Motor cortex dysfunction in complex regional pain syndrome

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Abstract

Objective: Most patients with complex regional pain syndrome (CRPS) exhibit debilitating motor symptoms. The effect of continuous pain on motor system in CRPS, however, is not well known. We searched for signs of motor cortex dysfunction in chronic CRPS type 1 patients with motor impairment.

Methods: We recorded rhythmic brain activity with magnetoencephalography (MEG) during noxious thulium–laser stimulation of both hands in eight CRPS patients and eight control subjects. We measured excitability of the motor cortex by monitoring the reactivity of the ∼20-Hz motor cortex rhythm to laser stimuli. The reactivity was defined as a sum of the stimulus-induced suppression and the subsequent rebound of the ∼20-Hz rhythm.

Results: In CRPS, the reactivity of the ∼20-Hz rhythm in the hemisphere contralateral to the painful hand was significantly weaker than in control subjects. The reactivity correlated with the mean level of the spontaneous pain (r = 0.64, P = 0.04). Suppression of the ∼20-Hz rhythm correlated with the grip strength in the painful hand (r = 0.66, P = 0.04).

Significance: Continuous pain in CRPS is associated with attenuated motor cortex reactivity.

Conclusion: Abnormal motor cortex reactivity may be linked with motor dysfunction of the affected hand in CRPS.

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1. Introduction

The complex regional pain syndrome (CRPS) is a disabling chronic pain condition of the upper or lower limb characterized by somatosensory, autonomic, and motor symptoms. The patients typically experience positive somatosensory phenomena, such as hyperalgesia and allodynia to tactile stimuli, but they regularly also present with sensory impairment. The autonomic symptoms include changes in skin color and temperature as well as sweating abnormalities. Motor dysfunction manifests as a decreased range of motion, weakness, clumsiness, tremor, dystonia, or myoclonia (Schwartzman and Kerrigan, 1990). In clinical examination, a majority of CRPS patients have been found to have motor symptoms (Veldman et al., 1993). Most of the patients have difficulties in using the affected hand in everyday tasks; the hand is weak and clumsy, and they feel that the hand does not obey their commands. Hand movements worsen the pain and may therefore, lead to immobilisation that further hamper the hand motor functions. The symptoms may even spread to the other side of the body with the course of the disease (Schwartzman and Kerrigan, 1990).

It has recently been proposed that the motor symptoms should be included in the clinical diagnostic criteria of CRPS (Harden et al., 2007). Although the precise pathophysiological mechanism underlying the complex clinical picture of CRPS remains unknown, growing evidence suggests that central nervous system alterations are associated with the pathogenesis of CRPS (Juottonen et al., 2002; Maihofner et al., 2003; Pleger et al., 2004b). Therefore, it is possible that the motor symptoms in CRPS are associated with alterations in central motor networks.

In addition to CRPS, patients with other clinical pain conditions also have signs of motor dysfunction. On the other hand, electric stimulation of the motor cortex may alleviate chronic pain (Tsubokawa et al., 1991). A previous PET study on patients who underwent motor cortex electrical stimulation for treatment of chronic pain, revealed the most significant increase in cerebral blood flow in the ventral–lateral thalamus (Garcia-Larrea et al., 1999). The authors suggested that the effect of motor cortex stimulation could be synaptically mediated to the medial thalamus, anterior cingulate and insular cortex as well as the upper brainstem which are areas involved in pain processing, indicating a
clinical and central nervous systems. The close coupling of motor cortex and pain systems. Vice versa, studies in healthy subjects have shown that nociceptive stimulation activates the motor cortex, possibly for preparation of voluntary movements to avoid further pain (Raij et al., 2004; Stancak et al., 2007).

Prior studies have shown that the level of spontaneous ~20-Hz oscillations that predominantly arise from the primary motor cortex (M1) (Jasper and Penfield, 1949; Papakostopoulos et al., 1980; Salmelin and Hari, 1994), reflect the functional state of the cortex. The ~20-Hz oscillations are suppressed during movement, and increased substantially after it, as revealed by Temporal Spectral Evolution (TSE) analysis, which can be used to follow event-related changes in different frequency bands (Salmelin and Hari, 1994). Similarly, after somatosensory stimuli, the 20-Hz level is first suppressed and then subsequently enhanced. Suppression of the ~20-Hz level is associated with excitation or disinhibition of M1 (Hari et al., 1998; Silen et al., 2000), whereas a subsequent increase of the rhythm, the rebound, reflects increased inhibition of M1 (Salmelin and Hari, 1994). This is in line with a transcranial magnetic stimulation (TMS) study showing that the latency of the rebound corresponds well with the timing of reduced cortical excitability following median nerve stimulation (Chen et al., 1999).

We monitored the excitability of the motor cortex by observing changes in the ~20-Hz rhythm to noxious stimulation and correlated the findings with the clinical symptoms of the patients to clarify the association between chronic pain and motor cortex function in CRPS.

2. Materials and methods

2.1. Patients and control subjects

We studied eight patients with CRPS type 1 (all right-handed females; age 26–57, mean 45.5) and eight healthy age-matched female control subjects (seven right-handed, one ambidextrous; age 28–57, mean 46.3). The patients were included in our earlier study on cortical evoked responses to noxious stimuli (Vartiainen et al., 2008). The protocol had a prior approval by the local Ethics Committee, and all subjects gave written informed consent, according to the Declaration of Helsinki.

In our patients, the diagnosis of CRPS type 1 was set according to the criteria by Stanton-Hicks et al. (1995) and Harden et al. (2007). A neurologist and a physiatrist performed the clinical examination, which included testing of fine motor skills and the active range of movements. An occupational therapist measured the grip strength with a dynamometer. As reported in our earlier study (Vartiainen et al., 2008), the patients had no evidence of lesions in the peripheral nerves or in the brain, as verified with electromyography (EMG) and magnetic resonance imaging (MRI). The patients had spontaneous continuous pain (mean 6.4 on the Visual Analogue Scale, VAS; from 0 to 10) in the upper limb. The duration of pain was 1–9 years (mean 5.5 years). All patients had motor deficits in the painful side; both the strength and the range of movements of the affected limb were decreased. Finger movements were slow and clumsy, leading to difficulties in fine motor tasks. The strength of the hand grip of the patients was significantly decreased on the painful side, in comparison to the healthy hand (t-test, P < 0.0001).

The clinical details are shown in Table 1.

2.2. Stimuli

Whole-scalp MEG was recorded during noxious thulium-laser stimulation (BLM 1000 Tm:YAG; Baasel Lasertech, Starnberg, Germany) of the hand dorsum. We applied single pulses (duration 1 ms, wavelength 2000 nm) on an area of about 20 mm² to avoid adaptation and potential skin damage. Such stimulation has been shown to elicit earliest cortical response at about 165 ms corresponding with Aβ-fiber activity (Fossi et al., 2000b). The left and right hands were stimulated with a 4.5–5.5 s interstimulus interval in separate sessions in pseudorandom sequence across subjects. Prior to the MEG recording, individual pain thresholds were measured by gradually increasing the stimulation energy according to the pain percepts of each subject. We started with low intensity (about 200 mJ), which elicited a non-painful sensation, and proceeded in approximately 50 mJ steps to a level with pricking pain sensation (VAS = 1). This was repeated three times, and the mean intensity was then defined as the pain threshold. As reported

### Table 1

Clinical details of patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<td>57</td>
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<td>7</td>
<td>5</td>
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<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Duration of pain</td>
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<td>6</td>
<td>4</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
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<td>L</td>
<td>R</td>
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<tr>
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<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<tr>
<td>Impaired motor function</td>
<td>+</td>
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<tr>
<td>Tremor or dystonia</td>
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</table>

Mean pain intensity in VAS scale (1–10). Duration of pain in years. Side of pain: R = right; L = left. Hand grip strength measured by Jamar dynamometer in handle position 3 (age-matched normal values in parentheses). Impaired motor function: decreased range of active movements and clumsiness in fine motor skills.
in our earlier study (Vartiainen et al., 2008), CRPS patients have significantly lower pain thresholds in both their painful and healthy hands, in comparison to the pain thresholds of the healthy control subjects (CRPS painful vs. controls; t-test, P = 0.003, CRPS healthy vs. controls; P = 0.02). In the control subjects, the pain thresholds did not differ between the hands.

During the recording, we used stimulation energy of about 1.5 times the individual pain threshold. In patients, the mean ± SEM stimulation energy was thus 520 ± 31 mJ, and in the control subjects, 737 ± 23 mJ (called here ‘high intensity stimulation’). We were not able to use equally strong stimulation energy with the CRPS patients, since they found it too painful. Therefore, we performed on the healthy subjects, a control measurement with a comparable absolute stimulation energy of 542 ± 13 mJ (1.1 times the pain threshold, called here ‘low intensity stimulation’). Thus, the control subjects underwent two separate stimulation sessions: the high intensity stimulation with VAS matched with that of the patients, and the low intensity stimulation matched with the stimulation energy of the patients. The subjects were instructed to relax their upper limbs during the measurement; the nurse applying the laser stimuli observed the subjects for any possible movements. At the end of each laser stimulation session, we asked the subjects to report the perceived intensity of pain on VAS, as well as their other sensations to the stimulation. The laser stimuli were perceived by all subjects as pricking pain, occasionally followed by a longer-lasting burning pain.

In the laser stimulation with comparable energy, the patients rated the stimulation significantly more painful than the control subjects (CRPS painful hand 7.5 ± 0.7 vs. controls 2.3 ± 0.3; t-test, P < 0.001, and CRPS healthy hand 5.4 ± 1.0 vs. controls 2.3 ± 0.3; P = 0.005). Furthermore, the patients rated the noxious stimulation of the painful hand more intense than that of the healthy hand (t-test, P = 0.05). In control subjects, the ratings did not differ between the left- and right-sided stimulation.

3.2. MEG recordings

Recordings were performed with a 306-channel helmet-shaped neuromagnetometer (Vectorview™, Neuromag Ltd., Helsinki, Finland) in a magnetically shielded room. Four indicator coils were placed on the scalp, and their positions with respect to the anatomical landmarks were determined with a three-dimensional digitizer. The exact head position in relation to the sensors was defined by detecting the magnetic signals produced by currents led into the indicator coils. The signals were bandpass filtered through 0.03–200 Hz and digitized at 600 Hz. In each recording, 50–60 laser stimuli were given. Spontaneous brain activity was recorded during laser stimulation of the right and left hands in different sessions. Before the laser stimulation, we recorded spontaneous brain activity in each subject during rest (eyes open/eyes closed) for two minutes.

3.2.1. Time–frequency representation (TFR)

We calculated temporal changes in the frequency range of 15–30 Hz with TFR, in order to observe how brain oscillations in this frequency range react to painful stimuli. The baseline was –500 ms to 0 ms, which was subtracted from the whole time span rendering absolute amplitude quantifications pointless. The activity was quantified from the channel over the contralateral sensorimotor region that showed the largest signal changes.

3.2.2. Temporal spectral evolution (TSE)

The TSE method was applied to quantify the reactivity of the ~20-Hz oscillations. The MEG signals were first filtered through 20-Hz oscillations. The MEG signals were first filtered through 20 Hz with TFR, in order to observe how brain oscillations in this frequency range react to painful stimuli. The baseline was –500 ms to 0 ms, which was subtracted from the whole time span rendering absolute amplitude quantifications pointless. The activity was quantified from the channel over the contralateral sensorimotor region that showed the largest signal changes.

The measured, hemisphere-matched parameters were compared between the control subjects and patients with the unpaired t-test. In addition, a paired t-test was used for comparisons of the parameters within the subjects between the sides (right vs. left, painful vs. healthy side) and between the measurements with different stimulation intensities in control subjects. To further test the differences between the patient and control groups, we used repetitive ANOVA with hemispheres defined as the within-subjects factor and group defined as the between-subjects factor. Prior to the correlation analysis of the measured parameters and the clinical symptoms (grip strength, level of spontaneous pain, duration of pain), we performed the Kolmogorov–Smirnov test of normality on the variables. In variables with non-normal distribution, we used Pearson’s correlation coefficient. In variables with non-normal distribution, Spearman’s correlation coefficient was used.

3. Results

3.1. Spectrum of spontaneous activity

The spectrum of the spontaneous activity recorded before stimulation during rest (eyes open) showed spectral peaks at ~10 and ~20 Hz over the sensorimotor region in both hemispheres, both in the patients and the healthy control subjects. The ~20-Hz rhythm peaked at 18.8 ± 0.5 Hz (mean ± SEM) for both the patients and the control subjects. The amplitudes of the ~20 Hz peak did not differ between the control subjects and patients (10 ± 2 fT/cm and 11 ± 2 fT/cm in the right and left hemisphere vs. 10 ± 2 fT/cm and 11 ± 2 fT/cm in the contralateral and ipsilateral hemisphere to the painful limb, respectively).

3.2. Reactivity of the ~20-Hz rhythm to noxious laser stimulation

Fig. 2 shows the TFR of the oscillatory activity over the contralateral sensorimotor cortex in the frequency range of 15–30 Hz, during laser stimulation in patients and in control subjects. In control subjects, the strongest activity was observed around 20 Hz.
The ~20-Hz power started to decrease at ~100–200 ms after the stimulation and subsequently increase at 1000–1500 ms during both high and low intensity stimulation. In stimulation of the healthy hand of the patients, a similar pattern of the ~20-Hz activity modulation was seen, but the ~20-Hz power was weaker than that of the control subjects. In stimulation of the patients’ painful hand, the ~20-Hz power was even weaker, and the ~20-Hz activity modulation was less evident than in stimulation of the healthy hand.

To illustrate the temporal aspects of the reactivity of the contralateral ~20-Hz rhythm in more detail, Fig. 3 shows the TSE of the ~20-Hz rhythm to noxious stimulation in patients and in control subjects. In line with the TFR analysis, suppression was lower in amplitude, and rebound was strongly diminished in patients, compared with those of the control subjects.

Fig. 4 presents the mean amplitudes of suppression and rebound as well as the mean reactivity in the hemisphere contralateral to the stimulation side, in patients and in control subjects. The suppression and rebound were stronger in the control subjects than in the patients, irrespective of the stimulation intensity, and in particular when compared with the data from the painful side stimulation: in comparison to the patients, the suppression amplitude of the control subjects was three times stronger in high intensity stimulation and two times stronger in low intensity stimulation. However, this difference did not reach statistical significance (3 ± 1 fT/cm vs. 9 ± 3 fT/cm or 6 ± 1 fT/cm to high or low intensity stimulation, respectively, \( P = 0.08 \)). Again when comparing to the patients, the rebound amplitude of the control subjects during high intensity stimulation was seven times stronger and during low intensity stimulation three times stronger. Both the rebound amplitude and the reactivity to painful hand stimulation were significantly smaller in patients than those in control subjects during high intensity stimulation (1 ± 1 fT/cm vs. 7 ± 3 fT/cm, \( P = 0.05 \), and 4 ± 2 fT/cm vs. 16 ± 5 fT/cm, \( P = 0.03 \), respectively). Compared with the controls during low intensity stimulation, the differences did not reach statistical significance, although the rebound amplitude and the reactivity of the patients were only 33% and 44%, respectively of those of the controls. In the control subjects, there was no significant difference in the suppression amplitude, the rebound amplitude, or the reactivity during high

![Fig. 2. Time–frequency representations of the power of oscillatory activity, over the contralateral sensorimotor region, to laser stimulation (arbitrary scale). The vertical line depicts the stimulation time point. The top row presents the mean 15–30-Hz level of the patients: on the left, activation to the stimulation of the painful hand; on the right, activation to the stimulation of the healthy hand. The bottom row shows the mean 15–30-Hz level of the control subjects during high and low intensity stimulation.](image-url)
vs. low intensity stimulation. Suppression, rebound or reactivity following healthy hand stimulation of the patients, were not significantly smaller than those of the control subjects during either high or low intensity stimulation.

The suppression peak for both painful and healthy hand stimulation in patients occurred at 606 ± 116 ms and 737 ± 110 ms (P = 0.53), and the rebound at 2392 ± 748 ms and 1098 ± 333 ms (P = 0.54), respectively. No significant differences were seen in the latencies of suppression or rebound between the patients and control subjects with comparable stimulus intensity. In control subjects, the latencies of suppression onset and peak were shorter during high intensity stimulation than during low intensity stimulation on both sides (onset at 165 ± 22 ms vs. 354 ± 25 ms, or 224 ± 13 ms vs. 378 ± 70 ms, and peak at 403 ± 73 ms vs. 729 ± 83 ms, or 414 ± 61 ms vs. 900 ± 121 ms, P < 0.05).

In inter-hemispheric comparisons of the measured parameters, there were no significant differences within the patient group (painful vs. healthy side) or within the control subject group. The ANOVA analysis did not reveal any significant hemisphere × group interaction in the measured parameters. In the hemisphere ipsilateral to the stimulation, there were no statistically significant differences in the amplitude or latency parameters, or in the reactivity between the groups or between the sides within the groups.

3.3. Correlation of the ~20-Hz rhythm level and clinical symptoms

The ~20-Hz reactivity contralateral to the painful limb stimulation correlated inversely with the intensity of the long-term mean spontaneous pain in the painful hand (r = −0.64, P = 0.04); the more intense the pain, the less reactive the motor cortex rhythm (Fig. 5). Also the ~20-Hz reactivity contralateral to the healthy hand stimulation correlated in a similar manner with the pain intensity (r = −0.63, P = 0.05). A separate analysis of suppression and rebound amplitudes in patients indicated that both the suppression and the rebound contralateral to the painful hand were correlated with VAS (r = −0.83, P = 0.005, and r = −0.76, P = 0.01, respectively). In the hemisphere contralateral to the healthy hand, there was a similar inverse correlation between VAS and the suppression amplitude (r = −0.74, P = 0.02). The suppression amplitude of the painful hand stimulation correlated positively with the grip strength of the same hand (r = 0.66, P = 0.04), whereas no significant correlation was found between grip strength and the rebound amplitude (r = 0.45, P = 0.13) nor between grip strength and reactivity (r = 0.42, P = 0.15). In the healthy hand, grip strength did not correlate with the amplitudes of suppression, rebound, nor reactivity. The intensity of long-term mean spontaneous pain and grip strength in the painful hand did not correlate significantly (r = −0.43, P = 0.14). The duration of pain did not correlate with any of the aforementioned variables.

The stronger the suppression was in the hemisphere contralateral to the painful hand stimulation, the stronger the rebound in the same hemisphere (r = 0.76, P = 0.01). No such correlation was found in the case of stimulation to the healthy hand (r = 0.13, P = 0.38). Further, it was found that the stronger the suppression to stimulation of the painful hand, the stronger the suppression also to healthy hand stimulation (r = 0.80, P = 0.008). Between the corresponding rebound amplitudes, no such correlation was seen (r = −0.33, P = 0.21).

4. Discussion

Our results show that the modulation of the motor cortex rhythm to noxious stimuli is altered in CRPS patients. The results
indicate that the normal pattern of a brief suppression and a subsequent enhancement of the ~20-Hz rhythm observed in healthy subjects is significantly attenuated in the hemisphere contralateral to the painful hand in patients: TFR and TSE showed weaker reactivity and particularly weaker rebound of the motor cortex rhythm suggesting decreased inhibition of the motor cortex in CRPS.

Chronic pain, such as phantom limb and neuropathic pain, has been shown to be associated with disinhibition of the motor cortex (Dettmers et al., 2001; Lefaucheur et al., 2006). A recent fMRI study on 13 patients with phantom limb pain revealed extensive bilateral activation in motor cortices during imagined movement of the phantom hand and during executed movement of the intact hand (Maclver et al., 2008), suggesting bilateral disinhibition of the motor cortex following unilateral deafferentation. In CRPS, TMS studies have indicated increased excitability of the motor cortex, either bilaterally or contralaterally to the painful side (Eisenberg et al., 2005; Schwenkreis et al., 2003). However, the mechanism of how chronic pain modulates excitability remains unclear. In line with these studies, we found reduced rebound of the motor cortex rhythm as an indication of disinhibition. Our findings seemed to be bilateral, although we found significant changes predominantly in the hemisphere contralateral to the painful hand. The results of the hemisphere contralateral to the healthy hand stimulation failed to reach statistical significance, possibly due to the small number of patients. An earlier study on the ~20-Hz rhythms to tactile stimulation in CRPS indicated similarly a tendency toward bilateral disinhibition (Juottonen et al., 2002).

Another TMS study on CRPS showed that conditioning peripheral repetitive magnetic stimulation failed to facilitate the motor system bilaterally in CRPS in contrast to healthy subjects (Krause et al., 2005). The authors suggested that the afferent input to the motor cortical system was less effective than in healthy subjects. The results of the present study would be in line with this interpretation. In healthy subjects, nociceptive laser stimuli induced transient excitation of the motor cortex (Rai et al., 2004), whereas in CRPS patients stimulation of the painful hand failed to excite the motor cortex normally. It is possible that disinhibition of the motor cortex induced by chronic pain had caused a static hyperexcitation state, where external noxious stimulation cannot further activate the motor cortex due to a ceiling effect. The correlation of clinical pain and the attenuation of the motor cortex activation support this suggestion.

The decreased reactivity of the motor cortex found in this study could be explained by a reduced number of excitable neurons within the motor cortex. It is known that continuous pain may lead to maladaptive plasticity of the sensorimotor cortex (Flor et al., 1995). In CRPS patients, the representation area of the painful hand in the primary somatosensory cortex has been shown to be smaller than that of the healthy hand (Juottonen et al., 2002; Maihofner et al., 2003; Pleger et al., 2004b). Analogously, a TMS study on 14 CRPS patients revealed an asymmetry in the motor cortex; the motor representation area of the affected hand was smaller than that of the unaffected hand (Krause et al., 2006).

In CRPS patients, movement of the affected extremity elicits pain, leading to varying degrees of immobilisation that may cause shrinkage of cortical representations. It is possible that such reduction in the extent of excitable neurons of the hand representation area could lead to decreased reactivity of the motor cortex. On the other hand, immobilisation has been shown to induce a reversible enhancement of the excitability of cortico-motorneuronal structures, as verified with TMS (Zanette et al., 1997). Thus the influence of immobilisation alone on our findings remains ambiguous.

In addition, motor cortex excitability may be altered by medication for chronic pain. Amitriptyline (in three patients), benzodiazepines (in two patients), and muscle relaxant (in one patient) taken by our patients, are likely to increase cortical inhibition (Ziemann, 2004). Two of these patients used additional medication previously shown to reduce cortical inhibition: venlafaxine and gabapentin (Ziemann, 2004). Four patients took opiates, which have an ambiguous effect on motor cortex excitability. In summary it can be said that the medication taken by our patients is not likely to systematically affect our results. If any, the net effect of the medication would probably be reflected as increased cortical inhibition, meaning that the disinhibition observed in patients could be even more evident without medication.

The majority of CRPS patients have a variety of motor symptoms (Veldman et al., 1993). Recent kinematic analysis on CRPS patients revealed that especially the grasping movements were altered, and that the motor impairment during motor task in fMRI scanning correlated with the activation of the contralateral primary motor cortex (Maihofner et al., 2007). In line, in the present study, suppression of the motor cortex ~20-Hz rhythm correlated with grip strength, suggesting that imbalance of the excitation-inhibition cycle may be associated with motor performance. This observation is in accordance with a study on progressive myoclonus epilepsy of Unverricht–Lundborg type, which showed disinhibition of motor cortex in patients with impaired fine motor skills (Silen et al., 2000). Although the exact mechanism cannot be shown, the above examples suggest that abnormal modulation of the excitability of the motor cortex may disturb the motor performance.

Pain affects the excitability of the motor cortex, which may in turn influence motor performance. In CRPS, chronic nociceptive input and reduced tactile input may disturb the normal interplay of sensory input and motor output, further hampering motor performance.

Alterations in motor cortex activation have been shown to correlate with clinical pain in CRPS; Schwenkreis et al. (2003) found that disinhibition of the motor cortex increased with higher VAS. Our results are in line with this observation: the attenuation of the motor cortex reactivity correlates with clinical pain, in other words, the more painful the affected limb was, the less reactive the contralateral motor cortex rhythm. Similar significant correlation was observed in the ‘healthy’ hemisphere, suggesting that despite unilateral pain symptoms, motor cortex excitability is altered in both hemispheres. This is in line with earlier studies showing bilaterally decreased pain thresholds (Vartiainen et al., 2008) and the mirror-like spreading of symptoms to the other side (Fors et al., 2005a; Schwartzman and Kerrigan, 1990). These findings strongly suggest that CRPS does not affect only one extremity but rather is a disease of the whole nervous system.

Significant correlation between clinical pain and dysfunction of the motor cortex suggests a close coupling of chronic pain and the motor system. It is possible that the continuous pain experienced in CRPS dampens the motor cortex function by competing with the tactile and proprioceptive input, confounding the sensorimotor interference. Further, this motor cortex dysfunction might promote the sustenance of pain by an unknown mechanism. Alternatively, a common pathophysiology might cause both the continuous pain as well as the motor cortex dysfunction.

Successful management of motor symptoms has been suggested to be one of the most essential prognostic factors for CRPS (Baron, 2008). 10 Hz repetitive transcranial magnetic stimulation of the motor cortex caused temporary relief of the clinical pain in CRPS (Pleger et al., 2004a). Furthermore, mirror visual feedback from a moving, unaffected limb, and motor imagery of the affected hand led to a reduction of pain and disability of the affected limb in CRPS patients (McCabe et al., 2003; Moseley, 2004, 2006). These results suggest that restoration of the normal motor cortex activity could be important in controlling the disabling pain.

In addition to the motor component itself, motor rehabilitation includes also tactile and proprioceptive components. In tailored motor rehabilitation of the painful limb, the increased tactile and
propioreceptive inputs would compete with the nociceptive input, potentially reversing the cortical maladaptive change. This cortical restoration might re-establish the normal excitation – inhibition pattern of the motor cortex and promote normal sensorimotor integration, hopefully leading to better motor performance and reduced pain. The possible restoration of motor cortex reactivity in the course of therapeutic interventions could be quantified and followed by the TSE method used in the present study.

### Disclosure

The authors disclose financial interest and commercial considerations.

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