The antalgic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone

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Summary
Epidural motor cortex stimulation (MCS) could achieve good pain control in patients with drug-resistant chronic neurogenic pain. In the search for parameters associated with the favourable outcome of this surgical procedure, quantitative sensory testing was performed in a series of 31 patients treated by MCS for chronic pain. Non-nociceptive and nociceptive sensory thresholds were measured in the painful area and its contralateral homologous zone with the stimulator in ‘off’ and in ‘on’ position. All 13 patients who exhibited normal or quite normal non-nociceptive thermal thresholds within the painful area benefited from MCS. Of the remaining 18 patients with altered thermal sensory thresholds, eight patients nevertheless experienced good pain control by MCS. In these eight ‘good responders’, sensory thresholds were improved by switching ‘on’ MCS. In contrast, the last 10 patients showed abnormal thermal thresholds that were not modified by switching ‘on’ MCS, and did not respond clinically to MCS. Therefore, ‘good responders’ to MCS could be identified by the absence of alteration of non-nociceptive sensory modalities within the painful area, or by abnormal sensory thresholds that could be improved by MCS. These results additionally suggest that MCS acts on neural pathways involved in sensory discrimination that, in turn, are able to modulate the transmission of pain signals.

Keywords: chronic pain; clinical neurophysiology; deafferentation; motor cortex stimulation; quantitative sensory testing

Abbreviations: MCS = motor cortex stimulation; TMS = transcranial magnetic stimulation

Introduction
Chronic motor cortex stimulation (MCS) using implanted epidural electrodes has been shown to achieve good pain control in patients with previously intractable neurogenic pain (Tsubokawa et al., 1991, 1993; Meyerson et al., 1993; Nguyen et al., 1997). Although clinical results are altogether encouraging (Mertens et al., 1999; Nguyen et al., 1999; Carroll et al., 2000), some patients do not benefit from this form of neuromodulation therapy, and the characteristics of the patients who do not respond favourably to MCS are as yet unidentified.

In addition, the mechanisms underlying the pain control afforded by MCS remain largely unknown. PET imaging has revealed an activation of the anterior cingulate cortex [Brodmann area (BA) 32 region] by MCS (Peyron et al., 1995; Garcia-Larrea et al., 1999), suggesting that its analgesic effects may be mediated through a reduction of the affective-emotional components of pain in which this cortical area plays a well documented role (reviewed in Devinsky et al., 1995). However, the gate control theory proposes that pain signals are modulated by concurrent somatic inputs as well as by descending influences from the brain (Melzack, 1999). In the case of deafferentation or central pain, the anatomical and/or physiological connections between non-nociceptive fast-conducting sensory afferents and the transmission of noxious signals are altered. The existence of sensory loss within a painful area is a well-known feature of these alterations (Tasker, 1982), and it may be hypothesized that MCS restores, at least partially, the relationship between non-nociceptive and nociceptive sensory processing.

The present study has been designed on the basis of this latter hypothesis: since MCS could improve the control...
exerted by non-nociceptive sensory afferents on pain pathways, ‘good’ and ‘bad’ responders may demonstrate either differential preservation of sensory thresholds or differential effects of MCS upon these thresholds. Therefore, thermal and mechanical sensory thresholds were measured in 31 patients who had undergone MCS, with either good or poor outcome, while the stimulator was switched ‘on’ or ‘off’.

Patients and methods

Patients
Thirty-one patients who had undergone MCS for pain control between 1993 and 2000 were recruited into this study. They all gave informed consent to participate in the study which was approved by the local ethics committee. A general description of the patients is presented in Table 1, and shows, in particular, that most of the patients in the group of peripheral nervous system disorders had trigeminal neuralgia (13 of 18 patients) and that most of the patients in the group of CNS disorders had post-stroke pain (10 of 13 patients).

The implantation of the stimulator had been performed using neuro-navigation guidance and electrophysiological mapping by means of somatosensory and motor evoked potentials, as described elsewhere (Nguyen et al., 1999, 2000). The chronic stimulation was performed with an Itrel system (Itrel II; Medtronic, MA, USA) delivering monophasic square pulses (duration, 60 μs; frequency, 40 Hz; intensity, 1–3 mV) in a cycling mode (3 h of ‘on’ period alternating with 3 h of ‘off’ period). Parameters were individually adapted to the best pain control.

The patients were assessed clinically for pain level using a 0–10 visual analogue scale, pre-operatively and at least three times from 6 to 18 months post-operatively. As described previously (Nguyen et al., 1999), the patients were characterized as ‘good responders’ when a reduction of the mean pain level by >40% was recorded, and as ‘bad responders’ when the reduction was <40%.

Quantified sensory testing
The sensory thresholds for innocuous and noxious thermal stimulation were measured by the methods of limits using a TSA 2001 apparatus (Medoc, Ramat Yishai, Israel). A 16 cm² Peltier probe was applied to the skin and produced heating or cooling with a linear rate of 1°C/s. After an adaptation period at a neutral temperature of 32°C, temperature increased (up to 50°C) or decreased (down to 0°C) until the patient pressed a signal-button at the first perception of thermal sensation (warm and cold thresholds), and then again at pain perception (heat and cold pain thresholds). The thresholds, expressed in degrees centigrade, were calculated as the average value of five consecutive trials.

Vibratory thresholds were additionally measured using a VSA 3000 vibrameter (Medoc). This computerized device vibrated at a constant frequency (100 Hz), with an amplitude increasing from 0 to 25 μm. The vibrator head was placed over the skin at a constant force pressure and the patient was asked to press a signal-button immediately at the first perception of vibration. The vibratory threshold, expressed in micrometers, was defined as the mean of five consecutive trials.

Skin sensory thresholds were measured over the most painful area of the skin and over the homologous contralateral area. Two sensory testing sessions were performed in a randomized order, 20–30 min after stimulator extinction (‘off’ condition) and 20–30 min after the stimulator had been turned on (‘on’ condition). These examinations were performed using a double blind procedure. First, the switch of the stimulator was manipulated by a physician (not the one performing the sensory testing session). Secondly, the patients did not experience any sensory or motor sensation at stimulator switching, and therefore could not detect it.

Statistical analysis was carried out using the Wilcoxon signed rank test, with a 95% confidence limit.

Results
In the present series of 31 patients treated by MCS, good pain control was achieved in 21 patients (21 ‘good responders’, 12 with peripheral neuropathy and nine with central lesion), but not in the other 10 patients (10 ‘bad responders’, six with peripheral neuropathy and four with central lesions).

Sensory testing in ‘off’ MCS condition
Sensory testing when performed in ‘off’ condition defined two groups of patients.
Wilcoxon signed rank test. Statistical comparison [threshold measured in the painful side versus the contralateral side (pain versus contra)] was using the

Patients have been split into two groups, on the basis of the preservation (Group 1, \( n = 13 \)) or the alteration (Group 2, \( n = 18 \)) of non-nociceptive sensory thresholds within the painful area. All patients in Group 1 were ‘good responders’ to MCS. Group 2 has been further subdivided according to the pain relief obtained with MCS, into Group 2a (\( n = 8 \), ‘good responders’, and Group 2b (\( n = 10 \), ‘bad responders’). Statistical comparison [threshold measured in the painful side versus the contralateral side (pain versus contra)] was using the Wilcoxon signed rank test. \( P \) values indicating significant differences are in bold.

The first group (Group 1) included 13 patients. The non-nociceptive thermal thresholds measured in the painful area were close to normal values and were not significantly different from the thresholds measured in the homologous contralateral zone (Table 2). All 13 of these patients responded favourably to MCS.

The second group (Group 2) included 18 patients. The non-nociceptive thermal thresholds in the painful zone were largely outside the normal range, at the level of normal noxious thresholds (>44°C for warm thresholds and <20°C for cold thresholds). These highly elevated non-nociceptive thermal thresholds were significantly altered compared with the opposite side. Of these 18 patients, eight demonstrated satisfactory pain relief with MCS (Group 2a), whereas the other 10 patients formed the group of ‘bad responders’ (Group 2b) (Table 2).

### Table 2 Mean (± SEM) sensory thresholds in ‘off’ condition in the painful area and in the homologous area on the opposite side of the body

<table>
<thead>
<tr>
<th></th>
<th>Cold threshold</th>
<th>Warm threshold</th>
<th>Vibratory threshold</th>
<th>Cold pain threshold</th>
<th>Heat pain threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
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<tr>
<td>Painful side</td>
<td>28.2 ± 0.6</td>
<td>36.3 ± 0.6</td>
<td>16.3 ± 2.1</td>
<td>14.3 ± 3.2</td>
<td>45.8 ± 1.0</td>
</tr>
<tr>
<td>Contralateral side</td>
<td>29.2 ± 0.6</td>
<td>34.9 ± 0.6</td>
<td>15.4 ± 2.1</td>
<td>18.7 ± 2.8</td>
<td>43.5 ± 1.3</td>
</tr>
<tr>
<td>Pain versus contra (( P ) value)</td>
<td>0.08</td>
<td>0.06</td>
<td>0.68</td>
<td>0.41</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Group 2a</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Painful side</td>
<td>8.0 ± 3.1</td>
<td>48.7 ± 0.8</td>
<td>12.6 ± 3.8</td>
<td>1.2 ± 1.2</td>
<td>50.3 ± 0.2</td>
</tr>
<tr>
<td>Contralateral side</td>
<td>25.7 ± 2.1</td>
<td>38.1 ± 1.3</td>
<td>7.3 ± 1.8</td>
<td>6.8 ± 3.3</td>
<td>46.7 ± 1.5</td>
</tr>
<tr>
<td>Pain versus contra (( P ) value)</td>
<td><strong>0.02</strong></td>
<td><strong>0.008</strong></td>
<td>0.15</td>
<td>0.31</td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td><strong>Group 2b</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painful side</td>
<td>7.3 ± 3.7</td>
<td>49.7 ± 0.6</td>
<td>18.3 ± 2.6</td>
<td>1.3 ± 0.8</td>
<td>50.1 ± 0.4</td>
</tr>
<tr>
<td>Contralateral side</td>
<td>24.1 ± 2.9</td>
<td>38.5 ± 1.5</td>
<td>18.6 ± 2.4</td>
<td>12.7 ± 2.5</td>
<td>46.7 ± 1.3</td>
</tr>
<tr>
<td>Pain versus contra (( P ) value)</td>
<td><strong>0.004</strong></td>
<td><strong>0.004</strong></td>
<td>0.46</td>
<td><strong>0.004</strong></td>
<td><strong>0.015</strong></td>
</tr>
</tbody>
</table>

The main result of this study is the demonstration that patients who experienced an antalgic effect from MCS showed either a preservation of non-nociceptive sensory thresholds within the painful area or a better sensory discrimination by switching ‘on’ the stimulator. In contrast, the lack of efficacy of MCS was associated with altered sensory thresholds that are not receptive for improvement by MCS, probably due to more severe disturbances of the sensory systems. This strongly suggests that MCS modulates the transmission of pain signals, at least by acting on neural pathways involved in sensory discrimination.

**Discussion**

Pain inhibition is achieved by MCS at an intensity below the threshold for muscle contraction and in the absence of any evoked sensation, at least when the stimulation is strictly pre-central (Peyron et al., 1995). An initial hypothesis was that MCS could activate non-nociceptive neurones within the sensory cortex, in an orthodromic or antidromic manner (Tsubokawa et al., 1993). However, MCS was not shown to produce any significant cerebral blood flow changes in the parietal cortex, suggesting that the sensory cortex was not the key structure (Peyron et al., 1995; Garcia-Larrea et al., 1999). On the other hand, these PET studies exhibited a major involvement of the medial thalamus, the anterior cingulate cortex, the anterior insula and the upper brainstem. In addition, the attenuation of RIII spinal nociceptive reflex during MCS supported the hypothesis that MCS could exert an inhibitory control mediated by descending pathways down
to the spinal cord segments (Peyron et al., 1995; García-Larrea et al., 1999).

Indeed, some anatomical and/or physiological connections have been described between the motor cortex and various structures involved in sensory processing, such as the thalamic sensory nuclei (Shin and Chapin, 1990) and the dorsal column nuclei of the spinal cord (Shin and Chapin, 1989). These projections were found to be mostly inhibitory (Coulter et al., 1974; Andersen et al., 1986; Shin and Chapin, 1989, 1990). However, in experimental models or clinical cases of deafferentation pain, electrophysiological recordings have shown the existence of an abnormal neuronal hyperactivity in these structures (Guilbaud et al., 1990; Lenz et al., 1994; Jeanmonod et al., 1996; Miki et al., 1998). This hyperactivity was thought to disturb the control exerted by non-nociceptive sensory afferents on pain pathways and then to contribute to the occurrence of noxious sensations. The stimulation of the motor cortex or of the pyramidal tracts within the internal capsule was found to reduce the deafferentation-induced neuronal hyperactivity in trigeminal nuclei or ventrobasal thalamic nuclei in rats and cats (Namba et al., 1988; Hirayama et al., 1990). Regarding the results of the present study, one could speculate that, by reducing neuronal hyperactivity interfering with sensory processing, MCS could relieve pain and improve sensory discrimination at the same time. Thus, MCS may act by reinforcing the control of non-nociceptive sensory inputs on nociceptive systems, at least when these sensory afferents are partially preserved.

In several patients with pain and severe sensory disturbances, MCS improved sensory discrimination, not in the painful area, but in the contralateral zone, i.e. ipsilateral to the stimulation. This situation was probably related to a profound reorganization of the somatosensory connections at various levels of the CNS that, in turn, could explain the lack of clinical efficacy of MCS. Thus, altered sensory thresholds within the painful zone may compromise the indication of MCS to relieve chronic pain in some cases.

Epidual MCS displays a number of attractive features compared with deep brain stimulation for pain therapy, e.g. thalamic targets (Hosobuchi et al., 1973; Hosobuchi, 1986), because the surgical procedure is safer and easier. However, to optimize the clinical results of this technique, there is a need to develop pre-operative criteria predicting its favourable outcome (Katayama et al., 1998). The present results suggest that pre-operative measurement of sensory thresholds may be of good predictive positive value. The absence of thermal sensory threshold alteration within the painful zone may be a feature predicting a favourable response to implanted MCS, as the absence of clinical motor weakness (Katayama et al., 1998). In contrast, a severe sensory loss within the painful zone could be taken into account when discussing the indication of MCS for pain control.

In addition, a non-invasive stimulation of the motor cortex could be performed pre-operatively using transcranial magnetic stimulation (TMS). TMS has recently been shown to have the capability to reproduce the antalgic effects of implanted MCS in patients with chronic neurogenic pain (Lefaucheur et al., 2001a, b). The analysis of TMS effects on non-nociceptive thresholds in patients with chronic pain is currently in progress in our centre, in the search for a reliable pre-operative screening of the good candidates for implantation.

In conclusion, this study showed MCS-induced pain relief to be associated with an improved sensory discrimination within the painful zone. MCS acts on somatosensory pathways and sensory processing according to the degree of sensory loss within the painful zone: patients displaying mild

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**Table 3 Mean differences (± SEM) between the sensory thresholds measured after switching ‘on’ MCS and those measured after switching ‘off’ in the painful area and in the homologous area on the opposite side of the body**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Cold threshold (P value)</th>
<th>Warm threshold (P value)</th>
<th>Vibratory threshold (P value)</th>
<th>Cold pain threshold (P value)</th>
<th>Heat pain threshold (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful side</td>
<td>+0.94 ± 0.8</td>
<td>−2.25 ± 0.8</td>
<td>−2.10 ± 2.0</td>
<td>+3.84 ± 2.3</td>
<td>−6.20 ± 2.9</td>
</tr>
<tr>
<td>On versus off</td>
<td>0.20</td>
<td>0.003</td>
<td>0.85</td>
<td>0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>Contralateral side</td>
<td>+0.01 ± 0.3</td>
<td>−0.49 ± 0.6</td>
<td>+0.51 ± 1.5</td>
<td>−1.64 ± 2.9</td>
<td>+0.17 ± 1.3</td>
</tr>
<tr>
<td>On versus off (P value)</td>
<td>0.84</td>
<td>0.45</td>
<td>0.20</td>
<td>0.68</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Group 2a

| Painful side | +6.72 ± 2.7 | −3.40 ± 1.4 | −2.29 ± 1.4 | +0.76 ± 2.0 | −1.43 ± 1.0 |
| On versus off (P value) | 0.03 | 0.03 | 0.16 | 0.44 | 0.50 |
| Contralateral side | +1.36 ± 1.1 | −0.63 ± 0.6 | −1.14 ± 1.0 | +1.39 ± 2.3 | −0.64 ± 1.4 |
| On versus off (P value) | 0.47 | 0.38 | 0.15 | 0.44 | 0.94 |

Group 2b

| Painful side | +2.42 ± 2.4 | −0.96 ± 0.6 | −0.78 ± 1.7 | +0.14 ± 0.9 | +0.11 ± 0.1 |
| On versus off (P value) | 0.38 | 0.13 | 0.64 | 1.00 | 1.00 |
| Contralateral side | +2.16 ± 0.9 | −1.12 ± 0.6 | −4.57 ± 1.6 | +1.25 ± 2.8 | −1.45 ± 1.3 |
| On versus off (P value) | 0.03 | 0.04 | 0.02 | 0.46 | 0.10 |

The three groups of patients are as defined in Table 2. Statistical comparison [between the values obtained in ‘on’ condition and those obtained in ‘off’ condition (on versus off)] were using the Wilcoxon signed rank test. P values indicating significant differences are in bold.
sensory loss showed more favourable response than patients with severe sensory loss within the painful area.

References


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