Central processing of tactile and nociceptive stimuli in complex regional pain syndrome

Nuutti V. Vartiainen a,*, Erika Kirveskari a, b, Nina Forss a, c

a Brain Research Unit, Low Temperature Laboratory, Helsinki University of Technology, Puumiehenkuja 2 B, P.O. Box 5100, FI-02015 TKK Espoo, Finland
b Department of Clinical Neurophysiology, Helsinki University Central Hospital, FI-00029 HUS Helsinki, Finland
c Department of Clinical Neurosciences, Helsinki University Central Hospital, FI-00029 HUS Helsinki, Finland

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A B S T R A C T

Objective: Patients with complex regional pain syndrome (CRPS) suffer from continuous regional limb pain and from hyperesthesia to touch and pain. To better understand the pathophysiological mechanisms underlying the hyperesthesia of CRPS patients, we investigated their cortical processing of touch and acute pain.

Methods: Cortical responses to tactile stimuli applied to the thumbs, index and little fingers (D1, D2, and D5) and nociceptive stimuli delivered to dorsa of the hands were recorded with a whole-scalp neuromagnetometer from eight chronic CRPS patients and from nine healthy control subjects.

Results: In the patients, primary somatosensory (SI) cortex activation to tactile stimulation of D2 was significantly stronger, and the D1–D5 distance in SI was significantly smaller for the painful hand compared to the healthy hand. The PPC activation to tactile stimulation was significantly weaker in the patients than in the control subjects. To nociceptive stimulation with equal laser energy, the secondary somatosensory (SII) cortices and posterior parietal cortex (PPC) were similarly activated in both groups. The PPC source strength correlated with the pain rating in the control subjects, but not in the patients.

Conclusions: The enhanced SI activation in hyperesthetic CRPS patients may reflect central sensitization to touch. The decreased D1–D5 distance implies permanent changes in SI hand representations in chronic CRPS. The defective PPC activation could be associated with the neglect-like symptoms of the patients. As the SII and PPC responses were not enhanced in the CRPS patients, other brain areas are likely to contribute to the observed hyperesthesia to pain.

Significance: Our results indicate changes of somatosensory processing at cortical level in CRPS.

1. Introduction

The complex regional pain syndrome (CRPS) is characterized by continuous regional pain that does not follow a specific nerve territory and is disproportionate to the usual course of any initiating event (Harden et al., 1999). Other clinical features include sensory hypersensitivity and impaired motor function, as well as trophic, sudomotor, and vasomotor changes. The origin of these symptoms is not yet fully understood (Jänig and Baron, 2003), but recent brain imaging studies have demonstrated alterations in central sensorimotor processing in CRPS patients (Juottonen et al., 2002; Maihöfner et al., 2003, 2005; Pleger et al., 2004).

Laser-evoked potentials (LEPs) are useful for assessment of the nociceptive pathways (Cruccu et al., 2004). Lesions of these pathways at the peripheral, spinal, or supraspinal level have been associated with attenuated LEPs (Treede et al., 1991; Hansen et al., 1996; Garcia-Larrea et al., 2002; Truini et al., 2003), whereas normal or enhanced LEPs have been recorded from chronic pain patients who do not have any known nociceptive pathway lesion (Lorenz et al., 1996; Garcia-Larrea et al., 2002). Therefore, LEPs are considered to reflect the integrity of ascending nociceptive pathways (Treede et al., 2003). Because attenuated LEPs have been described in patients suffering from either decreased or increased sensitivity to nociceptive stimuli, the LEPs measured at the vertex apparently do not reflect the subjective pain percepts (Casey et al., 1996; Wu et al., 1999; Garcia-Larrea et al., 2002).

We recorded magnetoencephalographic (MEG) responses to innocuous tactile and painful laser stimuli in a group of CRPS type 1 patients who had continuous pain in the upper limb and were hyperesthetic to tactile and nociceptive stimuli. Our goal was to search for functional alterations in the ascending somatosensory tracts and somatosensory cortical areas that would reflect the observed hyperesthesia to touch and pain.
2. Methods

2.1. Patients and control subjects

Eight chronic CRPS patients (all right-handed females; ages 26–57, mean 45.5 yrs) and nine healthy age-matched female control subjects (eight right-handed, one ambidextrous; ages 28–57, mean 46.0 yrs) participated in this study. Six of the patients had also participated in the earlier study by Juottonen et al. (2002), but in the present study they participated in new measurements. The protocol had a prior approval by the local Ethics Committee, and all subjects gave written informed consent before participation. The patients had no evidence of a peripheral nerve lesion, and thus the diagnosis of CRPS type 1 was set according to the criteria by IASP (Stanton-Hicks et al., 1995). All patients had continuous spontaneous pain (5–8 on the Visual Analogue Scale, VAS; from 0 to 10) in the upper limb; the pain had lasted for 1–9 years and was best described as burning, stabbing, or tearing. All patients had brush allodynia and fluctuating edema in the affected hand and five had vasomotor or sudomotor dysfunction. The patients underwent clinical examinations by both a neurologist and a physiatrist. Occupational therapist tested tactile sensitivity with monofilament detection and two-point discrimination from several points of the glabrous and hairy skin. Motor function of the upper limb was evaluated by testing the range of active movement and the fine motor skills. Grip strength was measured with a dynamometer. Electroneuromyography (EMG) and magnetic resonance imaging (MRI) were performed to exclude lesions in the peripheral nerves and in the brain.

2.2. MEG recordings

During the MEG recording, the subject was sitting inside a magnetically shielded room with the head comfortably supported against the helmet-shaped array of the 306-channel neuromagnetometer (Vectorview™, Neuromag Ltd., Helsinki, Finland).

Tactile stimuli (26 ms rise time, 60 ms plateau, 186 ms return to baseline) were delivered to the fingertips with diaphragms driven by compressed air (Mertens and Lütkenhöner, 2000). The stimulus baseline) were delivered to the fingertips with diaphragms driven by thulium-laser stimulator (stimulation area 20 mm²), produced by thulium-laser stimulator (BLM 1000 Tm:YAG; Baasel Lasertech, Starnberg, Germany), were delivered to hand dorsum in all patients and control subjects. The left and right hands were stimulated in separate sessions, delivered to hand dorsum in all patients and control subjects. The left and right hands were stimulated in separate sessions, and the ISI was varied between 4.5 and 5.5 s to avoid predictability. The left and right hands were stimulated in separate sessions, and the ISI was varied between 4.5 and 5.5 s to avoid predictability. The stimulation site was changed by an assisting person between single pulses inside an area of approximately 5 cm in diameter to avoid skin burns and adaptation. Individual pain thresholds were defined before the MEG measurement by gradually increasing the stimulus energy until the subjects reported pain (VAS = 1). The pain threshold was evaluated three times in each individual, and the mean stimulus energy obtained from these measurements was defined as the pain threshold. During the measurement, the stimulation energy was set to equal 1.4–1.5 times the individual pain threshold; the goal was to induce pain that would be considered at least of moderate intensity in both groups. The mean ± SEM stimulation energy was thus 520 ± 31 mJ for the CRPS patients and 737 ± 23 mJ for the control subjects. With this stimulation energy, the CRPS patients described strong pain and could not tolerate additional increase in stimulation energy. As the maximal tolerated stimulation energy of CRPS patients was lower than that in the control subjects, a control measurement with comparable stimulation energy of 542 ± 13 mJ (1.1 times the pain threshold) was performed in the control subjects. After each laser stimulation session, the subjects verbally described their sensations and rated the pain with VAS. During both tactile and laser stimulation, the subjects were asked to concentrate on the stimulated hand.

The evoked responses were recorded with the MEG device’s 204 planar gradiometers and 102 magnetometers. Four indicator coils were placed on the scalp, and their positions with respect to the anatomical landmarks were determined with a three-dimensional digitizer to align the MEG and the MRI coordinate systems. The exact head position in relation to the sensors was found by measuring the magnetic signals produced by the currents that were led into the indicator coils. The head position was measured in the beginning of each stimulation session. The assisting person was monitoring the subject for possible head movement during the measurement; in case of head movement, the session was repeated. The signals were digitized at 600 Hz and band-pass filtered through 0.03–200 Hz. The analysis period was from −200 to 500 ms. In each subject, 50–60 responses to laser pulses and 110–120 responses to tactile stimuli were averaged for each condition. Responses that coincided with eye blinks in the simultaneously recorded vertical electro-oculogram were automatically excluded from the analysis.

2.3. Data analysis

The source localization was based on the recorded signals from the 204 planar gradiometers. For identification of the sources of the measured responses, deflections exceeding the noise level were found by a visual search to define time windows and cortical areas for further analysis. Equivalent current dipoles (ECDs) best describing the local source currents were then calculated at the peak of the response by least-squares fit in subset of 10–14 channels over the area showing maximal deflections. This calculation resulted in three-dimensional location, orientation, and strength of the dipole in a spherical conductor model. Goodness of fit (g) of the dipole was calculated to quantify how much of the measured signal variance it explained, and only ECDs with g ≥ 80% were accepted. The ECDs were found, one by one, by fitting a dipole for each separate peak of activation. After identification of single dipoles, the analysis was extended to include the whole time period and all channels. The multidipole model was then used to explain the measured data by keeping the dipoles fixed in location and orientation, but allowing them to vary in amplitude over time. The validity of the multidipole model was estimated by comparing the recorded signals with those predicted by the model. If data were inadequately explained by the model, we then re-evaluated the data for more accurate source estimation. This approach has been successfully used in previous MEG studies of healthy subjects and patients (Juottonen et al., 2002; Raij et al., 2003; Forss et al., 2005a) and is described in detail in Hämäläinen et al. (1993).

The size of the hand representation area in the SI cortex was estimated by calculating the distance (in xyz-space) between D1 and D5 sources. The peak amplitude of the ECD waveform was considered to reflect the strength of the source. The strengths and peak latencies of the sources were compared between the groups and between the painful and healthy hands with a two-tailed t-test. Pearson’s correlation coefficients were calculated to correlate the source strengths with the stimulation energy and intensity of perceived pain.
3. Results

3.1. Clinical testing

Table 1 summarizes the results of clinical testing. All patients had allodynia to light brushing of the painful hand. The two-point discrimination was statistically significantly decreased in the painful hand compared with the healthy hand \((P = 0.005)\), and monofilament detection showed a trend towards increased threshold in the painful hand compared with the healthy hand \((P = 0.07)\). All patients had impaired motor function and decreased grip strength in the painful hand \((P = 0.02)\). The six patients that participated in the earlier study \((2–5\text{ years before})\) had persistent clinical symptoms with mean ± (SEM) VAS scaling increasing from first \((58 ± 2)\) to second \((67 ± 2)\) measurement. The deficits in tactile discrimination were not improved between the measurements (see Juottonen et al., 2002).

3.2. Processing of innocuous tactile stimuli

In all subjects, the earliest cortical responses to tactile stimuli peaked at about 54–58 ms at the contralateral parietal cortex. The source of the response was identified in all subjects in the posterior wall of the central fissure, in the SI cortex. Longer-latency responses peaked bilaterally at 99–105 ms in the temporoparietal regions. These responses were generated in the upper lip of the Sylvian fissure in the secondary somatosensory (SII) cortex. A later response peaked at the contralateral parietal cortex at 95–152 ms, and it was generated in the bottom of the postcentral fissure in the posterior parietal cortex (PPC).

Fig. 1 shows the source waveforms of one healthy control subject and one patient to tactile stimulation. The SI cortex and the bilateral SII cortices were activated in both subjects. PPC activation was observed in the control subject but not in the patient. At group level, the SI sources were 33% stronger \((P = 0.05)\) to the stimulation of the painful than that of the healthy hand in the patients, whereas no such side difference was observed in the control group (Table 2). The strengths and latencies of the SII sources did not differ between the groups or between the sides in either group. PPC activation was observed in all control subjects but only in three CRPS patients. The mean \((±SEM)\) PPC source strength was weaker in the CRPS patients than in the control subjects (patients healthy hand \(1.0 ± 0.9\text{ nAm} vs.\) controls \(11.2 ± 3.1\text{ nAm}, P = 0.01\); patients painful hand \(7.1 ± 4.0\text{ nAm} vs.\) controls \(11.2 ± 3.1\text{ nAm}, n.s.)\). The PPC source strength did not correlate with the tactile sensitivity or discrimination in the patients.

3.3. Plastic changes in SI

Fig. 2A illustrates the locations of D1 and D5 representations of one patient superimposed on her MRI. The D1–D5 distance is obviously shorter for the painful than for the healthy hand. Fig. 2B shows the distances in \(xyz\)-space between D1 and D5 in both hands of the patients and control subjects. At group level, the D1–D5 distance was statistically significantly shorter for the painful than the healthy hand \((mean ± SEM; 6 ± 2\text{ mm vs.} 10 ± 2\text{ mm}, P = 0.02)\). In the control subjects, the distance was similar in both hemispheres \((10 ± 2\text{ mm vs.} 12 ± 1\text{ mm}, n.s.)\).

Table 1

<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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<tbody>
<tr>
<td>Age (yrs)</td>
<td>40</td>
<td>46</td>
<td>55</td>
<td>57</td>
<td>26</td>
<td>51</td>
<td>52</td>
<td>37</td>
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<tr>
<td>Duration of pain (yrs)</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Side of pain</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>L</td>
<td>R</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Brush allodynia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Impaired motor function of the painful hand</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Tactile sensitivity

| Painful side | Control | 4.31 | 5.46 | 2.83 | 4.08 | 3.61 | 3.61 | – | 2.83 |
| Healthy side | 4.31 | 2.83 | 2.83 | 2.83 | 2.83 | 2.83 | 2.83 | 2.83 |

Two-Point discrimination (mm)

| Painful side | >15 | >15 | 5 | >15 | 10–20 | >15 | >15 | 5–14 |
| Healthy side | >15 | 10 | 5 | 5 | 5 | 5 | 5 | 5 |

Hand grip strength (kg)

| Painful side | 0(32) | 0(32) | 18(28) | 6(28) | 4(31) | 12(28) | 0(28) | 25(33) |
| Healthy side | 0(32) | 40(32) | 30(28) | 20(28) | 30(31) | 25(28) | 11(28) | 28(33) |

Side of pain: R = right; L = left. Tactile sensitivity measured with Semmes-Weinstein monofilaments from the fingertip of digit 2: normal light touch <2.83, diminished light touch 3.22–3.61, diminished protective sensation 3.84–4.31, loss of protective sensation 4.56–6.65, unresponsive >6.65. Two-point discrimination (mm) measured from fingertip of digit 2: normal <6, fair 6–10, poor 11–15. Clumsiness in fine motor skills or restricted range of active movement was regarded as “impaired motor function of hand”. Hand grip strength measured by Jamar dynamometer in handle position 3 (age-matched normal values are shown in parentheses).
Table 2
Source parameters (mean ± SEM) to tactile stimuli delivered to index finger

<table>
<thead>
<tr>
<th>Source Parameters</th>
<th>Source Strengths</th>
<th>Source Latencies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRPS</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>Amplitude (nAm)</td>
<td>Latency (ms)</td>
</tr>
<tr>
<td>SLc</td>
<td>CRPS</td>
<td>Controls</td>
</tr>
<tr>
<td>Healthy/left</td>
<td>21.3 ± 2.7</td>
<td>27.6 ± 4.2</td>
</tr>
<tr>
<td>Painful/right</td>
<td>28.5 ± 2.9</td>
<td>30.2 ± 4.0</td>
</tr>
<tr>
<td>SLc</td>
<td>CRPS</td>
<td>Controls</td>
</tr>
<tr>
<td>Healthy/left</td>
<td>30.4 ± 3.4</td>
<td>29.6 ± 6.2</td>
</tr>
<tr>
<td>Painful/right</td>
<td>38.1 ± 7.3</td>
<td>23.9 ± 3.5</td>
</tr>
<tr>
<td>PPC</td>
<td>CRPS</td>
<td>Controls</td>
</tr>
<tr>
<td>Healthy/left</td>
<td>1.0 ± 0.9</td>
<td>15.0 ± 4.0</td>
</tr>
<tr>
<td>Painful/right</td>
<td>7.1 ± 4.0</td>
<td>7.3 ± 2.8</td>
</tr>
</tbody>
</table>

*SLc = contralateral primary somatosensory cortex; SIIc = contralateral secondary somatosensory cortex; PPC = posterior parietal cortex; *P < 0.05.

3.4. Pain thresholds and ratings

Fig. 3 shows the pain thresholds of the control subjects and the CRPS patients to the laser stimulation. The pain thresholds were lower in patients than in the control subjects, not only in the painful but also in the healthy hand (patients painful vs. controls; *P = 0.003, patients healthy vs. controls; *P = 0.02). In the control subjects, the pain thresholds were the same for both hands.

All subjects described the laser pulses as pricking pain that was sometimes followed by a longer-lasting burning pain. The stimulation energy of 1.4–1.5 times the pain threshold (740 mJ in controls, 520 mJ in patients) was rated more painful in the painful side of the patients than in the control subjects (patients painful 7.5 ± 0.7 vs. controls 4.1 ± 0.5, *P < 0.001; patients healthy 5.4 ± 1.0 vs. controls 4.1 ± 0.3, n.s.). The stimulation with similar energy (540 mJ in controls, 520 mJ in patients) was rated more painful on both sides of the patients than in the control subjects (patients painful 7.5 ± 0.7 vs. controls 2.3 ± 0.3, *P < 0.001; patients healthy 5.4 ± 1.0 vs. controls 2.3 ± 0.3, *P = 0.005). The patients rated the stimulation more painful in the painful than in the healthy hand (patients painful 7.5 ± 0.7 vs. healthy 5.4 ± 0.3, *P = 0.05), whereas the control subjects rated the left- and right-sided stimuli equally painful.

3.5. Processing of noxious laser stimuli

Fig. 4A shows that in a control subject, the earliest laser-evoked responses to left-hand laser stimulation (energy 1.4–1.5 times pain threshold) peaked bilaterally over the temporoparietal regions at 167 ms, followed by another response over the contralateral superior parietal region at 192 ms. These responses were best explained by bilateral SII sources and a contralateral PPC source (Fig. 4C, Table 3). In a CRPS patient (Fig. 4B), the laser stimulation (energy 1.4–1.5 times pain threshold) elicited responses in the bilateral SI cortex at 195 and 233 ms, but no other significant activations were detected.

Fig. 5A presents the contra- and ipsilaterial SII and the contralateral PPC source waveforms to the stimulation energy of 1.4–1.5 times the pain threshold in a representative control subject and CRPS patient. In both of them, contra- and ipsilaterial SII sources peaked at about 200 ms. In the control subject, the contralateral PPC was activated to stimulation of both hands, whereas in the CRPS patient, PPC activation was detected only to stimulation of the healthy hand.

Fig. 5B shows the corresponding grand average waveforms of the contra- and ipsilateral SII and contralateral PPC sources. In both groups, the SII sources peaked at 140–210 ms. The PPC source was observed in seven control subjects at about 150–220 ms to both left- and right-sided stimuli. In contrast, PPC was activated only in two CRPS patients to the painful and in three to the healthy hand stimulation.

The laser-evoked PPC source was 15–17 mm medial (*P < 0.001 left hemisphere, *P = 0.009 right hemisphere) and 8–17 mm posterior (*P < 0.001 left hemisphere, n.s. right hemisphere) to the touch-evoked SII source.

The mesial cortex was activated at 200–350 ms in two CRPS patients and in three control subjects. Additional activation was infrequently detected in some subjects in the prefrontal and insular regions. Because the bilateral SII and contralateral PPC sources were the most consistent across subjects, we focused on them in the further analysis.

Table 3 presents the SII and PPC source amplitudes and peak latencies in control subjects to 540 mJ and 740 mJ, and in CRPS patients to 520 mJ laser stimulation. To the stimulation energy of 1.4–1.5 times the pain threshold (520 mJ in patients, 740 mJ in controls), the mean contra- and ipsilateral SII source strengths were 38–42% weaker in CRPS patients than in control subjects, but this difference was not statistically significant. The SII source strengths did not significantly differ between hands in the patients nor did they differ in the control subjects. The mean PPC source strength was higher in the control subjects than in the patients (controls 13.8 ± 3.5 nAm vs. patients healthy hand 4.0 ± 2.0, *P = 0.03; controls 13.8 ± 3.5 nAm vs. patients painful hand 4.5 ± 3.7 nAm, *P = 0.09).

To similar laser energy (520 mJ in CRPS, 540 mJ in control subjects), the mean contra- and ipsilateral SII source strengths were

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**Fig. 2.** (A) Locations of D1 and D5 representations in SI in one CRPS patient. Black symbols correspond to painful and white symbols to healthy hand. (B) D1–D5 distance in xyz-space for painful and healthy hands in CRPS patients, and for left and right hands in control subjects. Black squares correspond to painful and white squares to healthy hand in patients; black triangles correspond to left and white triangles to right hand in control subjects. Small symbols represent single subjects, large symbols represent mean ± SEM. D1 = thumb, D5 = little finger, L = left, R = right.
85–84% stronger in patients than in control subjects, but this difference was not statistically significant. The PPC sources in the patients and in controls were equally weak (patients painful hand 4.5 ± 3.7 nAm, patients healthy hand 4.0 ± 2.0 nAm, controls 3.8 ± 1.1 nAm).

Fig. 6 presents the correlation of source strengths between the stimulation energy and pain rating. In the control subjects, the SII source strength correlated significantly with the stimulation energy ($r = 0.53, P = 0.03$) and with the pain rating ($r = 0.55, P = 0.02$). The PPC source strength correlated with the pain rating ($r = 0.60, P = 0.009$), but it did not correlate with the stimulation energy.

In the patients, the SII source strength correlated significantly with the stimulation energy ($r = 0.63, P = 0.01$), but it did not correlate with the pain rating. The PPC source strength did not correlate with the pain rating nor did it correlate with the stimulation energy.

4. Discussion

4.1. Responses to tactile stimuli

In line with earlier observations, the SI activations of the control subjects were similar to left- and right-sided tactile stimulation, but in the CRPS patients the SI activation was significantly stronger to tactile stimulation of the painful than that of the healthy hand (Juottonen et al., 2002; Maihöfner et al., 2003). As the patients were hypersensitive to touch in the affected hand, the enhanced SI activity could reflect central sensitization to tactile input. Other explanation for the stronger activation could be increased focusing of attention to the painful hand. To decrease the possible effect of attention, we asked the subjects to concentrate on the stimulated hand. We compared the amplitudes of the early SI responses that have been shown to be more resistant to attentional changes than

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Fig. 3. Mean ± SEM pain thresholds of control subjects and CRPS patients. Circle corresponds to controls (left and right hands pooled) and squares to CRPS patients. $P < 0.05$, $P < 0.005$.

Fig. 4. Spatial distribution of laser-evoked fields in one control subject (A) and in one CRPS patient (B). Laser stimuli were presented to dorsum of left hand (painful hand in CRPS patient). Head is viewed from top. Inserts show enlarged responses from selected channels. (C) Source locations superimposed on magnetic resonance image of a control subject. SIIc = contralateral secondary somatosensory cortex, SIIi = ipsilateral secondary somatosensory cortex, PPC = posterior parietal cortex.
the later responses; particularly the SII responses have been shown to be enhanced by attention to stimuli (Mauguière et al., 1997). In our study, we found no significant enhancement of SII responses to tactile stimulation of painful side, and therefore we consider it

\[ SIIc \]

\[ SIIi \]

\[ PPC \]

\[ Controls (n = 9) \]

\[ CRPS (n = 8) \]

\[ 10 \text{nAm} \]

\[ 0 \quad 200 \text{ms} \]

\[ 0 \quad 200 \text{ms} \]

**Fig. 5.** (A) Contra- and ipsilateral SII and contralateral PPC source waveforms to laser stimulation of hand dorsums in one control subject and in one CRPS patient. (B) Grand average waveforms to laser stimulation in both groups. For illustrative purposes, in CRPS patients without identified PPC sources (in six patients to painful and in five to healthy hand stimulation), a source was simulated according to mean PPC source location in controls. SII = contralateral secondary somatosensory cortex, SIIi = ipsilateral secondary somatosensory cortex, PPC = posterior parietal cortex.

**Fig. 6.** (A) Contra- and ipsilateral SII and contralateral PPC source waveforms to laser stimulation of hand dorsums in one control subject and in one CRPS patient. (B) Grand average waveforms to laser stimulation in both groups. For illustrative purposes, in CRPS patients without identified PPC sources (in six patients to painful and in five to healthy hand stimulation), a source was simulated according to mean PPC source location in controls. SII = contralateral secondary somatosensory cortex, SIIi = ipsilateral secondary somatosensory cortex, PPC = posterior parietal cortex.

**Table 3**

<table>
<thead>
<tr>
<th>Source parameters (mean ± SEM) to laser stimuli delivered to hand dorsum</th>
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<tr>
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<td>PPC</td>
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the later responses; particularly the SII responses have been shown to be enhanced by attention to stimuli (Mauguière et al., 1997). In our study, we found no significant enhancement of SII responses to tactile stimulation of painful side, and therefore we consider it...
unlikely that focusing of attention would explain the observed amplitude differences between the painful and healthy sides. Further, rather than focusing their attention, CRPS patients have been reported to neglect their affected limb (Frettloh et al., 2006).

The D1–D5 distance was decreased by 40% in the hemisphere contralateral to the painful hand. Recent studies in CRPS patients have repeatedly demonstrated marked reduction of D1–D5 distance in SI cortex of the affected hemisphere (Juottonen et al., 2002; Maihöfner et al., 2003; Pleger et al., 2004). Shortening of the D1–D5 distance in MEG measurement could result not only from diminished size of the hand representations but also from fusion of cortical finger representations, as MEG measures the center of gravity of activation (Elbert et al., 1998; Juottonen et al., 2002). Such a fusion has been detected in association with continuous and temporally correlated stimulation of the adjacent fingers by direct intracortical recordings in monkeys as well as by MEG recordings in patients with dystonia (Clark et al., 1988; Elbert et al., 1998). Fusion of cortical finger representations could also explain the increased amplitudes of SI responses in the affected side, as the overall cortical activation area to single finger stimulation would be increased. In our patients, the two-point discrimination was impaired in the affected hand. The SI response latencies, however, were within normal limits, implying that the somatosensory tracts relay the impulses normally up to the cortical level. It is possible that the distorted or fused finger representations had impaired the two-point discrimination of the distal phalanges of the affected hand.

Earlier studies have indicated that the plastic changes at the SI are reversible in CRPS patients in whom the clinical symptoms, including the chronic pain, are alleviated by rehabilitation or spontaneous recovery (Maihöfner et al., 2004; Pleger et al., 2005). It has remained unclear, whether the plastic changes in chronic cases of CRPS patients with prevailing clinical symptoms are permanent. Six patients, in whom the shortened D1–D5 distance was observed in our previous study, also took part in the present study. The deficits in tactile discrimination and the chronic pain were not alleviated, and in line with these prevailing symptoms, the present recordings showed that in these patients the D1–D5 distance was still shortened. This suggests that in chronic CRPS, the reorganization of the SI finger representations may be permanent.

The immobilization of the hand can also affect the size of hand SI representation through reduced proprioceptive input by several mechanisms that operate in different timescales (Stavrinou et al., 2007). In our patients, attempts to move the hand usually worsened the pain, which led to a tendency to keep the painful hand immobilized. However, in earlier studies the degree of immobilization did not correlate with the extent of the plastic changes; instead, the D1–D5 distance correlated with the mean intensity of clinical pain (Maihöfner et al., 2003; Pleger et al., 2004). Further, if the immobilization would have reduced the hand representation size in SI, one would expect that with smaller number of active neurons, the amplitudes of SI responses would also be reduced. Instead, the SI amplitude was stronger in the painful side. Taken together, our results suggest that plastic changes at the SI cortex are associated with the chronic pain. However, immobilization of the affected hand may further modify the cortical representations.

Possible head movements during recordings cannot affect the D1–D5 distance as both fingers were stimulated in the same session, and the extent of the hand representation was evaluated from their relative distance.

4.2. Activation of SII to acute phasic pain

To our knowledge, this is the first attempt to characterize central processing of selectively nociceptive stimuli in a group of CRPS patients, although a case report of LEP recordings in one CRPS patient has been earlier published (Moreau et al., 2007). Because CRPS patients are extremely sensitive to any kind of stimulation applied to the affected hand, the functional imaging of their nociceptive system is very challenging. However, the present study showed that such measurement can be successfully performed. The significantly lowered pain threshold to laser stimuli implies heat hyperalgesia in our CRPS patients. Interestingly, the pain threshold was significantly lowered not only in the painful but also in the healthy hand, implicating that altered pain perception is not restricted to the affected hand. In a recent study, originally unilateral pain of a chronic CRPS patient spread in a mirror-like fashion to the opposite side, and this was accompanied by the appearance of an abnormal ipsilateral response in SI (Forss et al., 2005b). Bilaterally decreased pain thresholds and spreading of symptoms to the opposite side suggest that CRPS affects the whole CNS and is not restricted to one side of the body.

We used two energy levels of the laser stimulation in the control subjects (540 mJ and 740 mJ), whereas only one in the CRPS patients (520 mJ). Because the CRPS patients experienced severe pain already at this energy level and could not tolerate further increase, higher intensity stimulation was not possible. For control purposes, we therefore used a lower energy in control subjects.

Painful laser stimulation elicited simultaneous activation of the SII and PFC, which are part of the somatosensory cortical network. In contrast to some earlier studies, we did not observe the activation of the SI cortex to painful stimuli. A meta-analysis of PET and fMRI studies showed that the activation of SI to painful stimuli was observed in only about half of the studies (Peyron et al., 2000), and it has been suggested that sufficient spatiotemporal summation of the stimuli would be required for significant activation of SI (Treede et al., 1999). Lack of SI activation to laser stimuli in the CRPS patients is in line with our earlier findings, and is discussed in Forss et al. (2005a).

As MEG allows the separation of several simultaneously active sources, we were able – for the first time – to analyze the sensory aspects of the acute pain processing in CRPS. However, comparison of the laser-induced cortical activity between the patients and control subjects was not straightforward because the energy level of the painful stimulation that was appropriate for the healthy control subjects was intolerable for the hyperesthetic CRPS patients. Nevertheless, the latencies and amplitudes of the SII activations of the CRPS patients were within normal range. Attenuated LEPs peaking at the vertex at 200–400 ms have been considered as a sign of lesion in the nociceptive pathways in neuropathic pain patients (Casey et al., 1996; Wu et al., 1999; Garcia-Larrea et al., 2002; Treede et al., 2003). Thus, these results suggest that the nociceptive pathways convey Aβ-input normally at least up to sensory cortex (Watanabe et al., 1998; Frot et al., 1999, 2001; Ploner et al., 1999; Timmermann et al., 2001; Forss et al., 2005a).

Strength of SII activation correlated with the stimulation energy in the control subjects and in the patients. This finding agrees with earlier MEG and intracortical recordings about S-shaped stimulus intensity–response strength curves for the SII cortex, with increasing response strength from non-painful to painful levels, but with a ceiling effect for further increase in intensity (Timmermann et al., 2001; Chen et al., 2006; Frot et al., 2007). Therefore, it has been suggested that SII contributes to the discrimination of stimulus intensity from non-painful to painful level. Our findings in CRPS patients agree with this view; hypersensitivity to noxious heat did not significantly enhance the SII activation when compared to control subjects, indicating that SII activation in the patients rather reflects the physical characteristics of the nociceptive stimuli, such as stimulus energy, than the intensity of perceived pain. Further, the SII activation strengths in the patients did not differ between hands, yet the pain percept was significantly stronger.
on the painful side. This suggests that higher pain processing areas, such as the anterior cingulate cortex (ACC), insula or PPC could contribute to the hyperesthesia to pain.

The SII activity has been also shown to be modulated by attention. Directed spatial attention was shown to increase the amplitude of the lateralized N160 response, although in another study this response appeared less sensitive to attention than the later vertex potential (Garcia-Larrea et al., 1997; Legrain et al., 2002).

4.3. PPC and higher pain processing areas

LEPs measured at the vertex receive strong contribution from the sensory cortical areas, but also from higher pain-processing areas such as the ACC, insula, and PPC. A dysfunction in these areas would probably not affect the sensory SI responses, but could alter the vertex responses (Valeriani et al., 1996; Garcia-Larrea et al., 2003). As MEG is rather insensitive to deep or radial sources, it is not optimally suited to detect activation in the ACC or insula. In this study, the activation of these areas was only infrequently found, and therefore it is not possible to evaluate the functional integrity of these areas from the present data. Instead, the PPC area was activated by painful laser stimuli in seven out of nine healthy subjects. Prior studies have indicated that the parietal cortex participates in acute pain processing (Flöner et al., 1999; Kanda et al., 2000; Timmermann et al., 2001; Raji et al., 2003; Forss et al., 2005a), and that the strength of PPC activation correlates with the pain rating in healthy subjects (Apkarian et al., 1995).

Accordingly, in this study, PPC activation correlated with the pain rating in the control subjects, suggesting that activation of this area may be associated with the evaluation of perceived pain. In contrast, the PPC activation to laser energy of 1.5 times the pain rating in the control subjects, suggesting that activation of this area may be associated with the evaluation of perceived pain. In contrast, the PPC activation to laser energy of 1.5 times the pain threshold was significantly weaker in the CRPS patients than in the control subjects although the patients rated the pain more severe (patients 7.5 ± 0.7 vs. controls 4.1 ± 0.5). Further, the PPC activation of the patients did not correlate with the pain ratings. These results may indicate malfunction of PPC in the CRPS patients. However, as the degree of malfunction of PPC was not associated with the abnormal pain perception, it is not possible from the present data to evaluate whether defective activation of PPC would explain the altered pain perception in CRPS.

On the other hand, weak PPC activation of the CRPS patients could be explained by lower stimulus energy used in this group. Unfortunately, we could not directly test this as the patients could not tolerate further increase in the stimulus energy. However, even in healthy controls, the PPC activation was not significantly correlated with the energy.

In the patients, the PPC activation was weak not only to the nociceptive laser stimulation but also to the innocuous tactile stimulation. This stimulation was delivered with equal intensity in both groups, and it elicited strong SI and SII responses in the both groups. Therefore, we suggest that the PPC area is abnormally activated both to tactile and to nociceptive stimulations in CRPS patients. Lesions in the PPC are known to cause neglect syndrome. Neglect-like symptoms have been reported in chronic pain patients and are especially common and severe in CRPS patients (Frot M, 2001). In line, our patients often described the affected limb as ”strange”, ”foreign”, and not belonging to the body. Although neglect-like symptoms were not systematically tested in our patients, it is possible that these symptoms could be associated with defective activation of the PPC. However, further studies are needed to examine this putative association.

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