

ORIGINAL ARTICLE

H-coil repetitive transcranial magnetic stimulation for pain relief in patients with diabetic neuropathy

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Conflicts of interest

Prof. Inghilleri, Dr. Onesti, Dr. Gabriele, Dr. Cambieri, Dr. Ceccanti, Dr. Di Stefano, Dr. Biasiotta and Dr. Truini report no biomedical financial interests or potential conflicts of interest. Prof. Zangen is a key inventor of the H-coils and has financial interest in Brainway. Dr. Raccah serves as a scientific consultant for ATID (Advanced Technologies Innovation Distribution), which is Brainway's distributor for Italy.

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Abstract

Background: Painful neuropathy is associated with plasticity changes in the nervous system. Standard repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique used to study changes in cortical excitability and to inhibit pain perception. Deep rTMS is a newer development that allows direct activation of deeper neuronal populations, by a unique coil design termed the H-coil. This study was designed to assess whether deep rTMS applied over the motor cortical lower-limb representation relieves pain in patients with diabetic neuropathy.

Methods: Patients were randomly assigned to receive daily real or sham H-coil rTMS for 5 consecutive days. After a 5-week washout period, they crossed over to the alternative treatment for additional 5 days (according to a crossover study design). Outcome measures were changes in the visual analogue scale (VAS) for pain and in area and threshold of RIII nociceptive flexion reflex (RIII reflex).

Results: Of the 25 patients randomized, 23 completed the study. After real rTMS, the VAS scores decreased significantly ($p = 0.01$), and so did RIII reflex area ($p < 0.01$), while no significant effects in these variables were induced by the sham rTMS treatment. The rTMS-induced changes in the outcome measures disappeared about 3 weeks after stimulation. All patients tolerated stimulation well.

Conclusions: Deep H-coil rTMS provides pain relief in patients with diabetic neuropathy. This innovative technique can induce a therapeutic effect on brain areas that otherwise remain difficult to target. rTMS may produce its analgesic effects, inducing motor cortex plasticity and activating descending inhibitory pain control systems.

1. Introduction

Neuropathy is common in the diabetic population, affecting approximately 50% of patients with long-lasting disease (Schmader, 2002; Kelkar, 2005). The most common type is symmetric distal sensorimotor polyneuropathy, in which pain is a dominant symptom.

Although painful neuropathy responds to antidepressants, anticonvulsants and opioid agonists, these

drugs are often ineffective or can induce severe adverse effects (Attal et al., 2010). Hence, to manage this disturbance effectively, we need to seek other safe and effective therapeutic options.

Invasive neurostimulation techniques are already used successfully to treat drug-resistant neuropathic pain, including deep brain stimulation and epidural motor cortex stimulation (Cruccu et al., 2007; Nguyen et al., 2011). A non-surgical technique modulating cortical excitability and inhibiting pain perception in

What's already known about this topic?

- Invasive neurostimulation techniques are already successfully used to treat drug-resistant neuropathic pain.
- Standard transcranial magnetic stimulation (TMS) coils permit stimulating only superficial cortical regions of the human brain and their effectiveness is limited.

What does this study add?

- Deep rTMS through the H-coil is a new, non-invasive tool for research and clinical applications in neurological disorders, allowing safe access to deep cortical areas that are otherwise difficult to reach.

the human brain is repetitive transcranial magnetic stimulation (rTMS; Lefaucheur et al., 2006; Fregni et al., 2007; Leo and Latif, 2007; Lefaucheur, 2008a). Some evidence shows specifically that rTMS applied to the motor cortical areas relieves refractory chronic neuropathic pain (Pleger et al., 2004; Khedr et al., 2005; Lefaucheur et al., 2006; Hirayama et al., 2006; Picarelli et al., 2010). However, the studies available today have been carried out on populations of patients with different kinds of neuropathic pain. A study of patients with pain due to a single disease would provide more reliable and reproducible data.

Standard TMS coils (such as the figure of eight coil) permit stimulating only superficial cortical regions of the human brain because higher stimulus intensities required to affect deeper brain areas increase the risk of adverse effects.

A newer cooled coil, the Heschl (H)-coil, now allows deep brain stimulation without significantly increasing fields induced in superficial cortical regions. Studies in healthy subjects and mathematical models show that whereas the figure of eight coil stimulates superficial areas less than 1 cm below the skull, the H-coil induces a safe and effective field at a depth of about

3 cm below the skull (Zangen et al., 2005; Roth et al., 2007). rTMS with the H-coil has already proved effective as an acute treatment for major depressive disorder, bipolar depression and focal dystonias (Zangen et al., 2005; Kranz et al., 2010; Harel et al., 2011; Harel et al., 2012). The H-coil can therefore be used to stimulate the motor lower-limb cortex, an area that lied deep in medial motor area sections folding into the medial longitudinal fissure. To our knowledge, no studies have used rTMS with an H-coil to stimulate the motor lower-limb cortex as therapy for patients with painful diabetic neuropathy. Having more information would extend the therapeutic options in managing this difficult-to-treat neuropathy.

The aim of the current study was to assess whether rTMS applied with an H-coil to the lower-limb motor cortex effectively relieves chronic distal diabetic neuropathic drug-resistant pain. As outcome measures, we evaluated changes in the visual analogue scale (VAS) for pain, and the area and the threshold (Th) of nociceptive flexion RIII reflex (RIII reflex), at various time points before and after rTMS.

2. Materials and methods

Twenty-five consecutive patients (11 females and 14 males) with neuropathic drug-resistant pain due to diabetic symmetric polyneuropathy in the lower limbs attending our neurology outpatients department were enrolled in this single-centre, randomized, double-blind, crossover, placebo-controlled trial. The diagnosis of peripheral neuropathy was based on clinical and electrodiagnostic findings, adhering to the criteria proposed by England et al. (2005) [i.e., patients with symmetrically reduced or absent ankle reflexes, decreased distal sensation and abnormal nervous conduction study (NCS) or skin biopsy findings]. Diagnosis of neuropathic pain was relied on the Douleur Neuropathique en 4 questions (DN4) questionnaire, a clinician-administered screening tool that comprises various clinical items and indicates neuropathic pain when the score is ≥ 4 . All patients were resistant to standard therapies for neuropathic pain taken for at least 1 year; dose, frequency and route of administration of these drugs are described in Table 1. We define patients as

Table 1 Drug treatments utilized in patients with diabetic neuropathic pain.

Drug	Dose	Frequency	Route of administration
Gabapentin	900–3600 mg/die	300 mg three times daily, until 400–1200 mg three times daily	Oral
Duloxetine	60–120 mg/die	60 mg once or twice daily	Oral
Tramadol	200 mg/die	50 mg daily or two times a day or 50 mg four times a day	Oral
Oxycodone	30–120 mg/die	Two times a day	Oral
Pregabalin	300–600 mg/die	150 mg two to three times a day or 300 mg two times a day	Oral
Amitriptyline	25–100 mg/die	25 mg once daily, until 50 mg two times a day	Oral
Venlafaxine ER	75–225 mg/die	Once daily	Oral

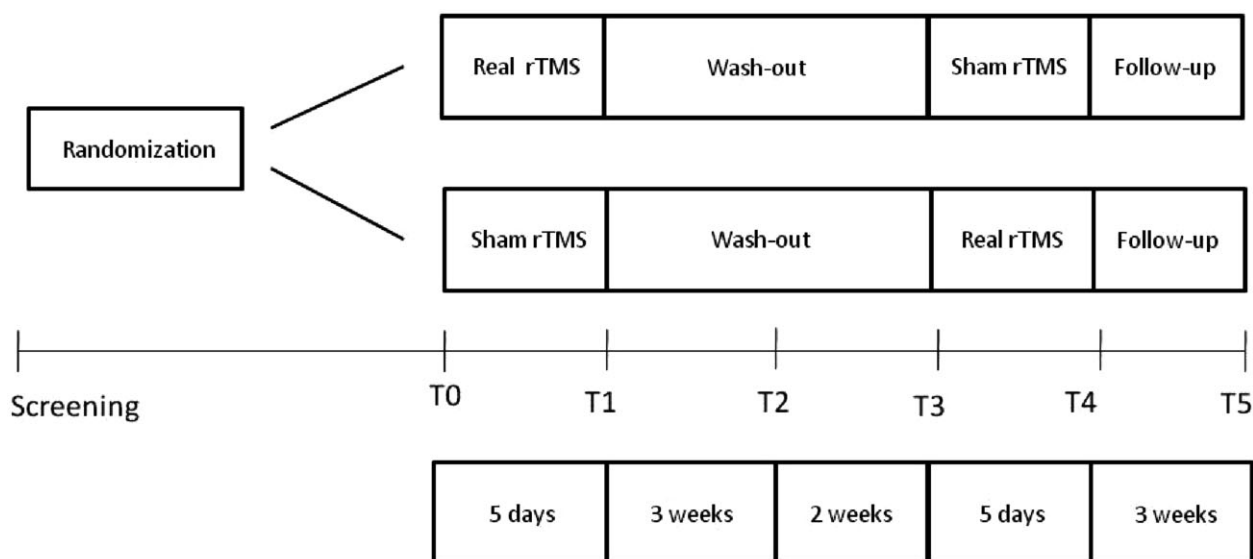


Figure 1 Study design. (Screening) Clinical assessment, neurophysiological procedures (RIII reflex, nerve conduction study, laser-evoked potentials), randomization. (T0) Clinical assessment and neurophysiological procedures (RIII reflex); successive real or sham repetitive transcranial magnetic stimulation (rTMS) session. (T1) Clinical assessment and neurophysiological procedures (RIII reflex). (T2) Last day session treatment; clinical assessment and neurophysiological procedures (RIII reflex). (T3) Clinical assessment and neurophysiological procedures (RIII reflex); successive sham or real rTMS session. (T4) Last day session treatment; clinical assessment and neurophysiological procedures (RIII reflex). (T5) Clinical assessment and neurophysiological procedures (RIII reflex).

drug-resistant if the severity of pain exceeded the rating of 40 at the VAS during the year before the enrolment into the study despite the usage of mono- or polytherapy drugs of proven efficacious in pain and an appropriate duration and dosage of treatment. Analgesic medications were stable for at least 4 weeks before study entry. Exclusion criteria for deep rTMS included history of epilepsy, implanted cardiac pacemaker or any intracardiac lines, implanted neurostimulators, surgical clips or medical pumps, history of frequent or severe headaches and history of migraine.

All patients gave informed consent and the study was approved by the Institutional Review Board. In a screening visit, before starting treatment, all patients underwent the following assessments: clinical examination; RIII reflex testing; an NCS; laser-evoked potentials (LEPs); and pain and depression questionnaires including the VAS for pain, the Italian version of the Neuropathic Pain Symptom Inventory (NPSI), the McGill pain questionnaire (MPQ), the DN4 and the Beck depression inventory (BDI). All patients also underwent skin biopsy to quantify the intraepidermal nerve-fibre (IENF) density at the proximal thigh and distal leg (Lauria et al., 2006). The NPSI, the MPQ, the BDI, the DN4 and the IENF were used only to describe the population.

After enrolment, patients were randomly assigned in a 1:1 ratio to two counterbalanced arms by receiving a sequential number from a computer-generated random list. Randomization scheme was generated prior to the study and blocked in groups of four by an operator not involved in study procedures. The first group received first real rTMS sessions and,

after a 5-week washout period, sham rTMS. The second group received the same treatment, but in reverse order, according to a double crossover study design (Fig. 1).

In each patient, sham and real rTMS sessions lasted 20 min and were delivered for 5 consecutive days.

The patient's clinical condition was evaluated before treatment began (T0), immediately after it ended (T1) and 3 weeks later (T2). After completing this first stage and further 2 weeks of wash-out, patients started the alternative treatment, and primary outcome variables were assessed again before the second treatment started (T3), immediately thereafter (T4) and 3 weeks later (T5).

Active rTMS sessions consisted of 30 consecutive trains of 50 stimuli delivered at 20 Hz, at 100% of resting motor Th (RMT), separated by intertrain intervals lasting 30 s.

Sham stimulation was delivered with a sham coil placed in the helmet encasing the active rTMS coil. The sham coil produced a similar acoustic artefact and scalp sensation as the active coil and could also mimic the facial muscle activation induced by the active coil. It induced only a negligible electric field inside the brain because its non-tangential orientation on the scalp and components cancelling the electric field ensured that it rapidly reduced the field as a function of distance (Roth et al., 2002; Isserles et al., 2012).

The analgesic effect of rTMS (real vs. sham) on pain relief was evaluated to the expected time (at T0-T1-T2-T3-T4-T5) in all patients through the VAS for pain and RIII reflex testing. Raters of the RIII reflex as well as patients were blinded to the treatment group during the entire duration of the study.

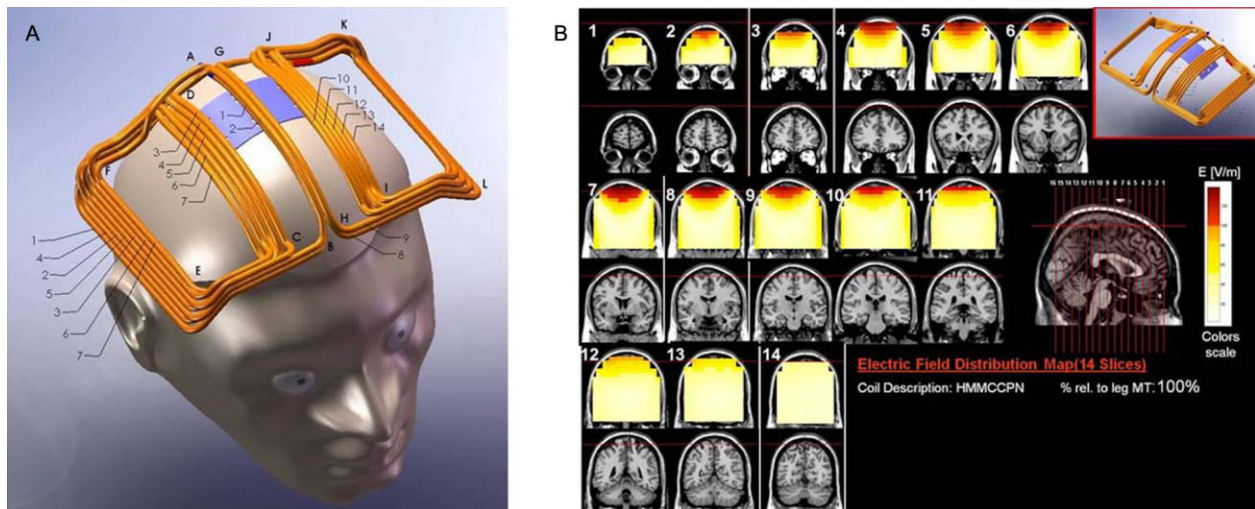


Figure 2 (A) A sketch showing the H-coil used in this study. The main electric field is produced by 14 strips divided into three groups. Each strip measures an average 12 cm in length. Coil elements A–B and G–H are in the central group, element D–C are in the right group, and elements J–I are in the left group. Elements L–K and E–F return currents in the opposite (antero-posterior) direction. (B) Coloured field maps for the H-coil indicating the electrical field absolute magnitude in each pixel, for 14 coronal slices 1 cm apart. The threshold (T_h) for neuronal activation was set to 100 V/m. The field maps were adjusted for stimulator power output level required to obtain 100% leg tibialis motor T_h , at a depth of 3 cm.

2.1 Clinical assessment

The subjective intensity of the pain sensation was assessed after real and sham rTMS treatment with a 100-step VAS for pain. The VAS used in this study and validated both for adults and for children over 5 years consists of a 100-mm line, either vertical or horizontal, anchored at the ends by labels with a minimum score of 0 (no pain) and a maximum score of 100 (worst possible pain) (Huskisson, 1974; Ho et al., 1996). Patients estimate the level of perceived pain sensation by marking the 100-step VAS.

3. Neurophysiological assessment

3.1 Deep TMS procedure

We delivered deep rTMS with the Brainsway H-coil (Brainsway, Jerusalem, Israel) applied via a helmet placed on the head (Fig. 2A). It is designed for safe and effective activation of hand or leg motor cortex, up to 3 cm within the brain. The coil contains 14 windings. Three medial groups conduce current along a postero-anterior axis, and two other groups return currents in the opposite (anterior-posterior) direction (Fig. 2A). Each coil element measures 10–13 cm in length.

The H-coil induces an electric field distribution as presented in Fig. 2B. The red pixels indicate field magnitude above the T_h for neuronal activation, adjusted for stimulator power output level required to obtain 100% of the leg tibialis motor T_h , at a depth of 3 cm.

Deep TMS was applied through the H-coil connected to a Magstim Rapid² stimulator (Magstim, Whitland, UK). The RMT for each patient was obtained by stimulating the leg primary motor area and defined as the minimum stimulator output intensity that evoke a motor response of more than 50 μ V in at least 5 out of 10 consecutive trials in the tibialis muscle. It was determined using the same H-coil. Sham stimulation was delivered with a sham coil placed in the same helmet and producing similar sounds and scalp sensations (Isserles et al., 2012). Before stimulation, all patients were instructed to insert earplugs to mitigate any possible adverse effects on hearing. The first step in the procedure was to locate the ‘hot-spot’ on the patient’s scalp in the point at which a minimum magnetic field causes a motor response, seen as a twitch in the tibialis anterior muscle. The spatial coordinates were then recorded with markings on a cap placed on the subject’s head to ensure placement reproducibility. The coil position was determined and motor T_h estimated immediately before active and sham rTMS sessions.

4. NCS

Patients underwent motor and sensory NCS testing using surface recording electrodes with standard placement. Methods used adhered to those recommended by the International Federation of Clinical Neurophysiology (Kimura, 2006). NCS testing com-

prised sensory nerve action potential amplitude and antidromic sensory nerve conduction velocities recorded from sural nerve, and orthodromic sensory nerve conduction velocity from ulnar nerve. Other nerve function variables examined were ulnar and plantar compound motor action potential amplitude and motor nerve conduction velocities. NCS data were compared with normative ranges established in our laboratory.

4.1 RIII reflex

The flexion reflex is a withdrawal reflex mediated by a complex network of interneurons at spinal level (Shahani and Young, 1971; Sandrini et al., 1993a,b; Burke, 1999). It consists of an early response, the RII reflex, and a late response, the RIII reflex. Some evidence suggests that the RIII reflex Th corresponds to the pain Th and the reflex area is related to the level of pain perception (Willer, 1977). These observations led some to propose the RIII reflex as a valid tool for assessing the mechanisms underlying pain perception (Sandrini et al., 2005).

The sural nerve was electrically stimulated percutaneously through superficial electrodes applied behind the right lateral malleolus with a Micromed Myoquick 1400 device (Micromed SpA, Mogliano Veneto, Italy). The RIII Th was defined as the stimulation intensity generating stable reflex responses at a rate of 60–90% after a series of 20 stimuli. A Th was accepted when three consecutive recordings yielded the same Th value. The RIII reflex was elicited and recorded from the lower limb according to a validated technique (Willer, 1977; Willer et al., 1989). The stimulus, 20-ms volleys of five rectangular pulses (1-ms duration), was delivered randomly every 5–20 s by a constant current stimulator. The intensity of stimulation was fixed at 1.2 Th. To ensure complete muscular relaxation during stimulation, the subjects sat comfortably reclined. As outcome to evaluate the analgesic effect of rTMS, we studied changes in the size of the RIII reflex in terms of area and Th.

4.2 LEP recording

To study LEPs, we used a neodymium : yttrium aluminum perovskite (Nd:YAP) laser (wavelength 1.34 mm, pulse duration 2–20 ms, maximum energy 7 J). The dorsum of the right foot, the left hand and the thigh were stimulated by laser pulses at relatively high intensity (150–200 mJ/mm²), short duration (5 ms) and small diameter (~5 mm) eliciting pinprick sensations (Truini et al., 2010). We measured peak

latency and amplitude (peak-to-peak) of the temporal N1 component and the N2–P2 vertex complex.

4.3 Statistical analysis

Given the exploratory nature of this pilot trial, no sample size determination was performed. Mann–Whitney *U* or the Fisher's exact test (for continuous and dichotomous variables, respectively) were used to check the well-balancing of the two groups.

Repeated measures analyses of variance (ANOVA) with time (T0, T1, T2, T3, T4 and T5 sessions) as the within-subject factor and treatment group (real/sham vs. sham/real groups) as the between-subject factor were run for each outcome variable. The treatment effect on each variable was tested in a *time* × *treatment* interaction analysis. Simple contrasts were conducted to determine where significant differences for each time main effect originated. In order to exclude a carry-over effect, washout differences were evaluate against the null hypotheses of no change during washout periods. To evaluate the sequence effect (i.e., whether real rTMS as first resulted more or less effective than sham as first), the two groups were considered as between-subject factor in the ANOVA.

Unless otherwise stated, all values are reported as means ± standard deviation (SD). *p*-Values equal or less than 0.01 in either direction were considered as significant. Data were analysed by an external statistician unaware of clinical data using the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, IL, USA).

5. Results

Of the 25 patients initially randomized, 13 patients received real rTMS first (real-sham group) and 12 patients sham rTMS first (sham-real group). Two patients in the real-sham rTMS group were lost to follow-up because they were unable to accomplish the study protocol. The data for 23 patients (9 females and 14 males, mean age 70.6 ± 8.5 years) were therefore used to test the effectiveness variables. At baseline, no significant differences were found between the two groups of patients in demographic and clinical characteristics (all *p*-values >0.05) (see Table 2). None of the patients suffered from depression, their mean BDI score was 5.8.

Repeated measures ANOVA identified a significant *time* × *treatment* effect on VAS scores, indicating a significant effect of rTMS in reducing level of VAS scores ($F_5 = 3.968$; $p = 0.01$) (see Table 3 and Fig. 3). In patients who underwent real deep rTMS stimulation

Table 2 Demographic and clinical characteristics of the 23 patients with painful chronic drug-resistant randomized to receive real-sham repetitive magnetic stimulation (rTMS) or sham-real rTMS.

Characteristics	Real-sham rTMS group (n = 11)	Sham-real rTMS group (n = 12)	All patients (n = 23)
Sex (F;M)	4 F; 7 M	5 F; 7 M	9 F; 14 M
Age (years)	70.7 ± 9.5	70.6 ± 7.9	70.6 ± 8.5
DN IV Questionnaire	5.5 ± 0.7	5.8 ± 1.4	5.7 ± 1
VAS (mm)	68.6 ± 5.5	63.7 ± 7.6	66.2 ± 6.6
NPSI Qtot	29.5 ± 4.8	30.1 ± 6.9	29.8 ± 5.8
MPQ			
PPI score	3.3 ± 0.9	2.7 ± 0.9	3 ± 0.9
tPRI score	35.2 ± 13.8	34.5 ± 8.2	34.9 ± 11
BDI	5.8 ± 4.1	5.8 ± 4.6	5.8 ± 4.3
Axonal sensory or sensorimotor neuropathy	Axonal sensory polyneuropathy in 9 patients; sensorimotor neuropathy in 2 patients	Axonal sensory polyneuropathy in 9 patients; sensorimotor neuropathy in 3 patients	Axonal sensory polyneuropathy in 18 patients; sensorimotor neuropathy in 5 patients
LEP	No evoked responses in 8 patients; Increased latency in 3 patients	No evoked responses in 11 patients; increased in latency in 1 patient	No evoked responses in 19 patients; increased latency in 4 patients
Skin biopsy (mm)			
Thigh	4.8 ± 3.3	5.3 ± 2.4	5.1 ± 2.9
Leg	3.4 ± 2.9	3.5 ± 3.2	3.4 ± 3.1

All measures are expressed as means ± SD. BDI, Beck depression inventory; DN4, Neuropathic Pain Diagnostic Questionnaire; LEP, laser-evoked potentials; MPQ, McGill Pain Questionnaire; NPSI, Italian version of the Neuropathic Pain Symptom Inventory; PPI, present pain intensity; tPRI, total pain rating index; VAS, visual analogue scale for pain.

first, VAS scores indicated significant within-group differences at T1 compared with T0, and persisted at T2, 3 weeks after the rTMS session ended (Fig. 3). The effect, however, dissipated 2 weeks later, at T3.

Patients that started real deep rTMS stimulation at T3 showed a significant reduction at T4 (after the end of treatment) that persisted at T5 (3 weeks after stimulation sessions ended) (Fig. 3).

Table 3 Results of the post hoc analyses performed after analysis of variance in visual analogue scale (VAS) scores and RIII area changes after real-sham repetitive magnetic stimulation (rTMS) or sham-real rTMS.

	Real/sham Mean value (SD)	Sham/real Mean value (SD)	Real/sham % change respect to baseline (T0)	Sham/real % change respect to baseline (T0)	Time × group effect F	p-Value
VAS						
T0	68.64	63.75	–	–	–	–
T1	44.54	58.67	–54%	–9%	6.48	0.008
T2	47.81	59.33	–43%	–7%	8.08	0.005
T3	60.91	55.41	–13%	–15%	0.02	0.91
T4	52.27	35.83	–31%	–78%	6.01	0.009
T5	58.64	37.21	–17%	–71%	5.46	0.01
RIII area						
T0	2.77	2.36	–	–	–	–
T1	2.01	2.25	–38%	–5%	5.78	0.01
T2	1.60	2.30	–73%	–3%	10.26	<0.001
T3	2.66	1.91	–4%	–23%	1.47	0.23
T4	2.48	1.42	–12%	–66%	11.58	<0.001
T5	2.52	1.65	–10%	–43%	8.16	0.006
RIII threshold						
T0	197	241	–	–	–	–
T1	169	236	–14%	–2%	2.38	0.14
T2	162	271	–18%	+12%	4.94	0.031
T3	170	267	–13%	+10%	4.23	0.054
T4	178	259	–10%	+7%	4.11	0.059
T5	182	245	–8%	+1%	1.092	0.31

SD, standard deviation.

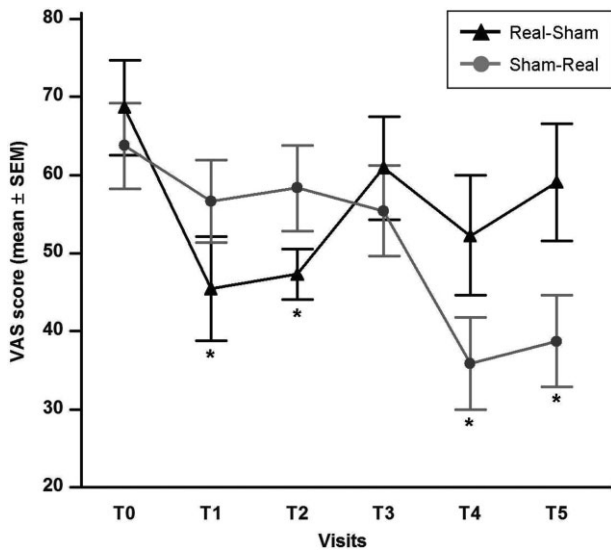


Figure 3 Mean ± standard error of the mean (SEM) changes induced by deep H-coil repetitive transcranial magnetic stimulation (rTMS) on visual analogue scale (VAS) scores over time in patients with painful drug-resistant chronic diabetic neuropathy. Repeated measures analysis of variance (ANOVA) disclosed a significant treatment x time interaction ($F = 3.968$; $p = 0.01$).

* $p \leq 0.01$ with respect to the baseline value.

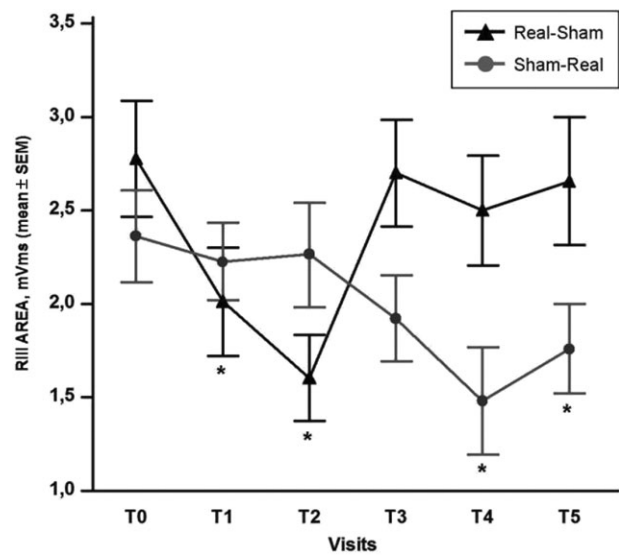


Figure 4 Mean ± standard error of the mean (SEM) changes induced by deep H-coil repetitive transcranial magnetic stimulation (rTMS) on changes in RIII area over time in patients with painful drug-resistant chronic diabetic neuropathy. Repeated measure analysis of variance (ANOVA) disclosed a significant treatment x time interaction ($F = 4.137$; $p < 0.01$).

* $p \leq 0.01$ with respect to the baseline value.

Repeated measures ANOVA identified a significant *time × treatment* effect on RIII area, indicating a significant effect of rTMS in reducing RIII area ($F_5 = 4.137$; $p < 0.01$) (see Table 3 and Figs. 4 and 5). In patients who underwent real deep rTMS stimulation first, RIII area was significantly reduced between T1 and T0, and was further reduced 3 more weeks after the rTMS sessions ended (at T2). This effect completely dissipated after 2 weeks, at T3 (Fig. 4). In patients who started real deep rTMS stimulation at T3, a significant effect was observed at T4 and persisted at T5 (3 weeks after stimulation ended) (Fig. 4).

Repeated measures ANOVA did not identify any significant *time × treatment* effect on RIII Th ($F = 2.745$; $p = 0.447$), indicating that rTMS had no significant effect on this Th sensitivity parameter (Table 3).

Unfortunately, LEPs were absent in so many patients (19 patients) that we could not analyse whether rTMS influenced their amplitude.

All groups tolerated deep rTMS well and none of them reported major or minor adverse effects.

6. Discussion

Our study provides new information showing that deep rTMS with an H-coil applied to the lower-limb cortex in 20-min sessions for 5 consecutive days reduces chronic

drug-resistant distal diabetic neuropathic pain and does so for at least 3 weeks.

Our study extends previous findings showing that standard M1 rTMS reduces various pain conditions including chronic intractable neuropathic pain (trigeminal neuralgia, deafferentation post-stroke pain, pain spinal cord injury), fibromyalgia and complex regional syndrome (Migita et al., 1995; Pleger et al., 2004; Khedr et al., 2005; Hirayama et al.,

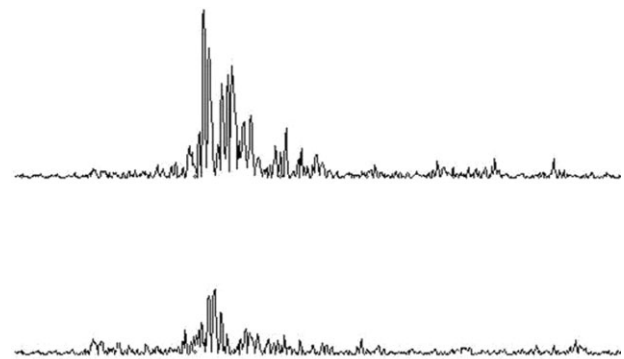


Figure 5 Repetitive transcranial magnetic stimulation (rTMS) induced effects on RIII reflex area in a representative patient. Above: before the treatment; below: after the real rTMS.

2006; Lefaucheur et al., 2006, 2008b; Defrin et al., 2007; Passard et al., 2007; Saitoh et al., 2007; Picarelli et al., 2010). To the best of our knowledge, this study is the first one to apply rTMS over lower-limb motor cortex in a selective population of patients suffering from pain associated with a single specific disease (Pleger et al., 2004; Hirayama et al., 2006; Lefaucheur et al., 2006; Defrin et al., 2007; Passard et al., 2007; Saitoh et al., 2007; Picarelli et al., 2010; Short et al., 2011). We also show that this innovative technique, by activating deeper cortical areas, relieves pain in the distal lower limbs, a brain area heretofore difficult to target when using a standard coil, without inducing adverse events. Moreover, the potential interest of an H-coil compared to a focal coil may be not only to activate deeper structures, but rather to activate a larger area or other neural circuits than those recruited by a figure of eight coil (Roth et al., 2007).

An interesting finding was the time-course for pain relief in patients with painful diabetic neuropathy, which was quite similar for the two outcome variables tested. Specifically, the rTMS effect on the VAS was evident at the end of the active treatment period, becoming slightly less evident 3 weeks after the rTMS ended, and disappeared completely after 5 weeks. On the other hand, the effect of deep rTMS on the RIII reflex area was evident at the end of the active treatment period and persisted for 3 weeks in all patients treated with real rTMS, even if the effect became even stronger after 3 weeks only in the group treated with real rTMS first. The rTMS effect disappeared completely after 5 weeks. We conjecture that this analgesic time-course depends on rTMS-induced cortical plasticity. In a previous study, rTMS sessions at 20 Hz given daily for 5 days reduced pain ratings in patients with trigeminal neuralgia and post-stroke pain for at least 2 weeks after treatment ended (Khedr et al., 2005). In a study on healthy volunteers, Nahmias et al. (2009) found that after a single rTMS session on M1 or dorsolateral prefrontal cortex, the thermal pain threshold increased but neither active or sham stimulation altered the RIII reflex, suggesting that a single rTMS session activates mechanisms other than descending modulatory systems. These results differ from our study, probably owing to the differences in the studied population (patients and not healthy subjects), the kind of pain (chronic and not acute) and the treatment schedule (continued for 5 days and then repeated or given in a single session). Given the RIII area reduction in our patients, we therefore conclude in contrast to others that rTMS might relieve pain by activating descending pain inhibitory controls (Nahmias et al., 2009). Similarly, in previous studies about invasive

brain stimulation, the attenuation of RIII reflex was justified with the hypothesis of a sustained synaptic activity in brain centres known to control pain and thus of descending inhibitory pathways down to the spinal cord segments (Peyron et al., 1995; García-Larrea et al., 2000). Since the pain is partly due to hyperexcitability of nociceptive dorsal horn neurons and RIII attenuation indicates a transient depression of spinal nociceptive neurons, it is not surprising to find an association between RIII attenuation during rTMS and pain relief.

A strength of our study is that to reduce a placebo effect, we took into account the timing of sham relative to active interventions. Indeed, after sham rTMS, both variables remained unchanged, and in patients treated before with real rTMS, a long-lasting maintenance of effect was not evident during the sham treatment period. We also checked the reciprocal relationship between active and sham interventions. A support for existence of intrinsic placebo rTMS effects comes from André-Obadia et al. (2011) who evaluated whether the sham intervention and active rTMS timing influenced placebo efficacy. They showed that placebo analgesia increased significantly when the sham intervention followed successful active rTMS and decreased when it followed unsuccessful rTMS (André-Obadia et al., 2011).

The patients with chronic painful drug-resistant diabetic neuropathy of this study underwent 20-min sessions daily for 5 consecutive days. Some evidence shows that multiple rTMS sessions can prolong the analgesic effect (Pascual-Leone et al., 1998; Lefaucheur et al., 2004). For example, Lefaucheur et al. (2004) reported that monthly sessions of motor cortex rTMS in a patient with drug-resistant neuropathic pain controlled pain for 16 months. In contrast, Topper et al. (2003) found that daily sessions of 10 Hz rTMS over the parietal cortex for 3 consecutive weeks in two patients with phantom limb pain-like syndrome induced no lasting reduction in pain.

Our findings could provide some help in explaining the mechanisms underlying rTMS-induced analgesia. The RIII is considered a quantitative index of spinal transmission of nociceptive signals and is modulated by a complex spinal interneuronal network under the control of the descending pain pathways, diffuse noxious inhibitory control systems or other descending serotonergic systems from the nucleus raphe magnus (Shahani and Young, 1971; Jankowska, 2001; Sagredo et al., 2006). The analgesia rated by our patients' VAS scores as confirmed by a decrease of RIII area could reflect spinal nociceptive neuron hypoexcitability arising when rTMS activates descending inhibitory

control pathways. We conjecture that rTMS might exert an antinociceptive action increasing cell firing rates in the human motor cortex, enhancing plasticity processes that induce changes in corticospinal excitability, thereby inhibiting pain-processing pathways and the RIII reflex. Neurostimulation techniques such as rTMS could change the normal interneuronal circuits within M1 inducing a metaplastic effect; however, some doubt remains about the connections of the recruited neuronal circuits (Hamada et al., 2009; Nguyen et al., 2011). Findings from functional neuroimaging studies also show that M1 rTMS induces activity changes in cortical and subcortical structures implicated in pain modulation, as well as the thalamus and anterior cingulate and insular cortices (Paus et al., 2001; Chouinard et al., 2003; Apkarian et al., 2005; Tracey and Mantyh, 2007; Yoo et al., 2008; Nguyen et al., 2011). Other types of coil such as the Double cone coil 110 mm from Magstim and the DB80 coil from MagVenture can modulate deep brain areas, but the H-coil induces more similar field superficially and deeply, so that the rate of reduction of the field with distance is much smaller and the superficial stimulation is not so strong as with the double cone coil (Hayward et al., 2007).

Our experience suggests that the deep penetration and electric field generated by H-coils may be of clinical importance in treating neurologic disorders, also opening a window on many basic research queries. In our study, an extension of the observation period would better define the effective duration of the real rTMS effect in patients that had the sham rTMS first. Future studies will confirm these missing data and will evaluate whether longer and more intense stimulation periods will product long-lasting beneficial effects and whether chronic maintenance TMS sessions are practicable.

7. Conclusions

Deep rTMS through the H-coil is a new non-invasive tool for research and clinical applications in neurological disorders, and allows safe access to deep cortical areas that are otherwise difficult to reach. Although deep rTMS applied in repeated sessions over the motor cortex with the H-coil provide moderately long-lasting reduction of pain, patients with chronic refractory neuropathic pain would need maintenance treatment.

Author contributions

The corresponding author declares that all co-authors have participated sufficiently in the work to take public responsi-

bility for appropriate portions of the content. Dr. Onesti and Prof. Inghilleri take responsibility for the integrity of the work as a whole, from inception to published article.

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