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Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand

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Abstract—Background: Complex regional pain syndrome type I (CRPS I) develops as a consequence of trauma affecting the limbs, without obvious nerve lesion. Its features include pain, edema, autonomic dysfunction, movement disorder, and trophic changes. CNS involvement is suggested by the symptoms, but the pathophysiology of CRPS I is unknown. Objective: To assess excitability changes in the motor cortex in patients with CRPS I. Methods: The authors studied 25 patients with unilateral CRPS I involving the hand by means of transcranial magnetic stimulation using a paired-pulse paradigm. Motor threshold (MT) and intracortical inhibition and facilitation were determined on the affected and the clinically unaffected side. A control group of 20 healthy subjects was studied. Results: The authors found a significant reduction of intracortical inhibition on both sides of patients with CRPS compared with control subjects, whereas intracortical facilitation and MT did not differ significantly. However, in the patients’ group, the presence of allodynia significantly decreased MT. Conclusions: The authors showed a bilateral disinhibition of the motor cortex in patients with complex regional pain syndrome.

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Complex regional pain syndrome type I (CRPS I; formerly reflex sympathetic dystrophy) is a syndrome that develops after a trauma affecting the limbs, without obvious peripheral nerve lesion. Its features include pain and related sensory abnormalities, edema, autonomic dysfunction, movement disorder, and trophic changes. Typically, spontaneous pain or allodynia is not limited to the territory of a
single peripheral nerve and is disproportionate to the inciting event.1–3 Numerous pathophysiologic components of the disease have been identified, including neurogenic inflammation,4 peripheral and central sensitization,5,6 and impaired sympathetic function.7–9 Despite these known pathophysiologic components of CRPS, a pathophysiologic explanation for the entire disease remains unknown.6 Based on clinical findings, such as tremor, dystonia, or hemisensory impairment, additional widespread involvement of the CNS has been suggested.3,10–12

Transcranial magnetic stimulation (TMS) is a useful noninvasive technique to assess the excitability of the motor system. Using paired-pulse TMS with a subthreshold conditioning and a suprathreshold test stimulus, the response to the test stimulus is inhibited at short and facilitated at longer interstimulus intervals (ISIs) in healthy humans.13–16 These phenomena are referred to as intracortical inhibition (ICI) and intracortical facilitation (ICF) because they are thought to reflect the activity of inhibitory and facilitatory interneuronal circuits in the motor cortex.13,15,17 In contrast, motor threshold (MT) assessed by single-pulse TMS is thought to reflect the excitability of the most excitable parts of the motor system in general.18 Abnormalities of ICI and ICF or MT were found in patients with several neurologic disorders involving the central motor system,19–21 but also after peripheral deafferentation.22,23 In the present study, we used TMS to assess changes of motor excitability and their possible relationship to clinical symptoms in patients with CRPS I to obtain further insight into the underlying pathophysiologic mechanisms.

**Methods. Subjects.** We studied 25 patients (16 women, 9 men) who fulfilled the clinical criteria of CRPS I at diagnosis. These criteria were 1) symptoms developed after an initiating noxious event; 2) spontaneous pain or allodynia and hyperalgesia occurred and were not limited to the territory of a single peripheral nerve and were disproportionate to the inciting event; 3) there was or had been evidence of edema, skin blood flow abnormality, or abnormal sensory activity in the pain since the inciting event; and 4) the diagnosis was excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction. Only patients with a unilateral affection of the upper limbs were selected. Patients with peripheral nerve lesions or other neurologic disorders were excluded. The patients’ ages ranged between 29 and 80 years (median, 50 years), and the period since diagnosis ranged between 0.5 and 231.0 months (median, 10.0 months). The patients did not take central acting drugs (expressed as a percentage of the use before trauma). The clinical features of the patients are reported in the table. Results obtained from the patients were compared with results recorded from a control group of 20 right-handed healthy volunteers (10 women, 10 men; aged 20 to 76 years; median, 49 years). All subjects participating in the study gave their informed consent. The local ethical committee approved the study.

**Transcranial magnetic stimulation.** TMS was performed using a Bistim module, which was connected to two Magstim 200 stimulators (Magstim Co., Whitland, Dyfed, UK). The stimuli were applied through a circular coil (outer diameter, 14 cm) positioned over the vertex with the current flowing counterclockwise in the coil to activate predominantly the left hemisphere, and clockwise to activate predominantly the right hemisphere. While stimulating the contralateral hemisphere, recordings were taken with Ag-AgCl surface electrodes from the first dorsal interosseus (FDI) muscle consecutively on both sides in the patients and only from the right FDI in the control group. They were stored on an EMG machine (Neuropack 8, Nihon Kohden, Tokyo, Japan) for further analysis. The signals were amplified with a bandpass of 20 Hz to 3 kHz, sweep duration of 10 to 50 ms/division, and gain of 0.1 to 1 mV/division. MT was determined at rest to the nearest 1% of the stimulator output and was defined as the minimum intensity that produced 5 motor evoked potentials (MEPs) >50 μV out of 10 trials. The corticocortical excitability (ICI and ICF) was tested in the resting muscle using a paired-pulse paradigm.11 The second stimulus (test stimulus) was adjusted to evoke an MEP of approximately 1.0 mV; the conditioning stimulus was set at 80% of the individual MT. The ISIs of 1, 2, 3, 4, 8, 10, 15, and 20 ms were chosen. For each interval, at least eight responses were collected. The paired pulses were mixed with 32 suprathreshold single control stimuli using the same stimulation intensity as for the second (test) stimulus. For each ISI, the amplitude ratio of the mean conditioned MEP to the control MEP was calculated. For all recordings, subjects were given audiovisual feedback at high gain to assist complete muscle relaxation. If EMG activity became ap-

### Table Clinical data of the CRPS patients

<table>
<thead>
<tr>
<th>Data</th>
<th>No.</th>
<th>Sex (WM)</th>
<th>Age (y; mean ± SD, range)</th>
<th>Affected side (1/r)</th>
<th>Inciting event</th>
<th>Duration since diagnosis (mo; mean ± SD, range)</th>
<th>Ongoing pain intensity during previous week</th>
<th>Use of the affected hand (in %; mean ± SD, range)</th>
<th>Number of patients with Hemisensory impairment</th>
<th>Alldynia</th>
<th>Tremor</th>
<th>Dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS</td>
<td>25</td>
<td>16/9</td>
<td>49.1 ± 13.8 (29–80)</td>
<td>12/13</td>
<td>Surgery</td>
<td>26.1 ± 47.0 (0.5–231.0)</td>
<td>Mean (VAS; mean ± SD, range)</td>
<td>3.8 ± 2.8 (0–8.7)</td>
<td>31.7 ± 33.1 (0–100)</td>
<td>4 (16%)</td>
<td>7 (28%)</td>
<td>5 (20%)</td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
<td>Maximal (VAS; mean ± SD, range)</td>
<td>6.2 ± 3.6 (0–10)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Actual pain intensity (VAS; mean ± SD, range)</td>
<td>3.5 ± 3.2 (0–8.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Data:** CRPS = complex regional pain syndrome; W = women; M = men; l = left; r = right; VAS = visual analogue scaling.
Figure. Time course of the mean amplitude ratio after paired-pulse transcranial magnetic stimulation at the different inhibitory (A) and facilitatory (B) interstimulus intervals. The different bars refer to recordings taken from the patients’ affected side (hatched), the patients’ clinically unaffected side (stippled), and the dominant hand of the control group (black). Error bars are SEM.

Statistical analysis. For the paired-pulse TMS, the inhibitory ISIs (1 to 4 ms) were analyzed separately from the facilitatory ISIs (8 to 20 ms). The results obtained from the patients’ affected side were compared with the patients’ clinically unaffected side using Student’s paired t-tests. For these paired t-tests, the significance level was adjusted by dividing it by the number of comparisons (0.05 ÷ 4 = 0.0125, Bonferroni correction for multiple comparisons). The results from the patients’ affected and clinically unaffected sides were compared separately with the results of the control group using an analysis of variance (ANOVA) for repeated measurements (within-subject factor “ISI,” between-subject factor “group”) with an adjusted significance level of 0.05 ÷ 2 = 0.025.

To detect a possible relationship between clinical features and ICI or ICF, an ANOVA for repeated measurements was calculated, with hemisensory impairment, allodynia, and tremor as between-subject factors, and age, duration since diagnosis, pain intensity, and use of the affected hand as covariates. For the MT, Student’s paired t-test was used to compare the affected and the clinically unaffected side, and Student’s unpaired t-test was used to compare patients and control subjects and clinical subgroups. Significance was assumed at the 0.05 level. For all statistical tests, the SPSS 11.0.1 software package (SPSS software, Munich, Germany) was used.

Results. Intracortical inhibition. Regarding the inhibitory 1- to 4-ms ISI (figure, A), no significant difference was found between the patients’ affected and clinically unaffected side at one of the ISIs. Comparing results of the patients’ affected side with the control group, ANOVA revealed a significant influence of the factor “ISI” (i.e., 1, 2, 3, or 4 ms) and a significant influence of the factor “group” (i.e., control group or patients’ affected side) with a reduced inhibition on the patients’ affected side (mean amplitude ratio, 49.8 ± 34.0% SD) compared with healthy control subjects (31.1 ± 22.9%, p = 0.006). There was no significant interaction between both factors. Comparing the results of patients’ unaffected side with the control group, there was also a significant influence of the factor “ISI” and the factor “group,” with a reduced inhibition on the patients’ unaffected side (48.5 ± 33.6%) compared with control subjects (p = 0.012). Again, there was no significant interaction between both factors.

Regarding the clinical features, the mean and the maximal pain intensity during the previous week were linked to a reduced ICI on the affected side but not on the clinically unaffected side (ANOVA, covariate effect on the affected side F = 6.354, p = 0.040 for the mean and F = 7.359, p = 0.030 for the maximal pain intensity). Other clinical features (hemisensory impairment, allodynia, tremor, age, duration since diagnosis, use of the affected hand) did not influence ICI on either the affected or clinically unaffected side.

Intracortical facilitation. Regarding the facilitatory 8- to 20-ms ISI (figure, B), there was also no significant difference between the patients’ affected and clinically unaffected side at one of the ISIs. Comparing the patients’ affected side and unaffected side with the control group, there was neither a significant effect of the factor “ISI” (i.e., 8, 10, 15, or 20 ms) nor of the factor “group” (i.e., control group and patients’ affected or unaffected side), and there was no significant interaction between these two factors. Mean amplitude ratio was 136.7 ± 96.0% SD on the patients’ affected side, 141.1 ± 69.8% on the patients’ clinically unaffected side, and 136.0 ± 37.2% for the control group. ICF was not influenced by one of the clinical features on either the affected or the clinically unaffected side.

Motor threshold. MT did not differ significantly between the patients’ clinically unaffected side (52.1 ± 10.0% of maximum stimulator output) and the patients’ affected side (51.6 ± 9.2%). There was also no significant difference between the control group (48.7 ± 9.2%) and either the patients’ affected or unaffected side. MT on the affected side was lower in patients with allodynia (45.0 ± 4.1%) than in those without allodynia (55.4 ± 8.2%, p = 0.005), whereas it did not differ between these two subgroups on the clinically unaffected side (49.0 ± 5.7% in patients with allodynia vs 54.2 ± 10.8% in patients without allodynia, p = 0.240).

MEP amplitudes after single control stimuli. MEP amplitudes after single control stimuli did not differ significantly between the patients’ clinically unaffected side (1.07 ± 0.61 mV), the patients’ affected side (1.00 ± 0.54 mV), and the control group (1.12 ± 0.44 mV).

Discussion. The main finding in patients with CRPS I was a reduced ICI in both the hemisphere contralateral to the affected and contralateral to the clinically unaffected hand. The phenomenon of ICI as assessed by TMS is the result of strong γ-aminobutyric acid (GABA)-dependent inhibitory
and weaker NMDA-dependent excitatory interneuronal circuits in the motor cortex. Therefore our results suggest a bilateral reduction of GABA-related motor cortical inhibition or an enhancement of NMDA-dependent excitatory mechanisms, or both.

In patients with limb amputation, a similar disinhibition was observed exclusively in the hemisphere contralateral to the amputation, which is discussed with respect to the altered peripheral input. An alteration of the peripheral input to the primary somatosensory and primary motor cortex, which are both closely linked via cortical horizontal connections, may also contribute to the observed disinhibition in the hemisphere contralateral to CRPS I. This disinhibition was particularly pronounced in patients with higher pain intensity. Because this finding was the result of an exploratory data analysis, further studies are required to firmly establish this relationship. However, it suggests that chronic pain in patients with CRPS induces central changes of sensorimotor processing, which may also result in clinical abnormalities such as hemisensory impairment in a subgroup of CRPS patients.

However, the disinhibition in the hemisphere contralateral to the clinically unaffected side is more difficult to explain. The finding of a bilateral motor cortex disinhibition in patients with CRPS is supported by the results of a MEG study, which showed a bilaterally altered reactivity of the 20-Hz motor cortex rhythm, with a significantly shorter and smaller 20-Hz rebound after tactile stimuli in patients with CRPS. Because the rebound of the 20-Hz rhythm is thought to reflect increased motor cortex inhibition, these findings also suggest a bilaterally modified inhibition of the motor cortex. Interestingly, in clinical reports CRPS was found not only to spread from the affected hand to the ipsilateral unaffected foot but also to the contralateral hand, or to show an initial bilateral distribution. There is evidence that unilateral nerve lesions may produce transsynaptic changes in the contralateral spinal cord dorsal horn, and a simultaneous appearance of bilateral pain hypersensitivity after unilateral nerve injury has been described in animal models of peripheral neuropathy. These effects are likely mediated by a central mechanism involving the system of commissural interneurons in the spinal cord and brainstem. It can be speculated that similar mechanisms could occur after subclinical traumatic nerve lesions in patients with CRPS I and therefore be related to the bilateral spread of CRPS in previous studies and to the bilateral motor cortex disinhibition seen in our study. Alternatively, the bilateral disinhibition could indicate a pre-existent increased susceptibility to CRPS.

Using the same TMS paradigm, a reduced ICI was found in patients with focal task-specific dystonia not only in the contralateral hemisphere but also in the ipsilateral hemisphere. This was attributed to a bilaterally disturbed motor cortex input from the basal ganglia. Further evidence for this hypothesis came from a recent fMRI study, showing an increased basal ganglia output via the thalamus to the motor and premotor cortical areas in patients with focal dystonia. Because dystonia is not an unusual clinical phenomenon in patients with CRPS I, and it may even show a multifocal or generalized distribution pattern in a subgroup of patients, our results could also be explained by a bilateral involvement of the basal ganglia during the course of the disease. However, this basal ganglia involvement might often be subclinical because dystonia was rarely observed in our patients. Interestingly, the amount of disinhibition in the hemisphere ipsilateral to CRPS I was not associated with pain intensity or duration since diagnosis. This leads to the assumption that the bilateral cortical disinhibition is not just a secondary phenomenon resulting from pain. It suggests a generalized involvement of the central motor system, which occurs early during the course of the disease and remains present years after its initiation.

Unlike changes in ICI, an alteration of ICF or MT was not a common phenomenon in patients with CRPS I when compared with healthy subjects. However, when analyzing clinical subgroups, MT was significantly lower in patients with alldynia than in patients without alldynia on the affected, but not on the clinically unaffected, side. A decrease in MT may be the result of increased excitability of the first (central) or second (spinal) motoneuron because MT reflects the excitability of the most excitable parts of the motor system in general. Therefore evoked pain as present in alldynia may exert a differential influence on motor excitability at different (spinal or cortical) levels on both sides. As for the relationship between pain and ICI, these findings have to be firmly established in further studies.

Considering the clinical relevance of our findings, the bilateral motor cortex disinhibition may not be a specific neurophysiologic marker for CRPS I because there is considerable overlap between patients and control subjects and because a reduced ICI has been reported not only in patients with dystonia and after amputation but also in patients with a wide range of other neurologic and psychiatric disorders, such as Parkinson’s disease, Alzheimer’s disease, Tourette’s syndrome, and schizophrenia. However, our findings give additional evidence for CNS involvement during the course of the disease and therefore encourage further research to develop therapeutical strategies that are able to target this CNS involvement in patients with CRPS I.

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References
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