Patterns of cortical reorganization in complex regional pain syndrome

Christian Maihöfner, MD; Hermann O. Handwerker, MD, PhD; Bernhard Neundörfer, MD; and Frank Birklein, MD

Abstract—*Objective:* To use magnetoencephalography to assess possible cortical reorganization in the primary somatosensory cortex (S1) of patients with complex regional pain syndrome (CRPS). *Background:* Patterns of pain and sensory symptoms in CRPS may indicate plastic changes of the CNS. *Methods:* Magnetic source imaging was used to explore changes in the cortical representation of digits (D) 1 and 5 in relation to the lower lip on the unaffected and affected CRPS side in 12 patients. *Results:* The authors found a significant shrinkage of the extension of the cortical hand representation for the CRPS affected side. The center of the hand was shifted toward the cortical representation of the lip. The cortical reorganization correlated with the amount of CRPS pain ($r = 0.792$), as measured by the McGill questionnaire, and the extent of mechanical hyperalgesia ($r = 0.860$). Using multiple regression analysis, the best predictor for the plastic changes was found to be mechanical hyperalgesia. Additionally, S1 sources following tactile stimulation were significantly increased on the CRPS side compared to the unaffected limb. *Conclusions:* This study showed reorganization of the S1 cortex contralateral to the CRPS affected side. The reorganization appeared to be linked to complaints of neuropathic pain.

NEUROLOGY 2003;61:1707–1715

The complex regional pain syndromes (CRPS) may develop after limb trauma or peripheral nerve lesions in up to 5% of all cases.[1-4] Based on the initial trauma, CRPS is classified as either CRPS type I (without apparent nerve lesion) or CRPS type II (with nerve lesion).[5] In combination with variable motor and autonomic symptoms,[2] the patients have spontaneous and stimulus-evoked pain,[2,4] which is not limited to a single nerve territory.[5,6] Even hemisensory deficits have been described.[7] Both the patterns of pain and the sensory symptoms observed in patients with CRPS may indicate that changes occur within the CNS.

In recent years, several investigations have suggested that cortical reorganization develops in response to pain. Changes of somatotopic maps in the primary somatosensory cortex (S1) were demonstrated to correlate with the experience of phantom limb pain in amputees, and also in patients with chronic back pain.[8,9] Therapeutic interventions that reversed cortical reorganization, e.g., a prostheses or somatosensory training, were associated with a decrease in pain.[10,11] However, cortical reorganization is not limited to chronic pain disorders. Rapid functional reorganization of S1 has also been shown in response to experimentally induced pain in healthy subjects and short term changes of spatial attention.[12-14] A recent study provided evidence for an altered central sensorimotor processing in CRPS.[15] The aim of the present magnetoencephalographic (MEG) investigation was to extend these findings and to correlate a potential cortical reorganization in CRPS to sensory, motor, or autonomic complaints. The findings presented here suggest that the major predictors for S1 cortex reorganization in patients with CRPS are the intensity of pain and the extension of mechanical hyperalgesia.

Methods and patients. *Subjects and psychophysical examination.* All patients were referred to the Neurologic Department of the University Hospital of Erlangen and met the current IASP diagnostic criteria for CRPS.[5] These criteria were extended according to the following points:

1) Preceding noxious event without (CRPS I) nerve lesion (CRPS II excluded, see below).

2) Presence of spontaneous pain or hyperalgesia not limited to a single nerve territory and disproportionate to the inciting event.

3) Presence of edema and a skin blood flow (temperature) or sudomotor abnormality or both in the distal part of the affected limb.

4) Exclusion of other diagnoses.

Twelve patients with CRPS (nine female, three male) with a mean age of 57.4 ± 18.7 years were included. To get a comparable cohort for our MEG study, only patients with affected upper limbs were examined. Ten were right-handed, two were left-handed. The mean duration of CRPS symptoms was 14.8 ± 10.6 weeks. Except for physical therapy and nonsteroidal anti-inflammatory drugs, these patients were untreated at the time of investigation (table 1). Informed written consent was obtained from all subjects and the study adhered to the tenets of the Declaration of Helsinki. The study was approved by the local ethics committee.

As CRPS comprises sensory, motor, and autonomic symptoms, we tried to assess each of these different modalities in a detailed neurologic examination. All measurements were performed on the affected and the contralateral unaffected side.

From the Departments of Neurology (Drs. Maihöfner and Neundörfer) and Physiology and Experimental Pathophysiology (Drs. Maihöfner and Handwerker), University of Erlangen-Nuremberg, Erlangen; and Department of Neurology (Dr. Birklein), University of Mainz, Germany.

Supported by the German Research Network "Neuropathic Pain Syndromes" (German Federal Ministry of Education and Research, BMBF) and the Novartis Foundation for therapeutic research.

Received April 16, 2003. Accepted in final form August 13, 2003.

Address correspondence and reprint requests to Dr. Christian Maihöfner, Institute for Physiology and Experimental Pathophysiology, University of Erlangen-Nuremberg, Germany, Universitätsstrasse 17, D-91054 Erlangen, Germany; e-mail: maihoefner@physiologie1.uni-erlangen.de

Table 1 *Demographic data, diagnoses, symptoms, and treatment of patients*

Patient no.	Age, y	Sex	Diagnosis	Affected limb	Inciting event	Pain	Hyperalgesia, area/weighted area	Motor symptoms	Autonomic disturbances	Time from onset, wk	Therapy	Comorbidity
1	58	Female	CRPS I	Left hand	Radius fracture	NRS 20 McGill 47	50/250	PoM: 30 DASH: 55.3 a: 50° b: 8 cm	Cyanotic skin, nails ↑	22	PT, NSAID	Hypertension
2	53	Female	CRPS I	Left hand	Supracondylar humerus fracture	NRS 80 McGill 30	0/0	PoM: 80 DASH: 60.2 a: 70° b: 13 cm	Cyanotic skin, edema, hair/nails	10	PT	None
3	22	Female	CRPS I	Right hand	Sprain	NRS 75 McGill 2	0/0	PoM: 0 DASH: 0 a: 0° b: 0 cm	Edema	36	PT, NSAID	Asthma
4	41	Male	CRPS I	Right hand	Distal radius fracture	NRS 0 McGill 36	69/345	PoM: 70 DASH: 84.3 a: 70° b: 12	Cyanotic skin, edema, hair ↑, sweating ↑, skin temperature ↑	4	PT, NSAID	Pollinosis, hyperuricaemia
5	82	Female	CRPS I	Right hand	Distal radius fracture	NRS 30 McGill 20	80/400	PoM: 60 DASH: 37.3 a: 40° b: 8 cm	Reddish skin, edema, skin temperature ↑	5	PT, NSAID	Asthma
6	48	Female	CRPS I	Right hand	Sprain	NRS 20 McGill 48	200/600	PoM: 20 DASH: 17.2 a: 20° b: 6 cm	Edema	12	PT	Atopic eczema
7	83	Female	CRPS I	Left hand	Distal radius fracture	NRS 50 McGill 46	235/885	PoM: 70 DASH: 100 a: 70° b: 10 cm	Cyanotic skin, edema, skin temperature ↑	4	NSAID	Chronic low back pain
8	49	Male	CRPS I	Left hand	Distal radius fracture	NRS 30 McGill 15	0/0	PoM: 90 DASH: 90.3 a: 75° b: 12 cm	Reddish skin, edema	10	PT	None
9	48	Female	CRPS I	Right hand	Hand surgery	NRS 50 McGill 33	40/200	PoM: 20 DASH: 40 a: 20° b: 2 cm	Edema	14	None	Tension type headache
10	46	Male	CRPS I	Left hand	Phanlanx fracture	NRS 30 McGill 59	224/1,120	PoM: 20 DASH: 40 a: 35° b: 0 cm	Cyanotic skin, edema, sweating ↑, hair/nails ↑	36	PT	None
11	83	Female	CRPS I	Left hand	Distal radius fracture	NRS 30 McGill 12	36/180	PoM: 20 DASH: 30 a: 30° b: 5 cm	Edema	11	None	None
12	76	Female	CRPS I	Left hand	Distal radius fracture	NRS 30 McGill 20	140/280	PoM: 20 DASH: 20 a: 10° b: 4 cm	Reddish skin, edema, skin temperature ↑	14	PT, NSAID	Hypertension, coronary heart disease, diabetes

Weighted area = weighted area of hyperalgesia (see Methods); CRPS = complex regional pain syndrome; NRS = numeric rating scale; PoM, pain on movement; DASH = disability score of arm, shoulder, and hand; a = difference in the active range of motion at the wrist between the CRPS and unaffected side; b = distance between fingertips and palms while making a clenched fist on the CRPS side; PT = physical therapy; NSAID = nonsteroidal anti-inflammatory drugs.

Sensory symptoms (pain and hyperalgesia). The magnitude of CRPS pain was quantified using the German counterpart of the McGill questionnaire (MPQ).[16] Patients were instructed to fill in the MPQ at home in order to quantify their pain in a familiar environment. In addition, patients quantified pain intensity at the time of the MEG recordings on a numeric rating scale (NRS), ranging from 0 (no pain) to 100 (intolerable pain). For the assessment of pinprick hyperalgesia, a von Frey filament with a rounded tip (diameter 0.8 mm, exerted force 200 mN) was used. To delineate the border of the hyperalgesic zone, probes were repeatedly

pushed onto the skin beginning in the periphery and advancing toward the painful skin area along at least eight separate lines radiating from the affected site. The border around the area of hyperalgesia was then traced onto an overlying acetate sheet and evaluated planimetrically. To assess the intensity of mechanical hyperalgesia, the same stimulus intensity was applied to areas with and without hyperalgesia and rated on the NRS scale. The quotient of NRS ratings obtained from affected and unaffected skin was then multiplied by the area of hyperalgesia to obtain the "weighted area of hyperalgesia" in arbitrary units.

Motor symptoms. Impairment of hand function was assessed by 1) measuring the distance between fingertips and palms while clenching a fist and 2) determining the active range of motion at the wrist (volar and dorsal flexion) using a goniometer. Pain experienced during movement of the hand was determined using a numeric rating scale, ranging from 0 (no pain) to 100 (intolerable pain). To further elucidate the impairment of daily activities, we also assessed CRPS-related disability employing the DASH questionnaire (Disability of Arm, Shoulder, and Hand Questionnaire). The DASH is an outcome data collection instrument that has been developed in order to assess different patient groups with musculoskeletal disorders of the upper extremities.[17] Using a self-report system, patients attribute scores between 1 and 5 to each of 30 items relating to functional activities and symptoms. The raw score is then transformed to a 0 to 100 scale, whereby 0 reflects a minimum and 100 a maximum disability. Recently, the DASH score has been validated for a German population.[18]

Autonomic and trophic symptoms. For the evaluation of autonomic disturbances a clinical sum score ranging from 0 to 5 was constructed, depending on the presence of the following symptoms (a score of one for each):

1) Significant skin temperature difference (>1 °C) compared to the unaffected side. After acclimatization, skin temperature was recorded on the volar aspect of the unaffected and affected extremity with an infrared thermometer (Thermohunter).

2) Changes in skin color (reddish, cyanotic, or white).

3) Presence of sweating abnormalities (hypo- or hyperhydrosis).

4) Presence of distal edema.

5) Trophic changes of skin, nail, or hairs.

Tactile stimulation and MEG recordings. For the assessment of potential shifts in the cortical representation of the fingers, somatosensory evoked magnetic fields were recorded following subsequent tactile stimulation of digits (D) 1 and 5 and the lower lip, each in separate runs. The sequence of the runs was identical in each patient (D1, D5, lower lip, starting with the affected limb). For tactile stimulation, an air-puff-derived tactile stimulator (9037–953, Biomagnetic Technologies, San Diego, CA) was used. This device has been extensively used in previous studies to explore the cortical representation of various body parts.[19-21] The skin contact area was a circular rubber bladder, 10 mm in diameter, and the intensity of mechanical stimulation was 40 g/cm^2. The rise time was 20 msec as measured from 10 to 90% of the intensity increment. No joint movement was observed during stimulation. The stimulation device was attached to the mid-volar aspect of the distal phalanges of D1 and 5 and to the outer part of the lower lip. Two hundred stimuli were applied and the interstimulus interval was randomized between 980 and 1,020 msec. The patients did not consider the tactile stimuli painful.

Cortical responses were recorded with a dual 37-channel neuromagnetometer (Magnes II; 4D Neuroimaging, San Diego, CA) in a magnetically shielded room. The detection coils of the neuromagnetometer were arranged in a uniformly distributed array in concentric circles over a spherically concave surface (144 mm diameter). MEG was performed by placing a single Dewar above the contralateral parietotemporal cortex, i.e., above C3 and C4, according to the international 10-20 EEG system. Cerebral evoked magnetic fields were recorded in the time interval between 200 msec before and 1,000 msec after the stimulus trigger with a bandwidth of 0 to 200 Hz. The sampling rate of the analogue signal was 1,041 Hz. For offline analysis, data were filtered (1 to 70 Hz, 50 Hz notch) and visually scanned for artifacts. Only epochs without obvious artifacts were averaged.

Magnetic source imaging was performed as described previously.[20-22] Briefly, a sphere locally fitted to the head shape underneath the sensor was used as a volume conductor model. Afterwards, a mathematic process based on the least-squares method[23] was applied if the evoked magnetic fields showed an approximately dipolar distribution. The time interval between 30 and 75 msec was analyzed, as this interval is known to cover activations in area 3b of SI.[19-21] Only stable clusters of dipoles of at least 10 msec duration were analyzed. For each localization, a correlation coefficient between the measured and the ideal magnetic dipole field was calculated. The predetermined criteria for the final dipole selection were a map correlation and a goodness of fit greater than or equal to 0.96. Latencies were calculated relative to the time of stimulation. To visualize results with respect to brain anatomy, the dipole locations were superimposed on MR images. A 1.5 Tesla Magnetom (Symphony, Siemens, Germany) was used and three skin markers were placed at fiducial points on the subject's head. The location of each fiducial point was also recorded relative to the neuromagnetometer position, thus establishing a common spatial reference for the transposition of three-dimensional coordinates between MEG and MRI data.

For the assessment of potential shifts of cortical representations, a modification of a previously described method[9] was applied (figure 1). The respective equivalent current dipole (ECD) localizations were mapped onto the cortical surface of area 3b. The center of the hand representation was found to be at the midpoint between the cortical representation of D1 and D5. The distance between the representation of the lower lip and the midpoint of the hand was then calculated. To obtain an estimate of the extent of the reorganization that had occurred, this distance on the affected and unaffected hand side was compared. Furthermore, to assess the total extension of the hand, the distance between the cortical representations of D1 and D5 was calculated.

Statistical analysis. The data are presented as mean ± SEM. Statistical evaluation was performed using the STATISTICA software package (version 5.5). To assess statistically significant differences the Wilcoxon signed-ranked test was employed. Correlations were assessed with the Pearson correlation coefficient and multiple regression analysis with adjustment for multiple comparisons, if necessary. $p < 0.05$ Was considered statistically significant.

Results. *Neurologic symptoms.* All patients reported spontaneous pain on the affected limb (NRS = 37.1 ± 22.0). The mean McGill pain rating index (PRI) was 33.5 ± 16.2 points, which was highly correlated to the number of words chosen (12.2 ± 5.1; r = 0.92; $p < 0.05$). Skin sensory testing revealed no symptoms associated with segmental or peripheral nerve territories. However, on the affected extremity, nine patients had hyperalgesia to punctate stimulation with von Frey filaments, i.e., pinprick hyperalgesia. The hyperalgesic skin area was distributed in a glove-like manner and covered a mean area of 136.3 ± 84.3 cm^2. Calculating the product of the area of pinprick hyperalgesia and the pinprick related pain index (see Methods) resulted in a weighted area of hyperalgesia of 493.2 ± 302.2 units.

Eleven patients had pain during movement of the affected hand, i.e., when clenching a fist (NRS = 41.7 ± 28.8). The range of motion on the affected side was significantly reduced compared to the unaffected side in 11 patients, for both the distance between fingertips and the palmar side of the hand (6.4 ± 4.4 cm versus 0.0 ± 0.0 cm, $p < 0.05$), and the extent of volar and dorsi flexion at the wrist (65.8° ± 22.5 versus 108.3° ± 6.6, $p < 0.05$). The DASH score for the assessment of the disease-related hand disability revealed that the CRPS-induced motor impairment had significant consequences for the patients' daily living activities (mean DASH score 47.9 ± 29.7).

Other clinical symptoms like trophic changes, edema, sweating abnormalities, changes of skin color, and skin temperature differences are listed in detail in table 1.

Somatosensory evoked magnetic responses in patients with CRPS. Representative somatosensory evoked mag-

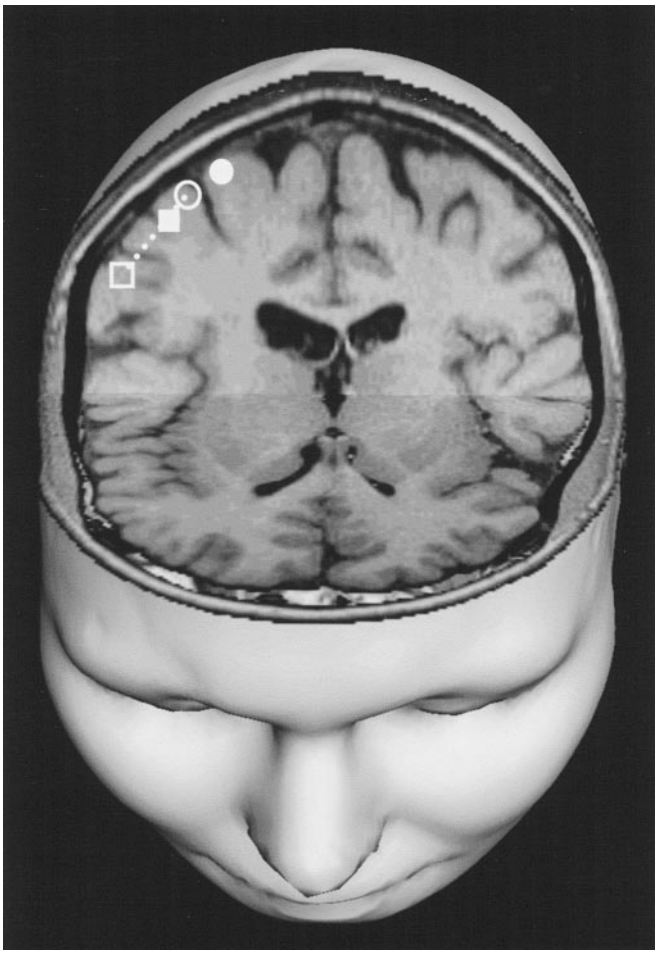

Figure 1. Magnetic source imaging showing the anatomic position of the equivalent current dipoles (ECD) for the left lower lip (open square), D1 (filled square), and D5 (filled circle) in a somatotopic manner along the postcentral gyrus. For the assessment of cortical reorganization, the following method[9] was used: the center of the hand representation was calculated as the midpoint between the ECD localization of D1 and D5 (open circle). The distance between the representation of the lower lip and the center of the hand was then calculated (line). To obtain an estimate of the extent of reorganization, the distances for the affected and unaffected limbs were compared.

netic fields (SEF) following tactile stimulation of digits (D) 1 and 5 and the lower lip in a patient with CRPS are shown in figure 2. For the whole group, the first main SEF deflection occurred at 46.9 ± 5.8 msec (for D1), at 44.8 ± 7.5 msec (for D5), and at 34.9 ± 7.6 msec for the lower lip. No significant difference was found between the unaffected and affected side for these peak latencies (stimulation on the affected side 46.2 ± 3.8 msec, 44.9 ± 2.3 msec, and 33.7 ± 1.6 msec for D1, D5, and the lower lip; NS). Furthermore, for the ECD parameters including the dipole map correlation and goodness of fit as well as the confidence volumes there were no differences detected between the affected and unaffected extremities (for details see table 2). However, as also demonstrated in the SEF recordings of figure 2, the mean strengths of the magnetic fields (dipole moment; nAm) for D1/D5 were significantly increased on the CRPS side compared to the unaffected side (22.8 ± 4.8 nAm versus 13.6 ± 4.6 nAm; $p < 0.05$; figure 3A). This increase in dipole moment on the painful side was independent of the side of pain (right or left, NS) or patient handedness (NS). However, the increase in dipole moment was significantly correlated with the intensity of spontaneous pain, evaluated on the NRS scale, at the moment of the MEG recordings ($r = 0.707$; $p < 0.05$; figure 3B).

There was no significant correlation with any other clinical signs regarding sensory (MPQ, area of hyperalgesia, weighted area of hyperalgesia), motor (pain on movement, impairment of hand function, DASH score), or autonomic (trophic changes, edema, sweating abnormalities, changes of skin color and temperature) symptoms.

Cortical reorganization in the S1 cortex of patients with CRPS. The time interval ranging from 30 to 75 msec after tactile stimulation was analyzed, as this interval was previously shown to represent the activation of area 3b in SI.[19-21,24] Projection of the computed ECD coordinates onto axial and coronal MRI slices demonstrated that the location of the SEF sources in the contralateral S1 cortex were arranged in a somatotopic manner, showing the cortical representation of the lower lip, D1, and D5 (see figure 1). To assess changes in the somatotopic map, the center of the hand representation itself was deemed to be the midpoint between the cortical representations of D1 and D5 (figures 1 and 4). As shown for one patient in figure 4, the distance between the cortical representation of the hand and the lip was decreased on the affected CRPS side compared to the unaffected side. The mean distance on the unaffected side was 2.76 cm compared with 1.95 cm on the affected side ($p < 0.05$; figure 5B). Additionally, the distance between D1 and D5 was reduced on the painful affected side (1.37 versus 0.80 cm for the unaffected and affected sides; $p < 0.05$; figure 5A). There was no effect of CRPS side (right or left, NS) or the handedness of the patients (NS). However, the degree of cortical reorganization was significantly correlated to the magnitude of CRPS pain, assessed with the MPQ ($r = 0.792$; $p < 0.05$; figure 5C), the area of hyperalgesia ($r = 0.810$; $p < 0.05$), and the weighted area of hyperalgesia ($r = 0.860$; $p < 0.05$; figure 5D). Using a multiple regression model, where the McGill pain rating index, the area of hyperalgesia, and the area of weighted hyperalgesia were independent variables, the best predictor for cortical reorganization was found to be the weighted area of hyperalgesia (beta weight: 0.77; $p < 0.05$).

There was no correlation with other clinical symptoms or epidemiologic data. In particular, there was no correlation between the duration of CRPS, pain during movement, the impairment of hand function (range of motion or DASH score), or autonomic symptom scores.

Discussion. In the current MEG study, we provide evidence of cortical reorganization of the primary somatosensory cortex in patients with CRPS. These changes were correlated with pain intensity and the presence of mechanical hyperalgesia. Furthermore, the strength of the S1 dipole sources following tactile stimulation was significantly increased on the painful side.

Previous research in humans and animals has provided evidence that lesions of the afferent nervous system may lead to cortical reorganization. In upper extremity amputees, the cortical representa-

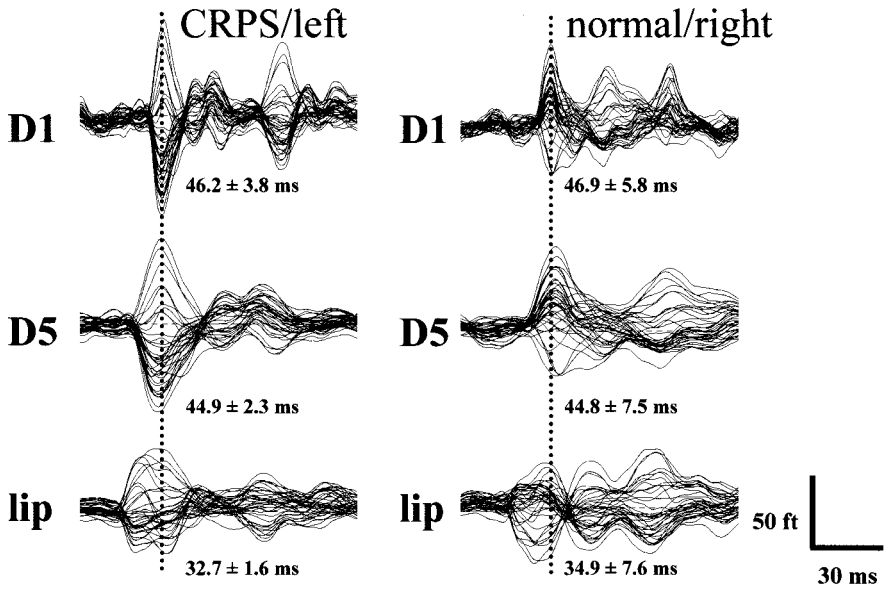

Figure 2. Chart showing somatosensory evoked magnetic fields following tactile stimulation of D1, D5, and the lower lip for one representative patient with complex regional pain syndrome (CRPS) in the left upper extremity. Waveforms recorded from the 37 channels of the sensor are superimposed (sensor position contralateral to the stimulation side, i.e., above C3 and C4). The first main SEF deflection occurred at 46.9 ± 5.8 msec for D1, at 44.8 ± 7.5 msec for D5, and at 34.9 ± 7.6 msec for the lower lip on the unaffected side. No significant difference between the unaffected and affected sides was found for any of these peak latencies (stimulation on the affected side 46.2 ± 3.8 msec, 44.9 ± 2.3 msec, and 33.7 ± 1.6 msec for D1, D5, and the lower lip; NS). The first activation was chosen for analysis because the ECD localizations are indicative of the cortical representation of the lower lip, D1, and D5. Note the higher amplitudes for this response on the affected side (left).

tion of the lip area extended into the cortical area corresponding to the amputated hand and arm.[9,10,25] The extent of cortical reorganization in these patients was positively correlated with the occurrence of pain. Obviously, cortical reorganization is not restricted to amputation, because shifts of cortical somatotopic maps have also been demonstrated in cases of non-amputee pain,[12,14,22,26] indicating that pain itself may be associated with reorganization of the primary somatosensory cortex for certain body regions. On the other hand, prolonged non-painful afferent stimulation during physical strain, e.g., in string players[27] or Braille readers,[28,29] led to an extension of the cortical representation of the hand into adjacent zones.

Our results corroborate and clearly extend these findings. In our CRPS I patients these changes occurred without nerve lesions. We intentionally excluded patients with CRPS II, because evoked magnetic responses may be difficult to localize precisely following nerve lesions. That is, in contrast to previous studies, the reorganization in our patients cannot be explained by cortical deprivation due to a loss of peripheral input. Furthermore, we found a shrinkage of the region representing the hand in CRPS rather than an extension—a striking contrast to previous studies in healthy subjects during experimental pain or training paradigms.[12,30] There is only one investigation suggesting that the cortical hand field within the S1 cortex is reduced within 5 minutes after injection of capsaicin at the thenar eminence.[14]

Our results indicate that the cortical representation of the hand—besides being reduced in extent—is moved to a more lateral and inferior position toward the lip. Cortical reorganization in our study was predicted by both pain and mechanical hyperalgesia. We assessed spontaneous pain acutely during the MEG recordings, and also by employing the MPQ. The advantage of the MPQ is that it measures sensory, affective, and evaluative components of chronic pain. It seems to be essential to assess these different dimensions in order to comprehensively assess pain and its correlation with cortical reorganization.[9] Accordingly, pain, as assessed with the MPQ, was related to cortical reorganization, whereas the

Table 2 *Equivalent current dipole parameters (means ± SD) of somatosensory evoked magnetic fields (SEF) responses following tactile stimulation of the lower lip and D1 and 5 on the unaffected and complex regional pain syndrome affected side*

Area	Latency, ms	Dipole moment, nAm	Corr.	GoF	Volume, cm^3
D1 affected	46.2 ± 3.8	24.0 ± 3.0	99 ± 0.01	99 ± 0.01	0.34 ± 0.43
D5 affected	44.9 ± 2.3	22.1 ± 2.4	98 ± 0.01	98 ± 0.01	0.23 ± 0.23
Lip affected	32.7 ± 1.6	14.6 ± 3.1	97 ± 0.01	97 ± 0.01	0.45 ± 0.54
D1 unaffected	46.9 ± 5.8	14.1 ± 32	98 ± 0.01	98 ± 0.01	0.23 ± 0.12
D5 unaffected	44.8 ± 7.5	13.1 ± 3.5	98 ± 0.01	98 ± 0.01	0.32 ± 0.42
Lip unaffected	34.9 ± 7.6	14.5 ± 2.9	97 ± 0.01	97 ± 0.01	0.53 ± 0.64

Latency = peak latency of the first major SEF component; corr = correlation coefficient; GoF = goodness-of-fit; Volume = confidence volume.

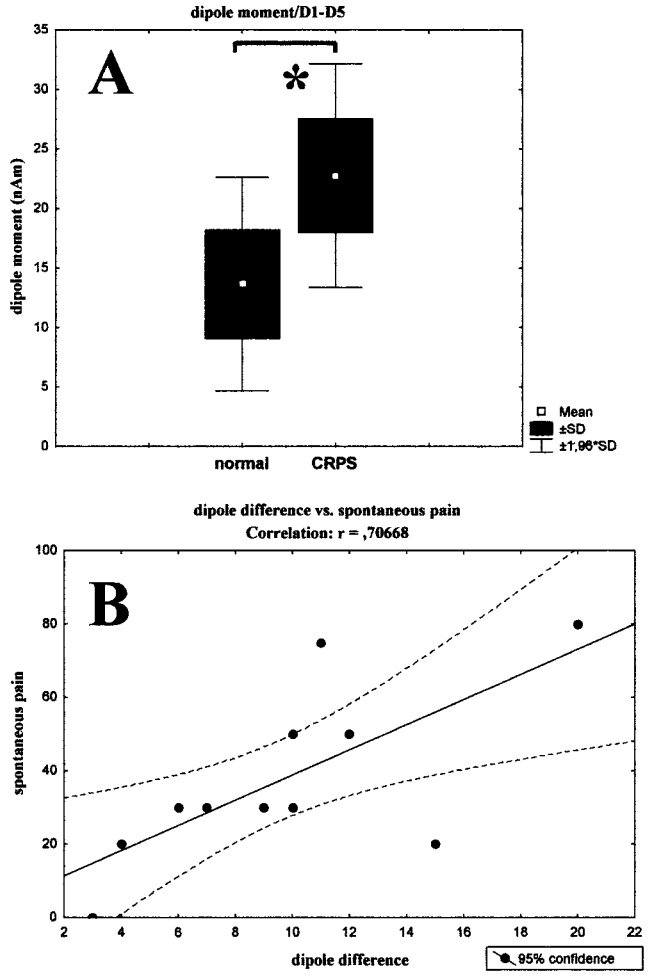

Figure 3. (A) Mean dipole moments (nAm) of the first somatosensory evoked magnetic fields response following tactile stimulation of D1/D5 on the normal and complex regional pain syndrome (CRPS) side. *$p < 0.05$. *(B) Correlation between spontaneous pain and the difference between the normal and CRPS side for the mean dipole moments of D1/5 ($r = 0.707$).*

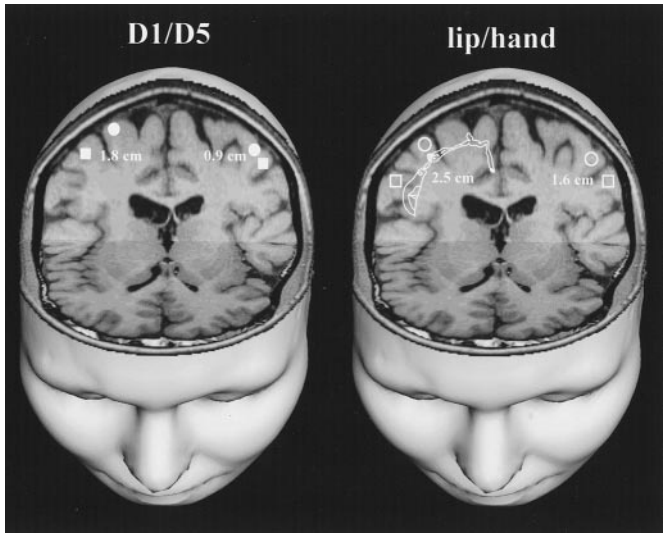

Figure 4. Left: Projection of the equivalent current dipole (ECD) localizations for D1 (filled square) and D5 (filled circle) onto individual MRI slices for one representative patient. Note the reduction in the cortical extension of the hand from 1.8 cm (unaffected side) to 0.9 cm (complex regional pain syndrome [CRPS] side). Right: Projection of the ECD for the center of the hand (open circle) and the lower lip (open square) onto individual MRI slices. Note the inferior and lateral shift of the hand position toward the lip on the CRPS side (distances between lip and hand 2.5 cm for the normal and 1.6 cm for the CRPS side).

rating of acute pain alone was not. Recently, similar results were presented for pain associated with carpal tunnel syndrome.[26] The reversibility of both cortical reorganization and pain after therapy is a further argument for a major role of pain in inducing cortical reorganization. This also agrees with the finding that nociceptive afferents can alter the excitability of mechanoreceptive neurons in the S1 cortex of monkeys.[31]

Alternatively, attention alone is known to interfere with both body representation in the cortex and somatosensory processing.[12,13,32,33] One is tempted to assume that increased attention to the painful limb might be a particular problem in CRPS and that this might account for modifications of cortical maps. However, a previous study showed that, compared to pain, attention plays a minor role in S1 reorganization.[12] Influences of attention are primarily mirrored in the somatosensory association cortex S2.[34] Furthermore, some patients with CRPS tend to ignore the affected limb rather than focusing attention to it.[35] Therefore, we do not think that attention alone is a convincing explanation for the extensive cortical reorganization observed in this study.

Continuous and chronic pain from a particular body region might lead to central nociceptive sensitization, possibly by gating the sensory volley to spinal, subcortical, and cortical relays. Besides cortical reorganization, both subcortical and spinal mechanisms may contribute to central sensitization. In the spinal cord, a number of neurotransmitters and changes in the electrophysiologic properties of wide dynamic range and nociceptive neurons have been demonstrated.[36,37] Similar changes have been postulated at the thalamic level. Pinprick hyperalgesia is regarded to be a hallmark of central nociceptive sensitization in both human pain models and patients with CRPS.[38] The correlation of cortical reorganization with the area and strength of pinprick hyperalgesia observed in this study suggests that an important connection between cortical reorganization and central nociceptive sensitization exists. Further support for central nociceptive sensitization in patients with CRPS can be taken from the observation that stimulation of the painful side produced higher dipole moments of the S1 response. The increase in this cortical response was dependent on the pain reported during mechanical stimulation. This is in accordance with previous MEG studies showing similar results for patients with other types of

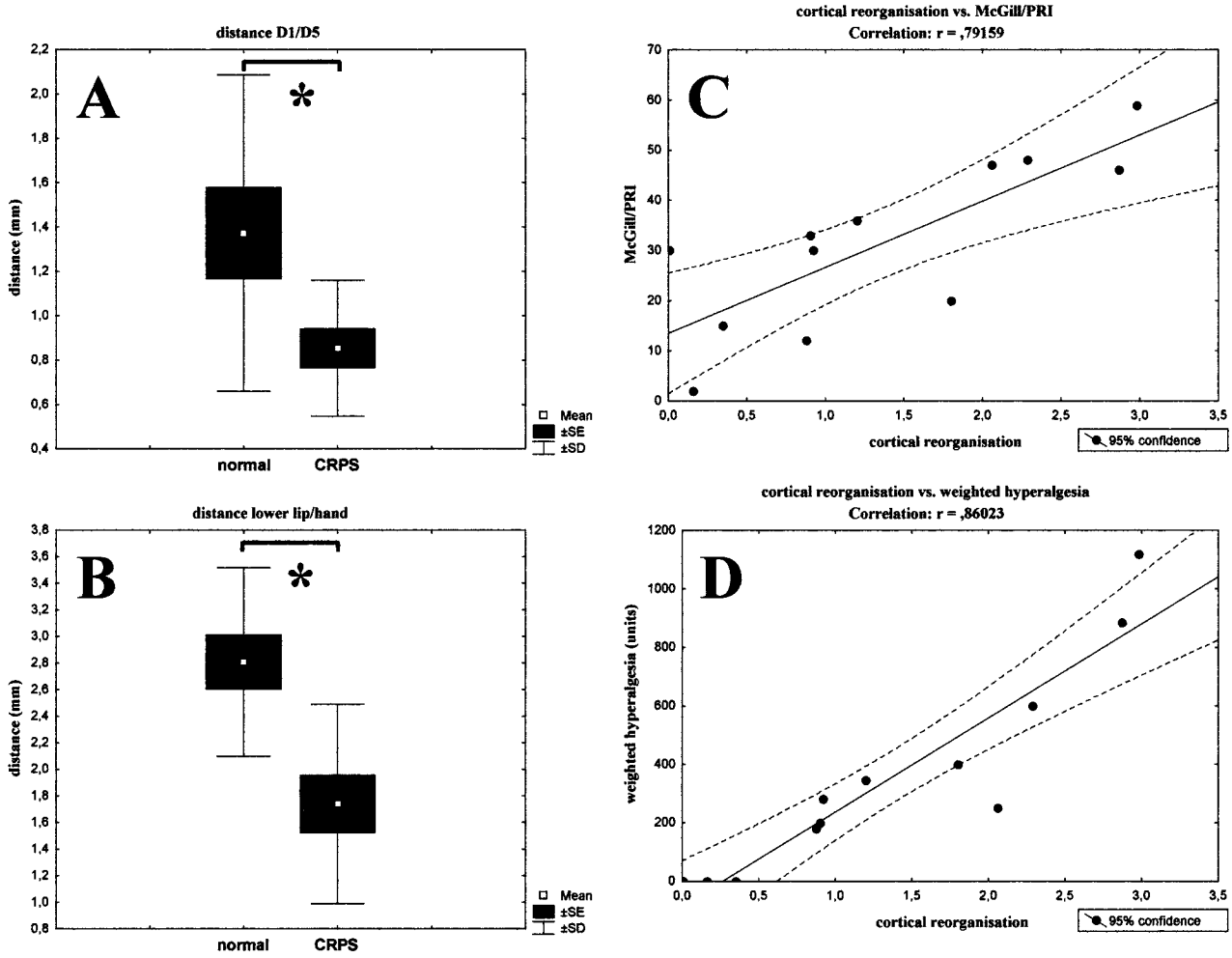

*Figure 5. (A) Euclidean distance between the center of gravity of the representation of D1 and D5 on the normal and complex regional pain syndrome (CRPS) side. *p < 0.05. (B) Euclidean distance between the center of gravity of the representation of the hand and the lower lip on the normal and CRPS side. *p < 0.05. (C) Correlation between the amount of cortical reorganization and McGill questionnaire pain rating index (r = 0.792). (D) Correlation between cortical reorganization and the weighted area of mechanical hyperalgesia (r = 0.860).*

chronic pain.[22,26] This observation may be the surrogate of enhanced cortical reactivity in chronic pain.

This study has several technical limitations that are immanent to MEG and magnetic source imaging. Modeling cortical sources of evoked magnetic fields by equivalent current dipoles assumes point-like activations. Therefore, the dipole localization corresponds to the center of the cortical electrical activity, which does not necessarily mirror the whole cortical representation of a distinct skin area. However, this limitation is the same for both body sides. Therefore, changes of the somatotopic map of one side may not be considered an artifact. In fact, most studies regarding pain and cortical reorganization were done by means of MEG.[8,9,25] MEG may be of minor sensitivity for the convexity of the cortex where the primary current spreads radially. Therefore, magnetic responses to stimulation of the upper limb should arise mainly from area 3b of the S1 cortex,[39] which is situated in the fissural wall, whereas weaker MEG signals are expected from areas 1 and 2. For this reason and to obtain a reliable signal for the source localization we focused on the time interval between 30 and 75 msec after tactile stimulation, as this interval is known to cover activations in area 3b of SI.[19-21,40]

Are the cortical changes CRPS specific? Besides pain, CRPS is characterized by motor and autonomic symptoms. Because the area of cortical representation for the hand is decreased, one might assume that this decrease reflects misuse of the painful hand and CRPS induced motor disability. However, none of the examinations used in our study to assess motor function were correlated with cortical reorganization. Motor function was assessed by determining the impairment of hand function—as measured by the range of motion—and the CRPS-induced upper limb disability—as evaluated by the DASH score. In this study we observed a lack of correlation between pain intensity during movement and cortical plasticity. Although more subtle effects of CRPS-induced motor disability on cortical somatosensory reorgani-

zation cannot be excluded, this observation renders the notion that motor dysfunction significantly influences cortical reorganization unlikely.

To assess autonomic changes we determined differences in skin temperature, changes in skin color, the presence of sweating abnormalities, and trophic changes of the skin, nails, and hair. The presence of autonomic dysfunction is essential for CRPS diagnosis, although the underlying pathophysiology is still a point of lively discussion. For acute CRPS, either decreased sympathetic outflow[41] or facilitated neurogenic inflammation[42] or both are deemed to be responsible for the aforementioned clinical signs. Our present finding that autonomic disturbances do not correlate with cortical reorganization is in accordance with the independence of autonomic symptoms and pain in the clinical setting. Although there might be sympatho-afferent coupling in certain patients with CRPS,[43,44] attempts to unequivocally link the quantity or even the presence of autonomic symptoms to pain have failed.[4]

The lack of correlation between both motor and autonomic symptoms and cortical reorganization emphasizes the impact of pain and hyperalgesia. Because both clinical symptoms are essential features used to discriminate CRPS from other types of chronic limb pain,[41,45] we are tempted to conclude that cortical reorganization is not CRPS specific. However, the plastic changes observed within the CNS in this study may explain the complex sensory features occurring in CRPS. In particular, the distribution of sensory symptoms exceeding the innervation territory of single nerves may be the psychophysical correlate of cortical reorganization.

The patients included in this study were homogenous, having acute forms of untreated CRPS I. It would be of interest to investigate changes in time course of CRPS. Patients with chronic CRPS may have more pronounced or even diminished cortical reorganization, and therapeutic interventions may affect central changes, too. Our investigation was explicitly designed to explore changes of the S1 cortex in CRPS. Beyond this, there are several lines of evidence pointing to involvement of other brain areas, particularly those involved in autonomic or motor control. For instance, the attenuation of sympathetic vasoconstriction[41,46] and the simultaneous amplification of sweating pinpoint to a dysregulation of the central sympathetic nervous system. Also, motor symptoms[2,4] like tremor, dystonia, and myoclonus must be generated in the CNS. Nevertheless, the underlying functional neuroanatomy of these symptoms remains to be explored. The great advantage of our study is that it provides neuroimaging evidence for the assumption that the pathophysiology of CRPS is not limited to the affected limb—it rather involves the whole nervous system. Whether therapeutic interventions interfering with cortical reorganization processes might provide new treatment options for CRPS remains to be demonstrated in future studies.

Acknowledgment

The authors thank Gabi Göhring-Waldecker for assistance with care of the patients and data organization, Sieglinde Jakobi for technical assistance during data acquisition, and Dr. C. Forster for help with the statistics.

References

1. Birklein F, Handwerker HO. Complex regional pain syndrome: how to resolve the complexity? Pain 2001;94:1–6.
2. Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes—analysis of 145 cases. Acta Neurol Scand 2000;101:262–269.
3. Stanton-Hicks M. Complex regional pain syndrome (type I, RSD; type II, causalgia): controversies. Clin J Pain 2000;16:S33–S40.
4. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–1016.
5. Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995;63:127–133.
6. van de Beek WJ, Schwartzman RJ, van Nes SI, Delhaas EM, van Hilten JJ. Diagnostic criteria used in studies of reflex sympathetic dystrophy. Neurology 2002;58:522–526.
7. Rommel O, Gehling M, Dertwinkel R, et al. Hemisensory impairment in patients with complex regional pain syndrome. Pain 1999;80:95–101.
8. Flor H, Braun C, Elbert T, Birbaumer N. Extensive reorganization of primary somatosensory cortex in chronic back pain patients. Neurosci Lett 1997;224:5–8.
9. Flor H, Elbert T, Knecht S, et al. Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 1995;375:482–484.
10. Flor H, Denke C, Schaefer M, Grusser S. Effect of sensory discrimination training on cortical reorganisation and phantom limb pain. Lancet 2001;357:1763–1764.
11. Lotze M, Grodd W, Birbaumer N, Erb M, Huse E, Flor H. Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? Nat Neurosci 1999;2:501–502.
12. Buchner H, Richrath P, Grunholz J, et al. Differential effects of pain and spatial attention on digit representation in the human primary somatosensory cortex. Neuroreport 2000;11:1289–1293.
13. Noppeney U, Waberski TD, Gobbele R, Buchner H. Spatial attention modulates the cortical somatosensory representation of the digits in humans. Neuroreport 1999;19:3137–3141.
14. Soros P, Knecht S, Bantel C, et al. Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography. Neurosci Lett 2001;298:195–198.
15. 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.
16. Stein C, Mendl G. The German counterpart to McGill Pain Questionnaire. Pain 1988;32:251–255.
17. Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996;29:602–608.
18. Germann G, Wind G, Harth A. [The DASH (Disability of Arm-Shoulder-Hand) Questionnaire—a new instrument for evaluating upper extremity treatment outcome.] Handchir Mikrochir Plast Chir 1999;31:149–152.
19. Nakamura A, Yamada T, Goto A, et al. Somatosensory homunculus as drawn by MEG. Neuroimage 1998;7:377–386.
20. Maihofner C, Kaltenhauser M, Neundorfer B, Lang E. Temporo-spatial analysis of cortical activation by phasic innocuous and noxious cold stimuli—a magnetoencephalographic study. Pain 2002;100:281–290.
21. Druschky K, Kaltenhauser M, Hummel C, et al. Somatotopic organization of the ventral and dorsal finger surface representations in human primary sensory cortex evaluated by magnetoencephalography. Neuroimage 2002;15:182–189.
22. Maihofner C, Neundorfer B, Stefan H, Handwerker HO. Cortical processing of brush-evoked allodynia. Neuroreport 2003;14:785–789.
23. Marquardt DW. An algorithm for least-squares estimation of non-linear parameters. J Soc Ind Appl Math 1963;11:431–441.
24. Kakigi R, Hoshiyama M, Shimojo M, et al. The somatosensory evoked magnetic fields. Prog Neurobiol 2000;61:495–523.
25. Birbaumer N, Lutzenberger W, Montoya P, et al. Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. J Neurosci 1997;17:5503–5508.
26. Tecchio F, Padua L, Aprile I, Rossini PM. Carpal tunnel syndrome modifies sensory hand cortical somatotopy: a MEG study. Hum Brain Mapp 2002;17:28–36.
27. Elbert T, Pantev C, Wienbruch C, Rockstroh B, Taub E. Increased cortical representation of the fingers of the left hand in string players. Science 1995;270:305–307.

28. Sterr A, Muller MM, Elbert T, Rockstroh B, Pantev C, Taub E. Perceptual correlates of changes in cortical representation of fingers in blind multifinger Braille readers. J Neurosci 1998;18:4417–4423.
29. Pascual-Leone A, Torres F. Plasticity of the sensorimotor cortex representation of the reading finger in Braille readers. Brain 1993;116:39–52.
30. Braun C, Heinz U, Schweizer R, Wiech K, Birbaumer N, Topka H. Dynamic organization of the somatosensory cortex induced by motor activity. Brain 2001;124:2259–2267.
31. Tommerdahl M, Delemos KA, Favorov OV, Metz CB, Vierck CJ, Jr., Whitsel BL. Response of anterior parietal cortex to different modes of same-site skin stimulation. J Neurophysiol 1998;80:3272–3283.
32. Buchner H, Reinartz U, Waberski TD, Gobbele R, Noppeney U, Scherg M. Sustained attention modulates the immediate effect of deafferentation on the cortical representation of the digits: source localization of somatosensory evoked potentials in humans. Neurosci Lett 1999;260:57–60.
33. Sawamoto N, Honda M, Okada T, et al. Expectation of pain enhances responses to nonpainful somatosensory stimulation in the anterior cingulate cortex and parietal operculum/posterior insula: an event-related functional magnetic resonance imaging study. J Neurosci 2000;20:7438–7445.
34. Mauguiere F, Merlet I, Forss N, et al. Activation of a distributed somatosensory cortical network in the human brain: a dipole modelling study of magnetic fields evoked by median nerve stimulation. Part II: effects of stimulus rate, attention and stimulus detection. Electroencephalogr Clin Neurophysiol 1997;104:290–295.
35. Galer BS, Butler S, Jensen MP. Case reports and hypothesis: a neglect-like syndrome may be responsible for the motor disturbance in reflex sympathetic dystrophy (complex regional pain syndrome-1). J Pain Symptom Manage 1995;10:385–391.
36. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;353:1959–1964.
37. Maihofner C, Tegeder I, Euchenhofer C, et al. Localization and regulation of cyclo-oxygenase-1 and -2 and neuronal nitric oxide synthase in mouse spinal cord. Neuroscience 2000;101:1093–1108.
38. Sieweke N, Birklein F, Riedl B, Neundorfer B, Handwerker HO. Patterns of hyperalgesia in complex regional pain syndrome. Pain 1999;80:171–177.
39. Hari R, Forss N. Magnetoencephalography in the study of human somatosensory cortical processing. Philos Trans R Soc Lond B Biol Sci 1999;354:1145–1154.
40. Hari R, Karhu J, Hamalainen M, et al. Functional organization of the human first and second somatosensory cortices: a neuromagnetic study. Eur J Neurosci 1993;5:724–734.
41. Wasner G, Heckmann K, Maier C, Baron R. Vascular abnormalities in acute reflex sympathetic dystrophy (CRPS I): complete inhibition of sympathetic nerve activity with recovery. Arch Neurol 1999;56:613–620.
42. Birklein F, Schmelz M, Schifter S, Weber M. The important role of neuropeptides in complex regional pain syndrome. Neurology 2001;57:2179–2184.
43. Baron R, Schattschneider J, Binder A, Siebrecht D, Wasner G. Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case-control study. Lancet 2002;359:1655–1660.
44. Drummond PD, Finch PM, Skipworth S, Blockey P. Pain increases during sympathetic arousal in patients with complex regional pain syndrome. Neurology 2001;57:1296–1303.
45. Birklein F, Kunzel W, Sieweke N. Despite clinical similarities there are significant differences between acute limb trauma and complex regional pain syndrome I (CRPS I). Pain 2001;93:165–171.
46. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. Brain 2001;124:587–599.