PAIN® 152 (2011) 1478–1485

PAIN®

www.elsevier.com/locate/pain

Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia

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

ARTICLE INFO

Article history:
Received 13 October 2010
Received in revised form 10 January 2011
Accepted 18 January 2011

Keywords:
Chronic pain
Muscle pain
Pain modulation
Transcranial magnetic stimulation

ABSTRACT

We assessed for the first time the long-term maintenance of repetitive transcranial magnetic stimulation (rTMS)-induced analgesia in patients with chronic widespread pain due to fibromyalgia. Forty consecutive patients were randomly assigned, in a double-blind fashion, to 2 groups: one receiving active rTMS (n = 20) and the other, sham stimulation (n = 20), applied to the left primary motor cortex. The stimulation protocol consisted of 14 sessions: an "induction phase" of 5 daily sessions followed by a "maintenance phase" of 3 sessions a week apart, 3 sessions a fortnight apart, and 3 sessions a month apart. The primary outcome was average pain intensity over the last 24 hours, measured before each stimulation from day 1 to week 21 and at week 25 (1 month after the last stimulation). Other outcomes measured included quality of life, mood and anxiety, and several parameters of motor cortical excitability. Thirty patients completed the study (14 in the sham stimulation group and 16 in the active stimulation group). Active rTMS significantly reduced pain intensity from day 5 to week 25. These analgesic effects were associated with a long-term improvement in items related to quality of life (including fatigue, morning tiredness, general activity, walking, and sleep) and were directly correlated with changes in intracortical inhibition. In conclusion, these results suggest that TMS may be a valuable and safe new therapeutic option in patients with fibromyalgia.

1. Introduction

Fibromyalgia is a chronic pain disorder characterized by widespread pain and muscle tenderness, often accompanied by sleep disorders, fatigue, and depression, affecting 1% to 3% of the general population [34,55]. Fibromyalgia remains one of the most difficult chronic pain syndromes to treat [3] and it may have an even greater impact on quality of life than other chronic pain conditions such as rheumatoid arthritis and osteoarthritis [21]. The etiology of fibromyalgia is poorly understood [1,46], but several studies in recent years have provided evidence for not only functional [8,15–17,38], but structural [26,33,48], electrophysiological [36], and neurochemical [19,20,57] changes in the central nervous system of fibromyalgia patients. These results highlight the role of central nervous system dysfunction in fibromyalgia, which is increasingly regarded as a prototypical "dysfunctional pain syndrome" related to changes in central pain processing primarily affecting pain modulatory systems [28,46,49,50].

Based on these findings, we hypothesized that noninvasive repetitive transcranial magnetic stimulation (rTMS) might be beneficial in fibromyalgia patients. Over the last decade, it has been repeatedly shown that rTMS of the primary motor cortex (M1) induces analgesic effects both in experimental pain [2,18,39,52,54] and in various chronic pain conditions [14,29], probably by activating pain modulation systems. Consistent with these findings, we recently showed that 10 daily sessions of unilateral M1 stimulation decrease chronic widespread pain and improve health-related quality of life of patients with fibromyalgia [42].

However, although these results were encouraging, their clinical relevance was unclear, as only the short-term effects induced by a single or a short series of daily stimulations were assessed. Only a few case reports describe the long-term analgesic effects – for up to

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0304-3959/$36.00
doi:10.1016/j.pain.2011.01.034

1 year – of monthly stimulations of M1 in some patients with neuropathic pain (eg, [31]). However, no controlled study has confirmed the possibility of maintaining the analgesic effects of rTMS over a long period of time in patients with chronic pain.

We report here the first randomized, double-blind, sham-controlled parallel group study, aiming to analyze the long-term maintenance, for up to 25 weeks, of the effects of unilateral rTMS of M1 on pain, quality of life, mood, and anxiety in patients with fibromyalgia. Based on our previous results [42] showing that the effects of rTMS lasted from 15 to 30 days after the stimulation and then subsided, we hypothesized that after an induction phase of 5 daily stimulations, a monthly periodicity would allow the analgesic effects to be maintained over a long period of time. Two series of weekly and fortnightly stimulation sessions were added to the stimulation paradigm in order to test whether it was possible to reinforce the effects of the induction phase.

Another objective of our study was to assess the effects of rTMS on cortical excitability during the course of treatment. It has been shown that the analgesic effects of rTMS in patients with chronic neuropathic pain are directly related to changes in cortical excitability [30] and we previously showed that fibromyalgia patients present significant changes in intracortical modulation, as assessed by paired-pulse stimulation paradigms [36]. Thus, we hypothesized that changes in cortical excitability might be related and predictive of the clinical effects of rTMS in fibromyalgia patients.

2. Methods

The study was approved by the appropriate local institutional review boards and all patients provided written informed consent before inclusion in the study.

2.1. Patients

Consecutive patients were recruited between October 2008 and September 2009. Right-handed patients of at least 18 years of age, who met the American College of Rheumatology criteria for fibromyalgia [56], had a score of at least 4 on the average pain intensity numerical scale of the Brief Pain Inventory (BPI) [11] at screening, and had suffered persistent pain for more than 6 months, were eligible for inclusion in the study. At screening, all patients underwent physical examination by a pain specialist, followed by laboratory tests if necessary. Patients were excluded if evidence was found of inflammatory rheumatic disease, autoimmune disease, or other painful disorders that might confound the assessment of fibromyalgia pain. Patients were not included if they presented a current primary psychiatric condition – including major depression or major personality disorders according to *Diagnostic and Statistical Manual of Mental Disorders-IV* criteria – or a history of substance abuse. All women of childbearing age included in this study had negative pregnancy tests at inclusion and were using contraception. Patients with contraindications for transcranial magnetic stimulation – a history of seizures, brain trauma, brain surgery, or intracranial hypertension, a pacemaker or other metallic implants – and patients with neurological disorders were also excluded. Concomitant medication for pain and sleep disorders was allowed, provided the dose administered had been stable for at least 1 month before enrollment and remained stable throughout the study.

2.2. Experimental design

After a 1-week baseline observation period during which daily average pain intensity was reported in a diary to check its stability, patients were randomly assigned to 2 groups (the active and sham stimulation groups), with equal numbers in each group. A study nurse prepared the concealed allocation schedule by computer randomization of these 2 treatment groups to a consecutive number series; the nurse had no further participation in the trial. Patients were assigned in turn to the next consecutive number.

The treatment protocol consisted of a total of 14 stimulation sessions over 21 weeks and one follow-up visit at week 25. An "induction phase" consisting of one session per day for 5 consecutive days was followed by a "maintenance phase" consisting of one weekly session for 3 weeks (ie, in weeks 1, 2, and 3 after the induction phase), 3 fortnightly sessions (in weeks 5, 7, 9 after the induction phase), and 3 monthly sessions (in weeks 13, 17, and 21 after the induction phase).

Cortical excitability was assessed systematically using the method described below, in all patients, before the treatment sequence on day 1 (D1) of the induction phase, at the end of the induction phase on D5, and then 3, 9, and 21 weeks (W3, W9, W21) after the induction phase. Patients then received either active or sham stimulation for the treatment sequence (see below), according to the group to which they had been assigned. Both patients and investigators were blind to treatment group. Cortical excitability measurements and transcranial stimulation were performed by an independent investigator not involved in the selection or clinical assessment of the patients.

2.3. Transcranial magnetic stimulation

Patients were seated in a comfortable reclining chair and asked to keep their hands as relaxed as possible. Magnetic stimulation was applied with a MagPROX100 machine (Magventure Tonika Elektronic; Farum, Denmark), using a figure-8-shaped coil oriented at a tangent to the scalp, with the main phase of the induced current in the anterior-posterior direction. The patients were fitted with ear plugs during TMS.

2.3.1. Assessment of cortical excitability

Motor cortical excitability testing included the determination of resting motor threshold (RMT), suprathreshold motor-evoked potentials (MEP), short intracortical inhibition (SICI), and intracortical facilitation (ICF) for the left hemisphere. Motor-evoked potentials were recorded for the first interosseous muscle of the contralateral hand, with an EMG amplifier module (Magventure Tonika Elecktronic) and surface electrodes (Alpine Biom, Skovlunde, Denmark). The RMT was defined as the lowest intensity eliciting a motor-evoked potential of at least 50 μV in 50% of trials. The relationship between stimulus intensity and MEP amplitude (ie, the stimulus response curve) was assessed as previously described [36], by measuring the MEP evoked by stimulation at 120% and 140% of the RMT and calculating the ratio of the MEP amplitude obtained at 140% of the RMT to that at 120% of the RMT (140/120 r). Intracortical modulation was investigated according to a previously described paired-pulse protocol [13,27,59]. Paired pulses were delivered, with the intensity of the conditioning stimulus set at 80% of the RMT, and the intensity of the test stimulus at 120% of the RMT. Interstimulus intervals (ISIs) of 2 and 4 ms were used for SICI, and ISIs of 10 and 15 ms were used for ICF. Conditioned stimuli were applied randomly and intermixed with control nonconditioned test stimuli. For each ISI, the results of 4 trials were averaged, and the changes in test MEP amplitude induced by conditioning stimuli are expressed as a percentage of the control MEP amplitude. The mean percentage inhibition with ISI 2 and 4 ms and facilitation with ISI 10 and 15 ms are used for statistical comparisons.

2.3.2. Treatment sequence

The rTMS parameters were similar to those used in our previous study [42]. Each stimulation session consisted of 15 series of 10-

Table 1
Characteristics of the patients and baseline values.

	Active rTMS group (n = 20)	Sham stimulation group (n = 20)	*P* value
Characteristics (mean ± SD)			
Age (years)	51.8 ± 11.6	49.6 ± 10.0	ns
Pain duration (years)	13 ± 12.9	14.1 ± 11.9	ns
BL pain intensity (0-10)	6.2 ± 1.4	6.5 ± 1.8	ns
Concomitant treatment			
Weak analgesics,% (n)	70 (14)	75 (15)	ns
Antidepressants,% (n)	50 (10)	50 (10)	ns
Benzodiazepines,% (n)	50 (10)	55 (11)	ns

rTMS, repetitive transcranial magnetic stimulation; ns, non significant; BL, baseline.

second pulses with a frequency of 10 Hz and an interval of 50 seconds between each train, giving a total of 1500 pulses per session. The stimulation intensity used was 80% of the RMT. Sham stimulation was carried out with a sham coil of identical size, color, and shape, emitting a sound similar to that emitted by the active coil.

2.4. Clinical outcome

The primary outcome was self-reported average pain intensity over the last 24 hours, measured with the numerical scale (0 = no pain, 10 = maximal pain imaginable) of the BPI [11]. Average pain intensity was assessed at the beginning of each session (before stimulation) during the induction and maintenance phases of the treatment (up to week 21) and at the follow-up visit in week 25 (1 month after the last stimulation).

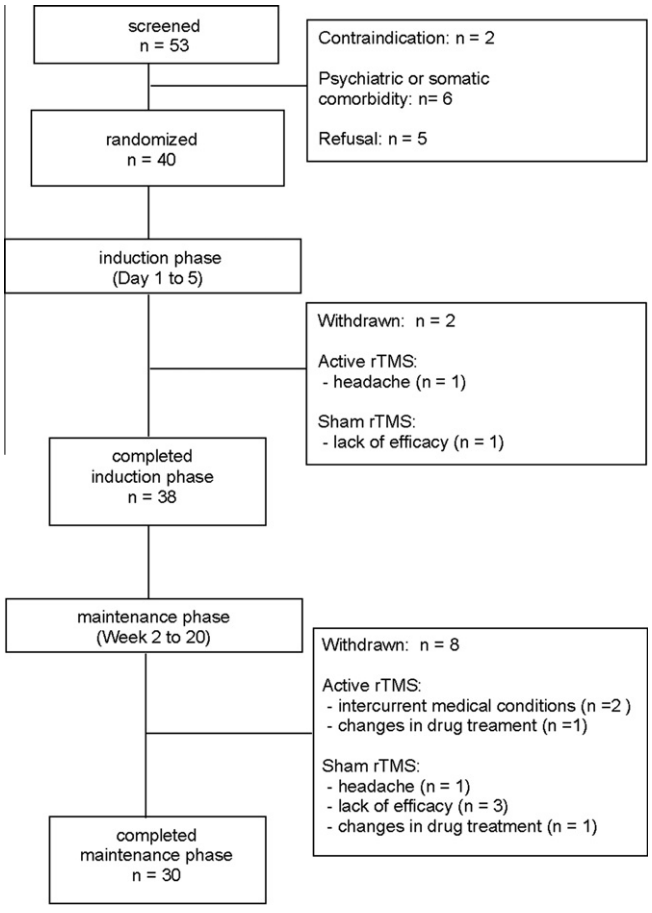

Fig. 1. Flowchart of the study.

The secondary outcome considered were the sensory and affective pain dimensions and the impact of pain and fibromyalgia on quality of life (before the treatment session) at baseline on day 1, on day 5, and then 3, 9, and 25 weeks after the induction phase.

The French version [6] of the McGill Pain Questionnaire [35] was used to measure the sensory and affective dimensions of pain. The BPI items for pain interference (from 0 = does not interfere, to 10 = complete interference) were used to measure the impact of pain on general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life [11].

The effects of the treatment on the health domains most affected by fibromyalgia were assessed with the French version [43] of the Fibromyalgia Impact Questionnaire (FIQ) [7]. Both the FIQ total score, with ranges from 0 (no impact) to 100 (maximum impact), and the FIQ subscales (from 0 to 10) for fatigue, morning tiredness, and stiffness were included in the analysis.

The effects of treatment on mood, anxiety, and catastrophizing were assessed before the treatment session on D1 and then in weeks 3, 7, 13, and 25 after the induction phase. Mood and anxiety were assessed with the 21-item Hospital Anxiety and Depression Scale (HAD) [61] and the 13-item short form of the Beck Depression Inventory (BDI) [4]. Catastrophizing was assessed with the Pain Catastrophizing Scale (PCS) [51].

2.5. Safety

The safety of rTMS was assessed by monitoring the occurrence of adverse effects during treatment and analyzing the pattern of treatment discontinuation for all patients randomized in the 2 treatment groups.

2.6. Statistical analysis

All analyses were performed on the intent-to-treat population, defined as all patients randomized to 1 of the 2 groups participating in at least one stimulation session. Based on our previous results and estimates of variance [42], we calculated that we would need 30 patients to complete the protocol for the study to have an 80% power to detect (2-tailed test with an alpha of 0.05) a mean difference in pain intensity of 1.2 on a scale from 0 to 10, from baseline to week 25. Based on an estimated dropout rate of 15% to 20%, we estimated that 40 patients should be enrolled.

All longitudinal continuous efficacy measures, that is, the primary outcome (average pain intensity score) and all secondary efficacy variables (ie, scores for the BPI-Interference, SF-McGill, FIQ, HAD, BDI, and PCS scales, and cortical excitability parameters), were analyzed with a mixed-effects model. The model included as explaining factors: treatment (active or sham stimulation), time, and the interaction of treatment with time. The patient was the random effect. The baseline-observation-carried-forward method was used for missing data. If a significant interaction between treatment and time was observed, pairwise comparisons were made between sham and active stimulation at the various time points, by *t* tests calculated from the model. Pearson's correlation test with Bonferroni correction for multiple comparisons was used to assess the correlation between the mean change in intracortical modulation (ie, SICI and ICF) and the mean changes in pain intensity, fatigue, anxiety, depression, and catastrophizing scores. Fisher's exact test was used to compare proportions. In all cases, P values <0.05 were considered significant. The Cohen's d, defined as the difference between the means of the 2 groups divided by the pool standard error, was used for the calculation of effect sizes. All the statistical analyses were carried out with JMP software, version 8.0 (SAS Institute Inc, Cary, NC).

3. Results

Forty female patients meeting the inclusion criteria were randomly assigned to the active rTMS (n = 20) or sham stimulation (n = 20) group. Sociodemographic variables, clinical characteristics, and concomitant analgesic treatments did not differ significantly between the 2 groups (Table 1). All but 2 patients completed the induction phase, and 8 other patients (3 in the active rTMS group and 5 in the sham stimulation group) withdrew during the maintenance phase (Fig. 1).

3.1. Effects of rTMS on pain intensity

Active rTMS had a significant effect on average pain intensity over the course of the treatment, as shown by comparison with the sham stimulation treatment (F = .02; $P = 0.007$). Pairwise comparisons showed that this effect was significant from day 5 onwards and was maintained until week 25, although the magnitude of the effect tended to decrease during the period of monthly stimulation, from week 16 to 25 (Fig. 2). This was reflected by changes in the effect size, which was 0.75 on day 5, 0.92 in week 3, 1.19 in week 9, and 0.66 in week 25.

3.2. Effects of rTMS on pain secondary outcomes

Both the sensory (F = 2.6; $P = 0.03$) and affective (F = 7.63; $P = 0.0001$) subscores of the SF-McGill questionnaire were significantly lower in the active rTMS group than in the sham stimulation group (Table 2). Over the course of treatment, the mean change in affective score was significantly larger than that in sensory score ($P < 0.001$).

3.3. Effects of rTMS on quality of life

Active stimulation significantly improved (F = 8.62, $P = 0.005$) the BPI interference score (Table 2), with patients reporting a marked decrease in the interference of pain with "general activity," "walking," "relations with other people," "enjoyment of life," and "sleep" (Fig. 3A-E). By contrast, the active treatment did not significantly decrease the interference of pain on "work" and "mood." In addition, active rTMS significantly decreased both the total score (F = 5.03; $P = 0.03$) of the FIQ (Table 2) and the 3 subscores relating to fatigue (F = 4.8; $P = 0.003$), stiffness (F = 11.7; $P = 0.001$), and morning tiredness (F = 7.47; $P = 0.009$) (Fig. 3F, G, H).

Mean depression and anxiety scores (as measured on the BDI and HAD scales) were not significantly affected by active or sham stimulation (Table 2). Catastrophizing score was significantly lower (F = 5.99, $P = 0.02$) after active rTMS than after sham treatment (Table 2).

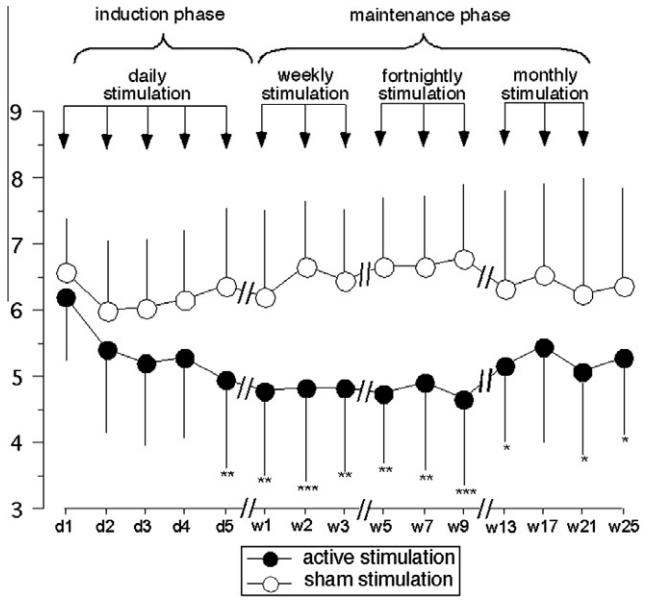

Fig. 2. Effects of active (black circles) and sham (white circles) stimulation on average pain intensity during the induction phase, from day 1 (d1) to day 5 (d5) and during the maintenance phase, from week 1 (w1) to week 21 (w21), and 1 month after the last stimulation at week 25 (w25). The arrows indicate the stimulation session. $^{*}P < 0.05$; $^{**}P < 0.01$ vs sham stimulation.

3.4. Effects of rTMS on cortical excitability

No significant difference was observed between the effects of active and sham stimulation on the motor threshold and suprathreshold motor-evoked potentials, as assessed with the 140/120 ratio (Fig. 4A, B). By contrast, both SICI (F = 5.37; $P = 0.0005$) and ICF (F = 4.98; $P = 0.001$) were significantly higher after active rTMS than after sham stimulation (Fig. 4C, D). At baseline there was no correlation between clinical variables (ie, pain, fatigue, and other secondary variables) and SICI and ICF, except a moderate correlation between SICI and the catastrophizing score ($r = 0.37$; $P = 0.03$). The mean change in SICI over the course of treatment was correlated with the mean change in pain intensity ($r = 0.64$; $P = 0.007$) in the group of patients who received the active treatment, but not in those who received sham stimulation. On the basis of this result, we also analyzed the relationship between the changes in SICI at the different times and the mean change in pain intensity. There was no correlation between baseline SICI and clinical effects of rTMS, but there was a moderate relationship between the change in SICI from day 1 to week 3 ($r = 0.47$, $P = 0.04$) and the change in pain intensity, and a much stronger correlation ($r = 0.71$, $P = 0.008$) between the change in SICI from day 1 to week 9 and the change in pain intensity.

The mean change in ICF was not correlated with the change in pain intensity ($r = 0.31$, ns), but it was directly correlated with the mean change in fatigue ($r = 0.52$, $P = 0.036$) and with the mean change in catastrophizing score ($r = 0.51$; $P = 0.043$), only in patients who received active rTMS.

3.5. Side effects

Two patients, one in the sham stimulation group and one in the active stimulation group discontinued the treatment because of headache. Nine other patients (5 in the active stimulation group and 4 in the sham stimulation group) reported transient (lasting <3 hours) mild headache during or just after one of the treatment sessions. Another patient in the active stimulation group reported transient dizziness after one session during the induction phase.

4. Discussion

This randomized sham-controlled study shows, for the first time, that the analgesic effects of rTMS of the primary motor cortex can be maintained for up to 6 months in patients with chronic pain. In our patients with fibromyalgia, the decrease in pain intensity was associated with a long-term improvement in other clinical features including fatigue, catastrophizing, and several items related to quality of life. The effects of rTMS were associated with changes in intracortical modulation, which may be involved in the mechanisms underlying its analgesic action. Our data suggest new therapeutic indications of this noninvasive brain stimulation technique.

Table 2
Comparison of the effects of active repetitive transcranial magnetic stimulation (rTMS) or sham stimulation from day 1 (D1) to week 25 (W25) on: the McGill Questionnaire sensory and affective scores, Brief Pain Inventory (BPI) interference score, Fibromyalgia Impact Questionnaire (FIQ) total score, the Hospital Anxiety and Depression (HAD) scores for anxiety and for depression, Beck Depression Inventory (Short Form) (BDI); Pain Catastrophizing Scale (PCS).

	D1		D5		W3		W9		W25	
	rTMS	Sham	rTMS	Sham	rTMS	Sham	rTMS	Sham	rTMS	Sham
McGill Sensory	20.8 ± 6.1	19.5 ± 6.5	17.0 ± 6.9	20.0 ± 6.2	16.5 ± 6.1	19.9 ± 6.5	16.9 ± 7.0	19.5 ± 6.8	16.9 ± 6.9	19.9 ± 6.7
McGill Affective	7.5 ± 2.5	6.8 ± 2.8	4.1 ± 2.8*	6.3 ± 2.7	4.2 ± 2.6*	6.4 ± 3.2	4.0 ± 2.8*	6.4 ± 2.8	3.5 ± 3.0**	6.3 ± 3.0
BPI Interference	5.8 ± 1.3	6.1 ± 1.7	4.8 ± 1.5**	6.2 ± 1.5	4.3 ± 1.9**	5.7 ± 1.4	4.3 ± 1.6**	5.8 ± 1.4	4.1 ± 1.7****	6.0 ± 1.5
FIQ total score	66.8 ± 12.5	67.2 ± 14.8	56.8 ± 14.7*	66.1 ± 8.7	55.2 ± 15.2**	67.5 ± 7.2	55.0 ± 16.6*	65.7 ± 11.0	56.0 ± 17.7	63.3 ± 15.0
HAD depression	8.4 ± 4.7	8.7 ± 3.5	8.7 ± 4.4	8.2 ± 4.3	8.8 ± 4.4	8.0 ± 4.6	9.3 ± 4.0	7.6 ± 4.5	8.6 ± 4.7	7.4 ± 4.3
HAD anxiety	11.8 ± 4.0	11.4 ± 4.4	9.9 ± 4.1	10.9 ± 4.4	10.9 ± 3.5	9.6 ± 5.2	10.1 ± 4.5	9.6 ± 5.6	9.2 ± 4.9	9.4 ± 5.7
BDI depression	9.6 ± 6.5	10.0 ± 5.8	9.1 ± 6.2	8.9 ± 5.8	9.2 ± 6.4	9.3 ± 5.6	9.2 ± 6.2	9.3 ± 5.3	8.8 ± 5.9	9.6 ± 5.2
PCS catastrophizing	24.8 ± 11.9	28.1 ± 8.8	21.0 ± 10.8*	28.1 ± 9.0	18.2 ± 10.2**	29.2 ± 9.3	17.7 ± 11.3*	26.0 ± 8.8	18.3 ± 11.2*	25.0 ± 8.9

Results are expressed as mean ± SD.
* $P < 0.05$.
** $P < 0.01$.
**** $P < 0.001$ vs sham stimulation.

The clinical applications of rTMS have expanded rapidly over the last few years. This technique, initially proposed for the treatment of depression, may also be useful for the treatment of other psychiatric and neurological conditions, including schizophrenia, Parkinson disease, epilepsy, and tinnitus [25]. Several studies have also shown that rTMS of the M1 has analgesic effects in various chronic pain conditions, including neuropathic pain [29,32], complex regional pain syndrome [44,45], and fibromyalgia [42].

Previous studies have generally considered the immediate analgesic effects of a single stimulation session [29]. Only a few studies in patients with neuropathic pain [12,24] or fibromyalgia [42] have evaluated the effects of repeated daily stimulations over a period of 5-10 days and reported analgesic effects lasting for 2-3 weeks after the last stimulation. In particular, in our previous study [42], we showed that the effects of rTMS lasted for 15–30 days after the stimulation and then subsided. The data presented here clearly demonstrate that it is possible to maintain the analgesic effects of rTMS over a long period of time, at least in patients with diffuse pain due to fibromyalgia. We found that rTMS not only reduced pain, but also improved several items relating to quality of life, such as the impact of pain on general activity, sleep, and walking, and other major clinical features of fibromyalgia, including fatigue and catastrophizing. Thus, the effects of rTMS in fibromyalgia patients were clearly not limited to the sensory component of pain, but reflected instead a more global improvement in the chronic pain state of the patients.

The pattern of stimulation selected here was derived from those used in studies on depression [41], including daily stimulation during the "induction phase" and weekly, fortnightly, and then monthly stimulation during the "maintenance phase." Due to the lack of data, it was not possible to define the optimal number of sessions or the ideal interval between 2 successive sessions for analgesic effects at the outset of the study. Our decision to use monthly periodicity stimulation at the end of the "maintenance phase" was a compromise based on our previous results, showing effects lasting not more than 30 days after 10 daily sessions, and the need to find a frequency of stimulation sessions that was both feasible and acceptable to chronic pain patients. However, we cannot rule out the possibility that our stimulation paradigm was not optimal. In particular, the analgesic effects of rTMS were weaker during the monthly stimulation period than during the weekly or fortnightly stimulation. In clinical practice, the use of weekly or fortnightly stimulation does not appear to be realistic. It is possible that more effective analgesia would have been achieved with an interval of 3 weeks between stimulation sessions, and this should be more feasible in patients with chronic pain. Also, it would be important to verify whether the 3 weekly and 3 fortnightly sessions are necessary to the maintenance of the analgesic effects. Thus, further studies are required in order to determine the optimal stimulation paradigm and also to test whether the stimulation of other cortical areas could also induce analgesic effects in these patients.

The mechanisms underlying motor cortex rTMS-induced analgesia remain unclear, but may be similar to that of chronic motor cortex stimulation through surgically implanted epidural electrodes, which is used to treat patients with refractory neuropathic pain [23,40,53]. Several neuroimaging studies have shown that the hemodynamic changes induced in the brain by rTMS are not confined to the motor system, but instead involve a set of cortical (cingulate, insular, orbitofrontal and prefrontal cortices, thalamus, and striatum) areas, involved in pain processing and modulation [5,9,58]. Thus, rTMS-induced analgesia may be mediated through the activation of pain modulating systems organized in the diencephalon and/or descending from the brainstem to the spinal cord [37]. The recently demonstrated involvement of endogenous opioid systems in rTMS-induced analgesia [10] is consistent with this hypothesis. However, no data are available concerning the brain activation associated with rTMS in chronic pain patients. The stronger effects of M1 rTMS on the affective than on the sensory dimensions of pain, as previously reported [42], suggests that motor cortex stimulation preferentially affects brain structures involved in the affective/emotional component of pain.

The analgesic effects of M1 rTMS have also been shown to be associated with changes in intracortical modulation in patients with neuropathic pain [30]. Intracortical modulation, which can be assessed by paired-pulse stimulation, depends on both the GABAergic and glutamatergic pathways [22,47,60]. The data presented here, consistent with the results of Lefaucheur et al. [30] for patients with neuropathic pain, indicate that the analgesic effects of rTMS are associated with an increase in both SICI and ICF. The change in pain intensity was correlated with the change in SICI, whereas the change in fatigue, another major symptom of fibromyalgia syndrome, was correlated with the change in ICF. These findings are consistent with our previous data [36] showing significant alteration of intracortical modulation in these patients, which were not related to medication. In the present study, it is unlikely that the pharmacological treatment (analgesics or other centrally acting agents) received by the patients biased significantly our results related to cortical excitability. Patients in the active or sham stimulation received similar pharmacological treatment. In addition, the correlations observed between the clinical effects and changes in cortical excitability tend to rule out the possibility that the clinical effects reported here were only due to unspecific effects. The clinical significance of intracortical modulation remains unclear.

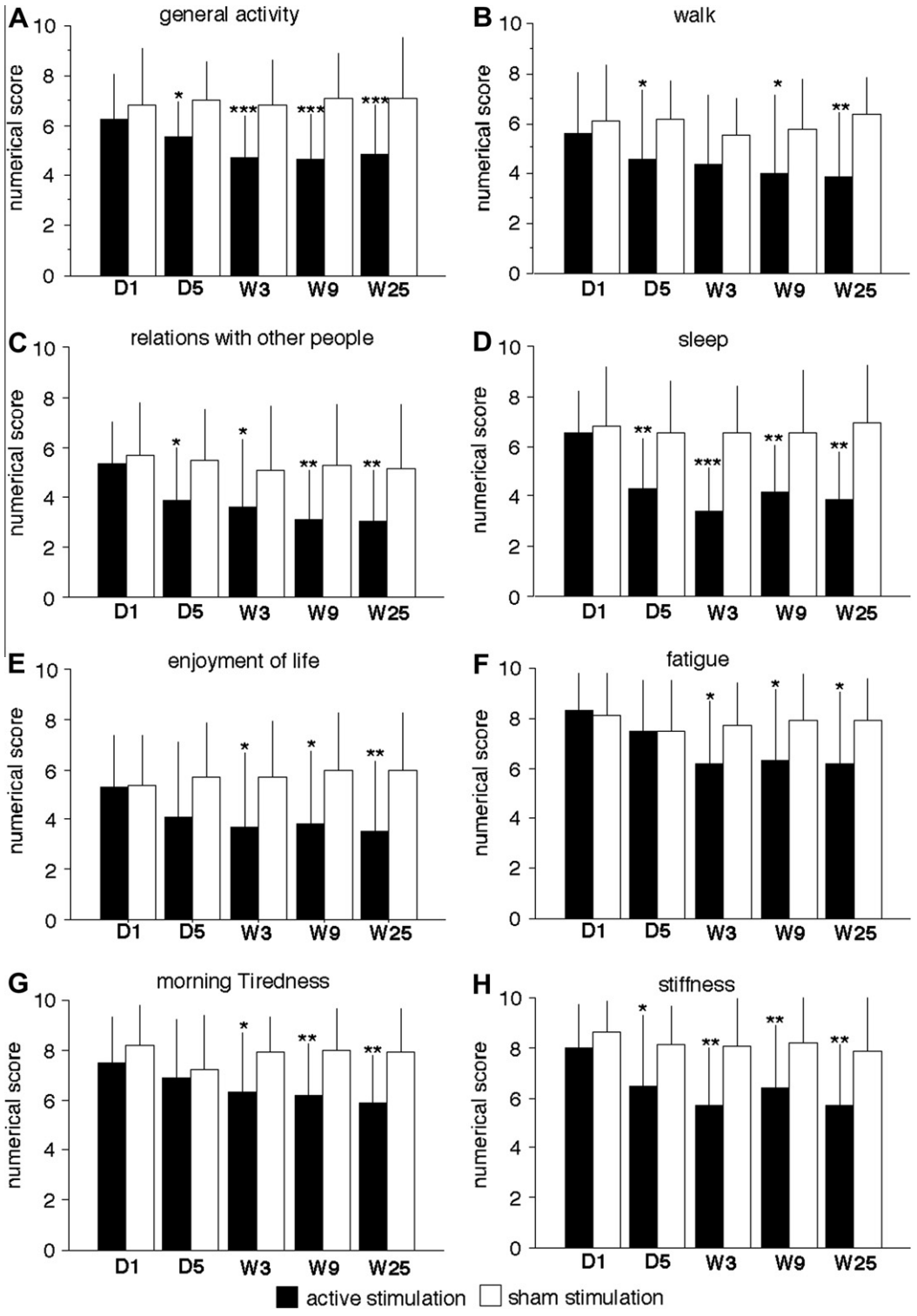

Fig. 3. Effects of active (black columns) and sham (white columns) stimulation from day 1 (D1) to week 25 (W25), on items of the Brief Pain Symptom Inventory relating to the interference of pain with general activity (A), walking (B), relations with others (C), sleep (D), enjoyment of life (E), and on the fatigue (F), morning tiredness (G), and stiffness (H) subscores of the fibromyalgia impact questionnaire (FIQ). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ vs sham stimulation.

Although one cannot formally exclude that changes in SICI and ICF were partly due to alteration in the input-output curve for MEP after active stimulation, our data suggest that the mechanism of action of rTMS is related to changes in intracortical modulation. From a clinical perspective, the relationship that we evidenced between the analgesic effects of rTMS and the changes in SICI in week 3 suggest that changes in intracortical modulation may be predictive of the efficacy of rTMS in patients with fibromyalgia and could therefore be used to select the patients most likely to respond to this treatment.

Our data also indicate that rTMS can be safely administered in an outpatient setting. The adverse events observed during the induction or maintenance phase were generally of mild to moderate severity, and only 2 patients (ie, <5%) discontinued treatment

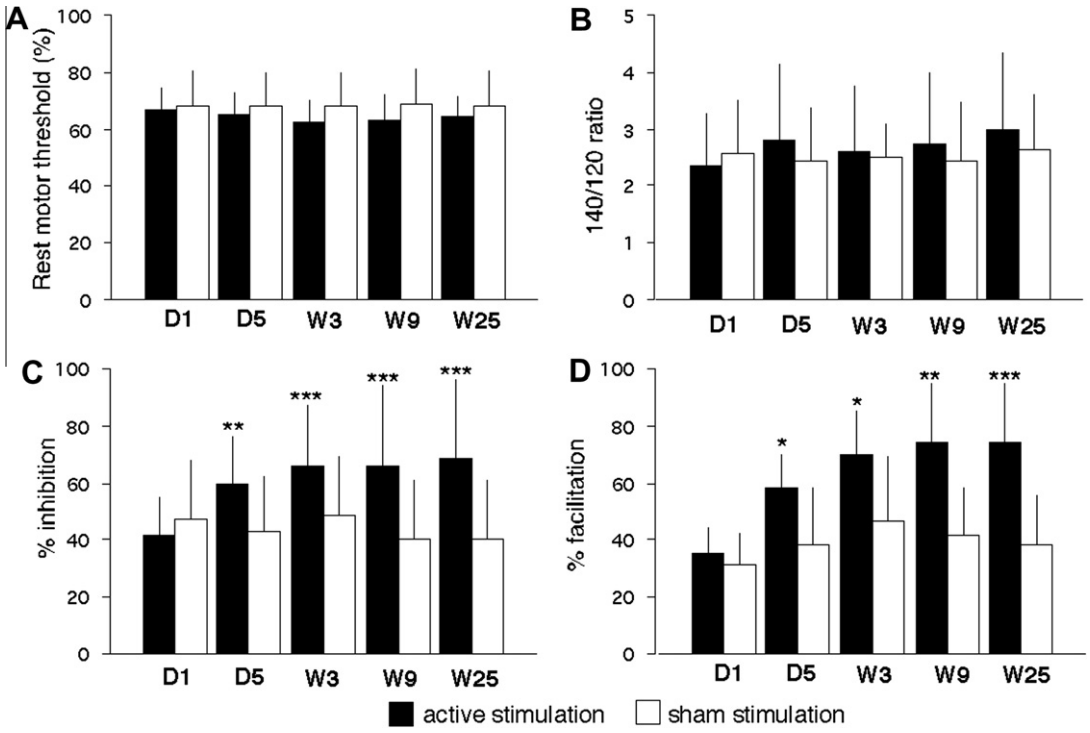

Fig. 4. Effects from day 1 (D1) to week 25 (W25) of active (black columns) and sham (white columns) stimulation on: resting motor threshold expressed as a% of the maximal intensity of stimulation of the TMS device (A); motor evoked potential amplitude ratio for stimulus intensities of 120% and 140% of resting motor threshold (B); short intracortical inhibition (SICI) expressed as% inhibition of the test response (C) and intracortical facilitation (ICF) expressed as% facilitation of the test response (D). $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ vs sham stimulation.

because of side effects (headache). These low incidences of adverse events and treatment discontinuation compare favorably with those for current pharmacological treatments of fibromyalgia (ie, antiepileptics and antidepressants). For example, in a recent double-blind placebo-controlled study of the antidepressant duloxetine, 38% of the patients did not complete the 12-week study, mostly because of side effects [3].

One limitation of this study, inherent to all studies using rTMS, is related to the blinding, because the person who places the active or sham stimulator in position cannot be blind to the treatment. As in our previous study [42], we overcame this problem by ensuring that the investigator placing the simulator in position was not involved in the recruitment and evaluation of the patients. In addition, the fact that the active coil can induce a slight tapping sensation on the skull in some patients could also have biased our results. We did not confirm that blinding was effective by asking the patients about the treatment they thought they had received after each session. However, the patients would be unlikely to identify their treatment correctly, as none had ever experienced rTMS before and very few side effects were reported for active or sham treatments. Furthermore, the possibility of our results being solely due to nonspecific effects of rTMS seems to be ruled out by the direct correlation observed between the improvement of clinical symptoms (pain, fatigue, and catastrophizing) and the changes in electrophysiological parameters (intracortical modulation).

In conclusion, the data presented here indicate that rTMS may be a valuable new therapeutic option in patients with fibromyalgia. Future studies should investigate whether long-lasting analgesic effects can also be obtained in other chronic pain syndromes.

Conflict of interest statement

The authors declare no conflict of interest related to this study.

Acknowledgements

This work was supported by grants from the "Fondation APICIL" and the "Fondation de France." We thank Françoise Morain for technical assistance and Pr Jacques Fermanian (Necker Hospital, Paris) for his help with statistical analyses.

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