HIGH LIGHT

Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain

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Abstract—*Objective:* To assess cortical excitability changes in patients with chronic neuropathic pain at baseline and after repetitive transcranial magnetic stimulation (rTMS) of the motor cortex. *Methods:* In 22 patients with unilateral hand pain of various neurologic origins and 22 age-matched healthy controls, we studied the following parameters of cortical excitability: motor threshold at rest, motor evoked potential amplitude ratio at two intensities, cortical silent period (CSP), and intracortical inhibition (ICI) and intracortical facilitation. We compared these parameters between healthy subjects and patients at baseline. We also studied excitability changes in the motor cortex corresponding to the painful hand of patients after active or sham rTMS of this cortical region at 1 or 10 Hz. *Results:* At baseline, CSP was shortened for the both hemispheres of patients vs healthy subjects, in correlation with pain score, while ICI was reduced only for the motor cortex corresponding to the painful hand. Regarding rTMS effects, the single significant change was ICI increase in the motor cortex corresponding to the painful hand, after active 10-Hz rTMS, in correlation with pain relief. *Conclusion:* Chronic neuropathic pain was associated with motor cortex disinhibition, suggesting impaired GABAergic neurotransmission related to some aspects of pain or to underlying sensory or motor disturbances. The analgesic effects produced by motor cortex stimulation could result, at least partly, from the restoration of defective intracortical inhibitory processes.

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In the beginning of the 1990s, chronic epidural stimulation of the motor cortex was shown to produce substantial relief of drug-resistant neuropathic pain.[1] Since then, cortical stimulators have been implanted in hundreds of patients with chronic pain.[2] Several studies also reported transient neuropathic pain relief following sessions of repetitive transcranial magnetic stimulation (rTMS) delivered at 10 to 20 Hz over the primary motor cortex.[3-5]

The anatomic location and neurochemical mediation of the analgesic effects induced by motor cortex stimulation have not been yet clearly identified. Metabolic changes have been found at a distance from the stimulated motor cortex, in orbitofrontal/anterior cingulate cortex, insula, and thalamic or brainstem nuclei.[6] These findings do not preclude that intracortical excitability changes occur in motor circuits.

Motor cortex excitability can be assessed by single- or paired-pulse TMS paradigms. Single-pulse parameters include motor threshold, measured at rest (RMT) or during facilitation; motor evoked potential (MEP) amplitude, measured at different levels of stimulus intensity or contraction force; and the electromyographic cortical silent period (CSP). Paired-pulse paradigms investigate intracortical inhibition (ICI) and intracortical facilitation (ICF) processes, related to neural activities in GABAergic and glutamatergic pathways.[7]

The goal of this study was to determine whether motor cortex rTMS induced changes in motor cortex excitability with respect to pain relief in a series of patients with chronic neuropathic pain located in one upper limb.

Methods. *Patients and controls.* We studied 22 right-handed patients, 10 women and 12 men, ages 28 to 75 years, with a mean (± SEM) age of 56.5 years (± 2.9), without a history of seizures (table). All patients had chronic, drug-resistant, unilateral neuropathic pain involving at least the hand, due to nerve trunk lesion (n = 4), brachial plexus lesion (n = 4), cervical spinal cord lesion (n = 4), or stroke located at the thalamus (n = 8) or the lateral medulla (n = 2). These patients were referred for evaluation of the indication of chronic motor cortex stimulation. This study was included in the framework of a research program on motor cortex stimulation for pain treatment that received authorization from both national and local ethical committees.

Prior to any rTMS session, first-perception thresholds for warm sensation and vibration were measured at the painful hand using a TSA-2001/VSA-3000 apparatus (Medoc, Ramat Yishai, Israel) and the method of limits.[8] Five trials were averaged. Some patients demonstrated severe sensory deficit in the painful zone,

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Table *Clinical characteristics of the patients*

Age, y	Pain origin	Pain location	Pain duration, y	Pain intensity (VAS/10)	Motor deficit in painful zone	Sensory deficit in painful zone	Analgesic medication
63	Thalamocapsulolenticular hemorrhagic stroke	Right hemibody, predominating at the hand	7	6.5	Mild	Severe	Clomipramine, fluoxetine, morphine sulfate
67	Traumatic lesion of the brachial plexus (car accident)	Entire right upper limb, predominating at the hand	3	8.0	Mild	Mild	Amitriptyline, clomipramine, clonazepam
44	Traumatic lesion of the median and ulnar nerves at the wrist (self-cutting, suicide attempt)	Median and ulnar territories of the left hand	8	7.5	Mild	Severe	Buprenorphine, fentanyl
62	Traumatic lesion of the superficial radial at the distal forearm (fracture of the distal radius)	Dorsal aspect of the right thumb and thumb-index finger web space	12	6.5	No	Mild	Acepromazine, amitriptyline, clonazepam, morphine sulfate, oxazepam
66	Thalamic ischemic stroke	Right hand	18	9.8	No	Severe	Amitriptyline, clonazepam, lamotrigine, morphine sulfate
42	Lateral medullary infarction	Right hemibody, predominating at the hand	2	5.4	No	Mild	Clomipramine, clonazepam, gabapentin
72	Cervical spinal cord ischemia (C7-D1, complication of posterior decompressive laminectomy)	Right hand	4	6.7	Mild	Severe	Clonazepam, tramadol
64	Lateral medullary infarction	Left hemibody, predominating at the hand	2	6.0	Mild	Mild	Carbamazepine, clomipramine
50	Thalamic ischemic stroke	Left hemibody, predominating at the hand	2	5.2	No	No	Gabapentin
34	Traumatic lesion of the ulnar nerve at elbow (crush injury)	Ulnar territory of the right hand	10	8.2	Mild	Mild	Buprenorphine, carbamazepine, clomipramine, clonazepam, codeine, paracetamol, tramadol
75	Thalamic ischemic stroke	Left hemibody, predominating at the hand	2	8.8	No	No	Carbamazepine, clomipramine, dextropropoxyphene, gabapentin, paracetamol
63	Radiation-induced lesion of the brachial plexus (lung carcinoma)	Right hand	5	5.6	Mild	Mild	Clonazepam, paroxetine
61	Traumatic lesion of the cervical spinal cord (neck trauma after a fall from a height)	Left hand	4	5.8	No	Mild	Clonazepam, fentanyl, gabapentin
34	Surgical lesion of the brachial plexus (complication of thoracic outlet syndrome surgery)	Left hand	7	7.3	No	No	Carbamazepine, clomipramine, clonazepam, dextropropoxyphene, gabapentin, morphine sulfate, paracetamol
62	Radiation-induced lesion of the brachial plexus (breast carcinoma)	Left hand	5	8.0	Mild	Severe	Bromazepam, clonazepam
53	Thalamic ischemic stroke	Right hemibody, predominating at the hand	2	4.8	No	No	Bromazepam, dextropropoxyphene, gabapentin, paracetamol
28	Thalamic hemorrhagic stroke	Right hemibody, predominating at the hand	2	9.0	No	Severe	Clomipramine, clonazepam
71	Surgical lesion of the cervical spinal cord (after decompression for spondylotic cervical stenosis)	Left hand	7	6.3	No	No	Clomipramine, dextropropoxyphene, paracetamol
65	Thalamic ischemic stroke	Left hemibody, predominating at the hand	9	6.5	No	Severe	Dextropropoxyphene, paracetamol
48	Posttraumatic cervical syringomyelia (C6-D1)	Right forearm and hand	3	6.1	Mild	Severe	Clonazepam, clorazepam, morphine sulfate
52	Thalamic ischemic stroke	Right hemibody, predominating at the hand	2	6.1	Mild	Mild	Clomipramine, clonazepam, gabapentin
68	Lesion of the median nerve at the wrist (complication of carpal tunnel syndrome surgery)	Median territory of the left hand	3	8.9	No	No	Acepromazine, clomipramine

defined by warm threshold above 42°C and vibratory threshold above 10 μm.[9] In contrast, no patients demonstrated severe motor deficit (Medical Research Council scores were ≥4/5 for the painful hand).

The study also included 22 healthy right-handed volunteers, 12 women and 10 men, aged from 33 to 71 years, with a mean (± SEM) age of 54.8 years (± 2.5). These subjects did not present any sign or medical history of neurologic symptoms or medication.

Motor cortex excitability testing. Subjects were seated in a comfortable reclining chair with a tightly fitting Lycra swimming cap placed over the head. They were instructed to keep their hands as relaxed as possible. TMS was performed with a Magstim 200 stimulator (Magstim Company, Carmarthenshire, UK) and a figure-of-eight double 70-mm coil (no. 9925-00, Magstim). Two Magstim 200 stimulators connected through a Bistim module served to deliver paired pulses. The optimal site for evoking motor responses in the first dorsalis interosseus (FDI) muscles was determined over the scalp (motor hot spot) and marked on the cap. The MEPs were recorded through a 20- to 1,000-Hz bandpass using a standard electromyograph (Phasis II, EsaOte, Florence, Italy) and pregelled self-adhesive disposable surface electrodes (no. 9013S0241, Medtronic Functional Diagnostics, Skovlunde, Denmark), placed on the belly and tendon of the FDI muscle. A Velcro bracelet was strapped around the forearm as ground electrode (no. 9013S0711, Medtronic). The coil was positioned tangentially to the surface of the head, with the handle pointing occipitally along a sagittal axis.

Cortical excitability testing included the determination of five parameters. RMT was defined as the minimal intensity of stimulation required to elicit MEPs of >50 μV in amplitude in at least five of 10 trials performed during complete muscle relaxation.[10] The relationship between stimulus intensity and MEP amplitude was assessed by studying the most variable part of the stimulus-response curve. This was previously found to correspond to TMS intensities ranging between 120 and 140% of RMT.[11-13] We calculated, therefore, the amplitude ratio of the MEP obtained at 140% of RMT to that obtained at 120% of RMT (140/120r). The CSP was determined as the duration of the post-MEP EMG activity interruption following single TMS pulses delivered at 140% of RMT. Stimulations were performed while patients exerted a tonic maximal voluntary contraction of the FDI muscle against the examiner's resistance. Four rectified traces, each consisting of three averaged trials, were superimposed. The minimal CSP duration was measured from the end of the MEP until the first reoccurrence of EMG activity. Finally, paired-pulse paradigms were applied, with a conditioning stimulus set at 80% of RMT and a test stimulus set at 120% of RMT, while the FDI muscle was at rest. Various interstimuli intervals (ISIs) were randomized (2 and 4 msec for ICI; 10 and 15 msec for ICF) and intermixed with control trials (test stimulus alone). For each ISI, four trials were averaged and the resulting MEP amplitude was converted into a percentage of the control MEP amplitude ($_{pp/c}$MEP%). Paired-pulse parameters were expressed as the amount of inhibition (ICI = 100% − $_{pp/c}$MEP%) and facilitation (ICF = $_{pp/c}$MEP% − 100%). The maximum degrees of inhibition and facilitation achieved at any ISI were retained for analysis.[14]

Motor cortex excitability was studied for the hemisphere corresponding to the painful hand of patients before and after each rTMS session. For the hemisphere corresponding to the nonpainful hand, testing was performed only once, prior to any rTMS session. In healthy volunteers, data were acquired from the right hand in 11 subjects and the left hand in the 11 remainders, and then pooled to avoid any influence of the dominant hemisphere.

rTMS procedure. In patients, after having completed excitability testing for the motor cortex corresponding to the painful hand, the coil was maintained fixedly on the head at the motor hot spot, using a specifically designed mechanical device for rTMS procedure.

Three sessions of motor cortex rTMS, separated by at least 3 weeks, were performed in random order with a Super-Rapid stimulator (Magstim): i) a series of 20 trains of 6 seconds in duration (54-second intertrain interval) at 10 Hz and 90% of RMT using an active coil (1,200 pulses); ii) the same protocol using a sham figure-of-eight coil (no. 1730-23-00, Magstim); iii) a single train of 20 minutes in duration at 1 Hz and 90% of RMT using an active coil (1,200 pulses). For the sham condition, the use of the Magstim Placebo Coil System was preferred to hold an active coil at 45 degrees away from the skull because this was shown to produce substantial stimulation of the cortex.[15] The patients were not informed about the existence of a sham condition. They only knew that three sessions of rTMS using different parameters of stimulation were tested for their respective efficacy to relieve pain.

Immediately after each rTMS session, we checked on the absence of coil shift from the motor hot spot marked on the cap and repeated excitability testing for the motor cortex corresponding to the painful hand. In all cases, the examiner who conducted excitability studies left the room during the rTMS session and was blinded for the type of session.

Pain level was self-scored by the patient on a 0 to 10 visual analogue scale (VAS) before and after each rTMS session. The short-term effects of rTMS on pain were assessed in this study, to correlate with concomitant excitability changes, even if optimal pain relief is usually delayed for some days after rTMS.[16]

Statistical analyses. We compared excitability values obtained for the motor cortex corresponding to the painful hand at baseline (mean of the three pre-rTMS values) to those obtained for the contralateral motor cortex in patients and to normal control values using one-way analysis of variance (ANOVA) and Bonferroni's post-tests. The correlation between pain scores and the excitability parameters that significantly differed between patients and controls was assessed using Pearson's test. The possible influence of the origin of pain (stroke vs other etiologies), the sensory deficit in the painful hand (severe vs mild or none), or the use of tricyclic antidepressants (yes vs no) on cortical excitability parameters was studied using unpaired t test. In all cases, $p < 0.05$ was considered as significant.

Second, we compared excitability values obtained for the motor cortex corresponding to the painful hand before and after rTMS sessions using repeated-measures ANOVA under six conditions that resulted from the combination of two nominal variables as within-subject factors: treatment, with three group levels (10 Hz, 1 Hz, and sham) and time, with two group levels (before and after). Between factors included i) the origin of pain (stroke vs other etiologies) and ii) the severity of sensory loss within the painful zone (severe vs mild or none). Post hoc tests were applied including a Bonferroni correction ($p < 0.0033$). Finally, the correlation between any significant rTMS-induced change in excitability parameters and the corresponding effect on pain level was assessed using Pearson's test, not corrected for multiple comparisons.

Results. *Baseline excitability changes in the motor cortex corresponding to the painful hand.* One-way ANOVA test showed differences in CSP duration ($p = 0.0005$) and ICI ($p < 0.0001$) between patients and healthy controls (figure 1). For CSP duration, the values obtained in patients, whatever the hemisphere, were shorter vs controls ($p < 0.01$, Bonferroni's post-test). For ICI, the values obtained for the motor cortex corresponding to the painful hand of patients were lower vs motor cortices corresponding to the painless hand of patients ($p < 0.01$) or to the hand of controls ($p < 0.001$). The other parameters, RMT, 140/120r, and ICF, did not vary with the groups ($p = 0.34$, 0.56, and 0.25, ANOVA), although ICF tended to be reduced in patients' hemispheres vs controls ($p = 0.10$, Bonferroni's post-test).

Regarding correlation analyses between baseline values, pain scores correlated with CSP duration for the hemisphere corresponding to the painful hand ($r = -0.33$, $p = 0.03$, Pearson's test), but not with ICI ($r = -0.17$, $p = 0.27$).

Finally, neither CSP nor ICI values differed regarding i) the origin of pain, i.e., stroke (n = 10) vs other etiologies (n = 12) ($p = 0.12$ for CSP and 0.65 for ICI, unpaired t test); ii) the presence (n = 8) or absence (n = 14) of severe sensory deficit in the painful hand ($p = 0.43$ for CSP and 0.75 for ICI); iii) intake of tricyclic antidepressants (n =

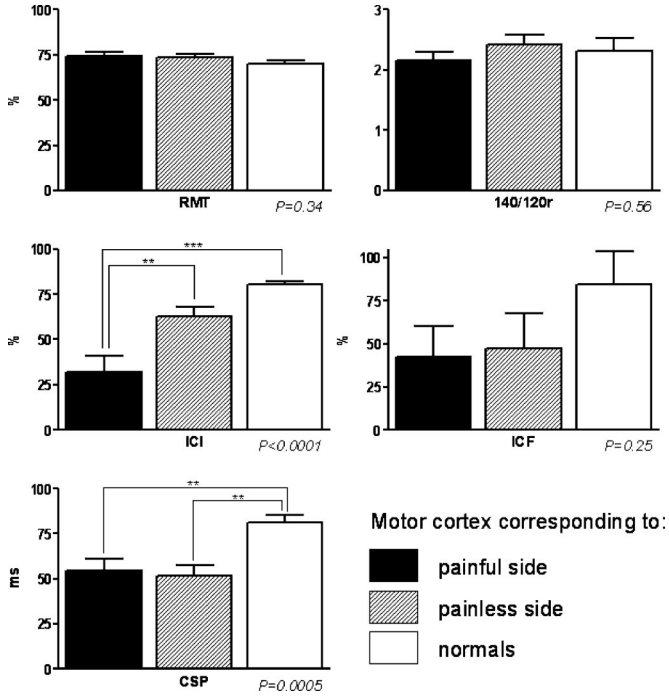

*Figure 1. Mean values (SEM) of rest motor threshold (RMT), motor evoked potential amplitude ratio for stimulus intensities set at 140% to 120% of RMT (140/120r), intracortical inhibition (ICI), intracortical facilitation (ICF), and cortical silent period (CSP) duration in the motor cortex corresponding to the painful (black bars) or painless (hatched bars) hand of patients or to the hand of healthy controls (white bars). p Significance of the one-way analysis of variance is presented at the right lower corner of each graph. Significant results for Bonferroni's post-tests: **$p < 0.01$; ***$p < 0.001$ (not significant otherwise).*

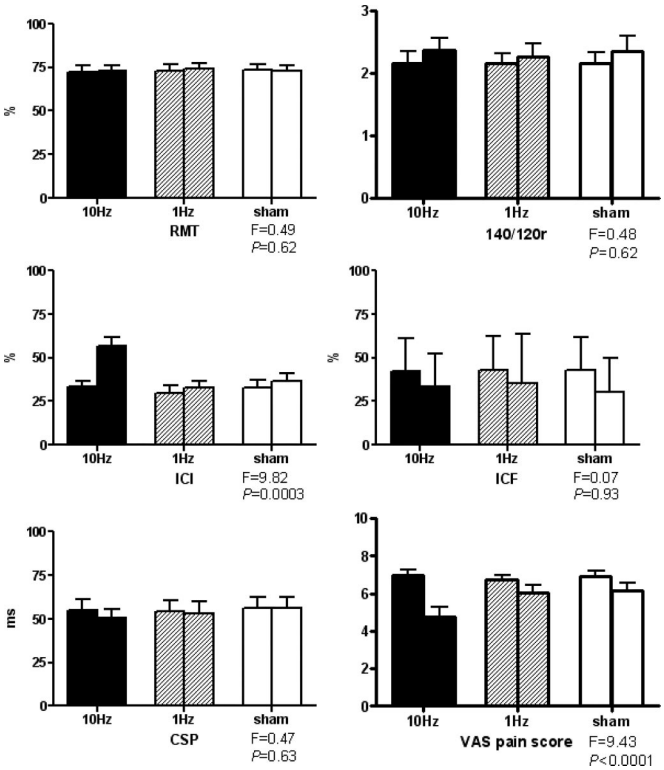

Figure 2. Mean values (SEM) of rest motor threshold (RMT), motor evoked potential amplitude ratio for stimulus intensities set at 140% to 120% of RMT (140/120r), intracortical inhibition (ICI) and intracortical facilitation (ICF), and cortical silent period (CSP) duration in the motor cortex corresponding to the painful hand of patients, and pain score on a 0 to 10 visual analogue scale (VAS) before and after three types of rTMS session: active (10 Hz), active (1 Hz), or sham. F(2,21) and p values of the repeated-measures ANOVA for treatment × time interaction are shown in the lower right corner of each graph.

13) or no intake (n = 9), (p = 0.91 for CSP and 0.90 for ICI).

rTMS-induced changes in the excitability of the motor cortex corresponding to painful hand. There were effects of treatment and time for ICI and VAS pain scores ($p <$ 0.0001, repeated-measures ANOVA), with treatment × time interaction for both parameters, F(2,21) = 9.82 and 9.43, p = 0.0003 and < 0.0001 (figure 2). The other parameters of cortical excitability (RMT, 140/120r, CSP, ICF) did not vary among the conditions. The two between factors (origin of pain, severity of sensory loss) did not interact with the results ($p > 0.05$, repeated-measures ANOVA).

Post hoc tests did not reveal any differences between the three pre-rTMS assessments regarding excitability values or pain levels. These values neither changed after "sham" 10-Hz rTMS and "active" 1-Hz rTMS. In contrast, ICI increased and pain score decreased after active 10-Hz rTMS ($p < 0.0001$, Bonferroni's post-test). The increase in ICI correlated with the concomitant pain relief ($r = -0.56$, p = 0.007, Pearson's test) (figure 3).

Discussion. In patients with chronic hand pain, we found features of cortical disinhibition with ICI reduction in the motor cortex corresponding to the painful hand. The defective ICI was restored in correlation with pain relief following subthreshold rTMS delivered at 10 Hz over this cortical region.

Relationships between pain and cortical excitability changes. A few studies have dealt with the modulating effect of pain on motor cortex excitability.

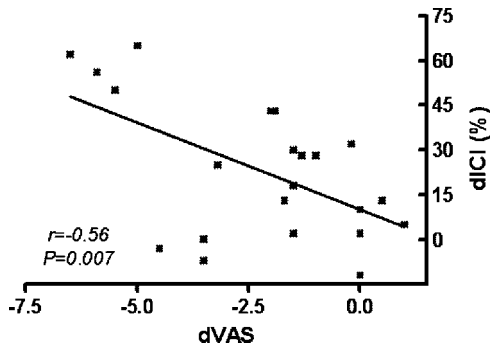

Figure 3. Correlation between changes induced by repetitive transcranial magnetic stimulation of the motor cortex at 10 Hz in pain level scored on a 0 to 10 visual analogue scale (dVAS) and intracortical inhibition (dICI) regarding the motor cortex corresponding to the painful hand (Pearson's test).

Most of these studies showed that MEP amplitude could be reduced in normal subjects by various types of conditioning noxious stimuli[3] (e.g., electrical stimuli, laser pulses, capsaicin cutaneous application, intramuscular hypertonic saline injection). From these observations, it was proposed that phasic or tonic provoked pain led to reduced motor cortical output.[17] However, high-frequency transcutaneous electrical nerve stimulation conventionally used to treat pain was also shown to reduce MEP amplitude.[18]

The relationships between chronic pain and motor cortex activity were thought to be totally different from acute pain condition. For instance, MEP amplitude was found enhanced in muscle adjacent to a chronic painful joint.[19] Motor cortex excitability was rarely assessed in patients with chronic pain. Patients with fibromyalgia showed increased RMT, normal MEP amplitude, shortened CSP, and reduced ICF and ICI (for long ISIs and suprathreshold paired pulses).[20] Patients with complex regional pain syndrome (CRPS) showed normal RMT, MEP amplitude, and ICF, but reduced ICI in the both hemispheres[21] or only in the hemisphere corresponding to the side of pain.[22]

The present results were consistent with these data, revealing normal RMT and MEP amplitude, a tendency toward ICF reduction, and significant ICI reduction and CSP shortening. In this way, chronic neuropathic pain appeared to be mainly characterized by a reduction in intracortical and corticospinal motor inhibitory mechanisms. A comparative study of patients having similar neurologic lesions than our patients but without pain should have been of interest to better appraise the relationships between motor cortex disinhibition and either the presence of neuropathic pain or the underlying neurologic lesion. However, it appeared impossible to match a series of neurologic controls to our patients, when taking into account the variety of factors that could influence the parameters of cortical excitability. These factors included cortical plasticity favored by the neurologic lesion at the origin of pain or by the severity of sensory or motor deficit, various cognitive parameters, and the effect of analgesic drugs. The respective contribution of all these factors to the present results is discussed, as well as the possibility of pain-related imbalance between inhibitory (GABAergic) and excitatory (glutamatergic) neurotransmission in the CNS.

Influence of sensorimotor dysfunction. ICI reduction or CSP shortening has been observed in a wide range of neurologic diseases with motor dysfunction,[23] such as Parkinson disease, dystonia, Tourette's syndrome, myoclonic or partial epilepsy, ALS, and motor stroke. In the acute phase of a motor cortex stroke, ICI is reduced for the both hemispheres, and in the case of good recovery, ICI returns to normal values in the unaffected hemisphere and remains reduced in the affected one.[24] The loss of ICI was also observed in the affected hemisphere of patients with mild motor impairment but severe hypesthesia due to thalamic infarction.[25] Other conditions of sensory deafferentation (e.g., amputation[26] and peripheral nerve transection[27]) were associated with ICI reduction. Sensory deafferentation is thought to induce a loss of GABAergic inhibition in the corresponding sensory cortical areas that could extend in homologous motor areas.[28] ICI also decreases with immobilization[29] due to functional reorganization in cortical motor maps, compensatory mechanisms regarding motor output maintenance, or reduced sensory inputs.

In this way, the patients enrolled in the present study presented several potential causes of ICI reduction in the affected side: good motor recovery from stroke, sensory deafferentation, and relative immobilization of the painful hand compared to the normal hand. Nevertheless, motor cortex disinhibition was also likely to correlate with the presence of pain, as evidenced by CSP duration at baseline and as suggested by the concomitant effects of 10-Hz rTMS on ICI and pain. A more convincing argument for the association of motor cortex disinhibition with pain would have resulted from analyzing data between hemispheres of patients with unilateral pain but bilateral lesions and deficits. Since there were none in this series, we have to acknowledge a limitation of the interpretation of the present results.

Influence of cognitive factors or medication. A reduction of ICI or CSP duration has been reported in various mental disorders, such as Alzheimer disease, obsessive-compulsive disorder, schizophrenia, or major depression.[30] A decreased ICI was also observed after sleep deprivation[31] and was suggested to be a trait marker for anxiety.[32] These cognitive factors might have contributed to the reduction of cortical inhibition found in the present series of patients, who frequently experienced anxious-depressive and sleep disorders along with chronic pain. The bilateral reduction of CSP duration, rather than ICI asymmetry according to the pain side, might reflect the influence of some cognitive factors, involved in affective or emotional aspects of chronic pain.

Pharmacologic influences were also considered. Among all the medications taken by our patients to treat their neuropathic pain, only norepinephrine reuptake inhibitors were previously shown to decrease cortical inhibition.[33] However, we did not observe any differences in ICI or CSP values according to tricyclic antidepressant intake. The reduced cortical inhibition at baseline likely revealed the inefficiency of drug treatment to restore defective GABAergic inhibitory activities in the patients included in this study.

Influence of GABA/glutamate imbalance. Various experimental studies emphasized that the reduction in GABAergic neurotransmission in the CNS was a leading cause of chronic neuropathic pain.[34] In animal models of neuropathic pain, reduced

GABAergic tone was found at the level of dorsal spinal cord, thalamus sensory nuclei, and somatosensory cortex, resulting in neuronal hyperactivity in the sensorimotor cortex.[35] CNS hyperactivity associated with deafferentation pain was also attributed to abnormal recruitment of NMDA glutamatergic receptors.[36]

ICI and CSP explore different GABAergic pathways[37] that are intracortical and mediated by GABA-A receptors for ICI and corticospinal with activation of GABA-B receptors for CSP. Glutamate antagonists may also influence these parameters of excitability.[38] Therefore, the impairment of cortical inhibition observed here could reveal an imbalance between GABAergic and glutamatergic transmission related to the development of neuropathic pain.

Changes induced by rTMS in cortical excitability and correlation with pain relief. In this study, the defective ICI was restored after active subthreshold 10-Hz rTMS but remained unchanged after 1-Hz rTMS. This observation differed from rTMS effects reported in healthy subjects. In normal subjects, subthreshold rTMS applied at high frequency increased MEP size and reduced ICI.[39] In contrast, subthreshold rTMS applied at low frequency reduced MEP size or ICF, but did not modify inhibitory parameters.[40]

The effects of rTMS depend on the state of cortical excitability before stimulation, as demonstrated by conditioning rTMS with previous ischemic deafferentation[41] or transcranial direct current stimulation.[42] Owing to a preexisting decrease in cortical inhibition due to pain or the underlying lesion, GABAergic synaptic connections could have been enhanced by rTMS applied at high frequency and not at low frequency. This result was possibly related to the restoration of 20-Hz frequency cortical oscillations that are known to be associated with motor cortex inhibition in healthy subjects, reduced by 1-Hz rTMS over M1[43] and lost in the case of chronic or provoked pain.[44,45]

CSP duration, but not ICI, correlated with pain scores at baseline, while rTMS-induced pain relief paralleled changes in ICI, but not in CSP duration. Such apparent contradictory results probably reflect both the multifactorial nature of excitability parameters and the multifaceted aspect of pain. In addition to pain, the underlying neurologic lesions and deficits might have contributed to ICI reduction, leading to the absence of a significant correlation between ICI and pain score at baseline. Conversely, rTMS might have induced changes in some aspects of pain, e.g., sensory-discriminative aspects, involved in the ICI process but not in CSP duration. In any case, the fact that pain relief resulting from rTMS application correlated with ICI changes strengthened the hypothesis of the influence of pain, among other factors, on ICI reduction presented in the affected side by patients with drug-resistant neuropathic pain.

References

1. Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Chronic motor cortex stimulation for the treatment of central pain. Acta Neurochir (Wien) 1991;52(suppl):137–139.
2. Nguyen JP, Lefaucheur JP, Keravel Y. Motor cortex stimulation. In: Simpson BA, ed. Pain research and clinical management, volume 15. Electrical stimulation and the relief of pain. Amsterdam: Elsevier Science, 2003:197–209.
3. Lefaucheur JP. Transcranial magnetic stimulation in the management of pain Clin Neurophysiol 2004;57(suppl):733–744.
4. Lefaucheur JP, Drouot X, Ménard-Lefaucheur I, et al. Neurogenic pain relief by repetitive transcranial magnetic cortical stimulation depends on the origin and the site of pain. J Neurol Neurosurg Psychiatry 2004;75:612–616.
5. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC. Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 2005;76:833–838.
6. Garcia-Larrea L, Peyron R, Mertens P, et al. Electrical stimulation of motor cortex for pain control: a combined PET scan and electrophysiological study. Pain 1999;82:1–15.
7. Ziemann U, Rothwell JC, Ridding MC. Interaction between intracortical inhibition and facilitation in human motor cortex. J Physiol (London) 1996;496:873–881.
8. Fruhstorfer H, Lindblom U, Schmidt WG. Method for quantitative estimation of thermal thresholds in patients. J Neurol Neurosurg Psychiatry 1976;39:1071–1075.
9. Drouot X, Nguyen JP, Peschanski M, Lefaucheur JP. The antalgic efficacy of chronic motor cortex stimulation is related to sensory changes in the painful zone. Brain 2002;125:1660–1664.
10. Rossini PM, Barker AT, Berardelli A, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalogr Clin Neurophysiol 1994;91:79–92.
11. Davey NJ, Smith HC, Savic G, Maskill DW, Ellaway PH, Frankel HL. Comparison of input-output patterns in the corticospinal system of normal subjects and incomplete spinal cord injured patients. Exp Brain Res 1999;127:382–390.
12. Han TR, Kim JH, Lim JY. Optimization of facilitation related to threshold in transcranial magnetic stimulation. Clin Neurophysiol 2001;112:593–599.
13. Liepert J, Restemeyer C, Kucinski T, Zittel S, Weiller C. Motor strokes. The lesion location determines motor excitability changes. Stroke 2005;36:2648–2653.
14. Chen R, Corwell B, Yaseen Z, Hallet M, Cohen LG. Mechanisms of cortical reorganization in lower-limb amputees. J Neurosci 1998;18:3443–3450.
15. Lisanby SH, Gutman D, Luber B, Schroeder C, Sackeim HA, Sham TMS. Intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiatry 2001;49:460–463.
16. Lefaucheur JP, Drouot X, Nguyen JP. Interventional neurophysiology for pain control: duration of pain relief following repetitive transcranial magnetic stimulation of the motor cortex. Neurophysiol Clin 2001;31:247–252.
17. Farina S, Tinazzi M, Le Pera D, Valeriani M. Pain-related modulation of the human motor cortex. Neurol Res 2003;25:130–142.
18. Mima T, Oga T, Rothwell J, et al. Short-term high-frequency transcutaneous electrical nerve stimulation decreases human motor cortex excitability. Neurosci Lett 2004;355:85–88.
19. On AY, Uludag B, Taskiran E, Ertekin C. Differential corticomotor control of a muscle adjacent to a painful joint. Neurorehabil Neural Repair 2004;18:127–133.
20. Salerno A, Thomas E, Olive P, Blotman F, Picot MC, Georgesco M. Motor cortical dysfunction disclosed by single and double magnetic stimulation in patients with fibromyalgia. Clin Neurophysiol 2000;111:994–1001.
21. Schwenkreis P, Janssen F, Rommel O, et al. Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand. Neurology 2003;61:515–519.
22. Eisenberg E, Chistyakov AV, Yudashkin M, Kaplan B, Hafner H, Feinsod M. Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychophysical and transcranial magnetic stimulation study. Pain 2005;113:99–105.
23. Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurol 2003;2:145–156.
24. Cicinelli P, Pasqualetti P, Zaccagnini M, Traversa R, Oliveri M, Rossini PM. Interhemispheric asymmetries of motor cortex excitability in the postacute stroke stage: a paired-pulse transcranial magnetic stimulation study. Stroke 2003;34:2653–2658.
25. Liepert J, Restemeyer C, Münchau A, Weiller C. Motor cortex excitability after thalamic infarction. Clin Neurophysiol 2005;116:1621–1627.
26. Schwenkreis P, Witscher K, Janssen F, et al. Changes of cortical excitability in patients with upper limb amputation. Neurosci Lett 2000;293:143–146.

27. Farkas T, Perge J, Kis Z, Wolff JR, Toldi J. Facial nerve injury-induced disinhibition in the primary motor cortices of both hemispheres. Eur J Neurosci 2000;12:2190–2194.
28. Levy LM, Ziemann U, Chen R, Cohen LG. Rapid modulation of GABA in sensorimotor cortex induced by acute deafferentation. Ann Neurol 2002;52:755–761.
29. Zanette G, Manganotti P, Fiaschi A, Tamburin S. Modulation of motor cortex excitability after upper limb immobilization. Clin Neurophysiol 2004;115:1264–1275.
30. Bajbouj M, Lisanby SH, Lang UE, Danker-Hopfe H, Heuser I, Neu P. Evidence for impaired cortical inhibition in patients with unipolar major depression. Biol Psychiatry 2006;59:395–400.
31. Civardi C, Boccagni C, Vicentini R, et al. Cortical excitability and sleep deprivation: a transcranial magnetic stimulation study. J Neurol Neurosurg Psychiatry 2001;71:809–812.
32. Wassermann EM, Greenberg BD, Nguyen MB, Murphy DL. Motor cortex excitability correlates with an anxiety-related personality trait. Biol Psychiatry 2001;50:377–382.
33. Ziemann U. TMS and drugs. Clin Neurophysiol 2004;115:1717–1729.
34. Canavero S, Bonicalzi V. The neurochemistry of central pain: evidence from clinical studies, hypothesis and therapeutic implications. Pain 1998;74:109–114.
35. Guilbaud G, Benoist JM, Levante A, Gautron M, Willer JC. Primary somatosensory cortex in rats with pain-related behaviours due to a peripheral mononeuropathy after moderate ligation of one sciatic nerve: neuronal responsivity to somatic stimulation. Exp Brain Res 1992;92:227–245.
36. Koyama S, Katayama Y, Maejima S, Hirayama T, Fujii M, Tsubokawa T. Thalamic neuronal hyperactivity following transection of the spinothalamic tract in the cat: involvement of N-methyl-D-aspartate receptor. Brain Res 1993;612:345–350.
37. Sanger TD, Garg RR, Chen R. Interactions between two different inhibitory systems in the human motor cortex. J Physiol (Lond) 2001;530:307–317.
38. Ziemann U, Chen R, Cohen LG, Hallett M. Dextromethorphan decreases the excitability of the human motor cortex. Neurology 1998;51:1320–1324.
39. Wu T, Sommer M, Tergau F, Paulus W.. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. Neurosci Lett 2000;287:37–40.
40. Romero JR, Anschel D, Sparing R, Gangitano M, Pascual-Leone A. Subthreshold low frequency repetitive transcranial magnetic stimulation selectively decreases facilitation in the motor cortex. Clin Neurophysiol 2002;113:101–107.
41. Ziemann U, Corwell B, Cohen LG. Modulation of plasticity in human motor cortex after forearm ischemic nerve block. J Neurosci 1998;18:1115–1123.
42. Lang N, Siebner HR, Ernst D, et al. Preconditioning with transcranial direct current stimulation sensitizes the motor cortex to rapid-rate transcranial magnetic stimulation and controls the direction of after-effects. Biol Psychiatry 2004;56:634–639.
43. Tamura Y, Hoshiyama M, Nakata H, et al. Functional relationship between human rolandic oscillations and motor cortical excitability: an MEG study. Eur J Neurosci 2005;21:2555–2562.
44. Juottonen K, Gockel M, Silen T, Hurri H, Hari R, Forss N. Altered central sensorimotor processing in patients with complex regional pain syndrome. Pain 2002;98:315–323.
45. Raij TT, Forss N, Stancak A, Hari R. Modulation of motor-cortex oscillatory activity by painful Aδ- and C-fiber stimuli. Neuroimage 2004;23:569–573.