Effectiveness of Repetitive Transcranial Magnetic Stimulation on Fibromyalgia Patients Responding to a First Repetitive Transcranial Magnetic Stimulation Induction Course After Six Months of Maintenance Treatment: A Randomized Pilot-Controlled Study

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Effectiveness of repetitive transcranial magnetic stimulation (rTMS) on fibromyalgia subjects responding to a first rTMS induction course after six months of maintenance treatment: a randomized pilot-controlled study

Short running title: rTMS efficacy in fibromyalgic subjects

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Abstract

Background: Fibromyalgia is a chronic painful condition without real effective treatment. The administration of repetitive transcranial magnetic stimulation (rTMS) has been shown to have a therapeutic effect on pain, but there are still questions about the maintenance of its effect over time. Continuation of the treatment upon clinical response through maintenance sessions is promising and merits further exploration.

Materials and Methods: We thus conducted a randomized, parallel-group, controlled study involving 78 patients to evaluate the effect of rTMS versus sham stimulation after a three-week induction treatment and six months of maintenance treatment (3-week periodicity) on 22 patients who presented a clinical response to the induction treatment. The clinical response was defined as a ≥ 30% decrease of the baseline visual analog scale (VAS) for pain and a score for the patient global impression of change (PGIC) >5. The clinic global impression (CGI), fibromyalgia impact questionnaire (FIQ), symptom severity score (3S), and Beck's depression inventory (BDI) were also studied.

Results: A significant clinical response to treatment with rTMS was observed after the induction phase and maintained over six months, particularly as measured by the PGIC parameter of pain, as well as on the intensity of fatigue and depression, with an absence of adverse effects induced by this method.

Conclusion: A three-week rTMS treatment, characterized by a reduction in pain, as evaluated by VAS, should be continued with the administration of rTMS maintenance sessions for an additional six months to maintain the best possible long-term effects.

Keywords: fibromyalgia, Transcranial Magnetic Stimulation, Long-Term Effects, pain, responders

Introduction

Fibromyalgia is a chronic painful condition that causes muscle or joint pain throughout the body at varying times and locations. Other symptoms (fatigue, non-restorative sleep, mood, and cognitive disorders) are common, and influence the quality of life.[1] The world prevalence of fibromyalgia is approximately 2%,[2] and mainly affects women.[2,3] Abnormalities in central pain processing play an important role in hyperalgesia and allodynia, reflecting central sensitization. There is also evidence of dysregulated descending inhibitory pathways and altered resting-state functional connectivity.[4,5] Psychiatric co-morbidities are often associated, especially mixed anxiety-depressive disorders.[6] The European League Against Rheumatism (EULAR) published new recommendations in 2016 for the management of fibromyalgia.[7] EULAR recommends monitoring pain, fatigue, sleep disturbance, and daily disability in a personalized, graded, and multidisciplinary approach. Drug treatment should be prescribed in the second intention when first-line treatment does not significantly improve the quality of life. As the etiology of fibromyalgia is not fully understood, the identification of adapted and efficient therapies is difficult.

One promising non-drug therapy is repetitive transcranial magnetic stimulation (rTMS), which consists of applying a magnetic field to the cerebral cortex to stimulate targeted areas of the brain.[8] This technique is a recognized treatment for major depression, some neurological diseases, and has been already used in pain pathologies: chronic pain, and

particularly neuropathic pain.[9,10] A grade B recommendation has also been attributed to rTMS in fibromyalgia[11], and treatment conditions have to be further explored for optimization. Conditions of rTMS stimulation for pain vary, but the cerebral zone to be stimulated is mainly the primary motor cortex of area M1.[12] The initial treatment generally consists of 10 daily sessions (five per week) targeting this area. This stimulation has been shown to improve the quality of life. However, the optimal conditions of stimulation require further study,[13] especially for maintenance of the effect.

Indeed, the long-term effects of rTMS maintenance sessions on pain relief (> 3 months) are not well known.[13] Such effects have been studied in resistant or refractory major depression,[14] with an effect on sleep quality,[15] and in refractory facial pain.[16] One study explored the long-term effect of rTMS in fibromyalgia and showed long-term changes in central pain regulation.[17] In this case, the treatment for all patients consisted of an induction phase (one session per day for five consecutive days), followed by a maintenance phase consisting of one weekly session for three weeks, three fortnightly sessions, and three monthly sessions. The analgesic effect of rTMS on overall pain was observable for 25 weeks.

In a preliminary pilot study[18], we observed a reduction of pain in 20 fibromyalgia patients after 15 sessions of rTMS treatment and determined the stimulations parameters to use according to this study, and the parameters listed by Lefaucheur and colleagues (frequency of stimulation, number of sessions).[9] The positive effect was maintained without additional sessions for 13 subjects for 35 days, and for five subjects for 90 days. However, whether the maintenance sessions stabilize the effect of the first rTMS treatment is yet to be established.

We therefore conducted a randomized controlled study to evaluate the effect of rTMS versus sham stimulation 1) at the end of a three-week induction treatment and 2) after a six-month maintenance treatment in responders to the first induction phase. .

Materials and Methods

Population *(NCT01942538)*

Patients between 18 and 70 years of age with a primary fibromyalgia diagnosis (CHRU Limoges) with the presence of ACR criteria (2010) by their referent rheumatologist, pain lasting more than six months, the absence of therapeutic modification in the month before and during treatment, and the failure of past or current drug-based treatment (pregabalin, duloxetine, minalcipran, gabapentin, venlafaxine, amitriptyline, or analgesic) were included in the trial from 2013 to 2017 at CH Esquirol Limoges (including patients from preliminary pilot study). Non-inclusion criteria included the existence of a non-stabilized psychiatric comorbidity (mixed anxiety-depressive disorders, depressive disorders), active epilepsy, a medical history of cerebral problems or brain surgery, the existence of any metallic implants in the body, and receiving drug therapy (clozapine, bupropion, methadone, or theophylline) or other alternative therapy (physiotherapy, balneotherapy, relaxation, cognitive behavioral therapy, hypnosis therapy, or acupuncture) started within the month preceding the study. Being pregnant, under legal protection, or lacking health insurance were also exclusion criteria, as required by French regulations. Participation in another biomedical research study was not allowed. All patients provided informed written consent and the study received legal authorizations from the Committee for the Protection of Persons and the French Agency for the Security of Health Products.

Patients were randomized (R1) at inclusion (D0) either to rTMS (n = 41) or sham stimulation (n = 37). After completion of the rTMS induction treatment, on day 21 (D21), subjects were evaluated, and the clinical response assessed; efficacy of the clinical response was based on a composite criterion consisting of a ≥ 30% decrease in the visual analogue scale (VAS) for pain from baseline and a Patient Global Impression of Change (PGIC) score >5. Patients who maintained a clinical response during the following three weeks (time between induction and

maintenance sessions) were submitted to a second round of randomization (R2) either to rTMS (n = 9) or sham stimulation (n = 13). The flowchart of the study is presented in Figure 1.

The clinician who realized the evaluations as well as the participant were blind to the treatment (rTMS or sham groups). Only the qualified rTMS technician who delivered the sessions knew which treatment was applied and did not communicate about it with anyone: this prevented any influence of the knowledge in the declaration of the patient and in the evaluation.

Randomization was performed by the rTMS technician responsible for administering the rTMS sessions with a list prepared in advance.

For non-responders, unblinding was realized. If it was sham non-responders, a proposal of rTMS sessions over 3 weeks for integration into the classic therapeutic scheme after 6 months was made. If it was rTMS non-responders, a withdrawal from the study and from the therapeutic scheme was done (continuation of the treatment seen by the referring clinician). Responders to the sham treatment continued the maintenance sessions in the sham group with data analysis as a sham group to assess the maintenance over time of this sham effect only.

rTMS treatment

Induction phase

The treatment included five daily sessions per week for three weeks. A daily session consisted of 20 min of stimulation at a high frequency of 10 Hz (Magstim Rapid^2, Magstim Company Limited, United Kingdom), with 20 trains of 10s stimulation (100 pulses) and an inter-train interval of 50s. This corresponded to 2,000 stimulations per session at 90% of the resting motor threshold (RMT). The cerebral area stimulated was the left primary M1 motor cortex either with the placebo coil (= sham stimulation) or with the “treatment” coil (= rTMS

stimulation). Sham stimulation coil delivered the same electrical stimulation as rTMS stimulation coil, with the same noise, and feeling on the scalp, but there was no induction of magnetic field (MAG&MORE PMD70-pCool-Sham). A neuronavigation process (Visor^{TM} Inomed) allowed real-time monitoring of the specific position of stimulation with reference to medical imaging of a "standard head" obtained by magnetic resonance imaging (MRI) (it included the brain, the scalp, and the skull ; the whole brain volume defined the sources spaces and considered 12 mm of grid spacing) (Asalab software, ANT, Netherlands). Potential secondary effects were recorded.

Maintenance phase

The maintenance phase consisted of a unique rTMS or sham session every 21 days until six months (M6). Potential secondary effects were recorded.

The flowchart of the study (Figure 1)reports the distribution of the participants used for the intent-to-treat analysis.

An exit from the study is proposed in case of epileptic seizure, occurrence of a side effect attributed to rTMS such as migraine or discomfort in the scalp during stimulation but also for participants who no longer meet all the inclusion and exclusion criteria such as the appearance of a preponderant co-morbidity, a pregnancy, a legal protection measure, a hospitalization under constraint, and a non-response at the end of rTMS sessions.

A "lost to follow-up" notation will be mentioned if rTMS sessions are interrupted and the person cannot be contacted again after three missed sessions.

A discontinuation of the sessions at the participant's request can be made. The person is still called in and assessed at the scheduled end of the maintenance sessionsthe exit occurs during the maintenance phase, his/her data can be analyzed in intent to treat.

Upon withdrawal of participant consent, the participant's data was deleted from the data entry file and the file/observation book was destroyed.

Refusal to participate during the course of the study was considered as withdrawal from the study. If the participant does not specify anything about the data collected about him/her, the data were kept for the global analysis, or for a complementary analysis, depending on the moment of withdrawal.

Discontinuation of treatment does not imply discontinuation of the study (statistical analysis intent-to-treat analysis).

Data collection and follow-up

Psychometric evaluations

Subjects were followed up at D21, D42 (± 5 days), and M6 (± 7 days).

Socio-demographic data, the extent of pain, clinical characteristics, and psychometric evaluations were reported at inclusion (D0), which was considered to be baseline.

The pain VAS, fibromyalgia impact questionnaire (FIQ), Beck depression inventory (BDI), clinic global impression (CGI), and symptom severity score (3S) were determined at inclusion (D0). The PGIC score was determined at the end of rTMS induction, as was the pain VAS, to constitute the composite criterion for clinical response.

The FIQ and BDI were completed at D21, D42, and M6 and the CGI and 3S evaluated at the same time.

The VAS for pain allows evaluation of the current severity of pain and was performed on the day of the rTMS session using a scale from 0 (absence of pain) to 10 (intolerable pain).[19] During maintenance phase, patients evaluated their pain during the previous week.

The CGI is a global evaluation that uses three independent item scales. It is easy to use and generalizable to all pathologies or co-morbidities.[20] The scales consist of the severity of illness (0 to 7), the global improvement after treatment (0 to 7), and a composite score on a four-point scale that addresses treatment efficiency and secondary effects.

The FIQ is a brief 10-item, self-administered instrument that measures physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well-being. The French version, validated in 2003, was used.[21] It is more adapted for women and takes 5 min to complete. The 10 items, distributed into various groups, correspond to the previous week, with a maximal global score of 100. The first item includes 10 questions (scored from 0 to 3) related to functional inability. The second tests well-being. The third addresses the consequence of the disease on work status. Items 4 to 10 address the symptoms of depression, anxiety, sleep, pain, stiffness, and fatigue. It is the only specific and sensitive composite test adapted to the pathology of fibromyalgia.

The BDI is a 21-item, self-reported rating inventory that measures the intensity of depression.[22] Each item is comprised of four sentences corresponding to four increasing degrees of intensity relative to a symptom and is scored from 0 to 3. The highest score obtained is the only one selected for the same set. The global score is determined by summing the scores of the 21 items. A score < 10 indicates the absence of depression, from 10 to 18 mild depression, from 19 to 29 moderate depression, and >30 severe depression.

The 3S evaluates four distinct categories from the ACR criteria (2010),[23] scored from 0 to 3 (no symptoms to severe symptoms): fatigue, waking-up tired, cognitive symptoms, and extent of somatic symptom severity. The global score is 12 but composite scores of each category can be used.

The PGIC is a self-reported measure and reflects a patient's beliefs about the efficacy of treatment.[24] The PGIC consists of a seven-point scale depicting a patient's rating of overall

improvement. Patients rate their change as “very much worse”, “much worse”, “minimally worse”, “no change”, “minimally improved”, “much improved”, or “very much improved”. Responses 6 or 7 correspond to a significant improvement of the global status of the subject.

The clinical response, i.e., the efficacy of rTMS, was assessed using a composite criterion consisting of in the VAS for pain from baseline and a PGIC score > 5 not before defined in the literature: the combined assessment of the VAS for pain and the patient’s own evaluation of improvement using the PGIC.

Statistical analysis

Intent-to-treat analysis was performed. Quantitative variables are described as means ± standard deviations. Qualitative variables are described as numbers and/or percentages. Comparisons of the distribution of the quantitative data between groups were performed using Student t tests or Mann Whitney tests, according to the distribution of the variables, and chi squared tests or Fisher exact tests when group size was small. In the preliminary pilot study, 13 out of 18 patients had a 30% decrease in overall VAS at the end of treatment (72%). An efficiency of 80% of maintenance of response at the 6th month compared to D42 is considered in the experimental group for the end of the maintenance sessions versus 20% in the sham group. Such a difference was demonstrated with 12 people per group for an alpha risk of 5% and a beta risk of 20%: that is to say 24 responders to the rTMS treatment. These 24 responders to the initial rTMS treatment correspond to 72% of the patients receiving a first rTMS treatment. Thus, it is necessary to have 35 people in each of the two groups rTMS and sham for the first rTMS treatment, i.e., 70 people with fibromyalgia in total. Considering the 10% of people included and not evaluable, it appears necessary to include 78 people (calculation carried out with the Nquery Advisor® v7.0 software). Results with p-values <

0.05 were considered to be significant. Analyses were performed using SAS® Enterprise Guide 7.1 (SAS Institute Cary, NC).

Results

Inclusion

This comparative randomized study with parallel controlled groups included 78 patients (73 females, 5 males). The characteristics of the studied population at inclusion are presented in Table 1. The mean age was 47.6 ± 8.1 years (range 27 to 64 years). Nearly a half of the patients (53.8%, n = 42) lacked or had a poor level of education and 51.3% had a job (n = 40). They were characterized by mild depression (BDI 13.4 ± 6.4) and the absence of anti-depressant treatment for 75.6% (n = 59). The associated stable comorbidities were mixed anxiety-depressive disorders (41%, n = 32) and major depression (39.7%, n = 31).

The FIQ score was intermediate (56.2 ± 9.7). The VAS score for pain was high (6.9 ± 1.2), combined with a wide range for the pain index (13.3 ± 3.3). The first item of the CGI was high (5.5 ± 0.6) as was the 3S for each item evaluated (fatigue: 2.7 ± 0.5, waking-up tired: 2.5 ± 0.6, cognitive symptoms: 2.2 ± 0.8, and extent of somatic symptom severity: 2.7 ± 0.5). The two randomization groups were similar for these characteristics (Table 1).

Induction phase

The evolution of the population studied during the induction phase of rTMS treatment is presented in Table 2. On D21, the clinical response according to the composite criterion was 35.6% in the sample: 37% of the subjects (n = 27) showed a decrease in the VAS from baseline ≥ 30% and 41.1% had a PGIC score > 5 (n = 30).

Furthermore, this clinical response was significantly higher for the rTMS group (47.4%, n = 18) than in the sham group (22.9%, n = 8) (p = 0.029) (Figure 2). The proportion of subjects with a ≥ 30% reduction in pain, according to the VAS, was greater in the rTMS group (47.4%,

n = 18) than in the sham group (25.7%, n = 9) (p = 0.055), and the proportion of subjects with a PGIC > 5 was 41.1%, with no difference between groups (p = 0.256).

In addition, the FIQ score (Figure 3A) significantly decreased between D0 and D21, especially in the rTMS group (FIQ difference (D21-D0) -10.1 ± 12.4 in the sham group versus -18.5 ± 17 in the rTMS group, p = 0.032). The depression intensity (BDI score) (Figure 3B) and 3S showed a trend towards decreasing between D0 and D21 for both groups. The item related to fatigue in the 3S decreased significantly more in the rTMS than sham group (difference (D21-D0) -0.5 ± 0.9 in the sham group versus -1.1 ± 1.0 in the rTMS group, p = 0.024).

No side effects were observed during treatment. Only 5 of 78 patients suffered from migraine headaches during the induction phase (3 under sham stimulation and 2 under rTMS), but they were non-responders to the treatment and did not participate in the maintenance phase.

At D21, two patients from each group were lost to follow-up and were consequently absent of intent-to-treat analysis.

Maintenance phase

Maintenance of the clinical response at D42

The observed clinical response at D21 was maintained in the rTMS group for 94.4% (n = 17) of the patients on D42. Nine patients were randomized on D42 to rTMS and eight to sham stimulation for the maintenance sessions (Figure 1). In the sham group a lower maintenance although non-significant than in the rTMS group was observed with six patients (75%) maintaining their clinical response on D42 (Figure 2). These patients were automatically assigned to sham stimulation (Figure 1).

On D42, the pain associated with the severity of the illness showed a trend towards decreasing (VAS for pain 3.6 ± 1.3, first CGI item 3.2 ± 0.8) for respondents after the rTMS induction

phase. The global improvement and efficacy index of the treatment were high (second CGI item 1.9 ± 0.6, third CGI item 3 3.7 ± 2).

At the same time, responders after the induction phase showing great improvement (PGIC value = 7) all belonged to the rTMS group (n = 3).

At D42, three patients did not maintain the clinical response observed at D21 (two in the sham stimulation group and one in the rTMS group) (Figure 1).

Maintenance of the clinical response at M6

The evolution of the clinical characteristics of the two randomized groups during the maintenance course of the treatment is presented in Table 3.

At M6, the clinical response was maintained for a large part of the sample (61.9%, n = 13): 14.3% of the patients (n = 3) showed a ≥ 30% decrease in the VAS from baseline and 66.7% (n = 14) had a PGIC score > 5.

In the rTMS group, 5 of 9 subjects (62.5%) maintained their therapeutic response to M6, as did 8 of 13 (61.5%) in the sham group (Figure 2) (p =1.000). The proportion of patients at M6 with a PGIC score > 5 was greater in the rTMS group than in the sham group (75.0%, n = 6 versus 61.5%, n = 8).

The intensity of depression did not differ relative to that at D42 and remained low relative to baseline (BDI difference (M6-D42) 0.3 ± 4.4, p = 0.825) (Figure 3B).

Between D42 and M6, the FIQ (Figure 3A) showed a trend towards increasing in the rTMS group (p = 0.073) (FIQ difference (M6-D42) 4.1 ± 13.9 in the sham group versus 24.2 ± 21.1 in the rTMS group). Although the 3S score was comparable to the values obtained at D42, the "waking-up tired" item showed a significant increase in the rTMS group (difference (M6-D42) 0.2 ± 0.6 in the sham group vs. 0.9 ± 0.6 in the rTMS group, p = 0.041).

At M6, nine patients missed the visit or deadlines (four in the sham stimulation group and five in the rTMS group), and one in the rTMS group was lost to follow-up but were included in the intent-to-treat data analysis.

No other adverse events were reported for any of the participants during the six-month follow-up.

Discussion

This study demonstrates the effectiveness of maintenance sessions of rTMS treatment for six months versus sham stimulation in fibromyalgia patients who were clinical responders to an initial three-week rTMS induction treatment.

Our results confirm the efficiency of rTMS for the treatment of pain in fibromyalgia. After the induction phase, the clinical response (composite criterion: decrease in pain VAS $\geq$ 30% and PGIC > 5) was significantly higher for patients receiving rTMS than for the sham group. The efficacy of the rTMS treatment was confirmed up to the end of the induction phase on D42, as 94.4% of patients who received this treatment maintained an observed clinical response at the end of the induction phase according to the composite criterion. These results are consistent with the conclusions of a meta-analysis in which rTMS showed efficacy for the treatment of pain, as assessed by VAS, in patients suffering from fibromyalgia.[13] The improvement in pain in our study was concomitant with a significant improvement in the quality of life, as well as fatigue, as illustrated by the evolution of the FIQ and 3S score for the fatigue item, respectively, at the end of the induction phase of rTMS treatment. These results are consistent with those reported concerning the potential effectiveness of high frequency rTMS stimulation to the left M1 zone on improving the quality of life of fibromyalgia patients, in parallel with the improvement in pain.[11]

We mainly explored the results of the maintenance phase on the stabilization of the clinical response during the six-month treatment. The clinical response during this phase appeared to be characterized by a greater improvement in pain as evaluated by the PGIC, which was not the case in the first phase, in which pain evaluated by VAS scores improved to a greater extent. The clinical response was greater in the rTMS than sham group based on the previously defined composite criterion, as for the induction phase.

The clinical response was assessed using a composite criterion corresponding to the combined assessment of pain by VAS and PGIC. VAS is widely used and considered to be the gold-standard for the evaluation of pain but is also criticized because it does not address all the components of pain, especially its evolution and associated perceptions. Thus, the PGIC was used in the study and included in the evaluation criterion to account for the patient's own sense of improvement.[25] Our observations suggest that assessment by VAS within the composite criterion is more reliable over a short period of time, whereas assessment by PGIC seems more reliable over the duration of a long-term study, such as ours, reinforcing the fact that these two different assessments appear to be complementary and provide a more reliable and rigorous assessment of improvement. [26] This finding suggests that this type of evaluation of fibromyalgia through the patient's reported outcome differs from the only VAS pain and the two may be representative of different clinical outcomes during the "acute" phase of the treatment, in which pain initially decreases, and the "chronic" phase of the treatment, in which the responding patients may better sense the consequences of the reduction in pain.

The only two patients who did not maintain their clinical response during the rTMS maintenance phase received sham simulation during the induction phase. The response to sham stimulation may indicate that different neurophysiological mechanisms are required during this phase and that they were probably not activated in the same way during rTMS

stimulation. This result is also enforced by the maintenance of clinical response for patients who first received rTMS during the induction phase and then sham stimulation.

Among the few studies on the efficacy of rTMS treatment after a maintenance phase in fibromyalgia, a consistent effect on pain during the maintenance phase was demonstrated on the same parameters as those assessed in our study (pain, quality of life, and depression) over 40 weeks, but after 14 weeks of inductive treatment (2 weeks with rTMS alone and 12 weeks of multi-component therapy combining rTMS with aerobic training, pool exercises, and relaxation).[27] Another study reported a reduction in pain after a 25-week maintenance phase.[16] Pain was assessed using the Brief Pain Inventory and thus the results are difficult to compare to ours. In addition, a higher number of patients were treated, which may have made it possible to show a reduction in pain that we were unable to observe under our conditions.

The significant reduction in fatigue observed in patients who received rTMS treatment relative to those who received sham stimulation during the induction phase was stabilized during the maintenance phase. This effect on fatigue in fibromyalgia has not been observed in the literature when the M1 area was stimulated, but rather when the left DLPC was targeted.[28] Indeed, rTMS has been shown to significantly relieve fatigue, providing a greater opportunity to achieve a clinically significant response in reducing the intensity of pain of fibromyalgia patients.

In addition, the intensity of the depression measured using the BDI also stabilized during the maintenance phase of rTMS treatment, after a non-significant decrease during the induction phase. This suggests that decreasing pain also contributes to decreasing the intensity of depression, as these two parameters appear to have evolved in parallel. Similarly, fatigue appeared to be highly present in patients suffering from depression, leading to concomitant evolution of these three parameters. Indeed, it has already been shown that pain, depression,

and quality of life evolve in the same way when targeting the M1 zone during rTMS treatment.[29]

The clinical response to treatment with rTMS exposed a strong trend of maintenance over six months in the absence of adverse effects and, in parallel, maintenance of the intensity of fatigue and depression.

Other studies have shown an improvement in the quality of life evaluated with the FIQ,[17,30,31] as in our study, during the induction phase but not the maintenance phase, using this questionnaire or, more broadly, another type of Health Survey Questionnaire (SF-36). This difference may explain why the results we obtained during the induction phase were not found during the maintenance phase of rTMS treatment for this characteristic or that of waking up tired. Indeed, only these two parameters did not evolve in favor of the long-term efficacy of rTMS treatment.

Our results confirm the interest of considering a maintenance phase by rTMS after improvement during a first rTMS induction phase. However, our study had several limitations that may reduce the scope of our results. First, the number of patients included in the maintenance phase was not high, probably because our composite criterion for qualifying improvement was relatively strict and rigorous. However, a sufficient number of patients were included in the first phase of rTMS in the study and this sample was sufficient to show significant differences between groups. Second, there is still no consensus on the conditions of rTMS stimulation during the induction phase (number of sessions, interval between sessions, choice of the stimulated area) and alterations of these conditions may help to improve the effectiveness of the induction phase and thus reinforce the effects of the maintenance phase. In addition, the frequency of maintenance sessions is not fixed and, for example, could be increased to two sessions per month.[17] The zone of stimulation could also

be alternated between the left M1 and DLFPC zones or they could be targeted simultaneously to achieve broader clinical effects. The physical benefits, in addition to the emotional benefits of stimulating the M1 zone in fibromyalgia patients, could thus be positively affected with,[28] for example, a better possible positive effect on the patients' quality of life. These experimentation conditions and these physiological effects may also give indications about the neurophysiological mechanisms involved in fibromyalgia, as some studies reported a potential effect through the endogenous opioid system,[32] and/or the activation of the cerebral dopaminergic system.[33-35] The long term effect have been suggested to involve several neurotransmitters systems (notably dopamine or serotonin or gamma-aminobutyric acid (GABA)) which have a known action on pain,[36] accompanied by the activation of synaptic plasticity.[10,37]

Conclusion

rTMS can be considered as an effective therapeutic strategy in fibromyalgia and maintenance sessions for those who clinically respond to treatment are indicated. Indeed, rTMS, in addition to its true and significant effect during the three-week inductive phase, showed a strong trend of sustained efficacy for the treatment of pain, as well as the intensity of depression and fatigue. However, further studies are still needed to better evaluate the stimulation conditions and explore the effectiveness of various frequencies of the administration of rTMS maintenance sessions.

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Figure 1. Flowchart of the study (applied to the intent-to-treat analysis)

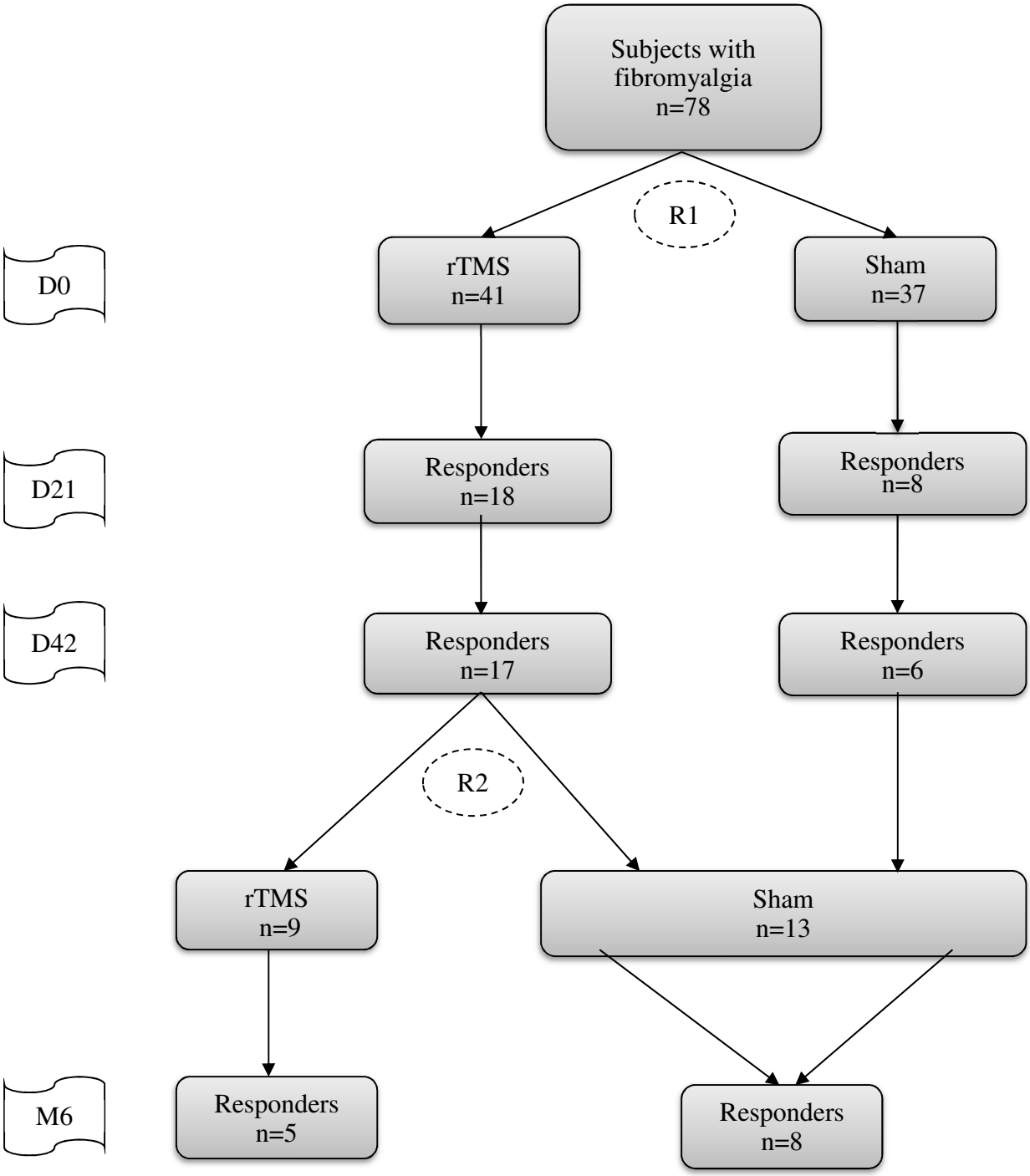


Table 1. Data for the whole population at inclusion, and for the rTMS treatment group (rTMS) and the sham stimulation group (sham) after randomization for treatment

	Global N=78	Sham N=37	rTMS N=41	p
Sex Ratio	0.068 (5/73)	0.088 (3/34)	0.051 (2/39)	0.664 (F)
Age (years) (mean ± SD)	47.6±8.1	47.2±8.5	47.9±7.7	0.923 (MW)
Level of education (n (%))				0.429 (F)
Without qualification	7 (9.0)	4 (10.8)	3 (7.3)	
Certificate of professional competence	35 (44.9)	18 (48.6)	17 (41.5)	
Bachelor	24 (30.8)	12 (32.4)	12 (29.3)	
College	12 (15.4)	3 (8.1)	9 (22)	
Job (n (%))	40 (51.3)	15 (40.5)	25 (61)	0.112 (F)
With comorbidity (n (%)) :				
Mixed anxiety-depressive disorder	32 (41)	14 (37.8)	18 (43.9)	0.649 (F)
Depressive disorder	31 (39.7)	13 (35.1)	18 (43.9)	0.492 (F)
Therapeutic drugs use (n (%)) :				
Antidepressants	19 (24.4)	11 (29.7)	8 (19.5)	1.000 (F)
Analgesic treatment	34 (43.6)	14 (37.8)	20 (48.8)	0.466 (F)
BDI (mean ± SD)	13.4±6.4	13.8±5.7	13±7.1	0.452 (MW)
Pain evaluation (mean ± SD) :				
VAS	6.9±1.2	6.8±1.1	7±1.3	0.481 (MW)
Extension score	13.3±3.3	13±2.9	13.6±3.6	0.245 (MW)
CGI first item (mean ± SD)	5.5±0.6	5.4±0.6	5.5±0.6	1.000 (MW)
3S (mean ± SD)				
Fatigue	2.7±0.5	2.7±0.6	2.7±0.5	0.947 (MW)
Waking-up tired	2.5±0.6	2.6±0.6	2.5±0.7	0.807 (MW)
Cognitive symptoms	2.2±0.8	2.2±0.8	2.1±0.8	0.539 (MW)
Extent of somatic symptoms severity	2.7±0.5	2.8±0.5	2.7±0.5	0.461 (MW)

SD : Standard deviation
BDI : Beck Depression Inventory
VAS : Visual Analogue Scale
CGI : Clinic Global Impression
3S : Symptom Severity Score
F : Fisher exact test
MW : Mann-Whitney's test

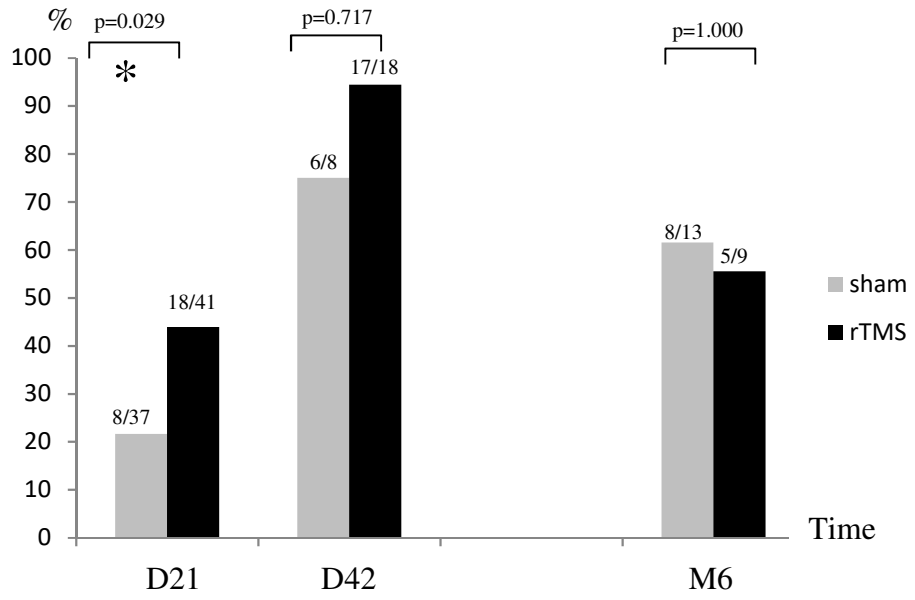
		Global N R1=78	Sham N R1=37	rTMS N R1=41	p
BDI (mean ± SD)	D21-D0	-4.2±5.7	-3.9±5.3	-4.4±6	0.965 (MW)
Evolution of VAS pain (%) with a minimum of 30% decrease	D21/D0	37	25.7	47.4	0.055 (X^2)
PGIC >5 (%)	D21/D0	41.1	34.3	47.4	0.256 (X^2)
Clinical response (%)	D21/D0	35.6	22.9	47.4	0.029 (X^2)
FIQ (mean ± SD)	D21-D0	-14.5±15.5	-10.1±12.4	-18.5±17.0	0.032 (MW)
3S (mean ± SD)					
Fatigue	D21-D0	-0.8±1.0	-0.5±0.9	-1.1±1.0	0.024 (MW)
Waking-up tired	D21-D0	-0.8±1.1	-0.7±0.9	-0.9±1.2	0.391 (MW)
Cognitive symptoms	D21-D0	-0.7±0.8	-0.6±0.7	-0.7±0.8	0.829 (MW)
Extent of somatic symptoms severity	D21-D0	-0.7±0.8	-0.7±0.8	-0.8±0.8	0.488 (MW)

Table 2. Psychometric evaluations in the sham and the rTMS group at inclusion (D0) and at the end of the treatment induction phase (D21)

Figure 2. Percentages of maintenance of the clinical response in the sham and the rTMS groups (above the histogram: number of responders at the observed time / total number at the previous time) at 21 days treatment (end of the

SD : Standard deviation
BDI : Beck Depression Inventory
VAS : Visual Analogue Scale
PGIC : Patient Global Impression Change
FIQ : Fibromyalgia Impact Questionnaire
3S : Symptom Severity Score
MW : Mann-Whitney's test
X^2 : Chi squared test

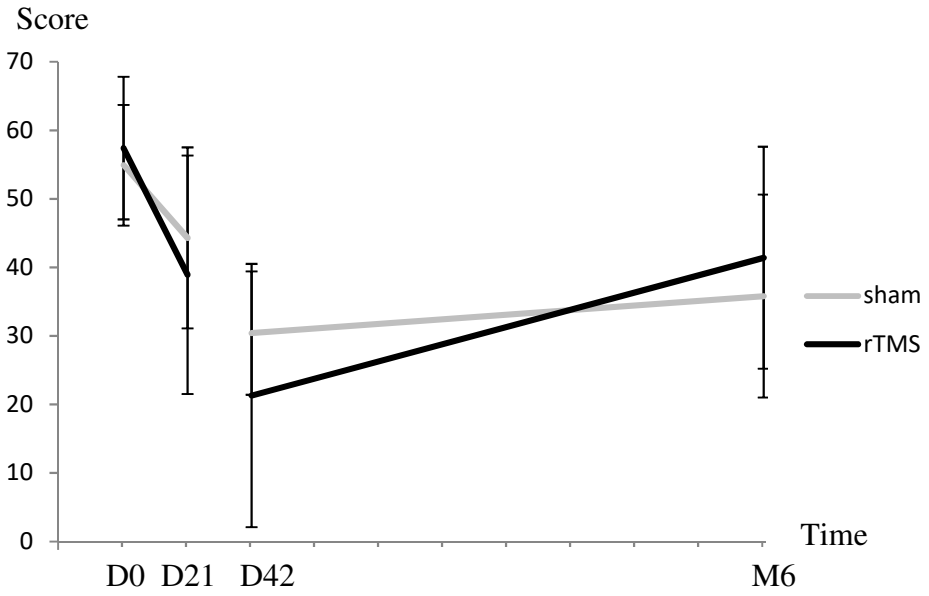
induction phase, D21), at 42 days (beginning of maintenance phase, D42) and 6 months (end of maintenance phase, M6) in relation to the previous follow-up.



p = significance for the difference between the two groups

Figure 3. Evolution of FIQ scores (A) and BDI scores (B) during the induction phase (day 0 to day 21) and the maintenance phase (days 42 to M6)

A



B

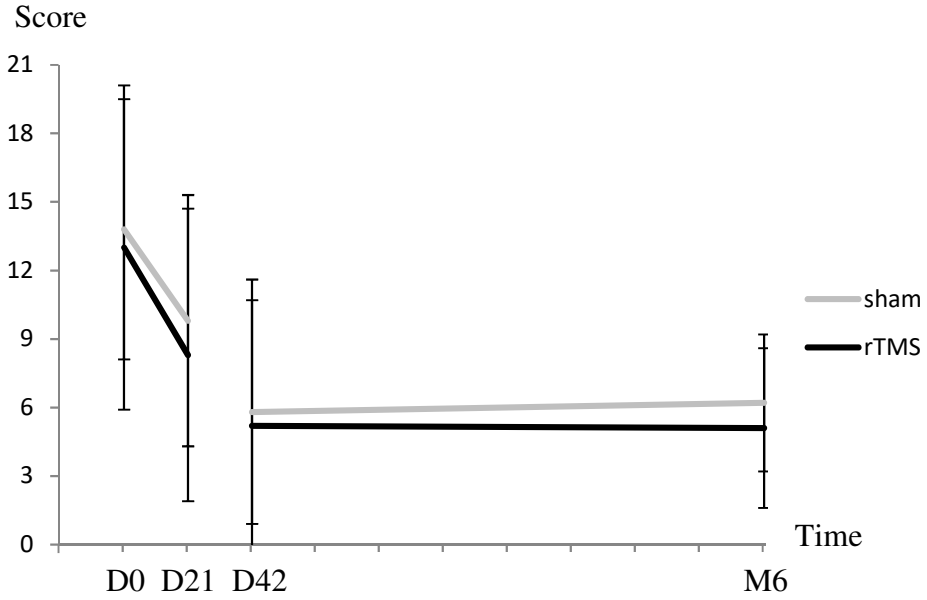


Table 3. Difference or ratio of psychometric evaluations score in the sham and the rTMS group between the beginning (D42) and the end (M6) of the maintenance phase

		Global N R2=22	Sham N R2=13	rTMS N R2=9	p
BDI (mean ± SD)	M6 - D42	0.3±4.4	0.1±5.1	0.6±3.5	0.825 (T)
Evolution of VAS pain (%) with a minimum of 30% decrease	M6 / D42	14.3	15.4	12.5	1.000 (F)
PGIC >5 (%)	M6 / D42	66.7	61.5	75	0.656 (F)
Clinical response (%)	M6 / D42	61.9	61.5	62.5	1.000 (F)
FIQ (mean ± SD)	M6 - D42	10.8±18.5	4.1±13.9	24.2±21.1	0.073 (T)
3S (mean ± SD)					
Fatigue	M6 - D42	0.6±0.9	0.5±0.9	0.6±0.9	0.874 (MW)
Waking-up tired	M6 - D42	0.5±0.7	0.2±0.6	0.9±0.6	0.041 (MW)
Cognitive symptoms	M6 - D42	0.3±0.9	0.5±1.1	0.3±0.5	0.554 (MW)
Extent of somatic symptoms severity	M6 - D42	0.4±0.8	0.4±0.8	0.3±1.0	0.726 (MW)

SD : Standard deviation
BDI : Beck Depression Inventory
VAS : Visual Analogue Scale
PGIC : Patient Global Impression Change
FIQ : Fibromyalgia Impact Questionnaire
3S : Symptom Severity Score
T : Student t Test
F : Fisher exact test
MW : Mann-Whitney's test