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Robot-guided neuronavigated rTMS as an alternative therapy for central (neuropathic) pain: Clinical experience and long-term follow-up

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Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) appears as a useful tool to alleviate neuropathic pain but only few data are available for the long-term benefit of this treatment.
Methods: Here we report the effects of rTMS sessions, considered as a possible therapy for pain relief after a failure of different medications in patients with central (neuropathic) pain. We review here the prospectively collected data of the first forty patients treated as follow: 20 Hz stimulation delivered over the contralateral primary motor cortex (M1), each 3–4 weeks.
Results: A total of 440 rTMS sessions was collected (mean sessions number: 11, range: 1–37, follow-up 312 days on average, maximum 2.8 years). After four sessions, nine patients (22.5%) discontinued rTMS because of a lack of efficiency (<10% pain-relief). The other 31 patients (77.5%) had a cumulative effect across sessions leading to a mean pain relief of 41% for a duration of 15.6 days. A correlation was observed between pain relief in the first session and long-term pain relief ($R = 0.649$. $p = 5.6*10^{-6}$). Both intensity and duration of pain relief were significantly better for patients with persistent laser evoked potentials (LEPs, $p = 0.049$ and 0.0018). We did not observe any adverse-effects.
Conclusion: These results suggest that repeated sessions of 20 Hz rTMS over M1 are interesting in clinical practice for the treatment of selected patients with central pain. Both the cumulative effects across the first sessions and the long duration of pain-relief should impact further randomized trials that are warranted to conclude formally on rTMS efficiency in central pain.

1. Introduction

Neuropathic pain is a chronic and disabling pain condition which incidence involves up to 7–8% of the general population (Hall et al., 2006; Torrance et al., 2006; Bouhassira et al., 2008; Dieleman et al., 2008). Neuropathic pain includes central pain (Schwartzman et al., 2001; Nicholson, 2004) which concerns up to 10–30% of spinal cord injuries (Schwartzman et al., 2001; Nicholson, 2004) and 1.5–8% of strokes (Andersen et al., 1995; Demasles et al., 2008; Klit et al., 2009). Medications are disappointing with only 30–40% of the patients describing more than

What's already known about this topic?
- rTMS appears as a useful tool to alleviate neuropathic chronic pain but few data are available on the long-term treatment of Neuropathic pain

What does this study add?
- Based on the clinical experience of long-term treatment, rTMS over primary motor cortex could be a possible therapy for pain relief in patients with neuropathic pain, after a failure of medications.

50% pain-relief (Finnerup et al., 2005; Attal et al., 2006; Dworkin et al., 2007). In these cases, non-invasive therapies such as repetitive transcranial magnetic stimulation (rTMS) over the motor cortex have been proposed (Lefaucheur et al., 2001a; Rollnik et al., 2002; Hirayama et al., 2006; Lefaucheur, 2006; Andre-Obadia et al., 2008) and are considered as safe (Bae et al., 2007; O'Reardon et al., 2007; Rossi et al., 2009). Thereafter, in people who experienced pain relief with rTMS, there is a place in their therapies, for invasive (neurosurgical) stimulation devices on the motor cortex (MCS) (Tsubokawa et al., 1991). In open studies, results have shown efficacy in 50–70% of patients (Nguyen et al., 1999; Nuti et al., 2005; Rasche et al., 2006) with an analgesic effect that may last for weeks or months after a washout of stimulation (Nuti et al., 2005; Velasco et al., 2008). Similarly, with rTMS, sustained post-stimulation benefits have been reported (Lefaucheur et al., 2004; Khedr, 2005) and should be taken into account when setting up a cross-over versus placebo trial. We investigated whether rTMS could be implemented in clinical practice as an intermediate therapy between drugs and invasive techniques. To this aim, we made a prospective audit in our first 40 patients treated with robot-guided rTMS over the primary motor cortex (up to 2 years and 37 rTMS sessions). The main objective of this study was to assess both the degree and the duration of analgesia induced by rTMS before entering in a cross-over design study that will investigate, versus placebo, the real analgesic effect of rTMS.

2. Material and methods

2.1 Patients

Patients treated with rTMS between October 2010 and April 2014 were all included in the study. All of them presented clinical symptoms typical of a unilateral central pain that was drug-resistant and lasted for at least 1 year with a moderate to severe intensity (Numerical Pain scale >4/10). In all except three patients, a lesion explaining symptoms was indentified. In three patients, in spite of a typical neuropathic pain syndrome, including a central distribution of the pain areas, clinical and/or neurophysiological evidence of sensory deficits on somatosensory evoked potentials (SEPs) or laser evoked potentials (LEPs) or quantitative sensory testing (QST) in the territory of the pain, we failed to identify a lesion, at the time of the diagnosis. These patients were nevertheless classified as having central pain of undetermined origin (see Table 1) and were included in the study. Plexus brachial avulsion was considered as central pain because of similar clinical features and anatomic root avulsion from the spinal cord.

Patients were all possible candidates for an epidural motor cortex stimulation (MCS). rTMS sessions were proposed as a step of therapy between drugs and surgery. Patients were systematically informed of the possibility for MCS treatment, regardless of

Table 1 Variables influencing pain relief and pain relief duration.

	Output variables (pain relief)		
Explicative variables	Mean intensity (%)	Mean duration (days)	Statistical test
% Relief of the first session	***$p = \mathbf{5.6 \times 10^{-6}}$, $R = \mathbf{0.649}$	**$p = \mathbf{0.0019}$, $R = \mathbf{0.476}$	Linear regression test
LEPs (impaired vs. absent)	*$p = \mathbf{0.048}$	**$p = \mathbf{0.0018}$	ANOVA
Isch. vs. haem.	ns ($p = 0.068$)	**$p = \mathbf{0.0074}$	ANOVA
Gender	ns ($p = 0.052$) ($F = 40.19$; $M = 24.57$)	**$p = \mathbf{0.0069}$ ($F = \mathbf{16.22}$; $M = \mathbf{9.05}$)	ANOVA
Allodynia (±)	ns	ns	ANOVA
Hyperpathia (±)	ns	ns	ANOVA
Lesion localization (brain vs. others)	ns ($p = 0.074$)	ns	ANOVA
SEPs (normal vs. impaired vs. absent)	ns	ns	ANOVA
Interval between pain and rTMS	ns	ns	Linear regression test

*$p<0.05$; **$p<0.01$; ***$p<0.001$.

the result of the rTMS sessions. They were free to ask for epidural motor cortex stimulation at any stage of the study.

Patients with ongoing depression, mood-disorders, opioid treatments or personality troubles (as assessed in a multi-disciplinary pain centre including psychiatric examination) were not included in the study. For each patient, we systematically collected (1) demographical data (age, gender), (2) clinical determinants of pain (aetiology, presence or absence of allodynia and hyperpathia, duration of symptoms), (3) neurophysiological status (LEPs, SEPs), except for patients with brachial plexus avulsion in whom SEPs and LEPs was not possible. SEPs were recorded by means of scalp electrodes after non-painful electrical stimulations of the median nerve at the wrist and of the tibial nerve at the ankle, bilaterally. LEPs were recorded by means of scalp electrodes after a painful CO_2 laser stimulation over the skin on the painful area and on the mirror area on the contralateral body (Garcia-Larrea, 2012). SEPs and LEPs investigated the lemniscal and the spinothalamic (mainly A-delta fibers) pathways, respectively. Both SEPs and LEPs were classified as 'normal', 'impaired' or 'abolished'. Patients were asked to keep their ongoing medications unchanged during the first four sessions. In case of unusual pain, they were allowed either to increase by one pill the daily dose of their treatment or to take 'emergency' medications [i.e. paracetamol, Non Steroidal Anti Inflammatory Drugs (NSAID), tramadol].

2.2 rTMS procedure

A 1 × 1 × 1 mm 3D-T1-weighted MRI was recorded in all patients to define the target of magnetic stimulation which was the primary motor cortex in its subdivision representing the hand. A trained operator identified the 'omega-shape' sulcus defining the central (Rolandic) sulcus. Target was considered as the centre of the 'omega-shape' in the primary motor cortex controlateral to pain. Then the accurate position of the target ('hot spot') was adjusted according to the amplitude of the motor response on the contralateral hand. Once the target was circumscribed, the stereotaxic coordinates of the target were fixed and saved for the present and the next sessions.

Magnetic stimulation was delivered with a MagPro stimulator (Magventure Tonika Elektronic, Farum, Denmark) through a figure eight-coil. To maintain the coil over the target during the entire session, its position was assisted by a robotized arm (Smartmove®; ANT, Enschede, Netherlands) coupled with a neuronavigation system (Visor2®; ANT). This device allowed a standardized selection of the target and compensated (in real-time) for head and body motions of the patients. Thus, once it has been defined, the target of the magnetic stimulation was kept constant during the 26 min of the rTMS session and, as an advantage over classical rTMS, almost 100% of the magnetic load was delivered over the target.

Stimulation parameters were based on french recommendations (Lefaucheur et al., 2011), and previous works in pain (Lefaucheur et al., 2001a, 2011; Passard et al., 2007; Andre-Obadia et al., 2008; André-Obadia et al., 2011; Mhalla et al., 2011). They consisted in 20 consecutive trains of 80 stimulations delivered at 20 Hz, at 80% of motor threshold, separated by inter-train intervals of 84 s (i.e. a total of 1600 stimulations during a 26-min session).

Patients were instructed that the effect of rTMS on their pain ('responder' status or not) was to be arbitrated after a test-period made of a series of four sessions, separated from each other by a 3–4 weeks interval. Then, sessions were repeated in 'responders', with intervals between sessions that were adapted to the patient and to the duration of the analgesic effect.

2.3 Pain assessment

For each session, pain relief was evaluated by a nurse who was not the investigator delivering the magnetic stimulations. She was trained to evaluate pain using the criteria mentioned below. She was unaware of the stimulation parameters and she collected the following variables, as declared by the patient, for an average period of time between prior and present rTMS session, with reference to the pain that the patient perceived, before the first rTMS session:

Pain being a subjective variable and the frame of reference for pain scoring being possibly variable between the beginning and the end of this long-duration study, it seems appropriate to measure pain changes through a subjective pain improvement score rather than through a classical pain score (for example Visual Analog Scale, VAS or Numerical Rating Scale). This choice is further justified by previous literature and by the fact that this study investigates chronic pain (Farrar *et al.*, 2001; Hurst & Bolton, 2004). The subjective pain improvement score (pain global impression of change, PGIC; Hurst et al., 2004) is appropriate to measure pain changes in rTMS studies (Hosomi et al., 2013) and it is highly

correlated with pain rating scale (Farrar *et al*., 2001). The main criteria of our study for the assessement of pain intensity changes was the *percentage of pain-relief (%R)*. Instead of being based on the 7-points scale of the PGIC, it was a continuous 0–100% scale which aim was similar to PGIC in the sense that it was also a relative score based on the appreciation of pain intensity changes by the patients. The advantages of this score over PGIC for the present study were its daily manipulation by the investigators and its previous validation for the long term evaluation of motor cortex stimulation (MCS; Nuti et al., 2005). With the aim to compare prospectively in the future the effects of rTMS and those of MCS, it was necessary to use the same primary criteria for the evaluation of pain relief. Patients were asked to quantify (if present) the level of pain relief between 0% (no pain relief) and 100% (complete pain relief) after the previous session. They were asked to quantify also, as a secondary evaluation criteria, the *duration of pain relief* (i.e. the number of days during which they felt pain relief). Other criteria, collected at the beginning of the rTMS session, were *pain intensity scores* through on a 0–10 numerical scale and changes in *medication doses*. For patients treated after April 2012, Neuropathic Pain Symptom Inventory (NPSI) *score* were also systematically collected.

After the initial test-period (four sessions), a first classification of patients was made according to their pain relief, as we did previously for MCS (Nuti et al., 2005): Patients who did not achieve the fourth session or for whom pain relief (%R) was $\leq$10% after the fourth session were definitely qualified as non-responders and were proposed to stop rTMS. Patients with %R > 10% were qualified as possible 'responders' and could continue the therapy.

2.4 Data analysis

Quantitative variables were expressed as mean $\pm$ SD and qualitative variables were expressed as percentage of incidence in the sample.

For one given patient, the global percentage of pain relief (Global %R) corresponded to the averaged %R along sessions. So was the Global duration of pain relief.

For the 20 patients who had at least the median number of rTMS sessions, the effect of the total number of sessions on %R and duration of pain relief was assessed using non-parametric tests (Friedman test and Wilcoxon signed rank test). $p < 0.05$ was considered as a significant value. Pain intensities before and after four rTMS sessions were compared with a student t-test for paired values. Medications information was transformed in a numerical variable in which positive values indicate medication increase, negative values indicate medication decrease and the number indicates the difference in the daily number of pills.

For the patients who underwent NPSI scoring, we assessed the global score and the NPSI subscore that was individually the most painful. Both of them were compared before and after the beginning of the treatment using Wilcoxon test.

We checked the possibility that different parameters could influence the results, as previously done for MCS (Nuti et al., 2005). Tested variables were gender, LEPs and SEPs status, type of lesion (ischaemia/hematoma), presence or absence of allodynia or hyperpathia and lesion localization. Considering the small sample of patients, we tested 'lesion localization' by comparing brain lesion against others. These variables were tested using a single factor ANOVA and a post-hoc student test. Percentage of pain relief and interval between pain and rTMS were tested using a linear regression model.

According to previous experience of categorizations of patients who underwent MCS (Nuti et al., 2005), patients with %R between 10 and 40% were considered as *low* responders, while those with %R between 40 and 70% were considered as *intermediate* responders. Only those with %R > 70% were *high* responders. This categorization of patients was made according to how it was done for MCS in previous reports (Nuti et al., 2005), with the aim to compare MCS and rTMS results and to establish (in the future) correlations on the basis of this variable (i.e. % of pain relief).

3. Results

3.1 Population and follow-up

3.1.1 Population

This study included 40 adult patients (19 women, 21 men) from 33 to 78 years old (mean age: 52.1 years). No patients had contra-indications for rTMS, only one patient had a previous (post-stroke) epilepsy and no one had pacemakers. All patients were treated for unilateral chronic central pain (Supporting Information Table S1). All patients had been treated with medications recommended in neuropathic pain (Supporting Information Table S2).

3.1.2 Sessions and follow-up

Except non-specific and slight tension-type headache immediately after or during the day following the rTMS session that was commonly reported elsewhere (Lefaucheur et al.), no serious side-effect attributable to rTMS (especially no seizure) was reported during or after the experiment. We only observed a poor tolerance in one patient in whom rTMS recalled her phantom limb pain. rTMS was discontinued after the 2nd session in 3 patients, after the third session in 4 and after the 4th session in 2 patients. Except for the patients who did not achieve the test-period, the mean session number per patient was 11 (±10.7, min: 4, max: 37). Follow-up was on average 311.8 days (maximum 1023 days). The interval between sessions was on average 28.4 (±12.2) days.

Nine (22.5%) of the 40 patients considered that pain relief was <10% after four sessions or discontinued rTMS before the fourth session, and were therefore qualified as non-responders. Among the 31 (77.5%) responders (pain relief >10%), the mean session number was 13.4 (±1, min: 1, max: 37). Follow-up was on average 381.6 days (maximum 1023 days). The interval between sessions was on average 28.6 days (±12.3 days).

3.2 rTMS efficacy (Fig. 1)

3.2.1 Intensity of pain relief

3.2.1.1 Percentage of pain relief (%R)

The averaged percentage of pain relief (Global %R) was 31.9% (range: 0–100%) in the whole population of patients. Global %R in the responders group was 41% (range: 10–100%). Sixteen patients (40%) belonged to the 'low responders' group. Twelve patients (30%) were considered as 'intermediate responders' and 3 (7.5%) were 'high responders'.

3.2.1.2 Visual Analogic Scale

Mean VAS scores before rTMS was 6.35 (±1.47) and was 6.16 (±1.71) after four sessions, but the difference did not reach significance ($p = 0.55$).

3.2.1.3 NPSI score

For the 15 patients who underwent NPSI evaluation, the global score was significantly higher before than after rTMS (44.7/100 ± 19.8 vs. 34.9/100 ± 23.9, $p = 0.04$). So was the NPSI subscore that was individually the most painful in each patient (14.7/20 ± 5.12 vs. 10.6/20 ± 5.79. $p = 0.03$).

3.2.1.4 Medications

Among the 32 responders patients, medications were decreased in eight patients, unchanged in 18 patients and increased in five. We found no significant link with %R ($p = 0.06$) or duration of pain relief (0.33).

3.2.2 Duration of pain relief

In the whole population of patients, the averaged duration of pain relief was 12 days (±11 days, range: 0–60 days). It was 16 days (±11 days, range: 0.33–60) in the responders group. Considering the 95% confidence interval, the high limit is 16 days.

We found a positive correlation between the percentage of pain relief and the duration of pain relief (linear regression test. $R = 0.764$. $p = 9.81 \times 10^{-9}$, Fig. 2).

3.3 Cumulative effect of repeated sessions

The median number of sessions per patient was 7. Among the 20 patients who had at least 7 rTMS

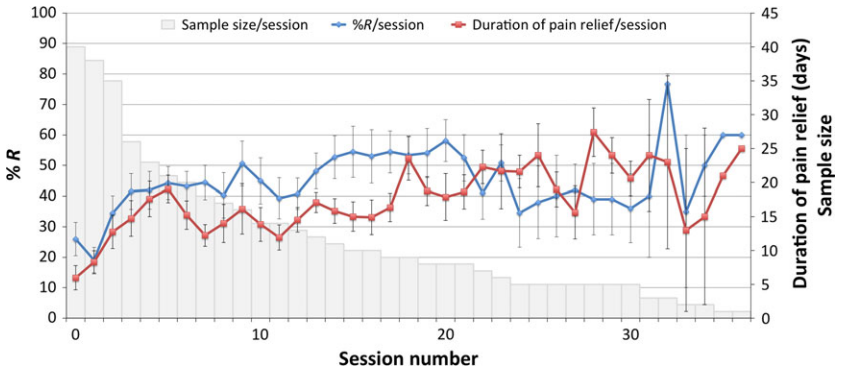

Figure 1 Pain relief, duration of pain relief (±SEM) and sample size per session according to session's number.

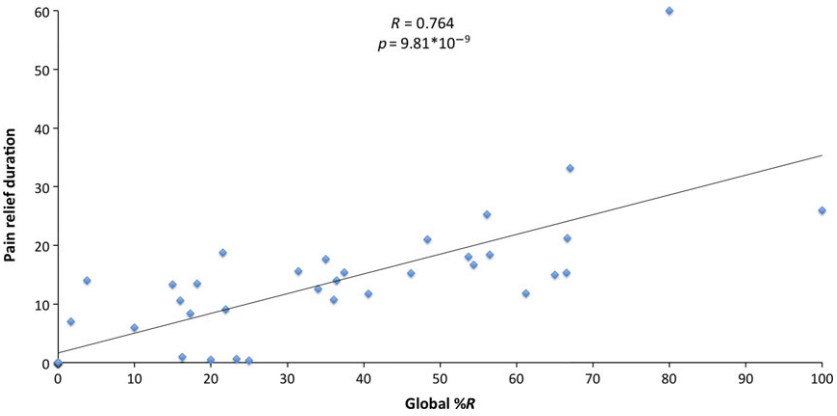

Figure 2 Linear regression between percentage of pain relief and duration of pain relief.

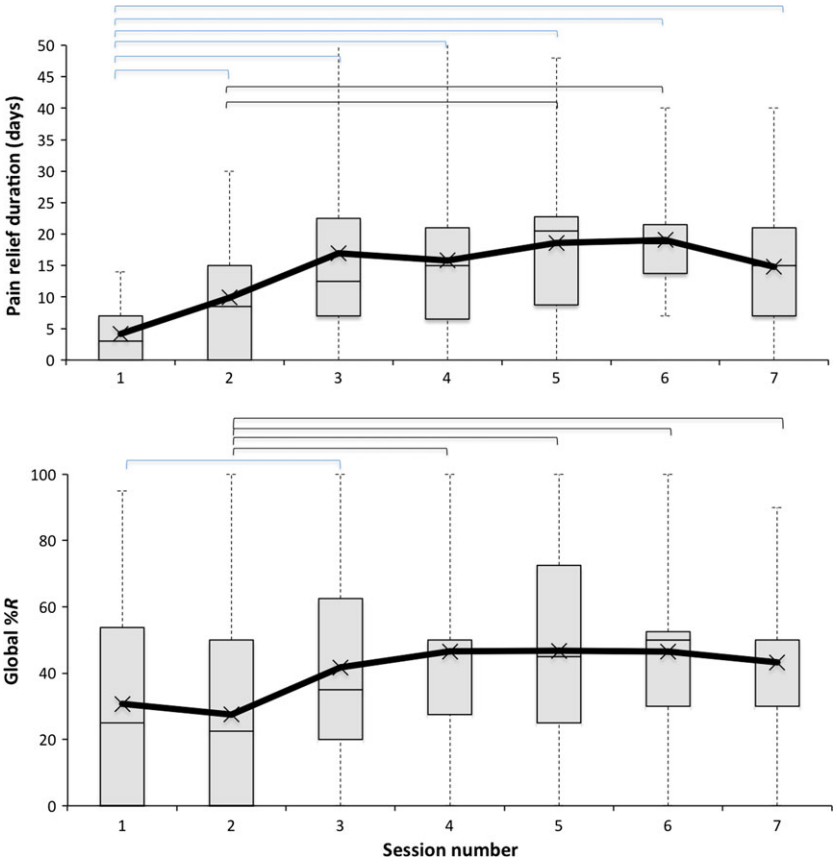

Figure 3 Percentage of pain relief and duration of pain relief (days) considering session number for patients who underwent at least seven sessions. (Pain relief percentage: Friedman test: $F = 19.43$; $p = 0.0035$; Pain relief duration: Friedman test: $F = 35.2$; $p = 3.96 \times 10^{-6}$. Square brackets above indicate significant Wilcoxon paired *post-hoc* test ($p<0.05$)
Blue = Difference between 1st session and other – Black = Difference between the second and others. All other comparisons were not significant.).

sessions (median follow-up), Friedman test showed an effect of session repetition on both percentage of pain relief ($p = 0.0035$) and duration of pain relief ($p = 3.96 \times 10^{-6}$). This effect, precised by post-hoc tests comparing sessions showed that the first two sessions induced significantly less pain relief and less relief duration than the ensuing sessions (Fig. 3). For repeated sessions (more than 3), no difference was observed (plateau).

3.4 Variables influencing the results

3.4.1 Variables influencing percentage of pain relief

We found a positive correlation between the percentage of pain relief after the first rTMS session and the averaged percentage of pain relief in the following sessions (regression test. $R = 0.649$, $p = 5.6 \times 10^{-6}$, Fig. 4). A similar correlation was

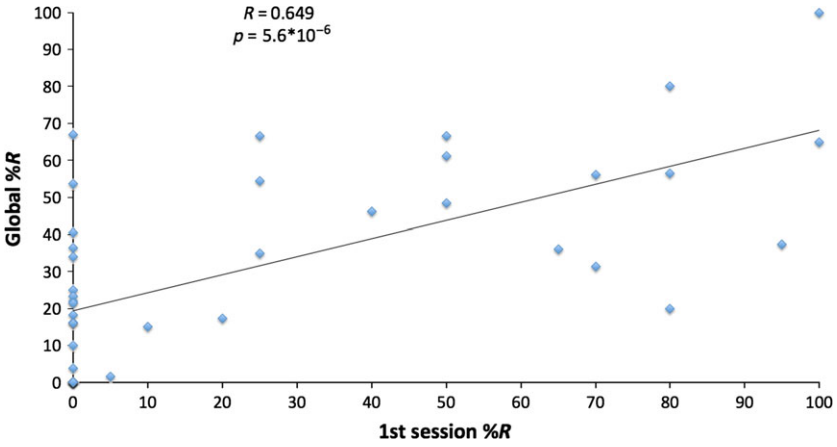

Figure 4 Linear regression between pain relief in the first session and the averaged pain relief during long-term therapy.

found for duration of pain relief between the first rTMS session and the ensuing sessions (regression test. $R = 0.476$ $p = 0.0019$).

Neurophysiological investigations were available in 25 patients (normal distribution. Shapiro–Wilk test). Patients with a persistent nociceptive evoked potentials in the territory of their pain, had a better pain relief (44.4% vs. 21.56%, $p = 0.049$) and a longer pain relief duration (17. 0 days vs. 6.0 days; $p = 0.0018$) than those with a complete spinothalamic deafferentation. No other factor showed any significant influence on the percentage of pain relief (Table 1). There was a tendency for women to have a better relief than men ($p = 0.052$). There was also a tendency for patients suffering from hemorrhagic stroke to have less relief than the general population ($p = 0.068$). Patients for whom no lesion was clearly identified had a trend to have less pain relief ($p = 0.0742$) as compared to the general population.

3.4.2 Variables influencing only the duration of pain relief

Women experienced longer duration of pain relief than men ($p = 0.0069$).

Patients with hemorrhagic stroke had shorter duration of pain relief than patients with ischaemic stroke ($p = 0.0074$) and than general population ($p = 0.0004$).

3.5 Considerations for clinical use

After three sessions, patients had a 43% chance of experiencing at least 40% of pain relief with a mean duration of 17.8 days.

Patients who had at least a 40% pain relief after three sessions have a 89% chance to experience at least a 40% pain relief at a 1-year follow-up.

Among the patients who still experienced more than 40% of pain relief at 1-year follow-up, 66% had more than 40% pain relief after the third session.

4. Discussion

This study is, to the best of our knowledge, the first one to describe the effects of repeated rTMS sessions over the motor cortex in patients with central pain. Most of the studies reported at that time in patients with chronic pain were limited to a maximum of five sessions and/or 1-month follow-up (Khedr, 2005).

Even though we preferred % pain relief as the main criteria because it introduced a relativity between two intensities of pain at different time, the amount of pain relief reported here (32%) was, on average, consistent with previous literature indicating a pain reduction on VAS between 2% and 34% (Leung et al., 2009). The results presented here are similar to other's studies reporting 25, 61 and 14% of poor, satisfying and good results, respectively (Khedr, 2005), or 50% of satisfying results for Hirayama et al. (2006). These results can also be compared to epidural motor cortex stimulation reporting 13, 35, 42 and 10% of poor, moderate, satisfying and good results, respectively (Nuti et al., 2005). In addition, the present study showed an improvement in the NPSI score that is consistent with results on pain relief and that is generally qualified as being more appropriate to the follow-up of chronic neuropathic pain than classical pain scores.

This analgesic effect is even more interesting if one consider the major difficulties in treating effectively this kind of pain, because of its intensity, and overall, the intractable characteristics of neuropathic

pain, explaining the general failure of medications. With rTMS, almost half of the patients experienced an interesting result and 15 patients described more than 40% relief in totally despaired situations of chronic pain refractory to medications. These results were also encouraging for those who experienced a slighter pain relief since 16 patients had an estimation of their improvement between only 10 and 40%, but they still wished to continue rTMS therapy. If we consider the overall response rate of about 77.5%, this is an additional argument in favour of meaningful clinical results in this context of poor response to classical (drugs) therapies. Moreover, this effect is accompanied by an excellent tolerance, and we did not observe any adverse event all along the 440 sessions.

The absence of a placebo condition is a serious limitation to the impact of this study, in terms of demonstration of a real efficacy because a participation of the placebo effect in these results cannot be excluded or even evaluated. This was however a deliberate choice to proceed to such an exploratory study, without a placebo condition, for the following reasons: First of all, the placebo effect may represent up to 30% of analgesic possibilities (André-Obadia et al., 2011), and therefore, from the point of view of care-givers, it can be an interesting tool that should be promoted if we are looking for analgesic solutions in patients. For this clinical study, we considered that a placebo effect, if any, should be considered as a simple tool to alleviate pain in patients, and not as a confounding factor to be excluded from the study. The main reason for this choice was that it was mandatory to evaluate both the effect and the number of rTMS sessions necessary to initiate an analgesic effect, these precisions being required to optimize the design of resulting placebo controlled cross-over trials. In that respect, our study demonstrated that it is necessary to perform several consecutive sessions to reach a level of pain relief, because of cumulative effects, and therefore, that a controlled trial with single rTMS sessions (or less than four sessions) would largely minimize the chance to find a significant effect. Conversely, our study also clearly demonstrated that after repeated rTMS sessions, pain relief has a remnant effect that may extend for several days or weeks. Therefore, a placebo (cross-over) controlled study that would alternate placebo and active sessions would necessarily minimize the chance to detect a differential effect between active and placebo sessions. Similarly, an experimental design in which the placebo sessions would not be preceded by a long wash-out period would minimize the chance to find a difference with the placebo condition. According to our results, 95% of the confidence interval for pain duration is between 11.4 and 18.3 days, and therefore, a minimal washout period of 18.3 days seems necessary in a double blind cross-over trial. These two last arguments (i.e. delayed (cumulative) effect and remnant pain relief) have also been reported in epidural motor cortex stimulation (Nuti et al., 2005), but these findings still not have lead to individualized clinical trials taking into account these possibilities of delayed and very long remnant effects. Indeed, many studies limited the wash-out or the placebo period to 4 weeks, what is probably not long enough to avoid such effects. Thus, for future controlled trials investigating rTMS for pain relief, our results should be helpful for selecting an appropriate timing of sessions, or, alternatively, to privilege experimental studies with two arms, one group with placebo and the other group with active rTMS.

For clinical practice, our study also confirmed that a gradual improvement of pain relief over the first sessions is a reality, as suggested by Khedr (2005). This period of cumulative effects could be set to the first three sessions with a plateau allowing to judge whether the rTMS therapy is effective or not. It is probably the same reason that has conducted several teams to realize an initial load of doses with daily stimulations. The persistent effect is also important to consider in clinical practice since one session every 2 weeks seems enough to maintain the pain relief, a result that did not differ so much from the results of a maintained effect from 8 to 15 days (Lefaucheur et al., 2001b; Khedr, 2005). Another finding that may be used in clinical practice is the increase of duration of pain-relief along the three first sessions and the increase of pain relief duration with the amount of pain relief.

These data can be considered to initiate a personalized rTMS therapy, for which the results to the first session is a predictor of long-term efficacy, as previously reported for epidural motor cortex stimulation (Nuti et al., 2005). Even though, this prediction at the group level is interesting for patients selection, individually, one should keep in mind that 11 patients for whom the first session was without effect could later benefit of rTMS, because of the cumulative effect. Thus, this predictor of efficacy should be considered cautiously, at the group level, only, but not for defining individual strategies with only one test based on one rTMS session. For the first time, another positive predictor of efficacy is identified, namely spared LEPs, as compared to

absent LEPs. Similar predictors of efficacy have been previously reported, for example with normal or spared SEPs as positive predictors for the success of spinal cord stimulations (Sindou et al., 2003). This information is very important for the prediction of post-operative results and it may be useful for the selection of patients, to improve patients selection and overall rate of success. The present study should also make the clinicians confident in the techniques since no serious adverse events were observed. With a record of follow-up (440 rTMS sessions, 312 days, 11 sessions for the average, 1023 days maximum) that is to our knowledge, the longest follow-up study published in neuropathic pain.

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Author contributions

B.P., V.B. and R.P. participated in collecting the data and rTMS manipulations over the 3 years and a half length of the study. F.V., C.N. and R.P. participated in financial support of the device. C.C. and F.V. actively contributed to the redaction of the manuscript and statistical treatments.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Patients clinical characteristics.

Table S2. Medications previously used.