The Effect of a Series of Repetitive Transcranial Magnetic Stimulation of the Motor Cortex on Central Pain After Spinal Cord Injury

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Objective: To study the analgesic effect of repetitive transcranial magnetic stimulation (rTMS) of the motor cortex on central pain in patients with chronic spinal cord injury (SCI).

Design: Double-blind randomized controlled trial. Mean follow-up period was 4.5 weeks.

Setting: General hospital.

Participants: Twelve paraplegic patients due to thoracic SCI suffering chronic central pain (11 completed the study) who were randomly selected from a list of eligible patients.

Intervention: Real or sham 10 daily motor rTMS treatments (500 trains at 5Hz for 10s; total of 500 pulses at intensity of 115% of motor threshold) using figure-of-8 coil over the vertex.

Main Outcome Measures: Chronic pain intensity (visual analog scale [VAS], McGill Pain Questionnaire [MPQ]), pain threshold, and level of depression (Beck Depression Inventory).

Results: Both real and sham TMS induced a similar, significant reduction in VAS scores (P<.001) immediately after each of the 10 treatment sessions and in VAS and MPQ scores after the end of the treatment series. However, only real rTMS conferred a significant increase in heat-pain threshold (4°C, P<.05) by the end of the series. Most important, the reduction in MPQ scores in the real rTMS group continued during the follow-up period. Depression scores were equally reduced in both groups but similar to pain relief, depression continued to improve at follow-up in the real rTMS group.

Conclusions: Whereas the pain alleviation induced by a single rTMS treatment is probably due to placebo, patients with SCI may benefit from a series of rTMS treatments.

Key Words: Pain; Rehabilitation; Spinal cord injuries.

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TRAUMATIC INJURY TO the spinal cord generates severe motor, sensory, and autonomic disturbances. One of the worst consequences of a spinal cord injury (SCI) is the development of chronic pain below the level of the lesion.1-3 The chronic pain in the partially or completely paralyzed body regions, also termed “central pain,”2,12 is severe and excruciating and has considerable impact on daily activity and the quality of life. Most important, central pain is relatively resistant to pharmacologic and nonpharmacologic treatment.2,4,5

In recent years, electric stimulation of the motor cortex with implanted electrodes has been shown to affect chronic central pain.6-14 However, this brain stimulation procedure is both costly and invasive, which limits its application, and it might have additional side effects (eg, infections, intracranial hemorrhages). On the other hand, transcranial magnetic stimulation (TMS) is a noninvasive and relatively safe technology in which electromagnetic currents in a coil produce magnetic pulses that cross the scalp unimpeded and induce neuronal depolarization.15-17

Moreover, it has been suggested that repetitive TMS (rTMS) stimulates the motor cortex in a way similar to that produced by epidural stimulation.18 Migita et al8 found that in poststroke patients, magnetic coil stimulation of the motor cortex can predict the outcome of motor cortex stimulation by implanted epidural electrodes so that if TMS attenuated the pain, chronic motor cortex stimulation with an electrode array was effective and vice versa. This finding uncovered the potential of rTMS as a possible stand-alone treatment for central pain.

Indeed, several authors reported that a single session of motor rTMS19-22 or repeated single TMS23 can reduce the intensity of chronic pain by various degrees in patients with central poststroke pain (CPSP), central pain due to brain stem lesions, and SCI or pain of peripheral origin, although in 1 study, the difference between active and sham stimulation did not reach a significance level.24 In some cases, the analgesic effect lasted for several hours after treatment. No clear conclusions were drawn regarding the beneficial effect of a single rTMS treatment in patients with SCI and central pain.20,22,23 Nevertheless, because central pain is chronic, the transient short-term relief usually obtained with a single rTMS treatment is not sufficient. Therefore a series of rTMS treatments that could have potentially long-term effects on pain warranted investigation.

Only 2 such studies exist. One study was conducted on a single patient with peripheral pain,25 and the other on patients with trigeminal neuralgia or CPSP,26 both with very encouraging results. The long-term effect of rTMS on patients with SCI and central pain was not tested. Our aim was therefore to conduct a randomized controlled trial to evaluate both the acute and long-term analgesic effect of motor rTMS on central pain of spinal origin.

METHODS

Participants

Twelve patients with SCI participated in the study (average age, 54±6y). One patient withdrew due to logistic reasons;
therefore 11 patients completed the study. Patients were recruited from the outpatient population of the rehabilitation center, located at the general hospital (see patients' characteristics in Table 1). All patients were paraplegics with traumatic injury restricted to thoracic spinal segments, 2 patients with complete SCI, and 9 with incomplete SCI. Inclusion criteria were: (1) chronic traumatic closed or penetrating SCI; (2) chronic central pain of a minimum duration of 12 months (central pain was diagnosed according to its definition and characteristics); (3) pain not attributable to causes other than central (eg, peripheral inflammation, diabetes); and (4) pain resistant to medications of various kinds (eg, narcotics, antidepressants, anti-epileptic), physical and complementary medicine treatments.

The screening process for candidates was very strict for 2 reasons: (1) the side effects and contraindications of TMS, and (2) our desire to exclude patients suffering pain other than that of spinal cord origin. Therefore, patients having the following conditions were not included in the study: presence of chronic pain above lesion, acute pain anywhere in the body, family or personal history of epilepsy, other concomitant neurologic diseases, any kind of metal implants in the head and neck region, brain injury, heart diseases including cardiac pacemaker, pregnancy, psychiatric illnesses, and difficulties to communicate verbally and coherently or to understand instructions. In addition, patients on anticonvulsants and/or long-term benzodiazepines were not included unless they reported that the treatment was not effective and that they were willing to undergo a gradual washout period of 3 weeks prior to the experiment under the supervision of a specialist. Patients taking other pain medications (eg, nonsteroidal anti-inflammatory drugs, antidepressants, short-term benzodiazepines) were instructed not to change the dosage throughout the experiment and follow-up period. They were also asked to report if an urgent need to increase dosage occurred and to report the dose added as a result of such need.

Testing took place in a quiet room. Patients were seated in a comfortable armchair or in their wheelchair. All patients were trained for the sensory testing before the actual testing had started. In all patients, testing was conducted on the hands and legs, for example, body regions above and below the level of injury, respectively. All patients signed an informed consent for participation in the study. The study was approved by the human rights committee of the hospital.

### Table 1: Characteristics of the SCI Patients and Sensory Status Below the Lesion

<table>
<thead>
<tr>
<th>Patient</th>
<th>Group</th>
<th>Age (y)</th>
<th>Sex</th>
<th>SCI Level</th>
<th>Pain Topography</th>
<th>Sensations</th>
<th>Thermal</th>
<th>Mechanical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Real</td>
<td>60</td>
<td>Female</td>
<td>T12</td>
<td>Diffusely located in both legs</td>
<td>MO</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Real</td>
<td>47</td>
<td>Male</td>
<td>T4</td>
<td>Diffusely located in both legs</td>
<td>SE</td>
<td>SE</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Real</td>
<td>60</td>
<td>Female</td>
<td>T8</td>
<td>The entire body below the lesion</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Real</td>
<td>59</td>
<td>Male</td>
<td>T12</td>
<td>Diffusely located in both legs</td>
<td>SE</td>
<td>MI</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Real</td>
<td>60</td>
<td>Male</td>
<td>NA</td>
<td>Left leg</td>
<td>SE</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Real</td>
<td>51</td>
<td>Male</td>
<td>T6</td>
<td>Diffusely located in both legs</td>
<td>SE</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Sham</td>
<td>45</td>
<td>Male</td>
<td>T10</td>
<td>Thighs and shins</td>
<td>SE</td>
<td>MI</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Sham</td>
<td>60</td>
<td>Female</td>
<td>T4</td>
<td>Right leg and pelvis</td>
<td>MO</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Sham</td>
<td>55</td>
<td>Male</td>
<td>T5</td>
<td>The entire body below the lesion</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Sham</td>
<td>44</td>
<td>Male</td>
<td>T9</td>
<td>Buttock, both thighs and shins</td>
<td>MO</td>
<td>MI</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Sham</td>
<td>60</td>
<td>Female</td>
<td>T9</td>
<td>Diffusely located in both legs</td>
<td>SE</td>
<td>MO</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MI, mild alterations; MO, moderate alterations; NA, not available; P, preserved; SE, severe alterations.

*Complete SCI.

### Equipment

**Transcranial magnetic stimulation.** We conducted TMS of the motor cortex with a Neotonus magnetic stimulator connected to a figure-of-8 coil. Two coils were used; real and sham, both of which were identical in shape and produced a similar background noise. The coil was attached to a rigid frame by a ball and socket joint and adjustable clamps. The stimulation parameters could be preprogrammed, adjusted, and controlled.

**Thermal stimulator.** Thermal stimuli were delivered using a Peltier-based computerized thermal stimulator with 3×3cm contact probes. A passage of current through the Peltier element produces temperature changes at rates determined by an active feedback system. As soon as the target temperature is attained, probe temperature actively reverts to a preset adaptation temperature by passage of an inverse current. The adaptation (baseline) temperature was set to 35°C.

### Main Outcome Measures

**Chronic pain intensity.** We evaluated the intensity of chronic pain with a visual analog scale (VAS). The VAS consists of a 15-cm plastic ruler with a slider in the middle. Moving the slider exposes a horizontal red bar (the visual side) to the subject; the side facing the experimenter displays an analog scale with values between 0 and 10. The end points were set as “no pain sensation” and “the most intense pain sensation imaginable.” Patients were requested to slide the ruler to present their current pain intensity. This measurement was conducted before, every 5 minutes during each session, and immediately after each treatment session, in order to evaluate both the acute effect of each treatment as well as the effect of the series. In addition, patients were asked to report the degree of pain reduction perceived, in percent.

**Chronic pain experience.** To evaluate the sensory, affective, and cognitive components of the chronic pain, patients filled out the McGill Pain Questionnaire (MPQ). The MPQ provides a quantitative evaluation of the patient’s pain experience with a separate measure of its sensory, affective, and cognitive dimensions (a full description of the MPQ and its indices has been reported previously). In short, the MPQ has 3 parts. In the first part, the patient is asked to outline, on a body chart, the body regions from which chronic pain is perceived. The second part consists of a list of descriptors out of which 2 quantitative parameters can be derived: the pain...
rating index (PRI) is based on summing the values of the words chosen by the subject from the list, and the number of words chosen (NWC) from that list. In the third part, the subject is asked to rate the present pain intensity (PPI) on a 5-word and number scale. Each subject filled out the MPQ before the first treatment, after the 5th and 10th treatments to evaluate the effect of the series on the pain experience, and also at the end of the follow-up period in order to evaluate the long-term effect of the treatment.

Acute pain threshold. We measured the pain threshold in pain-free body regions above the lesion (subjects’ nondominant dorsal hand) and in painful body regions below the lesion level (subjects’ lateral shin), by means of a thermal stimulator, using the method of limits. For threshold determination, patients received 4 successive, increasing stimuli, starting from an adaptation temperature of 35°C, at a rate of 2°C per second with interstimulus intervals of 30 seconds. The subject was asked to press a switch at the first pain sensation perceived, at which point the temperature was recorded by the computer. Pain threshold was the average reading of the 4 successive stimuli. Pain threshold was measured before and immediately after the 1st, 5th, and 10th treatment sessions to evaluate the acute effect of the treatments and the effect of the series.

Depression. All patients filled out the Beck Depression Inventory (BDI) prior to the 1st treatment, after the 10th treatment, and at the end of the follow-up period. Because rTMS is used to treat depression, we aimed at assessing whether possible reduction in chronic pain might be due to improved mood. The BDI consists of 21 items describing various depressive manifestations. Total scores range between 0 and 63, with higher scores indicating more severe depression. The BDI is among the most common self-report scales for depression, and has satisfactory psychometric properties.

Interview. After an initial screening process, potential candidates underwent an extensive semi-structured interview on the causes, circumstances, mechanism of the injury, and age at injury. The nature of the chronic pain, its location, time of onset after injury, its dynamics, and ameliorating or exacerbating factors were also recorded. Patients were asked about past and present analgesic medication, additional treatments for pain alleviation, treatment effectiveness, prior operations, as well as other health problems and relevant medication. The personal and family medical histories were documented and the data obtained in the interview was confirmed with the patients’ medical records. In addition to the interview, patients underwent a physical examination by a rehabilitation specialist. The information obtained in the interview and in the examination was further analyzed and discussed in order to exclude inadequate candidates.

Experimental design. The study had several phases: (1) screening the patients suitable for rTMS; (2) baseline evaluation, in which patients were interviewed and outcome measures obtained; (3) 2-week double-blind treatment consisting of 10 daily treatment sessions of real or sham rTMS (during this period several outcome measures were obtained daily and others, after the 5th and 10th treatments) (see Main Outcome Measures above), and (4) follow-up period ranging from 2 to 6 weeks at the end of which the outcome measures MPQ and BDI were obtained.

Patients were randomized into 2 groups that received either real or sham rTMS (see table 1). The patients as well as the person conducting the outcome measurements were blind to the type of treatment received. They were informed of the type of treatment at the end of the follow-up period and those receiving sham TMS were offered a series of 10 real TMS treatments.

Repetitive TMS. During the treatment, patients sat either in their wheelchair or in a comfortable chair. The magnetic coil was adjusted to a constant position with reference to the subject’s head. The position of the specially designed coil holder was freely adjusted and secured, and the coil then placed at the optimal position over the motor cortex for eliciting motor-evoked potentials (MEPs) in the abductor pollicis brevis (APB) muscle (recorded by a surface electromyography electrode). This muscle was chosen because of the paraplegia. To determine the MEP threshold, the minimal amount of machine output producing an MEP in 5 of 10 trials was used. After recordings of the MEP threshold, the coil was slowly and carefully moved medially towards the midline and was placed on the intersect point of the imaginary anteroposterior and mediolateral lines (vertex) of the skull. This point symbolizes the area in the motor cortex in which the legs and lower back are represented and was chosen because all the patients had chronic pain in their legs.

This position remained fixed for the duration of the experiment. This procedure was repeated in each of the 10 treatment sessions.

We should point out that because we aimed at stimulating the somatotopic areas representing the legs in the 2 hemispheres, the motor threshold of APB of both the right and left hand was measured and the average of the 2 MEPs was then used to determine stimulation intensity for treatment.

The 10 treatment sessions (each lasting 15–30min) were given at the same time of day. In each session, using magnetic coils, 500 trains were delivered at a frequency of 5Hz for 10 seconds at an inter-train interval of 30 seconds (ie, a total of 500 pulses). Total duration of TMS was 15 minutes at intensity equal to 115% of the motor threshold.

Data Processing

Data were processed with SPSS software. Analyses of variance for repeated measures were conducted to evaluate the effect of rTMS (real, sham) on the values of the outcome measures (pain threshold, VAS ratings, MPQ scores, BDI scores). The analyses included main effects, contrasts, and interactions. Those with P less than .05 were considered significant.

RESULTS

Pain Intensity

Figure 1 presents the average VAS ratings of chronic pain before and immediately after each of the 10 treatment sessions of the real and sham TMS groups, evaluating the acute effect of the treatment. The effect of group (real and sham) (P=.26) and the interaction group by time (before and after treatment) (P=.22) was not significant. However, the effect of time was significant (P<.001), indicating that the reduction in VAS ratings was significant and similar for the 2 groups. The reduction in pain ratings during each treatment (real TMS change, 1.2; P<.001; sham TMS change, 1.3; P<.001) indicate an acute effect of both TMS treatments. There was no difference in the magnitude of pain reduction between the groups. Note that due to randomization, the initial VAS values of the sham group were lower than those of the real TMS group.

Figure 2 presents the changes in VAS ratings throughout the real and sham series. The values are the average pain ratings before each treatment trial. A moderate reduction in pain ratings with time was observed in both groups (real VAS change, 1.7; sham VAS change, 1.5) and the effect of time was only borderline significant (real, P=.09; sham, P=.06). The
interaction group by time was not significant \(P = .46\), meaning that the effect of the series on pain ratings was similar for the 2 groups.

In the follow-up period, patients of the real TMS treatment reported that they perceived a 30% (scale range, 0%–100%) reduction in the intensity of chronic pain whereas those in the sham treatment reported 10% reduction of pain (data not shown).

The Pain Experience

Table 2 presents the values of the MPQ obtained before, after the 5th and 10th treatment, and at the end of the follow-up period. There was a significant effect of time \((P < .01)\) on the PRI, but not of group \((P = .26)\), namely, that in general the PRI was reduced in both the real and sham groups with time. Contrasts revealed that in both real and sham groups, the significant decrease in the PRI occurred after the 10th treatment \((P < .05, P < .05, \text{respectively})\) but not after the 5th treatment. However, only in the real TMS group did the decrease in the PRI continue during follow-up \((P < .05)\) whereas in the sham TMS, PRI values increased \((P < .05)\).

With respect to NWC, there was a significant effect of time \((P < .05)\) but not of group \((P = .14)\) and the interaction group by time was not significant. Contrasts revealed that in both the real and sham groups NWC significantly decreased following the 10th treatment \((P = .05, P = .05, \text{respectively})\) but not after the 5th treatment. In addition, NWC of the real TMS group (but not of the sham group) continued to decrease during the follow-up, but the decrease did not reach a significant level \((P = .1)\). There was no significant effect of time and group on the PPI \((P = .73, P = .89, \text{respectively})\) (see table 2).

Two patients of the real treatment group reported that the extent of the body region in which pain was felt decreased following the treatment, but the rest of the group as well as patients of the sham group reported that the extent of the pain region remained the same throughout the series.

Heat-Pain Threshold

Heat-pain threshold in pain free body regions above the lesion (in the hands) did not change significantly during the real or sham treatment series. With regard to heat-pain threshold in the painful body regions below the lesion, there was a borderline effect of time \((P = .057)\) and a significant interaction group by time \((P < .05)\). Only in the real TMS group did pain threshold increase, by 4°C from 47.8°±3.5°C to 51.7°±1.0°C (fig 3), indicating an analgesic effect in this group. The difference between the real and sham groups in the magnitude of change in pain threshold was significant \((P < .05)\).

Depression

Table 2 presents the values of BDI obtained during the treatment series and at the end of the follow-up period. Time significantly affected BDI scores \((P < .01)\) and the effect of group was only borderline significant \((P = .07)\). Both real and sham groups exhibited a significant reduction in BDI values at the end of the treatment series compared with pretreatment levels \((P < .01)\). The reduction in depression level was maintained at follow-up in both groups, compared with the levels measured prior to the series \((P < .01)\). However, only in patients receiving real TMS, did the level of depression continue to drop during follow-up compared with the values at the end of the series \((P < .05)\).

General Remarks

At follow-up, several patients of both real and sham treatment groups reported that the quality of everyday life improved after TMS treatments. One patient in the real TMS and 1 in the sham TMS group reported a dulling of the pain, making it more bearable than that experienced prior to the treatment. One patient in the real TMS group reported that the pain was no longer constant and described it as “coming and going” enabling her to function better. One patient in the real TMS and 1 in the sham TMS group reported that they feel stronger emotionally and could better endure their pain. Three patients of the real and 2 patients of the sham TMS group reported that they felt that their quality of life, mobility, and functioning improved. Two patients (1 from each group) reported a significant improvement in the quality of their sleep.
DISCUSSION

The aim of the study was to evaluate the acute and long-term effects of motor rTMS on central pain of spinal origin. Both real and sham rTMS induced a similar, significant reduction in pain ratings (VAS scores) after a single treatment, and after each treatment throughout a series of 10 consecutive sessions (VAS and PRI scores). Real rTMS had an advantage over sham TMS in that it increased the heat-pain threshold by 4°C in the painful body regions and resulted in a continuous decrease in chronic pain scores during the follow-up period of 4.5 weeks. Depression scores were also equally reduced in both groups at the end of the series, but similar to the pain relief, depression improved at follow-up only in the real rTMS group. It may be concluded that a series of rTMS treatments, but not a single treatment, may have a potential long-term clinical effect on central pain of SCI patients.

The acute effect of a single TMS session on SCI patients with central pain was not studied in depth. In 2 studies,22,23 central pain of SCI patients treated with rTMS in that it increased the heat-pain threshold by 4°C in the painful body regions and resulted in a continuous decrease in chronic pain scores during the follow-up period of 4.5 weeks. Depression scores were also equally reduced in both groups at the end of the series, but similar to the pain relief, depression improved at follow-up only in the real rTMS group. It may be concluded that a series of rTMS treatments, but not a single treatment, may have a potential long-term clinical effect on central pain of SCI patients.

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With regard to the long-term analgesic effects, it appears that repeated treatments with rTMS intensify the effect of a single treatment because our SCI patients reported as much as a 30% pain relief, and a significant reduction in chronic pain intensity at the end of 10 sessions, whereas patients receiving sham TMS experienced a 10% reduction in chronic pain. In addition, only the real rTMS group exhibited an increase of 4°C in the heat-pain threshold at the end of the series. Johnson et al41 recently reported that a single session of 20Hz rTMS induced a significant elevation of 2.4°C in the pain threshold of patients with chronic back pain, a change that was not observed following a sham session. Similarly, an increase in cold-pain threshold was observed in healthy controls following a single session of a real, but not a sham motor rTMS.24 The 4°C increase in pain threshold observed in our study is considered clinically significant and reflects a true reduction in the sensitivity of the patients to noxious stimuli.25 These findings emphasize the advantage of a series of rTMS sessions over a single session, with regard to the analgesic effect.

To our knowledge, this is the first study on the long-term effect of rTMS on central pain of spinal origin. Two previous studies deal with the long-term effects of rTMS using clinical entities other than ours. In 1 instance, a patient with peripheral neuropathy received 16 monthly sessions of 10Hz rTMS over the motor cortex with satisfactory results.25 Recently, Khedr et al26 reported treating patients with central poststroke pain and trigeminal neuralgia with a series of 5 daily 20-Hz sessions of real or sham rTMS. Although both treatments induced a reduction in pain scores, the reduction obtained with real rTMS was greater than that of the sham TMS after follow-up of 2 weeks. These results are in agreement with ours and point toward the clinical potential of a series of rTMS for chronic central pain. The frequency of rTMS and number of treatments that would induce the optimal long-term effect still remains to be tested.

The series of TMS treatments also induced a reduction in depression scores, in both real and sham groups, with a slight advantage of the real TMS in that the depression level continued to decrease at follow-up. It is therefore not clear whether the reduction in depression is due to a placebo effect. Several
authors have reported that rTMS can improve the mood of patients with depression\textsuperscript{17,43,44} and of healthy subjects\textsuperscript{43,45} although recently Grisaru et al\textsuperscript{46} failed to produce significant changes in the emotions of healthy people. Despite the fact that rTMS treatments for depression are applied to the frontal cortex, motor rTMS might have affected the brain regions associated with depression, but such an effect is yet to be established.

We may also speculate that the reduction in depression and perhaps the reduction in chronic pain may result from the mere participation in the experiment. Most of the SCI patients reported that they had to rearrange their lives in order to be able to reach the hospital every other day. Some of them reported that because assistance was not always available they had to manage on their own (eg, driving by themselves or taking taxis to the hospital), which was not customary for them. Visits to the hospital also invigorated their life and many specifically stated that this was a big change for them. Central pain is known to dramatically affect the life of SCI patients who suffer very intense pain for many years.\textsuperscript{3,4,7,48} Pain and suffering may lead to avoidance behavior and consequently to a reduction in activities of daily living.\textsuperscript{49,50} Overcoming such tendencies in order to participate in the rTMS series might have improved their mood and reduced their depression level, whether or not they received real or sham TMS.

Because depression is closely related to chronic pain,\textsuperscript{51,52} it is impossible to determine whether the reduction in depression following the TMS treatment induced amelioration in chronic pain or vice versa. It should be pointed out that although depression was similarly reduced in both real and sham TMS, only in the real TMS group did the pain threshold increase significantly. In addition, only patients receiving real TMS continued to display reduced depression at follow-up. Therefore, the reduction in depression cannot account for the entire analgesic effect of rTMS.

The mechanism underlying the analgesic effect of rTMS is still not clear and we can only speculate on the processes leading to the changes observed. Positron emission tomography conducted in patients undergoing epidural electric motor cortex stimulation (MCS) reveal activation of the anterior cingulate cortex\textsuperscript{10,13} suggesting a possible alteration of the affective-emotional aspects of pain. Such activation may underlie both the reduction in pain experience and in depression scores in our patients. Changes in nociceptive and non-nociceptive thresholds during MCS propose that MCS modulates the transmission of pain signals by acting on neural pathways involved with sensory discrimination.\textsuperscript{53} This effect might underlie the increase in pain threshold observed in our study. It is not clear however, whether rTMS induces similar changes as MCS.\textsuperscript{18,22} The correlation recently found between the subhypnotic propofol test and rTMS suggests that TMS might induce a GABA-mediated renormalization of cortical activity.\textsuperscript{53}

Study Limitations
Within the limitations of this study (the small sample and a relatively short follow-up period), the preliminary findings are encouraging and call for further investigation with a larger population sample. It should be pointed out that a coin coil instead of a figure-of-8 coil might have been more appropriate to stimulate the leg area of the motor cortex due to its location relative to the skull. It should also be pointed out that baseline VAS scores of chronic pain in both the real and sham TMS groups were not as high as expected from patients presenting pain resistant to treatment. However, PPI scores and other MPQ indices were relatively high in the same patients, suggesting that patients may have difficulties in rating their chronic pain on a blank scale with anchor points only at the 2 extremes (ie, VAS).

CONCLUSIONS
Although the acute effect of rTMS observed herein is probably due to a placebo effect, the long-term effects may have true clinical significance for pain relief in SCI patients. It is recommended that the effect of other rTMS frequencies and coil location should be tested in future studies.

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Suppliers
a. Neotonus magnetic stimulator; Neotonus, 30 South Park Sq, Marietta, GA 30060.
b. TSA 2001; Medoc Ltd, 1502 W Hwy 54, Ste 404, Durham, NC 27707.
c. SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.