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TECHNICAL NOTE

A practical algorithm for using rTMS to treat patients with chronic pain

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Summary High-frequency repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex has a good level of evidence of efficacy as a method for providing analgesic effects in patients with chronic pain. However, there is still no consensus regarding the parameters of stimulation to use and the detailed protocol to apply for therapeutic practice. In this article, we review the main technical points to address, and we propose a practical algorithm of how to use rTMS for chronic pain treatment in daily clinical practice.

Introduction

Since a first report made more than 20 years ago [16], high-frequency repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) has been proposed as a method for treating patients with chronic pain [13,15], according to a good level of evidence of analgesic efficacy [21,22]. However, there is no consensus regarding the exact parameters of stimulation to use and the detailed protocol to apply in the context of rTMS pain therapy. In this technical note, we propose a practical algorithm of how to use rTMS for treating patients with chronic pain, neuropathic or not, in daily clinical practice.

Parameters of motor cortex stimulation

The type of magnetic field should be biphasic, since to our knowledge no commercially available rTMS machine is able to deliver more than a few monophasic rTMS trains during a single session. The type of coil should be a figure-of-8 coil, since there is no significant level of evidence of efficacy reported in the literature regarding the use of non-focal

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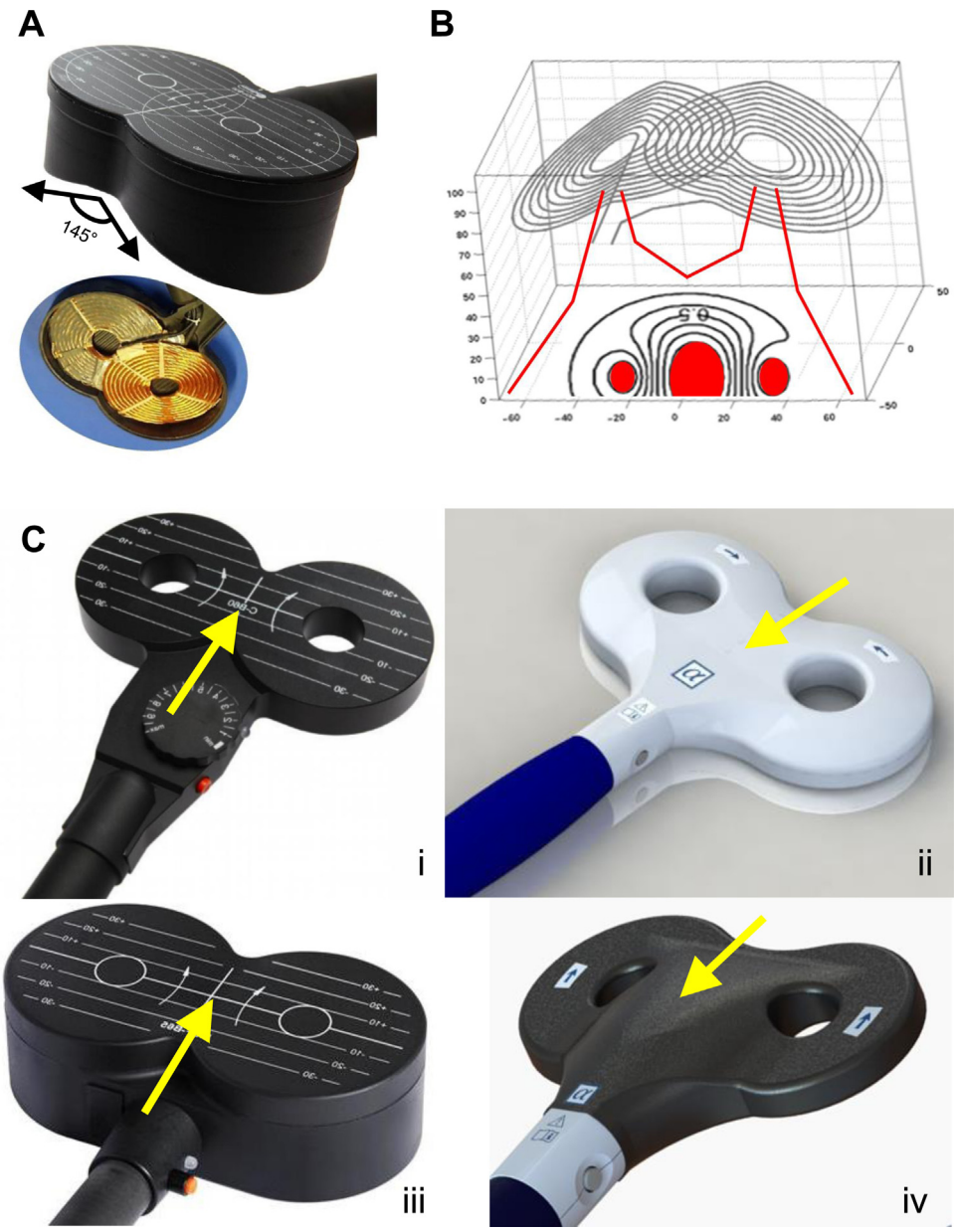

Figure 1 A. The B70 coil (manufactured by MagVenture ®), a non-flat figure-of-8 coil consisting of two overlapping windings forming an angle of 145°; B. Design of the B70 coil and geometry of the induced magnetic and electric fields with maximum values in red (adapted from Nadeem et al., 2003 [26] and Thielscher and Kammer, 2004 [32]); C. Examples of flat figure-of-8 coils manufactured by MagVenture ® (B60 (i) and B65 (iii) flat coils) and Magstim ® (D70 alpha uncoated (ii) or coated (iv) flat coils). The direction of the initial, rising phase of the discharge current waveform is shown as arrows on the coil encapsulation and is opposite between the two manufacturers. The current flows through the coil from the handle towards the front end of the coil for MagVenture ® coils (yellow arrow) but from the front end of the coil towards the handle for Magstim ® coils (yellow arrow). The direction of the current induced into the brain is opposite: the rising phase of magnetic pulse waveform enters the motor cortex anteroposteriorly for MagVenture ® coils and posteroanteriorly for Magstim ® coils if the coil-handle points backwards (i.e. the coil is handled behind the head). However, in the case of biphasic stimulation, the preferential orientation of the current into the brain corresponds to the second phase, i.e. posteroanterior for MagVenture ® coils and anteroposterior for Magstim ® coils, which is finally the same orientation as the current flowing into the coil (yellow arrows).

coils, such as circular, double-cone or H-coils, for pain therapy. However, there are different types of figure-of-8 coils. Most of them are flat coils consisting of two circular windings made of insulated copper wire (outer diameter of each winding: 70—75 mm), which are placed side-by-side in the same plane. This enables a flat figure-of-8 coil to stimulate neural structures with a focus right under its center. A more powerful type of figure-of-8 coil can also be used for rTMS, in which the two windings overlap in the central part, thus forming an angle of 145° (and not 180° as flat coils) (Fig. 1A-B).

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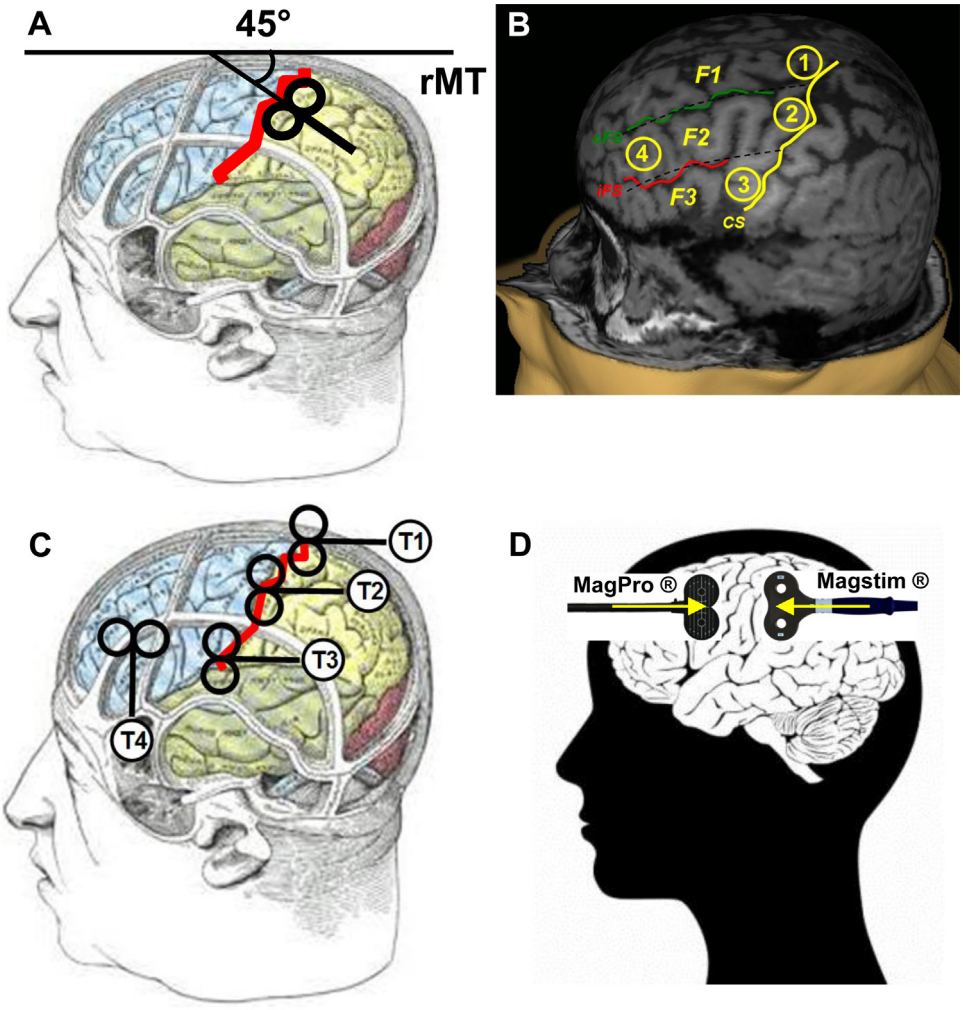

Figure 2 A. To determine motor hotspot location and the resting motor threshold (rMT), the figure-of-8 coil must be oriented at 45° away from the interhemispheric midline, i.e. perpendicular to the central sulcus (red line); B. Location of the navigated targets based on a three-dimensional reconstruction of the brain. F1, F2, and F3 correspond to the superior, middle, and inferior frontal gyri, respectively, separated by the superior frontal sulcus (sFS, in green) and the inferior frontal sulcus (iFS, in red). The sFS and iFS are projected (black dotted lines) onto the central sulcus (CS, in yellow) to divide the primary motor cortex into three segments: a medial segment (circle 1) facing F1 with lower limb representation, a central segment (circle 2) facing F2 with upper limb representation, and a lateral segment (circle 3) facing F3 with face representation. The dorsolateral prefrontal cortex (circle 4) is much more anteriorly located in F2; C. For therapeutic application, the figure-of-8 coil must be oriented parallel to the interhemispheric midline when stimulating the primary motor cortex (targets T1 to T3 for lower limb, upper limb, and face representation, respectively), but should have a more lateromedial orientation when stimulating the dorsolateral prefrontal cortex (target T4); D. For a preferential anteroposterior activation of M1, a Magstim ® figure-of-8 coil must be handled from behind the head, whereas a MagPro ®/MagVenture ® figure-of-8 coil must be handled in front of the face (otherwise the current direction flowing into the coil has to be reversed at the level of the stimulator control panel if the coil is handled from behind the head).

This coil, producing higher values of electric field strength to a greater depth in the brain than flat figure-of-8 coils [32], showed interesting therapeutic results, e.g. to relieve lower limb pain perhaps by more efficiently stimulating the corresponding M1 region [11].

The M1 target can be defined by two different methods, based on motor hotspot finding or image-guided navigation. Conversely, much fewer studies have used targeting of M1 based on cranial landmarks (i.e. C3/C4 site according to the International 10—20 system of electroencephalography (EEG) electrode location), which makes, therefore, this approach more difficult to recommend.

The most common targeting method is based on a ''function-guided'' procedure, i.e. the location of the motor hotspot, which corresponds to the scalp site at which stimulation evokes the largest motor evoked potentials (MEPs) in the targeted muscle territory. To determine motor hotspot location, the coil must be placed flat on the scalp oriented at 45° away from the interhemispheric midline, i.e. perpendicular to the central sulcus (Fig. 2A). This coil orientation is able to optimize corticospinal tract activation within M1. At this site and with this coil orientation, the resting motor threshold (rMT) can be determined. The rMT is defined as the minimum stimulus intensity that produces a MEP of about

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50 μV in at least 5 of 10 trials. The rMT will be used to individually dose the stimulation in each patient, taking into account any change in cortical excitability, e.g. related to medication intake such as anti-epileptic drugs in patients with neuropathic pain.

An alternative to target M1 is to use image-guided neuronavigation integrating brain magnetic resonance imaging (MRI) data of each individual treated by rTMS [14]. The location of M1 is at the anterior border of the central sulcus and it can be divided into 3 anatomofunctional regions along the mediolateral axis: a medial segment, facing the superior frontal gyrus (F1) and corresponding to the lower limb; a central segment, facing the middle frontal gyrus (F2), corresponding to the upper limb, also including the hand knob; a lateral segment facing the inferior frontal gyrus (F3) and corresponding to the face (Fig. 2B).

Neuronavigation allows inter-individual anatomical variations to be taken into account, a clear advantage over the ''function-guided'' procedure. Indeed, the location of the motor hotspot shows significant anatomical variability over the precentral gyrus, sometimes being located very much anterior to the central sulcus, even up to the level of the precentral gyrus in certain individuals [2]. However, it remains to determine whether targeting either the motor hotspot without navigation or the anterior border of the central sulcus using image-guided navigation has any impact on the outcome of rTMS pain therapy. Similarly, it remains to determine whether this outcome can be influenced by targeting either the motor cortical representation of the pain region in case of focal pain or the hand motor hotspot or hand knob whatever the pain location. This issue will also be addressed in our proposal of a practical algorithm.

Whatever the precise cortical site targeted within M1, the figure-of-8 coil orientation must be parallel to the interhemispheric midline (Fig. 2C), since it has been demonstrated that a lateromedial orientation of the coil led to losing the analgesic effects [5]. With a parallel-to-midline orientation of the coil, the electric current delivered to the brain can ''enter'' the precentral gyrus with either an anteroposterior or posteroanterior direction according to coil handle positioning in front or behind the head.

In the case of a biphasic magnetic pulse waveform, the most effective current direction to modulate M1 activity corresponds to the second phase of the stimulus. Therefore, it is important to know that the direction of the current in a figure-of-8 coil differs between manufacturers. For example, with the coil handle pointing backwards (i.e. the figure-of-8 coil is handled from behind the head), the second phase of a biphasic pulse preferentially stimulates M1 anteroposteriorly with Magstim ® coils but posteroanteriorly with MagPro ®/MagVenture ® coils (Fig. 1C). Since an anteroposterior activation of M1 is optimal for rTMS pain therapy [20], a Magstim figure-of-8 coil should be handled from behind the head, whereas a MagPro ®/MagVenture ® figure-of-8 coil should be handled in front of the face (Fig. 2D). An alternative with a MagPro ®/MagVenture ® figure-of-8 coil can be to reverse the current direction flowing into the coil if handled from behind the head.

Stimulation intensity should be set at 80—90% of the rMT and stimulus frequency should be 10 Hz, since better results were reported at this frequency [31], although high-frequency rTMS can theoretically range between 5 and 20 Hz. The other stimulation settings are as follows: 30 trains of 10s duration (100 pulses per train) with a 20s intertrain interval, for a total of 3,000 pulses per session of 15-min duration. A session duration of high-frequency rTMS longer than 10 minutes, whatever the number of pulses per session was shown to be a predictor of good outcome for rTMS pain therapy [10]. These settings remain within the safety limits for the use of rTMS in clinical practice [30].

Algorithm for rTMS pain therapy

Before starting treatment, it is necessary to screen rTMS candidates for any contraindications or risk of adverse events using a standard questionnaire [30]. It is also required to assess average daily pain intensity on a 0—10 numeric rating scale (NRS) or visual analog scale (VAS). Additional pain or quality of life questionnaires are welcome.

To start high-frequency rTMS therapy, one possibility is to target the motor cortical representation of the pain region. This objective can be achieved even without a navigation system by determining the motor hotspot of a muscle located in the pain region via mapping stimulations of motor cortical area and MEP recordings. In the case of no recordable MEP (amputation, paralysis or severe motor deficit in the pain region), a navigation system is mandatory to target the anatomical or functional motor representation of the pain region based on individual MRI data. In case of diffuse pain especially of non-neuropathic origin, such as fibromyalgia, the hand motor hotspot or hand knob is usually targeted on the left hemisphere, at least in right-handers.

However, it is conceivable to start high-frequency rTMS therapy by stimulating the M1 representation of the hand in all patients whatever the pain location or origin. Indeed, this region is easier to target and there is no convincing evidence of a somatotopic effect of rTMS-induced analgesia [6,19]. Therefore, rTMS therapy could be initiated in all cases by stimulating the hand area in M1, either contralateral to the painful side in cases of lateralized pain or on the left hemisphere in cases of diffuse pain, as aforementioned. This ''hand target'' can correspond to the hand motor hotspot (in the absence of a navigation system) or the hand knob (defined on morphological MRI with a navigation system). It must be recalled that the hotspot location is in any case stimulated to determine the rMT with a figure-of-8 coil oriented at 45° away from the interhemispheric midline, while therapeutic rTMS is performed with a figure-of-8 coil oriented parallel to this midline (Fig. 2C-D).

Firstly, an ''induction phase'' should be conducted by performing 3 to 5 daily sessions per week for 2 weeks. After 6 or 7 sessions, the level of analgesic response should be assessed on a 0—10 NRS or VAS and compared to scores before rTMS. The response to rTMS should be defined as a reduction in pain intensity of more than 2 points or 30% according to the 'Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials' (IMMPACT) criteria of ''clinically meaningful'' treatment [8]. If the patient does not respond to these initial sessions, an alternative target must be tried. The stimulation should be shifted to a more medial or more lateral part of the motor cortical strip, i.e. corresponding to lower limb or face representation, respectively. Again, the efficacy of high-frequency rTMS to provide

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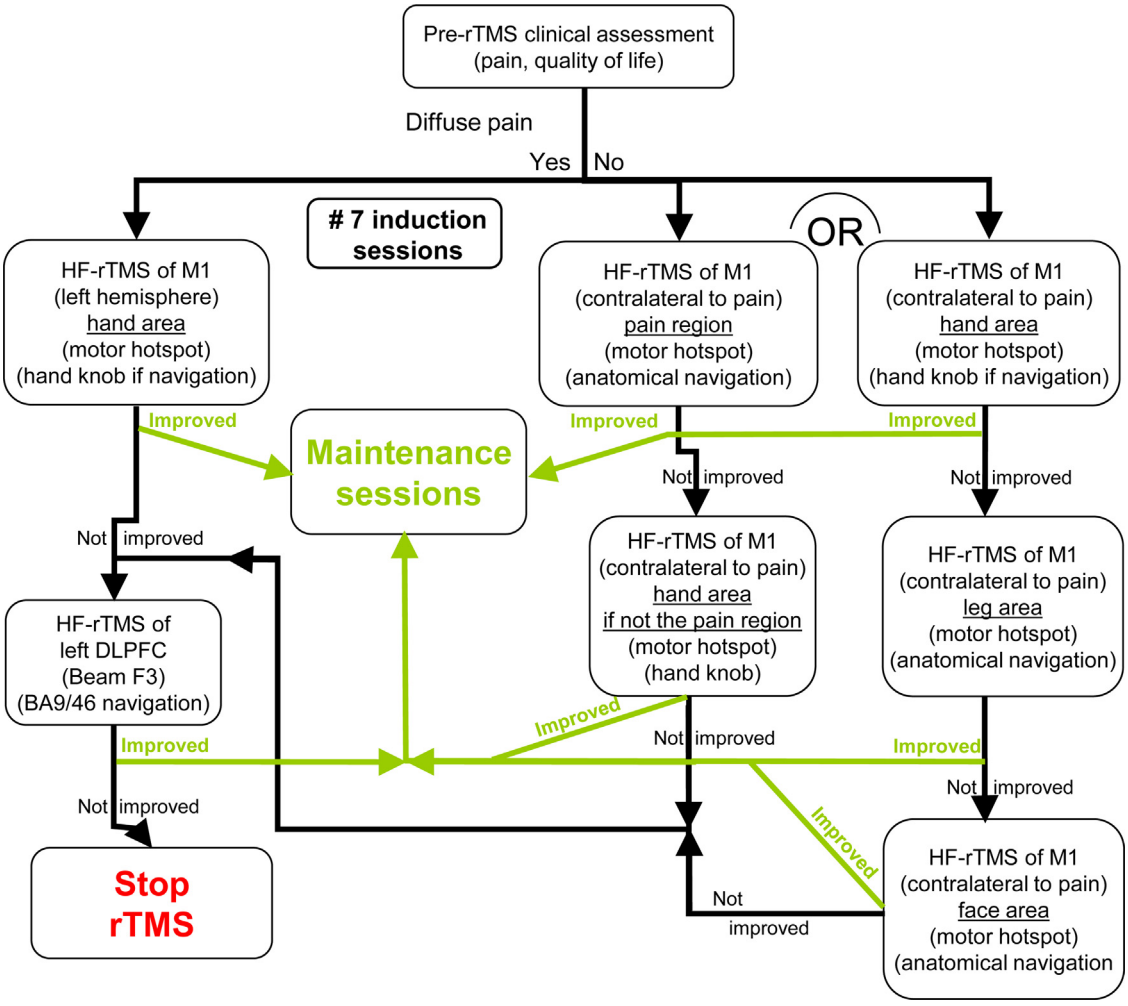

Figure 3 A practical algorithm for managing rTMS sessions and targeting in patients with chronic pain; HF: high-frequency; M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex.

pain relief should be assessed after 6 or 7 sessions. If the patient is still a non-responder, a last target should be tried, which is the left dorsolateral prefrontal cortex (DLPFC).

The DLPFC target was initially defined as being located 5 cm anterior to the hand motor hotspot [27]. However, it has been proven that this distance was anatomically incorrect [9], the DLPFC being located about 7 cm (in average) anterior to the hand motor hotspot [1]. Beside this ''function-guided'' procedure, various imaging algorithms were proposed to define the DLPFC target using navigation systems, either at the junction between BA 9 and BA 46 [25] or within BA 46 [28]. Finally, a non-navigated procedure with high anatomical accuracy has been developed according to the F3 site of the International 10—20 system of EEG electrode location. A simple method to determine F3 location from only three scalp measurements was published (''Beam F3 site'') [7] associated with the development of a free web interface calculator (http://clinicalresearcher.org/F3/calculate.php). The stimulation of the left DLPFC should be performed with the same settings as for M1 stimulation, except the intensity of stimulation (100—110% of rMT in place of 80—90%) and the orientation of the coil (lateromedial orientation in place of anteroposterior) (Fig. 2C).

In the case of significant response to stimulation of any M1 or DLPFC target (according to aforementioned response criteria), a ''maintenance phase'' should be considered. This ''maintenance phase'' can be standardized as two sessions for one week, then one session in weeks 4 and 6, and a monthly session for the following months. However, we propose that the frequency of rTMS session during this ''maintenance phase'' should rather be based on a more individual rhythm, depending on the duration of analgesia produced by the treatment. Indeed, it is known that pain relief is maximal beyond the time of stimulation and lasts for several days after a single high-frequency rTMS session over M1 [4,17]. Thus, pain can be significantly controlled in the long-term in some patients even with rTMS sessions being widely spaced in time owing to prolonged after-effects [18].

Conclusion

The number of reports of rTMS therapy used in daily clinical practice to treat patients with chronic pain syndromes is increasing over time and extends worldwide [24]. Several series have been published to date showing long-term benefit from at least 6 months of high-frequency rTMS

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delivered over M1 in patients with chronic pain of various origins [3,10,12,23,29]. However, a consensus is still awaited regarding the parameters of stimulation and the detailed protocol to use. The practical algorithm proposed in this technical note (Fig. 3) is an attempt to serve as a guide for physicians wishing to perform rTMS therapy in pain patients. Of course, this proposal remains to be validated on a larger scale by other investigators and researchers.

Disclosure of interest

The authors declare that they have no competing interest.

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