth penetration and a much slower rate of decay as a function of distance from the coil.<sup>24</sup> In our study, deep TMS using the H-coil induced muscle twitches even among patients who did not respond to TMS when using the figure-8 coil. In the current study, there were 2 patients in whom muscle twitches could not be induced by TMS using the figure-8 coil. In these 2 patients, deep rTMS provided a larger VAS reduction than the figure-8 coil immediately after and at 1 hour after stimulation. These results indicate that deep rTMS can generate a physiological effect more efficiently in the deeper region of the human brain. In the previous head model simulation study, electric field attenuation was directly proportional to the depth of the target. The results of our study also indicated that the resting motor threshold for each patient correlated to the distance from the coil to the superficial layer of the lower limb region of the M1 (Supplementary Materials). Therefore, it is our belief that the physiological advantage of the H-coil is attributable to the depth of the electric field that can be induced in the deep brain region. The possibility that the broadness of the distributed electric field is related to the physiological effect remains controversial.

In addition, our study also demonstrated that deep TMS using an H-coil was a safe, noninvasive method of stimulation and free from any serious adverse events. According to the results of the previous head model stimulation study, deep TMS using an H-coil did not cause any higher electrical field in the superficial brain regions, even when stimulating the brain regions.<sup>24</sup> Although a double-cone coil can produce very strong fields that can stimulate the leg motor area, these fields decay quite fast in relation to distance from the coil. As a result, since the double-cone coil must generate strong stimulations to superficial brain regions to effectively stimulate deep brain regions, it has been suggested that this method may cause greater pain to patients, making repetitive stimulations difficult.<sup>24</sup>

Onesti et al. previously reported that the effects of deep rTMS with an H-coil might last 3 weeks in patients with painful diabetic neuropathy.<sup>15</sup> The stimulation protocol consisted of 1500 pulses at 20 Hz and 100% intensity of

RMT for 5 consecutive days. In our experience, however, significant pain relief was no longer observed by 17 days after the end of 10 daily sessions of rTMS using a figure-8 coil (5-Hz stimulation of 500 pulses) in 64 patients with NP.<sup>8</sup> We suggest that the difference in the durability of pain relief following rTMS in these 2 studies was affected by the difference in the coils, the stimulating parameters (e.g., number of pulses per session), the frequency of stimulation, and also the background of the patients' pain conditions. The present study demonstrated that there was no carry-over effect at 17 days after the end of 5 days of stimulation with rTMS using either H-coils or figure-8 coils. The durability of the rTMS effect would be required for longer effectiveness. There were no statistically significant long-term effects of rTMS with either the H-coil or figure-8 coil. We think it is because SF-MPQ2-J measures, which consist of 22 questions and 4 group components, can consider not only the intensity but also the quality of the pain condition. In fact, subgroup analysis revealed that deep rTMS could significantly relieve only the neuropathic component (p = 0.021). Our finding that there are no significant long-term effects of rTMS for lower limb pain indicates that the stimulus conditions should be improved for a longer durability of effect in the clinical setting. Daily or weekly stimulation for more consecutive days is one solution for improving the long-term effect of rTMS. For daily rTMS, adaptation for home use may make it possible in the future.<sup>7</sup>

Our study has several potential limitations. First, the issue of blinding for the 2 coils needs to be considered. Since the obvious difference in the shapes of the 2 coils could not be concealed, we had to explain to patients prior

**TABLE 4. Adverse events**

Parameter	Figure-8		
	H-Coil	Coil	Sham
Total no. of patients reporting adverse events	2 (8)	4 (9)	3 (5)
Adverse event			
Headache	1 (4)	1 (1)	0
Dizziness	1 (1)	3 (8)	1 (4)
Pain in upper limbs	1 (3)	0	1 (1)
Fracture of phalanges in foot	0	1	0
Contact dermatitis	0	0	1

Data are expressed as numbers of patients (number of sessions).

to the study that we would be performing 3 types of stimulation without actually providing any details on the differences they might experience. Although the assessors were also blinded to the specific treatment being used, studies using a parallel design should be considered in the future. The second potential limitation involves the number of patients. Crossover studies with multiple arms often need a high number of patients. A larger-scale study is necessary to reach definitive conclusions. The underlying disease within our patients was heterogeneous and dominated by CPSP (66.7%). The heterogeneity of drugs may also be one of the study's limitations. The number of patients in the current study was not large enough to conduct subgroup analyses for investigating the effects of underlying diseases or drugs. In addition, the long-term effect and PGIC scores were not significant. Therefore, the results of our study should be applied to the general population of NP patients with caution, and a large-scale study is expected as a future task.

## Conclusions

In patients with NP, deep rTMS using an H-coil was a safe, noninvasive means of stimulation that achieved significant short-term pain relief of the lower extremities.

## Acknowledgments

We thank the Strategic Research Program for Brain Sciences from MEXT and AMED of Japan for partial support of this study.

## References

- André-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* **71**:833–840, 2008
- Dworkin RH, Turk DC, Revicki DA, Harding G, Coyne KS, Peirce-Sandner S, et al: Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). *Pain* **144**:35–42, 2009
- Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al: Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* **9**:105–121, 2008
- Hanajima R, Wang R, Nakatani-Enomoto S, Hamada M, Terao Y, Furubayashi T, et al: Comparison of different methods for estimating motor threshold with transcranial magnetic stimulation. *Clin Neurophysiol* **118**:2120–2122, 2007
- Harel EV, Rabany L, Deutsch L, Bloch Y, Zangen A, Levkovitz Y: H-coil repetitive transcranial magnetic stimulation for treatment resistant major depressive disorder: An 18-week continuation safety and feasibility study. *World J Biol Psychiatry* **15**:298–306, 2014
- Hirayama A, Saitoh Y, Kishima H, Shimokawa T, Oshino S, Hirata M, et al: Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. *Pain* **122**:22–27, 2006
- Hosomi K, Seymour B, Saitoh Y: Modulating the pain network—neurostimulation for central poststroke pain. *Nat Rev Neurol* **11**:290–299, 2015
- Hosomi K, Shimokawa T, Ikoma K, Nakamura Y, Sugiyama K, Ugawa Y, et al: Daily repetitive transcranial magnetic stimulation of primary motor cortex for neuropathic pain: a randomized, multicenter, double-blind, crossover, sham-controlled trial. *Pain* **154**:1065–1072, 2013
- Isserles M, Shalev AY, Roth Y, Peri T, Kutz I, Zlotnick E, et al: Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder—a pilot study. *Brain Stimulat* **6**:377–383, 2013
- Kammer T, Beck S, Thielscher A, Laubis-Herrmann U, Topka H: Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clin Neurophysiol* **112**:250–258, 2001
- Lefaucheur JP, Drouot X, Ménard-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* **79**:1044–1049, 2008
- Levkovitz Y, Roth Y, Harel EV, Braw Y, Sheer A, Zangen A: A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. *Clin Neurophysiol* **118**:2730–2744, 2007
- Maruo T, Nakae A, Maeda L, Shi K, Takahashi K, Morris S, et al: Validity, reliability, and assessment sensitivity of the Japanese version of the short-form McGill pain questionnaire 2 in Japanese patients with neuropathic and non-neuropathic pain. *Pain Med* **15**:1930–1937, 2014
- O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH: Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database Syst Rev* (9):CD008208, 2010
- Onesti E, Gabriele M, Cambieri C, Ceccanti M, Raccach R, Di Stefano G, et al: H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy. *Eur J Pain* **17**:1347–1356, 2013
- Roth Y, Amir A, Levkovitz Y, Zangen A: Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure-8 and deep H-coils. *J Clin Neurophysiol* **24**:31–38, 2007
- 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* **125**:336–343, 2014
- Roth Y, Zangen A, Hallett M: A coil design for transcranial magnetic stimulation of deep brain regions. *J Clin Neurophysiol* **19**:361–370, 2002
- Saitoh Y, Hirayama A, Kishima H, Shimokawa T, Oshino S, Hirata M, et al: 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* **107**:555–559, 2007
- Saitoh Y, Yoshimine T: Stimulation of primary motor cortex for intractable deafferentation pain. *Acta Neurochir Suppl* **97**:51–56, 2007
- Spagnolo F, Volonté MA, Fichera M, Chieffo R, Houdayer E, Bianco M, et al: Excitatory deep repetitive transcranial magnetic stimulation with H-coil as add-on treatment of motor symptoms in Parkinson's disease: an open label, pilot study. *Brain Stimulat* **7**:297–300, 2014
- Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al: Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology* **70**:1630–1635, 2008
- Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S: Treatment of thalamic pain by chronic motor cortex stimulation. *Pacing Clin Electrophysiol* **14**:131–134, 1991
- Zangen A, Roth Y, Voller B, Hallett M: Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. *Clin Neurophysiol* **116**:775–779, 2005

## Disclosures

Prof. Zangen is an inventor of the deep transcranial magnetic stimulation coil systems and supported us in the academic aspects

of deep rTMS. The department of Neuromodulation and Neurosurgery is a joint research chair established with sponsorship by Teijin Pharma Limited.

### Author Contributions

Conception and design: Saitoh, Shimizu, Hosomi, Maruo. Acquisition of data: Saitoh, Shimizu, Hosomi, Maruo, Goto, Yokoe, Kageyama. Analysis and interpretation of data: Shimizu, Hosomi, Shimokawa. Drafting the article: Shimizu, Goto. Critically revising the article: Saitoh, Shimizu, Hosomi, Goto, Shimokawa, Yoshimine. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Saitoh. Statistical analysis: Shimizu, Hosomi, Shimokawa. Administrative/technical/material support: Saitoh, Shimizu,

Hosomi, Maruo, Goto, Yokoe, Kageyama, Yoshimine. Study supervision: Saitoh, Shimizu, Hosomi, Yoshimine.

### Supplemental Information

#### Online-Only Content

Supplemental material is available with the online version of the article.

*Supplementary Materials*. <https://thejns.org/doi/suppl/10.3171/2016.9.JNS16815>.

### Correspondence

Youichi Saitoh, Department of Neuromodulation and Neurosurgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. email: [saitoh@nsurg.med.osaka-u.ac.jp](mailto:saitoh@nsurg.med.osaka-u.ac.jp).