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# Treatment of Chronic Facial Pain Including Cluster Headache by Repetitive Transcranial Magnetic Stimulation of the Motor Cortex With Maintenance Sessions: A Naturalistic Study

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ABSTRACT

*Objective:* To assess the long-term maintenance of analgesia induced by high-frequency repetitive transcranial magnetic stimulation (rTMS) of the motor cortex contralateral to pain in a naturalistic study of patients with chronic refractory facial pain.
*Methods:* 55 patients were included (cluster headache, $n = 19$; trigeminal neuropathic pain, $n = 21$; atypical facial pain, $n = 15$). The rTMS protocol consisted of an "induction phase" of one daily rTMS session for five days per week during two consecutive weeks, followed by a "maintenance phase" of two sessions during one week, then one session in weeks 4 and 6, and a monthly session for the next five months. In a subset of patients, navigated targeting was performed and session duration was shortened from 20-min to 10-min (with the same number of 2000 pulses per session). The analgesic effect of rTMS was assessed on a 0–10 visual numerical scale from 15 to 180 days after treatment initiation.
*Results:* All pain measures significantly decreased from baseline to D15: the intensity of permanent pain ($5.2 \pm 1.6$ to $3.2 \pm 1.9$) and paroxysmal pain ($8.6 \pm 1.5$ to $4.5 \pm 3.4$), as well as the daily number of painful attacks ($5.6 \pm 3.1$ to $2.3 \pm 3.1$). The percentage of responders (defined as pain score decrease $\geq$30%) was 73% at D15 and dropped to 40% at D180. The analgesic effect was similar regardless of the type of pain and was significantly lower when session duration was shortened, irrespective of the number of pulses.
*Conclusion:* This long-term maintenance rTMS protocol can be a therapeutic option in the clinical management of patients with chronic refractory facial pain, including cluster headache. However, only part of the patients respond to this technique and session duration should not be reduced.


## Introduction

Following the first reports of analgesia produced by surgically-implanted epidural motor cortex stimulation in the early nineties [1–4], facial pain was usually considered a good indication of this technique [5,6]. More recently, repetitive transcranial magnetic stimulation (rTMS) of the motor cortex, a non-invasive technique of cortical stimulation, was also used to relieve refractory neuropathic pain [7–15]. However, only few studies assessed the analgesic effect of rTMS specifically on facial pain or headache disorders. Most rTMS data concern migraine, targeting the occipital visual cortex [16], including with single-pulse TMS approach [17], the dorsolateral prefrontal cortex [18], or the primary motor cortex, which seems to be a good target [19,20]. Regarding facial neuropathic pain, beyond single cases reported separately [21] or included in large series of patients with pain of various origins [22,23], the main data consist of six controlled studies of 7–24 patients [24–29]. In these studies, facial pain was mostly secondary to surgical or traumatic lesion of the trigeminal nerve and high-frequency rTMS was delivered over the motor cortical area corresponding to the painful face [24,26,29] or to the hand of the painful side [25–28]. These trials were based on single rTMS sessions, except two studies in which patients were stimulated for five consecutive days [28,29]. These two series showed significant analgesic effects lasting for 2 weeks after the end of rTMS sessions. One series included only patients with facial pain [29] and the other included patients with trigeminal neuralgia or post-stroke pain at the face and upper limb, with no obvious

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differences in rTMS efficacy between these two clinical conditions [28]. Some studies showed a higher percentage of responders in cases of facial pain compared to other pain sites [25,26], while this difference failed to reach significance in other studies [24,27]. In the present study, we have evaluated the analgesic efficacy of rTMS not only in painful trigeminal neuropathy or neuralgia, but also in other types of facial pain syndromes refractory to conventional treatment.

Cortical stimulation produces analgesia through various possible mechanisms, including the activation of neural structures at a distance from the site of stimulation [30]. For example, motor cortex stimulation can reduce hyperactivity of thalamic relays involved in the transmission of painful stimuli [1,31]. Regarding the involved neurotransmitters, analgesia could result from the modulation of endogenous opioidergic control [32,33] or the restoration of intracortical gabaergic inhibition [34]. In the French [35] and international [36] recommendations for the use of rTMS, experts retained a level A of evidence regarding the analgesic effect of high-frequency motor cortex rTMS in patients with chronic neuropathic pain. However, the statistical difference between the analgesic effects produced by active and sham rTMS does not necessarily meet the threshold of clinical significance [37]. Further studies are still needed before considering rTMS in the therapeutic armamentarium against pain, especially to assess the value of this technique to produce a real clinical benefit in the long term.

Thus, our goal was not to demonstrate the actual analgesic efficacy of motor cortex rTMS compared to placebo, as it was already done, but to evaluate the benefits of this treatment in "real life", namely clinical practice, in which placebo stimulations are not performed. This is the reason why we designed a naturalistic study of rTMS therapy for pain, which also addressed the issue of prolonging rTMS-induced analgesia in the long term by means of maintenance sessions. In addition, the influence of rTMS session duration and image-guided navigation on rTMS efficacy has been studied.

## Methods

### *Patients*

In this open-label, naturalistic study, 55 patients (30 men and 25 women) underwent motor cortex rTMS for the treatment of chronic facial pain between January 2008 and January 2014. Pain was present for more than one year (or more than 6 months in case of postherpetic neuralgia) and was refractory to conventional therapy or associated with poor drug tolerance. In 19 patients, facial pain met the criteria for diagnosis of cluster headache (CH) according to the International Classification of Headache Disorders (ICHD), 3rd edition, of the International Headache Society [38]. In 10 patients, facial pain was secondary to a surgical or traumatic injury of the trigeminal nerve or ganglion (traumatic trigeminal neuropathic pain, traTNP), including surgical treatment of classical trigeminal neuralgia by percutaneous radiofrequency thermocoagulation, $n = 4$, microvascular decompression, $n = 2$, or percutaneous balloon compression, $n = 1$; posterior fossa (neuroma) surgery, $n = 2$; traumatic trigeminal nerve injury, $n = 1$. In 11 patients, facial pain was secondary to an inflammatory or infectious lesion of the trigeminal nerve or nuclei (inflammatory trigeminal neuropathic pain, infTNP), including herpes zoster infection, $n = 4$; other viral infection, $n = 1$; chronic inflammatory disease, such as Sjögren's syndrome, $n = 3$; brainstem lesion in the context of multiple sclerosis, $n = 3$. In 15 patients, facial pain was related to unclear pathophysiology in the context of dental surgery, $n = 7$; radiotherapy for meningioma, $n = 1$; stroke, $n = 1$; undetermined cause, $n = 6$. These cases met the criteria for diagnosis of atypical facial pain (AFP) according to the ICHD, 1st edition (persistent facial pain that does not have the characteristics of other cranial neuralgias and is not associated with physical signs or a demonstrable organic cause) [39]. The following versions of the ICHD have adopted the term "persistent idiopathic facial pain" (PIFP) [38], but the term AFP was preferred as it continues to be commonly used in other classifications [40] or by clinicians [41].

All patients with CH had previously received the reference treatments in this setting, including verapamil ($n = 15$), lithium ($n = 6$), and occipital nerve infiltration ($n = 8$) for attack prevention on the one hand, and oxygen therapy ($n = 17$) and sumatriptan ($n = 12$) for acute attacks on the other hand. They had also received analgesic treatments that are less specifically indicated in this disorder (including antiepileptics, $n = 9$ and antidepressants, $n = 7$). Antiepileptic drugs (mainly carbamazepine) were also administered in all patients with TNP or AFP, associated with antidepressants in 29 patients (81%) and trigeminal ganglion block in 15 patients (42%).

### *rTMS protocol*

Stimulation was performed using a MagPro stimulator (MagVenture, Farum, Denmark) with a dynamic cooled figure-of-eight coil. The stimulation target was the motor cortical representation of the face, contralateral to the painful side, according to motor evoked potential (MEP) recordings. A non-navigated procedure was performed in 33 patients, whereas from January 2011, in 22 patients, the site of cortical stimulation was determined using a TMS Navigator system (Localite, Sankt Augustin, Germany).

Stimulation was performed at 10 Hz with an intensity set at 80% of the resting motor threshold (RMT) determined as usual [42], using the MEP monitor amplifier of the MagPro stimulator. Between January 2008 and October 2010, each rTMS session consisted of 40 trains of 5-sec duration with intertrain interval (ITI) of 25 s, leading to deliver 2000 pulses in 20 min (20-min session) (22 patients). From November 2010, session duration was shortened from 20 to 10 min (10-min session) (33 patients), consisting of 20 trains of 10-sec duration with ITI of 20 s (15 patients, until March 2012), and then 40 trains of 5-sec duration with ITI of 10 s (18 patients, from April 2012). The therapy 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. Then, in patients with clinical response, defined as a decrease in pain score $\geq$30% on a 0–10 visual numerical scale (VNS), a maintenance therapy was undertaken, consisting of one session during weeks 4 and 6, and then a monthly session for the next five months, for a total of 7 sessions.

### *Clinical assessment*

Patients were assessed at baseline (before rTMS therapy) and 15, 30, 90, and 180 days after treatment initiation (D15, D30, D90, D180). In case of permanent pain, the average daily pain intensity was scored on a 0–10 VNS. In case of paroxysmal pain, the average pain intensity during attacks was also scored on a 0–10 VNS and the number of painful attacks per day was recorded. The average percentage of change for both permanent and paroxysmal pain was calculated following rTMS therapy compared to baseline at each time point, the result obtained at D15 being the primary endpoint of the study. Patients were classified into four groups according to their analgesic response [3]: very good response (pain reduction $\geq$70%), good response (pain reduction from 50% to 69%), moderate response (pain reduction from 30% to 49%), and poor or no response (pain reduction $<$30%). Finally, the global clinical effect of rTMS therapy was self-assessed by each patient at D90 on the Clinical