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J. Neurol. Neurosurg. Psychiatry published online 25 Jan 2008;
doi:10.1136/jnnp.2007.135327

JNNP Online First, published on January 25, 2008 as 10.1136/jnnp.2007.135327

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Keywords: motor cortex stimulation, neuropathic pain, quantitative sensory testing, thermal sensation, transcranial magnetic stimulation.

ABSTRACT

Background: Improvement in sensory detection thresholds was found associated with neuropathic pain relief produced by epidural motor cortex stimulation with surgically implanted electrodes.
Objective: To determine the ability of repetitive transcranial magnetic stimulation (rTMS) of the motor cortex to produce similar sensory changes.
Methods: In 46 patients with chronic neuropathic pain of various origins, first-perception thresholds for thermal (cold, warm) and mechanical (vibration, pressure) sensation were quantified in the painful zone and in the painless homologue contralateral territory, before and after rTMS of the motor cortex corresponding to the painful side. Ongoing pain level was also scored before and after rTMS. Three types of rTMS session, performed at 1Hz or 10Hz using an active coil, or at 10Hz using a sham coil, were compared. The relationships between rTMS-induced changes in sensory thresholds and in pain scores were studied.
Results: Subthreshold rTMS applied at 10Hz significantly lowered pain scores and thermal sensory thresholds in the painful zone but not mechanical sensory thresholds. Pain relief correlated with post-rTMS improvement of warm sensory threshold in the painful zone.
Conclusions: Thermal sensory relays are potentially dysfunctioning in chronic neuropathic pain secondary to sensitisation or deafferentation-induced disinhibition. By acting on these structures, motor cortex stimulation could relieve pain and concomitantly improve innocuous thermal sensory discrimination.

Epidural motor cortex stimulation (MCS) is an option for the treatment of refractory neuropathic pain.[1] However, the mechanisms by which MCS impacts on pain processing remain unclear. In patients with surgically-implanted epidural MCS, we previously found that switching 'on' the stimulator significantly lowered first-perception sensory thresholds in the painful zone, particularly in patients who were 'good responders' for the procedure.[2] From this observation, we suggested that MCS analgesic effects was associated with the modulation of sensory perception in the painful zone. Non-invasive stimulation of the motor cortex using repetitive transcranial magnetic stimulation (rTMS) at high frequency (10-20Hz) can also produce analgesic effects.[3] Whether these analgesic effects are associated with perception changes in the painful zone as for epidural MCS remains to demonstrate. Herein, a series of 46 patients with chronic neuropathic pain of various origins was studied. Detection thresholds for innocuous thermal (cold, warm) and mechanical (vibration, pressure) sensations were quantified before and after a session of rTMS delivered to the motor cortex. Sensory thresholds were measured in the painful zone and the non-painful contralateral homologue territory, while rTMS was applied over the motor cortex corresponding to the painful side. The effects of high (10Hz) and low (1Hz) frequencies of stimulation were compared to a sham condition. The influence of the localisation and origin of pain and that of the severity and type of sensory loss in the painful zone were also studied.

PATIENTS AND METHODS

Patients

The study included 46 right-handed patients (23 women, 23 men), aged from 27 to 79 years (mean 54.2 years), with chronic, unilateral, neuropathic pain. All patients were resistant to at least two drug classes used as first-line treatment of neuropathic pain for more than one year. They were receiving medication at the time of the study, including anticonvulsant drugs or benzodiazepins: bromazepam (n=4), carbamazepine (n=9), clonazepam (n=25), clorazepam (n=3), gabapentine (n=16), oxazepam (n=1); morphinics: buprenorphine (n=2), codeine (n=3), dextropropoxyphene (n=11), fentanyl (n=2), morphine sulfate (n=7), tramadol (n=4); antidepressants: amitriptyline (n=3), clomipramine (n= 21), fluoxetine (n=1), paroxetine (n=1); paracetamol (n=14). The patients had no past history of seizure. They have been referred to our hospital in order to evaluate the indication of surgical implantation of epidural electrodes for chronic MCS. This study was set up within the framework of a research program on neuropathic pain treatment by cortical stimulation. This program has received authorization from national and local ethical committees.

Regarding the site and origin of pain, the patients were divided into four subgroups: a group of patients with facial pain secondary to surgical or traumatic lesion of the trigeminal nerve (n=13), a group of patients with upper limb pain secondary to surgical, radiation-induced or traumatic lesion of the brachial plexus (n=10), a group of patients with pain predominating at upper limb secondary to thalamic stroke (n=13), a group of patients with lower limb pain secondary to syringomyelia or ischemic spinal cord lesion (n=10).

Quantitative sensory testing and pain scoring

Sensory perception was assessed within fifteen minutes before and after each rTMS session. In all cases, the examiner was blinded to the type of rTMS administered. First-perception sensory thresholds for cold sensation, warm sensation, vibration and pressure were measured in the area of maximal pain and in the non-painful contralateral homologue area. A 16 cm^2 Peltier probe attached to a TSA 2001 apparatus (Medoc, Ramat Yishai, Israël) was applied to the skin for the measurement of thermal thresholds (in °C). This device was able to produce cooling (down to 0°C) or heating (up to 50°C) at a linear rate of 1°C/sec from a starting neutral temperature of 32°C. Vibration thresholds were measured using a VSA 3000 vibrameter (Medoc). The vibrator head was applied to the skin at constant force pressure and produced

vibration at fixed frequency of 100Hz and increasing amplitude (0.1–25 µm). An electronic Von Frey apparatus (EVF2, Bioseb, Chaville, France) was used for pressure thresholds. This device consisted of a filament of fixed diameter attached to a strain gauge handle and applied to the skin at increasing pressure (0.1–500 g). In all cases, the patients pressed a signal-button at first perception of the stimulus. Sensory thresholds were determined as the average value from five trials using the method of limits.[4] A severe sensory deficit was defined by a marked alteration of first-perception thresholds in the painful zone,[2] i.e. less than 22°C for cold threshold and more than 42°C for warm threshold, 10 µm for vibration, and 38 g for pressure.

Before and after each rTMS session, pain level was self-scored by the patient on a 0-10 visual analogue scale (VAS). Pain levels were scored immediately before sensory testing, even if the maximal analgesic effects of rTMS are usually delayed for some days.[5] Individual responses to rTMS in terms of pain relief were evaluated by calculating the percentages of pain score variation [(post-rTMS – pre-rTMS scores)/(pre-rTMS scores)], first for the 'active' and 'sham' 10Hz rTMS sessions, and then by subtracting 'active' – 'sham' results to take into account the placebo effect. A good responder to rTMS was defined by an 'active' – 'sham' percentage of pain relief greater than 30%.[6]

Repetitive TMS procedure

Three different sessions of rTMS, i.e. 'active' 10Hz, 'sham' 10Hz and 'active' 1Hz, separated by at least three weeks were performed in a random order. The study was designed to perform each of the six possible order combinations in eight patients and therefore, to include 48 patients. Unfortunately, two patients did not complete the study, which was finally based on 46 patients.

All rTMS sessions were identical in their course and performed using a Super-Rapid magnetic stimulator (Magstim Co., Whitland, Carmarthenshire, Wales, UK) and a figure-of-eight coil (70mm Double Coil 9925-00, Magstim). Motor evoked potentials were recorded using a standard EMG machine (Phasis II, EsaOte, Florence, Italy) and pre-gelled self-adhesive disposable surface electrodes (#9013S0241, Medtronic, Skovlunde, Denmark). First, the site of cortical stimulation that evoked motor responses of maximal amplitude in the first dorsal interosseus muscle of the painful side was determined using single TMS pulses. Then, the coil was maintained fixedly at this site throughout the whole rTMS session, using a specifically designed mechanical device. Like in a previous study,[6] rTMS was delivered over the motor cortical area corresponding to the hand of the painful side, whatever the site of pain. The coil was positioned tangentially to the surface of the head, with the handle pointing occipitally along a postero-anterior sagittal axis. The rest motor threshold (RMT) was defined as the minimal intensity of stimulation required to elicit motor evoked potentials of more than 50 µV in amplitude in five out of ten trials performed during complete muscle relaxation.[7]

One of the three following rTMS protocols was applied: (i) a series of 20 trains of 6 seconds in duration (54-second intertrain interval) at a stimulation rate of 10Hz and at an intensity of 90% RMT using an 'active' coil (1200 pulses); (ii) the same protocol using a 'sham' figure-of-eight coil (Placebo Coil System 1730-23-00, Magstim); (iii) a single train of 20 minutes in duration at 1Hz and 90% RMT using an 'active' coil (1200 pulses). As placebo control, we preferred to use a sham coil than to hold an active coil at 45 degrees away from the skull, because this latter condition was found to produce substantial stimulation of the cortex.[8] The patients were not instructed about the existence of a 'sham' condition, but were informed that three rTMS sessions using different parameters of stimulation had to be tested for their respective efficacy in relieving pain.

Statistical analyses

Sensory thresholds and pain scores were analysed with repeated measures ANOVA under six conditions that resulted from the combination of two nominal variables as within-subject

factors: “Treatment”, with three group levels (10Hz, 1Hz and sham), and “Time”, with two group levels (before and after). In a second time, were introduced as between-factors: (i) the site and origin of pain (four subgroups) and (2) the severity and type of sensory loss within the painful zone (three subgroups). In addition, post-hoc tests were applied with Bonferroni’s correction ($P<0.0033$).

The influence of the site and origin of pain on the one hand, and the severity and type of sensory loss on the other hand, on the rate of responders to rTMS was studied with the chi-squared test. The correlation between the changes induced by rTMS in sensory thresholds and in pain scores was analysed with the Pearson test. The level of *P* significance was set at 0.05 for these analyses.

RESULTS

Severity and type of sensory loss within the painful zone

According to the severity and type of sensory loss determined preoperatively by quantitative sensory testing within the painful zone, patients were divided into three subgroups: group A, without severe thermal or mechanical deficit (n=15, including three patients with trigeminal nerve lesion, three patients with brachial plexus lesion, seven patients with thalamic stroke, and two patients with spinal cord lesion); group B, with severe mechanical but not thermal deficit (n=13, including eight patients with trigeminal nerve lesion, two patients with thalamic stroke, and three patients with spinal cord lesion); group C, with severe mechanical and thermal sensory deficit (n=17, including two patients with trigeminal nerve lesion, seven patients with brachial plexus, three patients with thalamic stroke, and five patients with spinal cord lesion). Only one patient (with thalamic stroke) presented severe thermal but no mechanical deficit. This patient was discarded from further analyses regarding the influence of the severity and type of sensory loss within the painful zone on rTMS efficacy.

Effects of rTMS on sensory thresholds and pain

Significant effects of ‘Treatment’ and ‘Time’ were observed for thermal (cold, warm) thresholds measured in the painful zone and for pain scores (repeated measures ANOVA, $P<0.01$), with a significant Treatment x Time interaction (table 1). In contrast, there were no significant variations between the conditions for mechanical (vibration, pressure) thresholds in the painful zone and for any sensory modality in the non-painful, contralateral zone.

Post-hoc tests revealed that both thermal thresholds and pain scores improved after ‘active’ 10Hz rTMS (Bonferroni’s post-tests, $P=0.0005$ and 0.0001 for cold and warm thresholds, respectively, and $P<0.0001$ for pain scores, table 1). For cold modality, thresholds increased in 35 patients, remained stable in 4, and were reduced in 7 patients. For warm modality, thresholds were reduced in 30 patients, remained stable in 5, and increased in 11 patients. Finally, pain scores were reduced in 33 patients, remained stable in 7, and increased in 6 patients. In contrast, thresholds and pain scores did not vary after ‘active’ 1Hz or ‘sham’ rTMS (Bonferroni’s post-tests, $P>0.0033$). There were also no significant differences between the various pre-rTMS values, even if pressure thresholds appeared to be not as stable as the thresholds measured for the other sensory modalities.

The changes induced by rTMS in sensory thresholds were not influenced by the localisation and origin of pain when considered as ANOVA between-factor. In contrast, the severity and type of sensory loss within the painful zone significantly interacted with rTMS-induced changes in cold thresholds (repeated measures ANOVA, $F(4,43)=2.53$, $P=0.046$). Cold perception in the painful zone specifically improved after ‘active’ 10Hz rTMS in the group of patients with severe mechanical and thermal sensory deficit (group C) (Bonferroni’s post-tests, $P<0.0033$).

The mean decrease in VAS score induced by 10Hz-rTMS was greater in patients with trigeminal neuropathic facial pain (-2.1) than in patients with limb pain due to brachial plexus

lesion (-1.7), thalamic stroke (-1.1), or spinal cord lesion (-1.5). Regarding the influence of sensory loss in the painful zone, patients of group B showed greater VAS score decrease following 10Hz-rTMS (-2.4) than patients of group A (-1.3) or C (-1.4). Patients of group B had severe mechanical but not thermal deficit. Eight of these 13 patients presented trigeminal neuropathic facial pain. However, none of these group differences regarding VAS score changes induced by rTMS was found to reach the level of statistical significance.

Table 1: Mean (± s.e.m.) values of first-perception thermal and mechanical sensory thresholds measured in the painful zone and the homologue, non-painful, contralateral zone, and of pain levels scored on a visual analogue scale (VAS), before and after 'active' 10Hz, 1Hz and 'sham' repetitive transcranial magnetic stimulation (rTMS) of the motor cortex corresponding to the painful side. The results are presented for the entire series of patients (n=46). Statistical comparisons used repeated measures (rm-) ANOVA, followed by Bonferroni's post-hoc tests. *P* values indicating significant differences are underlined. ANOVA disclosed significant variation for cold and warm thresholds of the painful zone, and for pain scores. Post-hoc tests showed that these parameters were significantly modified only by 10Hz rTMS.

	10Hz rTMS		**1Hz rTMS**		**Sham rTMS**		**rm-ANOVA**
	Pre-rTMS	**Post-rTMS**	**Pre-rTMS**	**Post-rTMS**	**Pre-rTMS**	**Post-rTMS**	**Treatment x Time (*F*(2,45)), *P***
Painful side:							
Cold threshold (°C)	22.1 ± 1.5	24.4 ± 1.3	22.4 ± 1.5	22.4 ± 1.6	22.4 ± 1.5	22.7 ± 1.5	(4.77), 0.011
Warm threshold (°C)	41.0 ± 0.9	39.4 ± 0.8	40.6 ± 0.9	40.2 ± 0.9	40.7 ± 0.9	40.5 ± 0.9	(5.25), 0.007
Vibration threshold (µm)	12.5 ± 1.3	11.5 ± 1.3	11.9 ± 1.3	12.0 ± 1.4	12.6 ± 1.4	11.9 ± 1.4	(2.30), 0.106
Pressure threshold (g)	74.0 ± 14.4	65.0 ± 14.0	70.5 ± 13.4	73.9 ± 14.4	66.3 ± 13.3	62.3 ± 13.3	(2.26), 0.113
Contralateral side:							
Cold threshold (°C)	29.0 ± 0.4	29.3 ± 0.3	29.1 ± 0.4	29.1 ± 0.4	29.3 ± 0.3	29.2 ± 0.4	(1.24), 0.295
Warm threshold (°C)	35.7 ± 0.4	35.6 ± 0.4	35.6 ± 0.3	35.5 ± 0.3	35.4 ± 0.3	35.6 ± 0.3	(1.24), 0.295
Vibration threshold (µm)	8.5 ± 1.2	8.4 ± 1.2	8.6 ± 1.1	8.2 ± 1.1	8.4 ± 1.1	8.4 ± 1.2	(0.52), 0.596
Pressure threshold (g)	9.4 ± 1.4	9.2 ± 1.7	9.3 ± 1.3	9.2 ± 1.2	9.4 ± 1.3	9.3 ± 1.3	(0.00), 0.998
VAS pain scores:	6.6 ± 0.3	5.0 ± 0.4	6.5 ± 0.2	6.1 ± 0.3	6.4 ± 0.3	5.8 ± 0.3	(13.64), <0.0001

Individual results to rTMS sessions

Regarding individual results, 12 patients were characterized as 'good responders' to 10Hz rTMS, but none to 1Hz or sham rTMS. Five of the good responders to 10Hz rTMS had facial pain due to trigeminal nerve lesion (38% of this group of patients). The seven remainders were equally representative of the groups of patients with upper or lower limb pain due to thalamic stroke, brachial plexus or spinal cord lesion (23% to 25% of these groups). Despite this higher percentage of responders in case of trigeminal neuropathic pain, we failed to find a significant influence of the site and origin of pain (chi-squared test, P=0.69).

Regarding the severity and type of sensory loss within the painful zone, 10 good responders had severe mechanical deficit: five patients of the group B (38% of this group with severe mechanical but not thermal deficit) and five patients of the group C (29% of this group with concomitant severe thermal deficit). The two remainders were from the group A (13% of this group without any severe sensory deficit). The severity and type of sensory loss did not influence the rate of rTMS responders (chi-squared test, P=0.23).

Relationship between rTMS effects on pain level and sensory thresholds

When the values obtained for the 'active' or the 'sham' 10Hz rTMS session were considered separately, no correlation was found between rTMS-induced changes in pain scores and in sensory thresholds, ipsilateral or contralateral to the stimulation. However, when the values obtained by subtraction between the two sessions ('active' – 'sham' rTMS session) were considered, pain relief was found to correlate to the improvement in warm threshold within the

painful zone (*P*= 0.001, Pearson test, table 2). No other significant correlation was observed between 'active' – 'sham' changes in pain scores and in sensory thresholds.

Table 2: Correlation coefficient and *P* significance of the Pearson correlation test between sensory threshold and pain score changes induced by repetitive transcranial magnetic stimulation (rTMS) of the motor cortex. The difference between 'active' and 'sham' 10Hz sessions was considered.

Correlation between rTMS-induced changes	**Pain scores**	
Sensory thresholds	**r**	***P***
Painful side:		
Cold threshold	0.02	0.89
Warm threshold	0.47	0.001
Vibration threshold	0.22	0.15
Pressure threshold	0.05	0.76
Contralateral side:		
Cold threshold	0.09	0.64
Warm threshold	-0.10	0.52
Vibration threshold	0.10	0.53
Pressure threshold	0.06	0.70

DISCUSSION

Motor cortex stimulation improved thermal sensory perception in the painful zone

This study mainly showed that subthreshold high-frequency rTMS (but not low-frequency rTMS) applied to the motor cortex improved thermal sensory perception in the painful region of patients with chronic, drug-resistant, neuropathic pain. Moreover, warm sensation perception improvement correlated with pain relief.

Pain is a powerful distracter. Therefore, pain decrease may have helped patients to reallocate their attention to cutaneous sensory perception, leading to sensory threshold improvement. The selectivity of improvement observed in this study (only for thermal thresholds), argued against a mechanism due to the reduction of an unspecific pain-related distracter effect. However, such mechanism could have been modulated according to pain relief characteristics. The reduction of a burning pain, for instance, could have competed with warm threshold measurement, as the reduction of a freezing pain with cold threshold. Pain characteristics were not assessed in detail, but the selective thermal sensory changes observed in this study were unlikely to be explained by a particular representation of thermal descriptors regarding baseline pain.

Perception thresholds have been recorded using the method of limits, which is a 'reaction-time inclusive' technique.[9] This should be noticed because high frequency rTMS can shorten reaction time in patients.[10] However, reaction time shortening could not explain that only thermal and not mechanical thresholds have been affected by rTMS in this study.

Previous studies showed that various TMS protocols applied to the motor cortex could modulate the perception of innocuous, sensory stimuli in healthy subjects. First, it was reported that single TMS pulses applied to hand motor cortical area could reduce or block the perception of non-painful electrical stimuli delivered to the index finger, contralateral to TMS pulses.[11-13] Paradoxically, single TMS pulses rather increased the amplitude of somatosensory evoked potentials (SEPs) for the intervals between TMS and peripheral stimulation that result in sensory perception attenuation.[14,15] In contrast to single pulses, subthreshold low-frequency rTMS (0.9-1Hz) reduced both tactile sensory perception and SEP amplitude.[16,17] Regarding thermal sensation, cold detection thresholds decreased (when expressed in absolute values of temperature, i.e. increased when expressed in differential values with respect to the starting temperature of 32°C) following motor cortex rTMS in healthy volunteers, whatever stimulation frequency (1, 5, or 20Hz).[18,19] In patients with chronic low back pain, a single

rTMS session applied at 20Hz over the motor cortex also reduced cold perception thresholds (expressed in absolute values of temperature).[20] In these studies, there was only a slight, and not significant increase in warm detection thresholds,[19,20] suggesting that motor cortex rTMS attenuated thermal stimulus perception at different magnitudes according to A-delta (cold) or C (warm) fibre mediation. Conversely, in the present study, motor cortex rTMS improved thermal stimulus perception, equally for cold and warm modalities. Thus, the impact of motor cortex stimulation on sensory perception is likely to depend on the existence of neurological lesions at the origin of pain.

Relationship between thermal sensory perception improvement and pain relief induced by motor cortex stimulation

At least for warm modality, this study showed that rTMS-induced modulation of sensory perception was associated with pain relief. The motor cortex is potentially connected to various structures involved in both innocuous and noxious sensory processing, located at various regions of the central nervous system, e.g., in dorsal horn, brainstem, or thalamus. Experimental animal studies suggested that MCS could modify neuronal activity at all these anatomical levels, but only a few studies were performed in models of neuropathic pain. These experiments mainly showed that MCS could reduce hyperactivity secondary to deafferentation or provoked pain in thalamic relays.[21-23]

The existence of thalamic neuronal hyperactivity in humans with chronic neuropathic pain was confirmed by single-unit recordings during functional stereotactic procedures.[24-26] Spontaneous pain was thought to be associated with a burst-firing pattern in the thalamus, even if thalamic bursts have been also observed in patients without pain.[27] Bursts may correspond to abnormal synchronization between the thalamus and the cortex or within the thalamus.[28] Via corticothalamic projections and intrathalamic connections, MCS could reduce thalamic hyperactivity or interfere with abnormal thalamo-thalamic or thalamo-cortical oscillations. Consequently, these changes will contribute to relieve spontaneous pain.

Positron emission tomography showed in patients with chronic neuropathic pain that epidural MCS led to regional cerebral blood flow changes in thalamus, anterior cingulate and orbitofrontal cortical regions, insula, and upper brainstem.[29] Functional imaging also showed that most or all of these structures were involved in both innocuous and noxious thermal sensation processing.[30-32] More specifically, stereotactic microstimulation revealed that thermal and pain sensations were processed in similar thalamic region.[33]

By acting on those structures involved in thermal sensory processing, motor cortex rTMS could improve innocuous thermal sensory discrimination concomitantly with pain relief. In contrast, the absence of any significant changes in mechanical sensory perception excludes a mechanism of reinforcement of the lemniscal 'gate control' over the nociceptive system. The functional integrity of the lemniscal system is required for the efficacy of neuromodulation strategies targeting the dorsal columns,[34] but not the motor cortex.

The relevance of this discussion is based on possible similarities between epidural MCS and non-invasive rTMS, in particular regarding the type of activated circuits and structures. However, these two techniques are not equivalent, considering, for instance, the range of stimulation frequencies (10-20Hz for rTMS vs. 40-60Hz for MCS) or the geometry of the induced current delivered into the brain, leading to different targeting strategies.[35] Thus, similar behavioural effects (i.e., pain relief) produced by MCS and rTMS could originate from different mechanisms of action.

Factors influencing sensory perception and pain level changes induced by motor cortex stimulation

The severity and type of sensory loss within the painful zone mildly interacted with the results: cold perception improved after 'active' 10Hz rTMS more particularly in the group of patients

with severe mechanical and thermal sensory deficit. Thermal sensory loss was found to be one of the main clinical features associated with neuropathic pain in case of stroke,[36-39] trigeminal neuralgia,[40] or spinal cord injury.[41,42] These observations suggested that spinothalamic tract alteration was necessary for the development of central pain. We did not confirm that neuropathic pain was closely linked to an altered perception of thermal sensation at baseline, since only one patient presented pure thermal deafferentation, while predominantly severe mechanical sensory deficit was observed in 13 patients. Sensory deficit was equally affecting both thermal and mechanical modalities in the remainders, sensory loss being severe in 17 patients and mild to moderate in 15 patients. In fact, similar thermal deficits can be observed in patients with or without pain.[43,44] There is no exclusive association between any pattern of sensory changes and the development of neuropathic pain of peripheral or central origin.[45]

In a previous study,[6] motor cortex rTMS targeted on hand area was found to produce better analgesic effects in case of facial versus limb pain. Using a similar design, this study also revealed a greater VAS score decrease and a higher percentage of rTMS responders in the group of patients with trigeminal neuropathic facial pain than in the other groups. However, these results did not reach statistical level of significance in the present study compared to the previous one, probably due to methodological differences (group sizes, statistical tests).

Conclusion

Subthreshold rTMS applied at 10Hz (but not at 1Hz) over the motor cortex improved thermal sensory perception in patients with refractory chronic neuropathic pain. The changes in thermal thresholds were selective (mechanical thresholds remained unchanged) and associated with pain relief, at least for warm modality. Even if neuropathic pain was not strictly dominated by abnormal temperature sensitivity in the present series, the modulation of thermal sensory perception within the painful zone was found to interact with the analgesic efficacy of cortical stimulation. A similar observation was made in patients who were 'good responders' for chronic epidural MCS.[2] Motor cortex rTMS seemed to mimic the effects of chronic epidural MCS and therefore, the determination of rTMS ability to improve thermal sensory discrimination in the painful zone could predict the good outcome of a subsequent surgical procedure. Further studies are needed to confirm this hypothesis.

Acknowledgments: The work was granted by the 'Institut UPSA de la douleur'.

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