



HAL
open science

Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex

Hasan Hodaj, Jean-François Payen, Enkelejda Hodaj, Anne Dumolard, Caroline Maindet, Jean-Luc Cracowski, Chantal Delon-Martin, Jean-Pascal Lefaucheur

► To cite this version:

Hasan Hodaj, Jean-François Payen, Enkelejda Hodaj, Anne Dumolard, Caroline Maindet, et al.. Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex. *Clinical Neurophysiology*, 2020, 131, pp.1423 - 1432. 10.1016/j.clinph.2020.03.022 . hal-03490923

HAL Id: hal-03490923

<https://hal.science/hal-03490923>

Submitted on 22 Aug 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Long-term treatment of chronic orofacial, pudendal, and central neuropathic limb pain with repetitive transcranial magnetic stimulation of the motor cortex

Hasan Hodaj^{a,c*}, Jean-François Payen^{a,c}, Enkelejda Hodaj^b, Anne Dumolard^a, Caroline Maindet^a, Jean-Luc Cracowski^b, Chantal Delon-Martin^c, Jean-Pascal Lefaucheur^d

^a*Centre de la Douleur, Pôle Anesthésie Réanimation, CHU Grenoble Alpes, F-38000, Grenoble, France.*

^b*Centre d'Investigation Clinique, CHU Grenoble Alpes, F-38000, Grenoble, France.*

^c*Grenoble Alpes University, Grenoble Institut Neurosciences, GIN, F-38000 Grenoble, France*

^d*EA 4391, Service de Physiologie – Explorations Fonctionnelles, Hôpital Henri Mondor, Université Paris Est Créteil, Créteil, France*

*** Correspondence:**

Dr. H. Hodaj

Pôle Anesthésie Réanimation, CHU Grenoble Alpes, BP217, 38043 Grenoble, France

Tel.: +33 476765213

Fax: +33 476765951

E-mail: HHodaj@chu-grenoble.fr

Abstract

Objective: To assess the long-term analgesic effects of high-frequency repetitive transcranial magnetic stimulation (rTMS) of the motor cortex in patients with chronic pain syndrome.

Methods: The study included 57 patients (orofacial pain, n=26, pudendal neuralgia, n=18, and neuropathic limb pain, n=13) with an "induction phase" of 12 daily rTMS sessions for 3 weeks, followed by a "maintenance phase" of bi-monthly sessions for the next five months.

Results: All pain measures significantly decreased from baseline to the end of the induction phase. Analgesic response, defined as pain intensity decrease $\geq 30\%$ compared to baseline, was observed in 39 patients (68%), who could be differentiated from non-responders from the 7th rTMS session. At the end of the maintenance phase (D180), 27 patients (47%) were still responders. Anxio-depressive symptoms and quality of life also improved. The analgesic response at the end of the induction phase was associated with lower pain score at baseline, and the response at the end of the maintenance phase was associated with lower anxio-depressive score at baseline.

Conclusion: The analgesic efficacy of motor cortex rTMS can be maintained in the long term in various chronic pain conditions. Patients with high pain level and severe anxio-depressive symptoms may have a less favorable profile to respond to the procedure.

Significance: The overall impact of rTMS treatment on daily life requires a multidimensional evaluation that goes beyond the analgesic effect that can be achieved.

Keywords: chronic pain; facial pain; long-term; neuropathic pain; predictive factor; pudendal neuralgia; rTMS treatment.

Highlights

- Analgesic effects of motor cortex rTMS were essentially evaluated in the short term.
- 57 patients with chronic pain underwent 3-week rTMS therapy followed by 5-month maintenance in responders.
- Most patients had a good outcome, associated with less severe pain intensity and anxio-depressive symptoms at baseline.

1. Introduction

Repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) is increasingly used to treat various types of chronic refractory pain. Meta-analyses of the literature argued for the efficacy of rTMS of M1 at high frequency (≥ 5 Hz), especially in neuropathic pain (Jin et al., 2015; Cruccu et al., 2016; Baptista et al., 2019). The main neuromodulatory property of rTMS relies on its prolonged effects lasting beyond the stimulation period, but rTMS sessions need to be repeated to achieve sufficient pain relief consistent with therapeutic use in clinical practice (Lefaucheur et al., 2004a). However, most published studies are short-term and only 4 studies reported the results of motor cortex rTMS therapy performed for at least 6 months. These studies included 80 patients with central neuropathic pain of various origins (Pommier et al., 2016; Quesada et al., 2018), 55 patients with facial pain (Hodaj et al., 2015), 20 patients with fibromyalgia (Mhalla et al., 2011), and 18 patients with central poststroke pain (Kobayashi et al., 2015) who received verum rTMS. Overall, motor cortex rTMS was found to be beneficial in these patients with refractory chronic pain syndrome.

The objective of this work was to reappraise the long-term efficacy of rTMS therapy in clinical settings for three types of chronic pain syndrome, i.e. orofacial pain, pudendal neuralgia, and neuropathic limb pain. We studied the analgesic effects of rTMS during an initial induction phase and the maintenance of its efficacy in responders by means of bi-monthly sessions for 6 months. In addition, using multidimensional assessment tools, we looked for predictive factors that could influence the therapeutic response to rTMS in the short and long term.

2. Methods

2.1. Patients

This observational study included 57 consecutive patients (21 men and 36 women) treated by rTMS between March 2014 and April 2018 in the Pain Center of Grenoble University Hospital, France. The patients were classified into three groups according to the type of pain: orofacial pain (26 patients), pudendal neuralgia (18 patients), and central neuropathic limb pain (13 patients). All patients had chronic pain refractory to conventional therapies for more than a year. At the time of inclusion, current analgesic medication included anticonvulsants (68% of patients), antidepressants (77%), and opioids (58%).

Orofacial pain was related to a definite lesion of the trigeminal nerve or nucleus in 8 patients, secondary to a neurosurgical procedure (Gasser's ganglion thermocoagulation (n=2),

microvascular decompression (n=2), neurinoma surgery (n=1)) or an infectious or inflammatory process (herpes zoster (n=2), multiple sclerosis (n=1)). In 12 patients, orofacial pain was of undetermined cause, including 6 patients with persistent idiopathic facial pain (PIFP), in a context of dental intervention (n=5) and facial trauma (n=1), and 6 patients with burning mouth syndrome (BMS), according to the most recent International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society (IHS), 2018). In patients with orofacial pain, the analgesic response was further analyzed into two subgroups: facial pain and BMS, given the specificities of this syndrome (Ariyawardana et al., 2019).

Pudendal neuralgia was diagnosed in 18 patients according to validated clinical criteria (Labat et al., 2008), confirmed by positive anesthetic pudendal nerve block in 14 patients. In 7 of these patients, pain was persistent despite previous surgical decompression of the pudendal nerve.

Central limb neuropathic pain was secondary to a definite lesion of the brain in 5 patients (brain surgery (n=2), trauma (n=1), stroke (n=1), multiple sclerosis (n=1)) or the spinal cord in 5 patients (spinal stroke (n=4), syringomyelia (n=1)). In two patients, upper limb pain was secondary to brachial plexus avulsion. The last patient had lower limb pain secondary to amputation (phantom limb pain).

2.2. rTMS procedure

Stimulation was performed using a MagPro stimulator (MagVenture (distr. Mag2Health), Farum, Denmark) using either a flat B65 coil (MagVenture) in patients with orofacial, upper limb or hemibody pain or an angled B70 figure-of-eight coil (MagVenture) in patients with lower limb or pudendal pain.

First, the resting motor threshold (rMT) was determined as the minimum stimulus intensity that produced a motor evoked potential (MEP) of about 50 μ V in at least 5 of 10 trials (Rossini et al., 2015). For this measurement, the MEP monitor amplifier of the MagPro stimulator was used. **When a B65 coil was applied, the MEPs were recorded in all cases on the abductor pollicis brevis (APB) muscle with the coil oriented perpendicular to the central sulcus. When a B70 coil was applied, the MEPs were recorded on the tibialis anterior (TA) muscle with the coil aligned to the interhemispheric fissure. However, if no MEPs could be obtained on the TA muscle, then they were recorded on the APB muscle, still with the B70 coil.**

For therapeutic stimulation, the motor cortical representation of the painful region was targeted with the coil held in posteroanterior orientation. In patients with orofacial pain, upper limb or hemibody pain, a flat B65 figure-of-eight coil was used and the site of cortical stimulation was determined using a TMS Navigator system, integrating individual brain magnetic resonance imaging (MRI) data (Localite, Sankt Augustin, Germany). Targeting was performed according to the previously described functional anatomy of the precentral gyrus (Ayache et al., 2016). For hemibody pain, the hand area was targeted.

In patients with pudendal neuralgia or lower limb pain, an angled B70 figure-of-eight coil was used (Hodaj et al., 2018) and the site of cortical stimulation was fixed at the vertex (Cz in the International 10–20 system). Compared to flat figure-of-eight coils, the B70 coil is more powerful, leading to lower the resting motor threshold (rMT) by 10 to 33% (Kammer et al., 2001). In addition, the B70 stimulates deeper and larger, able to bilaterally activate the motor cortex corresponding to pelvic-perineal and lower limb muscles when placed at the vertex due to its angle of 150°, without requiring an image-guided navigation system for targeting.

Stimulation was performed at 10 Hz with an intensity set at 80% of the rMT. Each rTMS session consisted of 40 trains of 5-sec duration with intertrain interval of 25 sec for a total of 2,000 pulses in 20 minutes. This protocol is in conformity with the expert recommendations for safety (Rossi et al., 2009; Lefaucheur et al., 2011). In all cases, the rTMS treatment protocol was initiated after the agreement of a multidisciplinary team meeting and the informed consent of the patient.

2.3. Clinical evaluation

The rTMS protocol consisted of an induction phase of one session per day for five days during two consecutive weeks (weeks 1 and 2), then 2 sessions in the next week (week 3) for a total of 12 sessions. Average daily permanent pain and paroxysmal pain intensities were scored on a 0-10 visual numerical scale (VNS) and the number of painful paroxysms was recorded before rTMS therapy (D0), and the day after each session up to the end of the induction phase (D21).

Then, in patients with analgesic response, defined as a decrease in the VNS score of permanent pain $\geq 30\%$ compared to baseline, a maintenance therapy was undertaken, consisting of one rTMS session in week 4 and then bi-monthly sessions for the next five months, for a total of 11 sessions. During the maintenance phase, pain scores were recorded on a VNS the day after each session and the rTMS therapy was stopped if pain score reduction became $<30\%$ compared to baseline.

In patients who completed the study, a multidimensional assessment was performed in addition to pain scores at the end of the maintenance phase (D180), including the Neuropathic Pain Symptom Inventory (NPSI) total score and subscores (Bouhassira et al., 2004) assessing the symptomatic pain profile (used in this study for both neuropathic and non-neuropathic pain, although "non-validated" in the latter indication), the Hospital Anxiety and Depression (HAD) scale (Zigmond and Snaith, 1983) assessing anxiety and depression, and the Physical and Mental Component Summaries (PCS, MCS) of the Short Form (36) Health Survey (SF-36) (Ware and Sherbourne, 1992) assessing the quality of life, scored with the RAND 36-Item Health Survey 1.0 (Hays et al., 1993). Finally, patients self-assessed the global effect of rTMS therapy at D180 on the Clinical Global Impression (CGI) scale (Busner and Targum, 2007).

2.4. Statistical analysis

Data are presented as mean \pm standard deviation (SD). The significance level of p value was set at 0.05. Statistical analyses were performed using the Stata 13.0 software (StataCorp, College Station, Texas, USA). Parametric or non-parametric tests were used depending on whether the data had a normal distribution or not, as shown by the Shapiro–Wilk test.

First, analyses on baseline data were performed according to the origin of pain: orofacial pain, limb neuropathic pain, and pudendal neuralgia. Kruskal-Wallis or one-way ANOVA test was used for quantitative variables (age, pain syndrome duration, VNS scores of permanent and paroxysmal pain, daily number of pain paroxysms, and NPSI, HAD, and SF-36 PCS and MCS scores) and Fisher's exact test for categorical variables (gender, medications).

Second, the effect of rTMS on pain scores (VNS scores of permanent and paroxysmal pain and daily number of pain paroxysms) was studied in the entire series of patients using repeated-measures ANOVA with Bonferroni's post-hoc test for comparisons to baseline. In addition, the scores measured at the end of the induction phase (D21) were compared to baseline in the entire series of patients and each of the three subgroups defined by the origin of pain using the Wilcoxon matched-pairs test.

According to the percentage of reduction of the VNS score of permanent pain, patients were classified into four groups (Hodaj et al., 2015): very good response (for pain reduction \geq 70% on VNS score), good response (pain reduction from 50% to 69%), moderate response (pain reduction from 30% to 49%), and poor or no response (pain reduction $<$ 30%). Overall, responders were defined by a decrease in this pain score \geq 30% compared to baseline. The groups of responders and non-responders were compared using unpaired t test or Mann-Whitney-Wilcoxon rank-sum test (quantitative variables) or Fisher's exact test (categorical

variables) regarding the following variables: age, gender, pain syndrome duration, pain origin, location (face, perineum, upper or lower limb) or side (bihemispheric, right- or left-sided) of the stimulated cortical target, rMT, current analgesic medication (anticonvulsants or not, and antidepressants or not, and opioids or not), the various clinical scores measured at baseline (VNS, NPSI, HAD, and SF-36 scores) and the VNS scores at the end of the induction phase. From the VNS scores of permanent pain recorded after each of session of the induction phase, repeated-measures ANOVA was performed, which was based on an interaction model between responders/non-responders and time. The objective of this analysis was to determine whether the time course of pain scores differed between responders and non-responders, and if so from which time point.

Third, in the patients who completed the study, excluding the patients who relapsed during the maintenance phase, the effect of rTMS on pain scores (VNS scores of permanent and paroxysmal pain and daily number of pain paroxysms) was studied using repeated-measures ANOVA. In addition, the pain scores (VNS scores of permanent and paroxysmal pain and daily number of pain paroxysms) measured at the end of the maintenance phase (D180) were compared to those measured at the end of the induction phase (D21) and to baseline using the Wilcoxon matched-pairs test in the entire series of patients and in each of the three subgroups defined by the origin of pain. The other clinical scores (NPSI, HAD, and SF-36 scores) measured at D180 were compared to baseline also using the Wilcoxon matched-pairs test in the entire series of patients.

The groups of responders and relapsing patients were compared using unpaired t test or Mann-Whitney-Wilcoxon rank-sum test (quantitative variables) or Fisher's exact test (categorical variables) regarding the same demographic and clinical variables as between responders and non-responders at the end of the induction phase. Finally, the association between patients' CGI and status in terms of responders or non-responders was studied using the Fisher's exact test.

3. Results

3.1. Differences in baseline characteristics between groups according to pain origin

Demographic and baseline data are presented in Table 1. The mean (\pm SD) age of the patients was 62.2 ± 15.0 years and did not differ between groups, as well as mean pain syndrome duration. Conversely, there were gender differences between groups: a majority of women was found in the cases of pudendal neuralgia and orofacial pain (72-73%), but not in the case of neuropathic limb pain (31%). In terms of treatment, the groups differed on opioid intake,

which was less frequent in orofacial pain (42%) than in pudendal neuralgia and neuropathic limb pain (67-77%). In terms of clinical scores, the groups differed on physical functioning (SF36), which was lower in neuropathic limb pain (35.6 ± 30.2) than in orofacial pain (66.8 ± 27.5) and pudendal neuralgia (61.6 ± 17.7). No other significant differences between groups according to pain origin were found.

3.2. Analgesic effect at the end of the induction phase

The rTMS protocol was well tolerated by all patients, without any report of serious adverse events. All pain measures significantly decreased over time during the induction phase ($p < 0.0001$, repeated-measures ANOVA) (Figure 1). Compared to baseline, all scores significantly improved at D21 ($p < 0.0001$, Wilcoxon matched-pairs or paired t-test): (i) the VNS score of permanent pain (from 6.0 ± 1.9 to 4.1 ± 2.9); (ii) the number of painful paroxysms per day (from 8.3 ± 7.8 to 3.3 ± 4.5); (iii) the VNS score of painful paroxysms (from 8.4 ± 1.4 to 3.9 ± 2.7). Regarding the type of pain, the VNS score of permanent pain significantly decreased from baseline to the end of the induction phase for orofacial pain (from 6.0 ± 2.0 to 3.7 ± 2.9 , $p < 0.0001$, paired t-test), limb neuropathic pain (from 7.0 ± 1.6 to 5.3 ± 2.8 , $p = 0.013$), and pudendal neuralgia (from 5.4 ± 1.9 to 3.7 ± 3.0 , $p = 0.013$).

According to the percentage of reduction of the VNS score of permanent pain, analgesic response was considered very good in 12 patients (21%), good in 8 patients (14%), moderate in 19 patients (33%), and poor in 18 patients (32%) (Table 2a). Thus, a total of 39 responders (68%) vs. 18 non-responders (32%) was found. Obviously, the VNS score of permanent pain at D21 was extremely different between these two groups (2.9 ± 2.3 vs. 7.6 ± 1.5 , $p < 0.0001$, unpaired t-test), as well as the VNS score of painful paroxysms (4.0 ± 2.7 vs. 8.7 ± 1.3 , $p = 0.008$, Mann-Whitney-Wilcoxon test), but not the number of painful paroxysms per day (3.4 ± 4.5 vs. 4.5 ± 2.2 , $p = 0.217$).

No difference in terms of analgesic response at the end of the induction phase was found according to age, sex, symptom duration, location or side of the stimulated cortical target, rMT, current analgesic medication, or paroxysmal pain features, and NPSI (total score and 4/5 subscores), HAD, or SF-36 scores at baseline (Table 3). Conversely, there was an influence of the VNS score of permanent pain at baseline, which was significantly lower in responders than in non-responders (5.5 ± 1.9 vs. 7.0 ± 1.4 , $p = 0.005$) as well as the NPSI subscore concerning the "burning spontaneous pain" (4.3 ± 3.2 vs. 7.5 ± 1.8 , $p = 0.002$) (Table 3). Regarding the type of pain, a lower rate of responders was observed in the patients with BMS

(33%) than in patients with other facial pain (80%), limb neuropathic pain (69%), or pudendal neuralgia (67%) (Table 2a).

Finally, repeated-measures ANOVA showed a significant interaction between patient's status (responders vs. non-responders) and time. The post-hoc analyses showed a significant decrease of permanent pain intensity over time only in responder group ($p < 0.0001$). In this group, the analgesic response was found to be significant from after the 7th session according to our interaction model between responders/non-responders and time. In addition, this response met the 'Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials' (IMMPACT) criteria of "clinically meaningful" treatment (Dworkin et al., 2008) with a mean decrease $\geq 30\%$ and reduction ≥ 2 points on the VNS score of permanent pain compared to baseline (Figure 2).

3.3. Analgesic effect at the end of the maintenance phase

Among the 39 patients who were responders at the end of the induction phase, 27 patients (47% of the initial series of patients) continued to be responders and to benefit from rTMS therapy until the end of the maintenance phase (D180). In 10 patients, rTMS was stopped because of reoccurrence of significant pain, which was defined as permanent pain score reduction $< 30\%$ compared to baseline. Withdrawal occurred before the end of the 2nd month for 4 patients, 4th month for 4 patients, and 5th or 6th month for two patients. On the other hand, 2 patients were lost to follow-up.

In the 27 final responders, repeated-measures ANOVA showed non-significant variation of pain measures over time during the maintenance phase (Figure 3). However, compared to the end of the induction phase, the VNS score of permanent pain tended to further decrease at the end of the maintenance phase (from 2.9 ± 2.3 to 2.4 ± 2.0 , $p = 0.059$, Wilcoxon matched-pairs test), as well as the VNS score of painful paroxysms (from 3.8 ± 2.8 to 2.5 ± 2.7 , $p = 0.044$), but not the number of painful paroxysms per day (from 2.9 ± 4.1 to 2.0 ± 3.3 , $p = 0.463$). Compared to baseline, all scores were significantly improved at D180 ($p < 0.001$, Wilcoxon matched-pairs test): (i) the VNS score of permanent pain (from 5.7 ± 2.0 to 2.4 ± 2.0); (ii) the number of painful paroxysms per day (from 8.8 ± 1.3 to 2.5 ± 2.7); (iii) the VNS score of painful paroxysms (from 8.4 ± 7.2 to 2.0 ± 3.3) (Figure 4a).

The change in the VNS score of permanent pain from the end of the induction phase (D21) to that of the maintenance phase (D180) showed a significant decrease only for patients with orofacial pain (from 2.6 ± 2.0 to 1.9 ± 1.8 , $p = 0.041$), but not for neuropathic limb pain (3.7 ± 2.8 vs. 3.5 ± 1.9 , $p = 0.833$) and pudendal neuralgia (2.9 ± 3.0 vs. 2.7 ± 2.3 , $p = 0.750$).

Concerning the multidimensional assessment performed at D0 and D180 in the responders who completed the study, a significant improvement was observed for the NPSI total score, the HAD total score and the PCS and MCS scores of the SF-36 (Figure 4b). Regarding the NPSI subscores, a significant improvement was observed for burning spontaneous pain (4.7 ± 3.2 vs. 2.5 ± 2.3 , $p=0.004$), paroxysmal pain (4.3 ± 2.7 vs. 2.1 ± 2.2 , $p=0.002$), and evoked pain (4.1 ± 2.8 vs. 2.6 ± 1.9 , $p=0.014$), but not for pressing spontaneous pain (2.9 ± 3.0 vs. 2.1 ± 2.4 , $p=0.14$) and paresthesia/dysesthesia subscores (2.7 ± 2.7 vs. 2.6 ± 2.2 , $p=0.818$).

According to the percentage of reduction of the VNS score of permanent pain in the 27 responder patients, analgesic response was considered very good in 10 patients (37%), good in 8 patients (30%), moderate in 9 patients (33%) (Table 2b). According to the CGI scale, 8 patients (30%) were found to very much improved, 15 patients (55%) to be much improved, and 4 patients (15%) to be minimally improved. The patients' impression was significantly associated with the patients' response regarding the percentage of reduction of the VNS score of permanent pain ($p=0.001$, Fisher's exact test).

No difference between responders and relapsing patients during the maintenance phase was found according to age, sex, symptom duration, pain origin, location or side of the stimulated cortical target, rMT, current analgesic medication, pain, NPSI total score and subscores, and SF-36 scores at baseline (Table 4). Conversely, the HAD total score at baseline was lower in responders than in patients who relapsed (14.9 ± 8.1 vs. 21.2 ± 7.8 , $p=0.049$) (Table 4). Regarding the influence of remaining pain symptoms at the end of the induction phase (D21), no difference was found between responders and relapsing patients for the VNS score of permanent pain (2.9 ± 2.3 vs. 2.7 ± 2.0 , $p=0.818$, t-test), the number of painful paroxysms per day (2.9 ± 4.1 vs. 4.5 ± 6.0 , $p=0.437$, Mann-Whitney-Wilcoxon test), and the VNS score of painful paroxysms (3.8 ± 2.8 vs. 3.9 ± 2.4 , $p=0.892$).

Overall, among the 27 responders, there were 13 patients with facial pain (orofacial pain excluding BMS): 65% of this group at baseline and 81% of this group at the beginning of the maintenance phase; 6 patients with neuropathic limb pain: 46% of this group at baseline and 67% of this group at the beginning of the maintenance phase; and 6 patients with pudendal neuralgia: 33% of this group at baseline and 50% of this group at the beginning of the maintenance phase. Although non-significant, facial pain may be a more favorable condition to rTMS therapy, especially in the long term.

Finally, analgesic medication has been able to be reduced or discontinued in 20 of the 27 responders (74%) at the end of the maintenance phase, but in none of the non-responders. Among these patients, 16 had anticonvulsants, which were reduced in all cases (100%), 15

had antidepressants, which were reduced in 10 patients (67%), and 9 had opioids, which were reduced in 4 patients (44%). Among the 12 patients on drug combinations, at least two drugs were reduced in 10 patients (83%).

4. Discussion

This study showed a significant pain relief at the end of the induction phase in the entire series of patients, including 68% of responders, defined by a decrease in pain VNS score $\geq 30\%$ compared to baseline. Such a change meets the IMMPACT criteria of “clinically meaningful” treatment (Dworkin et al., 2008). The rate of responders in this study is slightly above the range of values usually reported, i.e. 46 to 62% (Lefaucheur et al., 2014). In our study, only one factor was associated with the clinical response at short-term (D21), i.e. the intensity of pain at baseline, which was lower in responders than in non-responders. The fact that patients who did not respond to rTMS was, on average, more painful than the responders should be considered in the indication of rTMS therapy, which might be more cautious in patients with the highest levels of pain.

Conversely, we did not find that pain duration, origin, and location were relevant prognosis factors. Previous studies reported that pain location at the face was a relevant predictor of good outcome (Lefaucheur et al., 2004b, 2006; Hodaj et al., 2015). In the present study, orofacial pain other than BMS may be the most favorable condition to rTMS therapy, but BMS was clearly the least favorable. This could reflect the fact that patients with BMS had higher permanent pain intensity and anxiety score at baseline compared to the other groups (data not shown). Since BMS only represented a small subgroup in our series, further studies should be performed to confirm this observation.

One original finding of this study lies in the long-term treatment of pudendal neuralgia by motor cortex rTMS and the use of the B70 coil, more adapted than the conventional flat figure-of-eight coils to stimulate the bi-hemispheric cortical representation of the pelvis. Only a few studies describe the use of rTMS in chronic pelvic pain: in patients with endometriosis (Pinot-Monange et al., 2019), bladder pain syndrome (Cervigni et al., 2018; Nizard et al., 2018) or as a predictive test of the analgesic efficacy of cortical implantation (Nizard et al., 2015). In our series, the therapeutic response in pudendal neuralgia at the end of the induction phase was good (67% of responders), but during the maintenance phase, pain relapse tended to be more frequent than in case of orofacial pain (50% vs. 20% of relapses in these two groups, respectively). It is worth mentioning that although not significant, HAD anxiety score at baseline also tended to be higher in patients with pudendal neuralgia than orofacial pain

(mean HAD anxiety score: 10.3 vs. 6.7) (Table 1), reinforcing our hypothesis on the implication of anxiety in the recurrence of pain during the maintenance phase.

Concerning the site of cortical stimulation, we targeted the anatomical representation to the motor cortex of the pain zone. Conversely, in most studies, the hand cortical area contralateral to pain side is targeted regardless of pain location. Indeed, the somatotopic effect of rTMS-induced analgesia has not been demonstrated (Lefaucheur et al., 2006; Ayache et al., 2016; André-Obadia et al., 2018). In this study, face or upper limb motor targeting was based on individual MRI-guided navigation, while less focal stimulation using the B70 coil was delivered over perineal or lower limb motor cortical representation. No significant difference between these two approaches was found in terms of outcome. Thus, according to the few previous studies that addressed this issue (Hodaj et al., 2015; Ayache et al., 2016), our results cannot help in determining whether MRI-guided rTMS of M1 is more efficient or not to relieve pain than a non-navigated procedure.

Another original finding of this study concerns the comparison of the evolution of pain scores on VNS over time between patients who were classified as responders or non-responders at the end of the induction phase. This analysis showed that the difference became significant only from the 7th session. Thus, the level of pain relief after 7 sessions could predict the effect of rTMS in the longer term. However, depending on the various limitations of the study, it is premature to make it a reliable indicator to determine whether a patient suffering from pain is "responder" or "non-responder" to rTMS therapy and eligible for maintenance sessions after only 7 sessions. This deserves further specific study. Another group recently showed that the analgesic efficacy of motor cortex rTMS reached significance after just 4 sessions in central neuropathic pain, but with consecutive sessions, each separated by 3-4 weeks (Quesada et al., 2018). In any case, a few rTMS sessions are probably required to determine whether a patient is responder or not to the procedure and no prolonged protocols of "induction" are needed for this objective.

In the maintenance phase, regarding the 27 responders who completed the study, pain scores were stabilized or tended to further decrease between D21 and D180, including 23 patients who declared to be much or very much improved. Compared to baseline, all other clinical scores (NPSI, HAD, and SF-36) were improved at D180 in the patients who completed the study. However, the rTMS therapy was stopped in 10 patients who showed pain reoccurrence. The only variable differentiating these 10 patients from the 27 final responders was the HAD total score at baseline, which was higher in patients who relapsed.

As mentioned in the introduction, only 4 studies previously reported the long-term efficacy of rTMS over at least a 6-month period (Mhalla et al., 2011; Hodaj et al., 2015; Kobayashi et al., 2015; Pommier et al., 2016; Quesada et al., 2018). In the present study, 47% of the patients who initiated rTMS therapy were still responders with a clinically meaningful improvement at 6 months, including a significant improvement in pain perception, anxiety-depression, and quality of life. This result observed on multidimensional assessment well correlates with patients' impression of global improvement showing 23 of the 27 responders who felt much or very much improved. Thus, it appears important to evaluate the effect of rTMS in chronic pain patients in terms of daily functioning and quality of life and not only on pain scores.

In addition, during the maintenance phase, rTMS treatment made it possible to reduce or stop analgesic drug consumption in 74% of responders. Given the classes of the drugs used (anticonvulsants, antidepressants, and opioids) that are known to carry many side effects, reducing the daily dose might provide clinical benefit in daily life beyond the impact on economic aspects and cost savings. Reduction of side effects in patients who discontinued analgesics has not been specifically evaluated in this study, but it would be worth investigating these aspects in future studies.

Our study also confirms that repeating rTMS sessions for several weeks or months might be able to maintain or enhance rTMS-induced analgesia (Lefaucheur, 2008). However, in the present series of 57 patients with various chronic pain syndromes, the percentage of responders dropped from 68% at the end of the induction phase to 47% (-21%) at the end of the maintenance phase, but this drop was smaller in the subgroup of 20 patients with facial pain (excluding BMS), from 80% to 65% of responders at 6 months (-15%). In our previous study of 55 patients with facial pain (Hodaj et al., 2015), this reduction was twice as important, from 73% to 40% of responders at 6 months (-33%). The fact that the maintenance phase consisted of bi-monthly sessions in the present study vs. monthly sessions in our previous study may explain these differential results.

Another original finding of our study lies in the investigation of factors that can influence the long-term therapeutic outcome. We found that relapsed patients during the maintenance phase had more severe anxio-depressive symptoms at baseline than patients with consistent rTMS efficacy over time. This finding may prove useful in clinical practice. It can be assumed that psychological support and appropriate treatment of anxio-depressive symptoms may reduce the number of relapses in the long term.

Finally, we have to acknowledge some study limitations. First, the absence of control group cannot rule out a placebo effect. However, it is difficult to consider long-term sham-controlled

study in patients with refractory pain, according to the benefit already demonstrated of rTMS in clinical practice. Second, it is an observational study over 4 years with heterogeneity of pain site and origin. An empirical choice of periodicity of maintenance sessions should also be noted, which was based primarily on the few long-term studies published in this domain.

5. Conclusion

Our study confirms the cumulative analgesic efficacy of high-frequency rTMS of M1 by the repetition of sessions in the treatment of various chronic refractory pain syndromes. The advantage of rTMS lies in its safety and good tolerance. In responders, rTMS can reduce drug treatments thus avoiding side effects of medication. On the other hand, this technique suffers from various constraints, such as the cost of the equipment (especially regarding a system coupled with neuronavigation), the requirement for a specific training, and an incompressible medical or technician time because of the need to repeat sessions. Medico-economic studies will be essential to determine the role of rTMS in the therapeutic armamentarium and the interest of its use for the treatment of refractory pain in clinical practice. In this regard, studies with long-term maintenance therapy and assessment are needed.

On the other hand, rTMS studies require multidimensional assessment, since chronic pain has frequent and possibly serious effects on mood and quality of life. The improvement of these associated symptoms can contribute to the overall satisfaction of the patient even in the absence of reduction of pain intensity (Hodaj et al., 2018). In addition, with regard to the proper analgesic effect, it seems important to study paroxysmal pain or provoked pain if it exists, and not just the ongoing average permanent pain.

Pain is a complex perception and the goal is to obtain overall improvement of the patient beyond analgesic effects. Multidimensional evaluation, the search for predictive factors of therapeutic response, protocol harmonization and personalization are avenues to explore and integrate into our strategy. Although various double-blind controlled studies already demonstrated the efficacy of rTMS, the protocols were rather heterogeneous with short-term assessment, ultimately lacking relevance for current practice. Naturalistic observational studies are valuable to present long-term results and to define the place of the technique in the daily treatment of chronic pain syndromes. However, multicenter controlled studies are still needed to confirm the validity of this approach.

Conflict of interest statement

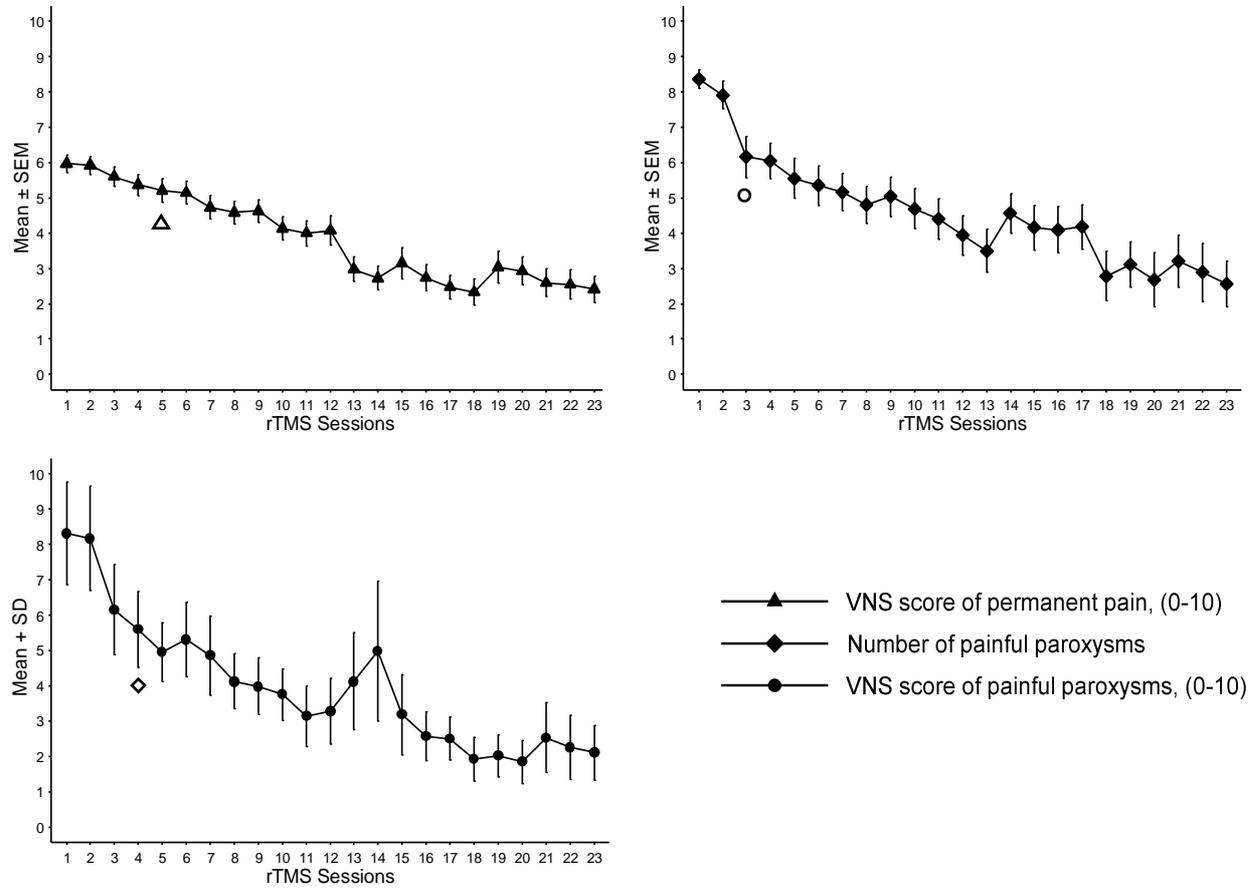
The authors have no relationship or financial interest related to this work that may have influenced or biased this article.

References

- Andre-Obadia N, Magnin M, Simon E, Garcia-Larrea L. Somatotopic effects of rTMS in neuropathic pain? A comparison between stimulation over hand and face motor areas. *Eur J Pain* 2018;22:707-15.
- Ariyawardana A, Chmieliauskaite M, Farag AM, Albuquerque R, Forssell H, Nasri-Heir C, et al. World Workshop on Oral Medicine VII: Burning mouth syndrome: A systematic review of disease definitions and diagnostic criteria utilized in randomized clinical trials. *Oral Dis* 2019;25 Suppl 1:141-56.
- Ayache SS, Ahdab R, Chalah MA, Farhat WH, Mylius V, Goujon C, et al. Analgesic effects of navigated motor cortex rTMS in patients with chronic neuropathic pain. *Eur J Pain* 2016;20:1413-22.
- Baptista AF, Fernandes AMBL, Sá KN, Okano AH, Brunoni AR, Lara-Solares A, et al. Latin American and Caribbean consensus on noninvasive central nervous system neuromodulation for chronic pain management (LAC(2)-NIN-CP). *Pain Rep* 2019;4:e692.
- Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, et al. Development and validation of the Neuropathic Pain Symptom Inventory. *Pain* 2004;108:248-57.
- Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)* 2007;4:28-37.
- Cervigni M, Onesti E, Ceccanti M, Gori MC, Tartaglia G, Campagna G, et al. Repetitive transcranial magnetic stimulation for chronic neuropathic pain in patients with bladder pain syndrome/interstitial cystitis. *Neurourol Urodyn* 2018;37:2678-87.
- Cruccu G, Garcia-Larrea L, Hansson P, Keindl M, Lefaucheur JP, Paulus W, et al. EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur J Neurol* 2016;23:1489-99.
- Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008;9:105-21.
- Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. *Health Econ* 1993;2:217-27.
- Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38:1-211.
- Hodaj H, Alibeu JP, Payen JF, Lefaucheur JP. Treatment of Chronic Facial Pain Including Cluster Headache by Repetitive Transcranial Magnetic Stimulation of the Motor Cortex With Maintenance Sessions: A Naturalistic Study. *Brain Stimul* 2015;8:801-7.
- Hodaj H, Payen JF, Lefaucheur JP. Therapeutic impact of motor cortex rTMS in patients with chronic neuropathic pain even in the absence of an analgesic response. A case report. *Neurophysiol Clin* 2018;48:303-8.
- Jin Y, Xing G, Li G, Wang A, Feng S, Tang Q, et al. High Frequency Repetitive Transcranial Magnetic Stimulation Therapy For Chronic Neuropathic Pain: A Meta-analysis. *Pain Physician* 2015;18:E1029-46.
- Kammer T, Beck S, Thielscher A, Laubis-Herrmann U, Topka H. Motor thresholds in humans: a transcranial magnetic stimulation study comparing different pulse waveforms, current directions and stimulator types. *Clin Neurophysiol* 2001;112:250-8.
- Kobayashi M, Fujimaki T, Mihara B, Ohira T. Repetitive transcranial magnetic stimulation once a week induces sustainable long-term relief of central poststroke pain. *Neuromodulation* 2015;18:249-54.
- Labat JJ, Riant T, Robert R, Amarenco G, Lefaucheur JP, Rigaud J. Diagnostic criteria for pudendal neuralgia by pudendal nerve entrapment (Nantes criteria). *Neurourol Urodyn*

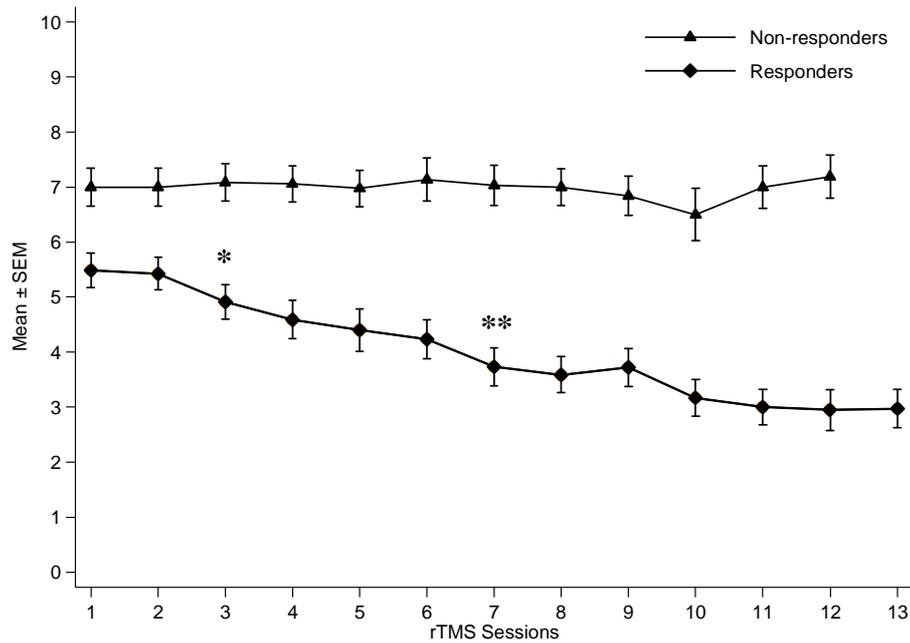
- 2008;27:306-10.
- Lefaucheur JP. Use of repetitive transcranial magnetic stimulation in pain relief. *Expert Rev Neurother* 2008;8:799-9.
- Lefaucheur JP, Drouot X, Ménard-Lefaucheur I, Nguyen JP. Neuropathic pain controlled for more than a year by monthly sessions of repetitive transcranial magnetic stimulation of the motor cortex. *Neurophysiol Clin* 2004a;34:91-5.
- Lefaucheur JP, Drouot X, Menard-Lefaucheur I, Zerah F, Bendib B, Cesaro P, et al. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. *J Neurol Neurosurg Psychiatry* 2004b;75:612-6.
- Lefaucheur JP, Hatem S, Nineb A, Ménard-Lefaucheur I, Wendling S, Keravel Y, et al. Somatotopic organization of the analgesic effects of motor cortex rTMS in neuropathic pain. *Neurology* 2006;67:1998-2004.
- Lefaucheur JP, André-Obadia N, Poulet E, Devanne H, Haffen E, Londero A, et al. Recommandations françaises sur l'utilisation de la stimulation magnétique transcrânienne répétitive (rTMS): règles de sécurité et indications thérapeutiques *Neurophysiol Clin* 2011;41:221-95.
- Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol* 2014;125:2150-2206.
- Mhalla A, Baudic S, Ciampi de Andrade D, Gautron M, Perrot S, Teixeira MJ, et al. Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. *Pain* 2011;152:1478-85.
- Nizard J, Levesque A, Denis N, de Chauvigny E, Lepeintre A, Raoul S, et al. Interest of repetitive transcranial magnetic stimulation of the motor cortex in the management of refractory cancer pain in palliative care: Two case reports. *Palliat Med* 2015;29:564-8.
- Nizard J, Esnault J, Bouche B, Moreno A, Lefaucheur JP, Nguyen JP. Long-Term Relief of Painful Bladder Syndrome by High-Intensity, Low-Frequency Repetitive Transcranial Magnetic Stimulation of the Right and Left Dorsolateral Prefrontal Cortices. *Front Neurosci* 2018;12:925.
- Pinot-Monange A, Moisset X, Chauvet P, Gremeau AS, Comptour A, Canis M, et al. Repetitive Transcranial Magnetic Stimulation Therapy (rTMS) for Endometriosis Patients with Refractory Pelvic Chronic Pain: A Pilot Study. *J Clin Med* 2019;8:508.
- Pommier B, Créac'h C, Beauvieux V, Nuti C, Vassal F, Peyron R. Robot guided neuronavigated rTMS as an alternative therapy for central (neuropathic) pain: clinical experience and long-term follow-up. *Eur J Pain* 2016;20:907-16.
- Quesada C, Pommier B, Fauchon C, Bradley C, Créac'h C, Vassal F, et al. Robot-Guided Neuronavigated Repetitive Transcranial Magnetic Stimulation (rTMS) in Central Neuropathic Pain. *Arch Phys Med Rehabil* 2018;99:2203-15.
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009;120:2008-39.
- Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 2015;126:1071-107.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- Zigmond AS, Snaith RT. The hospital anxiety depression scale. *Acta Psycho Scand* 1983;67:361-70.

Figure 1. Time course of the effect of rTMS therapy on the various pain scores during the induction phase in the entire series of patients.



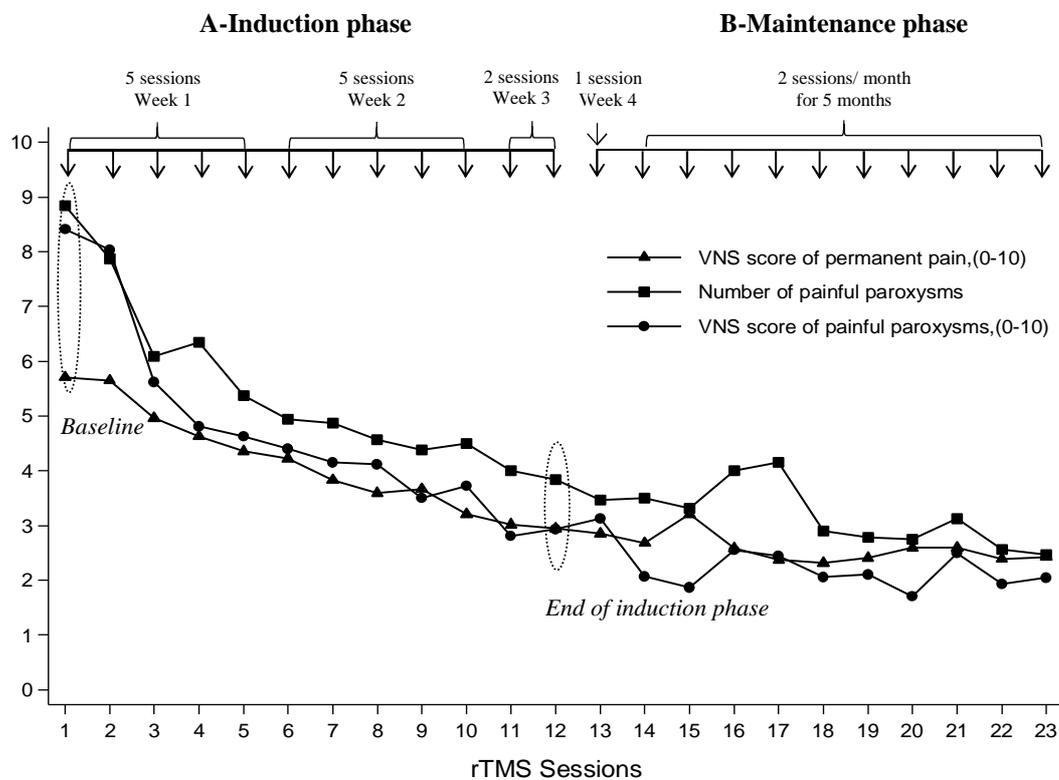
Mean values (with standard error bars), $P < 0.005$, Bonferroni's post-hoc test compared to baseline: Δ from the 5th session for the VNS score of permanent pain, \circ from the 3rd session for the VNS score of painful paroxysms, \diamond from the 4th session for the daily number of painful paroxysms.

Figure 2. Differential time course of the effect of rTMS therapy on permanent pain score during the induction phase according to the patient's status (responders vs. non-responders)



Mean values (with standard error bars), * $p < 0.0001$ from 3rd session, ** the analgesic response became clinically significant in responders from the 7th session with a decrease $\geq 30\%$ and a reduction of at least 2 points on VNS score of permanent pain [24].

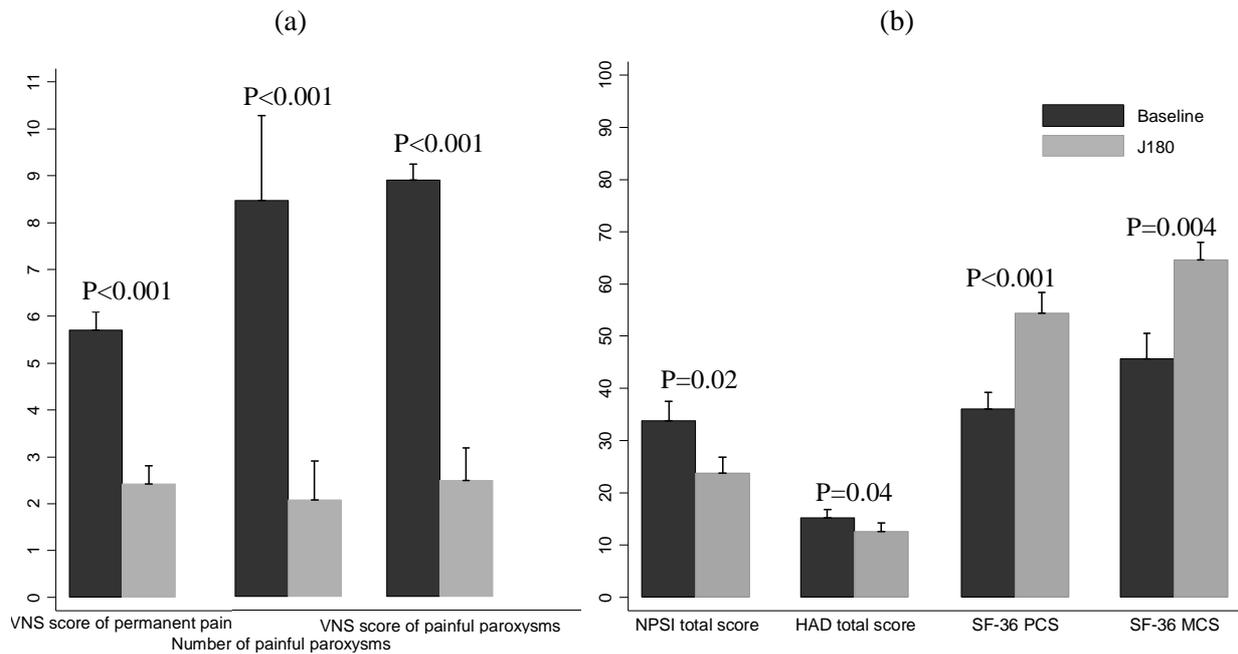
Figure 3. Time course of the effect of rTMS therapy on the various pain scores during the rTMS sessions in the 27 responders



3A- All pain measures significantly decreased over time during induction phase ($p < 0.0001$, repeated measures ANOVA).

3B- Pain scores assessed after the last session of the induction phase (session 12) and after the 11 sessions of the maintenance phase. P values of repeated-measures ANOVA are: $p = 0.163$ for VNS score of permanent pain, $p = 0.494$ for Number of painful paroxysms, $p = 0.132$ for VNS score of painful paroxysms.

Figure 4. Assessment of pain scores (4a) and multidimensional assessment (4b) at D0 and D180 in the 27 responders who completed the study (mean values with standard error bars)



VNS: 0-10 visual numerical scale, NPSI: Neuropathic Pain Symptom Inventory (0-100), HAD: Hospital Anxiety (0-21) and Depression scale (0-21), SF-36 PCS and MCS: Physical and Mental Component Summaries of the Short Form (36) Health Survey (0-100).

Table 1. Demographic and baseline data according to pain origin and in the entire series of patients

	Orofacial pain (n=26)	Neuropathic limb pain (n=13)	Pudendal neuralgia (n=18)	P	All patients (n=57)
Age, years	65.8 ± 14.0	57.7 ± 15.1	60.4 ± 15.9	0.237 [¥]	62.2 ± 15.0
Sex, women n (%)	19 (73.1)	4 (30.8)	13 (72.2)	0.028 [†]	36 (63.2)
Pain syndrome duration, months	87.5 ± 72.1	116.8 ± 166.5	94 ± 64.7	0.716 [§]	96.2 ± 98.3
Prior interventional gesture, Yes n (%)	9 (34.6)	2 (15.4)	15 (83.3)	0.000 [†]	26 (45.6)
Anticonvulsants, Yes n (%)	20 (76.9)	8 (61.5)	11 (61.1)	0.468 [†]	39 (68.4)
Antidepressants, Yes n (%)	23 (88.5)	10 (76.9)	11 (61.1)	0.112 [†]	44 (77.2)
Opioids, Yes n (%)	11 (42.3)	10 (76.9)	12 (66.7)	0.009 [†]	33 (57.9)
Permanent pain, VNS score (0-10)	6.0 ± 2.0	6.6 ± 2.0	5.4 ± 1.7	0.270 [¥]	6.0 ± 1.9
Painful paroxysms, number of patients	13	4	12		29
Painful paroxysms, number per day	7.3 ± 4.9	19.6 ± 15.7	5.7 ± 2.8	0.311 [§]	8.3 ± 7.9
Painful paroxysms, VNS score (0-10)	8.6 ± 1.4	8.6 ± 0.5	8.0 ± 1.6	0.448 [§]	8.4 ± 1.4
NPSI – Total score (/100)	32.9 ± 18.2	39.7 ± 16.8	42.4 ± 23.7	0.373 [¥]	36.5 ± 19.3
NPSI – Burning spontaneous pain (/10)	5.3 ± 3.3	6.0 ± 3.1	4.7 ± 3.4	0.692 [¥]	5.3 ± 3.2
NPSI – Pressing spontaneous pain (/10)	2.6 ± 3.1	4.1 ± 2.8	4.7 ± 2.7	0.119 [¥]	3.4 ± 3.1
NPSI – Paroxysmal pain (/10)	3.6 ± 2.8	3.7 ± 3.1	4.5 ± 3.6	0.718 [¥]	3.9 ± 3.0
NPSI – Evoked pain (/10)	3.9 ± 2.5	3.9 ± 3.7	4.8 ± 3.3	0.709 [¥]	4.1 ± 2.9
NPSI – Paresthesia/dysesthesia (/10)	2.5 ± 2.7	3.1 ± 3.3	4.7 ± 4.0	0.199 [¥]	3.1 ± 3.2
HAD – Total score (/42)	15.2 ± 8.8	18.1 ± 10.3	18.7 ± 5.5	0.344 [¥]	17.0 ± 8.2
HAD – Anxiety (/21)	7.9 ± 4.8	8.7 ± 5.1	10.3 ± 3.2	0.205 [¥]	8.9 ± 4.5
HAD – Depression (/21)	7.3 ± 4.9	9.4 ± 6.0	8.3 ± 3.5	0.464 [¥]	8.0 ± 4.7
SF-36 – Physical component score (/100)	41.1 ± 17.4	29.6 ± 18.9	34.8 ± 5.4	0.057 [§]	37.3 ± 15.8
SF-36 – Mental component score (/100)	45.7 ± 23.1	45.7 ± 24.4	40.4 ± 24.1	0.853 [§]	44.3 ± 23.2
SF-36 – Physical functioning (/100)	66.8 ± 27.5	35.6 ± 30.2	61.6 ± 17.7	0.039 [§]	59.9 ± 27.7
SF-36 – Role physical (/100)	24.0 ± 31.8	15.6 ± 35.2	12.5 ± 19.9	0.548 [§]	19.4 ± 29.6
SF-36 – Bodily pain (/100)	23.8 ± 23.1	16.5 ± 16.2	16.3 ± 10.9	0.765 [§]	20.5 ± 19.4
SF-36 – General health (/100)	49.7 ± 7.5	50.5 ± 9.8	48.6 ± 7.2	0.751 [§]	49.5 ± 7.7
SF-36 – Vitality (/100)	34.8 ± 19.1	31.9 ± 25.2	32.8 ± 24.7	0.821 [§]	33.7 ± 21.3
SF-36 – Social functioning (/100)	54.0 ± 26.7	51.6 ± 27.9	49.0 ± 34.3	0.976 [§]	52.2 ± 28.5
SF-36 – Role emotional (/100)	38.7 ± 42.7	45.8 ± 46.9	30.3 ± 37.9	0.820 [§]	37.9 ± 41.7
SF-36 – Mental health (/100)	55.2 ± 23.4	53.5 ± 20.2	51.8 ± 25.4	0.946 [§]	54.0 ± 22.9

NPSI: Neuropathic Pain Symptom Inventory, HAD: Hospital Anxiety and Depression scale, SF-36: Short Form (36) Health Survey. Quantitative variables are presented as mean±SD. ¥ one-way ANOVA; §: Kruskal-Wallis test; †: Fisher's exact test

Table 2. Response rate according to the origin of pain:**a) At the end of the induction phase**

	Responders			Non-responders
	Very good response	Good response	Moderate response	
Orofacial pain (n = 26)	6	7	5	8
<i>Facial pain (n = 20)</i>	6	6	4	4
<i>Burning mouth syndrome (n = 6)</i>	0	1	1	4
Neuropathic limb pain (n = 13)	2	1	6	4
Pudendal neuralgia (n = 18)	4	0	8	6
Entire series of patients (n = 57)	12	8	19	18

b) At the end of the maintenance phase

	Responders			Relapsing patients	Lost to follow-up
	Very good response	Good response	Moderate response		
Orofacial pain (n = 18)	8	3	4	2	1
<i>Facial pain (n = 16)</i>	8	2	3	2	1
<i>Burning mouth syndrome (n = 2)</i>	0	1	1	0	0
Neuropathic limb pain (n = 9)	1	2	3	3	0
Pudendal neuralgia (n = 12)	1	3	2	5	1
Entire series of responders at the end of induction phase (n = 37)	10	8	9	10	2

Very good response: pain reduction $\geq 70\%$; good response: pain reduction from 50% to 69%; moderate response: pain reduction from 30% to 49%; poor or no response: pain reduction $< 30\%$.

Table 3. Demographic and baseline data according to rTMS outcome at the end of the induction phase

	Responders (n=39)	Non-responders (n=18)	P
Age, years	61.4 ± 15.6	64.1 ± 13.8	0.540 [¥]
Sex, women n (%)	23 (59.0)	13 (72.2)	0.389 [†]
Pain syndrome duration, months	101.4 ± 111.1	85 ± 63.8	0.823 [§]
Pain origin, n (%)			0.981 [†]
Orofacial pain	18 (69.2)	8 (30.8)	
Neuropathic limb pain	9 (69.2)	4 (30.8)	
Pudendal neuralgia	12 (66.7)	6 (33.3)	
Motor cortex target, n (%)			
Face area	18 (46.1)	8 (44.4)	0.835 [†]
Hand area	5 (12.8)	1 (5.6)	
Leg area	4 (10.3)	3 (16.7)	
Perineal area	12 (30.8)	6 (33.3)	
Stimulation side, n (%)			
Bi-hemispherical	14 (35.9)	7 (38.9)	0.973 [†]
Right hemisphere	14 (35.9)	6 (33.3)	
Left hemisphere	11 (28.2)	5 (27.8)	
rMT (%)	51.0 ± 9.8	48.3 ± 7.6	0.307 [¥]
Anticonvulsants, Yes n (%)	29 (74.4)	10 (55.6)	0.156 [†]
Antidepressants, Yes n (%)	28 (71.8)	16 (88.9)	0.191 [†]
Opioids, Yes n (%)	24 (61.5)	9 (50.0)	0.412 [†]
Permanent pain, VNS score (0-10)	5.5 ± 1.9	7.0 ± 1.4	0.005 [¥]
Painful paroxysms, number of patients	25	4	
Painful paroxysms, number per day	8.9 ± 8.3	4.4 ± 2.2	0.427 [§]
Painful paroxysms, VNS score (0-10)	8.4 ± 1.5	8.1 ± 0.7	0.676 [§]
NPSI – Total score (/100)	35.1 ± 19.0	39.7 ± 20.5	0.484 [¥]
NPSI – Burning spontaneous pain (/10)	4.3 ± 3.2	7.5 ± 1.8	0.002 [¥]
NPSI – Pressing spontaneous pain (/10)	3.3 ± 2.9	3.7 ± 3.4	0.680 [¥]
NPSI – Paroxysmal pain (/10)	4.1 ± 2.8	3.2 ± 3.5	0.345 [¥]
NPSI – Evoked pain (/10)	4.2 ± 2.8	3.8 ± 3.3	0.672 [¥]
NPSI – Paresthesia/dysesthesia (/10)	2.9 ± 3.1	3.5 ± 3.4	0.587 [¥]
HAD – Total score (/42)	16.7 ± 8.5	17.3 ± 7.9	0.799 [¥]
HAD – Anxiety (/21)	8.8 ± 4.5	9.1 ± 4.5	0.785 [¥]
HAD – Depression (/21)	8.0 ± 5.0	8.2 ± 4.4	0.852 [¥]
SF-36 – Physical component score (/100)	37.1 ± 14.6	37.8 ± 18.9	0.797 [§]
SF-36 – Mental component score (/100)	45.8 ± 24.9	40.9 ± 19.2	0.455 [§]

NPSI: Neuropathic Pain Symptom Inventory, HAD: Hospital Anxiety and Depression scale, SF-36: Short Form (36) Health Survey. Quantitative variables are presented as mean±SD. ¥ unpaired t-test, § Mann-Whitney-Wilcoxon rank-sum test, † Fisher's exact test

Table 4. Demographic and baseline data according to rTMS outcome at the end of the maintenance phase

	Responders (n=27)	Relapsing patients (n=10)	P
Age, years	59.2 ± 12.8	68.3 ± 18.5	0.100 [¥]
Sex, women n (%)	19 (70.4)	4 (40.0)	0.132 [†]
Pain syndrome duration, months	106.4 ± 127.8	90 ± 65.3	0.631 [§]
Pain origin, n (%)			
Orofacial pain	15 (88.2)	2 (11.8)	0.134 [†]
Neuropathic limb pain	6 (66.7)	3 (33.3)	
Pudendal neuralgia	6 (54.6)	5 (45.4)	
Motor cortex target, n (%)			
Face area	15 (55.6)	2 (20.0)	0.168 [†]
Hand area	3 (11.1)	2 (20.0)	
Leg area	3 (11.1)	1 (10.0)	
Perineal area	6 (22.2)	5 (50.0)	
Stimulation side, n (%)			
Bi-hemispherical	8 (29.6)	5 (50.0)	0.583 [†]
Right hemisphere	11 (40.7)	3 (30.0)	
Left hemisphere	8 (29.6)	2 (20.0)	
rMT (%)	50.3 ± 9.1	53.8 ± 12.2	0.355 [¥]
Prior interventional gesture, Yes n (%)	11 (40.7)	5 (50.0)	0.716 [†]
Anticonvulsants, Yes n (%)	8 (80.0)	19 (70.4)	0.694 [†]
Antidepressants, Yes n (%)	20 (74.1)	7 (70.0)	0.999 [†]
Opioids, Yes n (%)	16 (59.3)	6 (60.0)	0.999 [†]
Permanent pain, VNS score (0-10)	2.9 ± 2.3	2.7 ± 2.0	0.918 [¥]
Painful paroxysms, number of patients	16	7	
Painful paroxysms, number per day	2.9 ± 4.1	4.5 ± 6.0	0.437 [§]
Painful paroxysms, VNS score (0-10)	3.8 ± 2.8	3.9 ± 2.4	0.892 [§]
NPSI – Total score (/100)	33.7 ± 17.8	32.7 ± 17.2	0.800 [¥]
NPSI – Burning spontaneous pain (/10)	4.7 ± 3.2	2.5 ± 3.2	0.156 [¥]
NPSI – Pressing spontaneous pain (/10)	2.9 ± 3.0	3.7 ± 2.5	0.557 [¥]
NPSI – Paroxysmal pain (/10)	4.3 ± 2.7	3.1 ± 2.7	0.332 [¥]
NPSI – Evoked pain (/10)	4.1 ± 3.0	3.6 ± 2.1	0.718 [¥]
NPSI – Paresthesia/dysesthesia (/10)	2.7 ± 2.7	2.9 ± 3.6	0.868 [¥]
HAD – Total score (/42)	14.9 ± 8.1	21.2 ± 7.8	0.049 [¥]
HAD – Anxiety (/21)	7.8 ± 4.2	10.8 ± 4.1	0.077 [¥]
HAD – Depression (/21)	7.1 ± 5.0	10.4 ± 4.2	0.078 [¥]
SF-36 – Physical component score (/100)	36.0 ± 15.9	41.9 ± 10.3	0.439 [§]
SF-36 – Mental component score (/100)	45.7 ± 23.8	49.8 ± 28.1	0.737 [§]

NPSI: Neuropathic Pain Symptom Inventory, HAD: Hospital Anxiety and Depression scale, SF-36: Short Form (36) Health Survey. Quantitative variables are presented as mean±SD. ¥ unpaired t-test, § Mann-Whitney-Wilcoxon rank-sum test, † Fisher's exact test