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Bilateral somatosensory cortex disinhibition in complex regional pain syndrome type I

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ABSTRACT

Objective: In a previous study, we found bilateral disinhibition in the motor cortex of patients with complex regional pain syndrome (CRPS). This finding suggests a complex dysfunction of central motor-sensory circuits. The aim of our present study was to assess possible bilateral excitability changes in the somatosensory system of patients with CRPS.

Methods: We measured paired-pulse suppression of somatosensory evoked potentials in 21 patients with unilateral CRPS I involving the hand. Eleven patients with upper limb pain of non-neuropathic origin and 21 healthy subjects served as controls. Innocuous paired-pulse stimulation of the median nerve was either performed at the affected and the unaffected hand, or at the dominant hand of healthy controls, respectively.

Results: We found a significant reduction of paired-pulse suppression in both sides of patients with CRPS, compared with control patients and healthy control subjects.

Conclusion: These findings resemble our findings in the motor system and strongly support the hypothesis of a bilateral complex impairment of central motor-sensory circuits in CRPS I. *Neurology*® 2011;77:1096-1101

GLOSSARY

ANOVA = analysis of variance; **CRPS** = complex regional pain syndrome; **ENG** = electroneurography; **GABA** = γ -aminobutyric acid; **pp-SEP** = paired-pulse somatosensory evoked potential; **PPS** = paired-pulse suppression; **SEP** = somatosensory evoked potential; **SOA** = stimulus onset asynchrony; **sp-SEP** = single-pulse somatosensory evoked potential.

Complex regional pain syndrome (CRPS) can occur following a trauma or surgical procedure.¹⁻³ Patients with CRPS have deep somatic pain, thermic hyperalgesia,⁴ motor disturbances,⁵ and autonomic dysfunction.⁶⁻⁹ Imaging studies described cortical changes, such as smaller representation of the CRPS-affected hand on primary somatosensory cortex (S1) during painless stimulation of the affected side.¹⁰⁻¹⁶ Recently, in spite of unilateral signs and symptoms, we found bilateral disinhibition in the motor cortex of patients with CRPS I.¹⁷ These findings were affirmed by a recent fMRI study showing bilaterally increased motor cortex activations during finger tapping.¹⁸ Such a bilateral cortical disinhibition might be related to bilateral behavioral impairments in motor-sensory tasks which patients with CRPS show in our clinical routine, although only one extremity is affected. Patients with CRPS might exhibit such patterns of disinhibition not only in motor, but also in sensory cortex.

Paired-pulse stimulation in combination with recordings of somatosensory evoked potentials (SEP) is a well-established tool to investigate cortical inhibition in the somatosensory system.^{19,20} Paired-pulse suppression (PPS) describes the phenomenon that at short stimulus onset asynchronies neuronal responses to the second stimulus are significantly reduced. PPS is quantified as the ratio of the second response amplitude divided by the first response amplitude. Small amplitude ratios are associated with strong PPS; large ratios are associated with

Supplemental data at www.neurology.org

Supplemental Data



From the Departments of Neurology (M.L., O.H., P.S., S.L., P.S., M.T.) and Pain Management (A.R., J.F., H.R., C.M.), Berufsgenossenschaftliches Universitätsklinikum Bergmannsheil GmbH, Ruhr-Universität Bochum, Bochum, Germany.

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This work is part of the doctoral thesis of M. Lenz.

Table 1 Summary of study patients' characteristics and clinical signs

	Patients with CRPS	Control patients
No.	21	11
Sex, female, n	12	11
Age, y, mean \pm SD	51 \pm 10.8	46.2 \pm 11.7
Affected side, right hand, n	10	7
Duration of illness, mo, mean \pm SD	4.9 \pm 3.7	7.0 \pm 3.7
Pain intensity		
Current (NRS), mean \pm SD	4.5 \pm 2.1	4.4 \pm 2.6
Average (NRS), mean \pm SD	6.1 \pm 1.8	6.7 \pm 1.8
Medication intake, n		
NSAID	13	6
Antidepressants	2	2
Anticonvulsives	7	5
Opioids	1	1
Other	6	4
Origin of illness, n		
Fracture	10	5
Surgery	2	1
Trauma	9	5
Joint impairment, n		
Moderate	6	3
Severe	8	2
ROM, mean \pm SD		
Wrist	0.7 \pm 0.3	0.9 \pm 0.2
MCP	0.6 \pm 0.3	0.8 \pm 0.2
Abnormal ROM values, n		
Edema, n	19	2
Skin color changes, n	12	4
Dystrophic signs, n	9	0
Impairment on ADL, mean \pm SD	1.4 \pm 0.5	0.9 \pm 0.6

ADL = activities of daily living; CRPS = complex regional pain syndrome; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drugs; MCP = metacarpophalangeal; ROM = range of motion.

reduced PPS. In the present study, we used paired-pulse SEP after innocuous stimulation to investigate whether in patients with CRPS I bilateral disinhibition is not restricted to the motor cortex, but can also be found in S1.

METHODS Subjects. We considered 37 patients (25 patients with CRPS I, 12 patients with non-neuropathic pain as controls) who were referred to the Department of Pain Management (BG Universitaetsklinikum Bergmannsheil, Ruhr-University Bochum, Germany) to participate in the study. Five patients (4 CRPS and 1 control) were excluded due to intolerable pain during stimulation. Thus, clinical features and SEP data are reported for 21 patients with CRPS (12 women, 9 men) aged

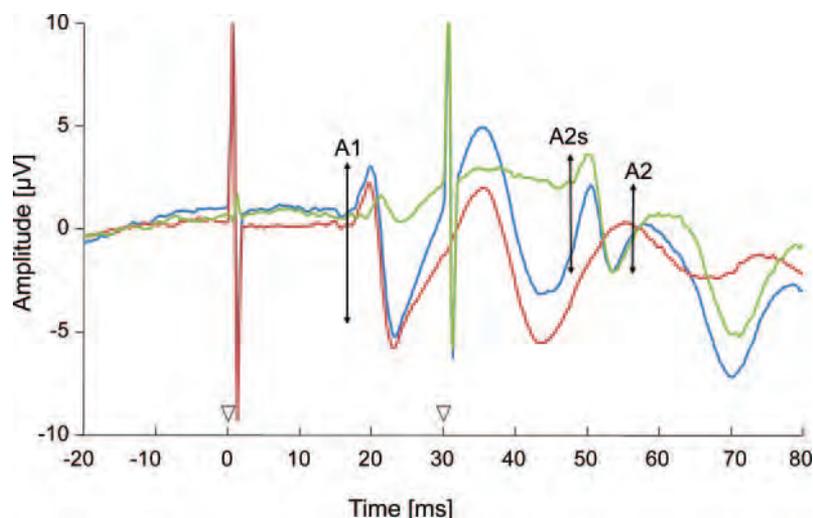
24 to 69 years (mean age 51 \pm 10.8 years) and 11 non-neuropathic control patients (11 women; aged 46.2 \pm 11.7 years). The duration since diagnosis ranged between 0.2 and 15.8 months (4.9 \pm 3.7 months) for the patients with CRPS and between 2.0 and 12.9 months (7.0 \pm 3.7 months) for the control patients. Pain intensities (current and average), as well as medication intake, origin of illness, and clinical signs, were assessed. Additionally, each patient was asked to estimate the remaining level of use of the affected hand (expressed as a percentage of the use before trauma). The clinical features of CRPS and control patients are reported in table 1. All patients with CRPS I fulfilled Budapest criteria for research,³ including an increased bone metabolism as revealed by 3-phase scintigraphy.²¹ Only patients with unilateral affection of the upper limbs were selected. Neurologic examination and electroneurography (ENG) was performed on each patient to exclude peripheral nerve lesions. Patients with peripheral nerve lesions or other neurologic disorders were excluded.

The results obtained from the 2 patient groups (CRPS and non-neuropathic control patients) were additionally compared to results of 21 healthy volunteers (12 women, 9 men; aged 28 to 67; mean age 51.3 \pm 10.9).

Standard protocol approvals, registrations, and patient consents. All subjects participating in the study gave their written informed consent. The study was approved by the Ethics Committee of the Ruhr-University Bochum, Germany, and was performed in accordance with the Declaration of Helsinki.

Paired-pulse stimulation and SEP recordings. To assess paired-pulse suppression in the somatosensory cortex, we applied a paired-pulse protocol consisting of innocuous paired electrical stimulation of the median nerve with a stimulus onset asynchrony (SOA) of 30 msec in combination with recordings of somatosensory evoked potentials (SEP). Nerve stimulation (pulse duration 0.2 msec, repetitive rate of the paired stimuli 3 Hz) was performed using a block electrode placed on the wrist of the affected and unaffected hand of patients or the dominant hand of controls, respectively. Subjects had to report a prickling sensation in the thumb, index, and middle finger of the stimulated hand to verify correct positioning of the stimulating block electrode. In all participants, the chosen stimulation intensity induced a small muscular twitch in the thenar muscles. During median nerve stimulation and SEP recordings, subjects were seated in a comfortable chair and were instructed to relax but stay awake with closed eyes. SEP signals were amplified and filtered using a BrainAmp magnetic resonance amplifier (Brain Products GmbH, Gilching, Germany) and digitized in a PC running the BrainVision Recorder software package (Brain Products GmbH). Paired-pulse SEP recordings were done using a 3-electrode array. Two electrodes (C3' and C4') were located over the left and right primary somatosensory cortex (S1), 2 cm posterior to C3 and C4 according to the international 10–20 system (American Electroencephalographic Society, 1994). A reference electrode was placed over the midfront (FZ) position. The electrical potentials were recorded in epochs from 0 to 200 msec after stimulus onset. Single-pulse SEP (sp-SEP) of both hands was recorded additionally using the same setup as for the paired-pulse SEP (pp-SEP). A total of 800 stimulus-related epochs were recorded at a time for single and paired stimuli on each side. The sequence of single and paired stimulation as well as stimulus presentation on affected and unaffected side was pseudorandomized to avoid bias effects. We analyzed peak-to-peak amplitudes of the cortical N20–P25 response component for the first and second paired-pulse stimulus. As exemplarily shown in

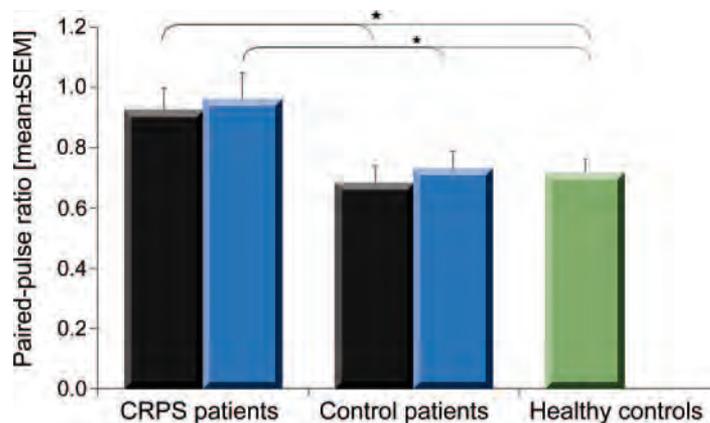
Figure 1 Representative evoked potentials of one healthy subject



Evoked potentials were measured over cortical CP3 after single (red trace) and paired-pulse (blue trace) stimulation of right median nerve. The green trace results by subtracting the single-pulse trace from the paired-pulse trace. The analyzed amplitudes of the first response (A1) and second response (A2) after paired-pulse stimulation are marked by vertical bars; amplitudes of the second response after subtracting the response to a single pulse are denoted as A2s. Onset of stimulation is marked by arrowheads.

figure 1, after paired-pulse stimulation the response to the second pulse rides on the response to the first pulse, leading to a superimposition of both evoked potentials. Therefore the amplitude of the response to the second pulse may misleadingly appear to be higher or lower. To assess “true” paired-pulse interaction, linear superposition effects had to be factored out by subtracting the response to the single-pulse stimulation from the paired-pulse stimulation trace. We analyzed the second pp-SEP amplitude after linear subtraction of the sp-SEP (A2s) and referred it to the first pp-SEP amplitude before linear subtraction (A1). PPS was expressed as a ratio (A2s/A1) of the amplitudes of the second (A2s) and the first (A1) peak (figure 1).²⁰

Figure 2 Paired-pulse suppression in patients and controls



Mean paired-pulse ratios \pm SE are plotted for the hemisphere contralateral to the unaffected (black) and affected (blue) hand of patients with complex regional pain syndrome (CRPS) and control patients and the dominant hand (green) of healthy controls. Patients with CRPS show increased amplitude ratios compared with control patients with non-neuropathic pain and with healthy controls (Student unpaired *t* test, $p < 0.05$).

Statistical analysis. Paired-pulse SEP ratios of the 2 patient groups were compared using analysis of variance (ANOVA) for repeated measurements with affected/unaffected “side” as within-subject factor and “diagnosis” as between-subject factor. To compare the results of the patients’ affected and unaffected side with the dominant side of healthy controls, we calculated Student unpaired *t* tests. Linear correlation analysis (Pearson) was utilized to test for significant correlation coefficients between paired-pulse ratios, current and average pain levels, duration of the disease, and stimulation intensities. We performed all statistical analyses using the SPSS 17.0 software package (version 17.0.0).

RESULTS ANOVA revealed no significant difference between the patients’ affected (mean amplitude ratio \pm SE; CRPS group = 0.96 ± 0.09 , control group = 0.74 ± 0.06) and clinically unaffected side (mean amplitude ratio \pm SE; CRPS group = 0.95 ± 0.07 , control group = 0.71 ± 0.06 ; $F = 0.311$, $p = 0.581$). In contrast, ANOVA revealed increased amplitude ratios in patients with CRPS compared with patients with non-neuropathic pain (CRPS group vs control group; $F = 5.622$, $p = 0.024$). The ANOVA result was confirmed by post hoc *t* tests (affected hand CRPS vs control group, $p = 0.045$; unaffected hand CRPS vs control group, $p = 0.006$), indicating that in patients with CRPS amplitude ratios in both affected and unaffected hands were increased.

Compared to the dominant hand of healthy subjects (mean amplitude ratio \pm SE, 0.72 ± 0.05), amplitude ratios in patients with CRPS’s affected (Student unpaired *t* test, $p = 0.027$) and unaffected ($p = 0.008$) side were also significantly increased (figure 2). We found no difference between the patients with non-neuropathic pain and the healthy subjects.

Paired-pulse ratios did not correlate with pain intensities, either current or average (1 week; table e-1 on the *Neurology*[®] Web site at www.neurology.org) pain intensities. We could not find any correlation between paired-pulse ratios and the duration of the disease (see table e-1).

Evaluation of the single response components A1 and A2s revealed no significant differences between patient groups and between the affected and unaffected sides in patients (ANOVA, between-subject factor group, A1, $F = 2.207$, $p = 0.148$; A2s, $F = 0.217$, $p = 0.644$, within-subject factor side, A1, $F = 2.461$, $p = 0.127$; A2s, $F = 2.602$, $p = 0.117$; see table e-2 for amplitudes and ratios). Comparing patients with healthy controls revealed reduced A1 responses for the affected side of patients with CRPS (Student unpaired *t* test, $p = 0.031$; see also table e-2) but no changes in the second amplitude A2s.

As well, stimulus intensities did not differ significantly between the affected and unaffected sides in patients, between patient groups (ANOVA, within-subject factor side, $F = 1.591$, $p = 0.217$; between-subject factor group, $F = 0.141$, $p = 0.71$) and

healthy subjects and patients (see table e-3 for intensities and *t* tests).

DISCUSSION In the present study, we found decreased somatosensory PPS in both the hemisphere contralateral to the affected and contralateral to the clinically unaffected hand in patients with CRPS I, indicating a bilateral disinhibition. These findings correspond to findings in the motor cortex using paired-pulse TMS¹⁷ and 2 other studies using MEG to assess the reactivity of the 20-Hz motor cortex rhythm to tactile or laser stimulation, which also indicated a tendency toward bilateral motor cortex disinhibition.^{10,22} Taken together, all these findings suggest a complex dysfunction of bilateral cortical sensory-motor networks in patients with CRPS I, which is not a normal reaction on chronic pain, since we found no correlation with current or average pain intensities in the present study. Furthermore, bilateral disinhibition in sensory-motor networks could not be found in control patients with non-neuropathic pain syndromes.²³ In the motor system, people with chronic neuropathic pain after incomplete peripheral nerve lesion (neuralgia) showed decreased PPS only in the hemisphere contralateral to the affected extremity.²³ Moreover, in our previous study we found that the mean and the maximum pain intensity during the week prior to the study were linked to a reduced intracortical inhibition in the motor cortex contralateral to the affected side but not to the clinically unaffected side.¹⁷ These findings indicate that the phenomenon of bilateral disinhibition cannot be driven by the sensation of pain alone. However, the mechanism of how chronic pain may modulate cortical excitability remains unclear.

In the human motor cortex, the phenomenon of PPS as assessed by TMS is assumed to be the result of strong γ -aminobutyric acid (GABA)-dependent inhibitory and weaker NMDA-dependent excitatory interneuronal circuits.^{17,24,25} Assuming this for the sensory system as well, our results suggest a bilateral reduction of GABA-related sensory-motor cortical inhibition or an enhancement of NMDA-dependent excitatory mechanisms, or both. However, our data cannot provide information about possible underlying mechanisms. Despite substantial experimental and theoretical work, the mechanisms mediating paired-pulse behavior are not fully understood. There is evidence that GABA_B receptors seem to be involved in regulation of PPS, as presynaptic blockade of GABA_B receptors causes a decrease in synaptic release probability consistent with the presynaptic inhibition of glutamate release.²⁶ Because of differences in the time course of recovery functions between cortical and thalamic cells, it has been argued that inher-

itance of thalamic response properties is unlikely to account for long-lasting forward suppression.²⁷ For human subjects, based on multichannel SEP recordings after paired median nerve stimulation, it can be reasonably assumed that somatosensory paired-pulse suppression is evoked on a cortical level since it has been shown that it is generated rostral to the brainstem nuclei.²⁰

Several imaging studies reported a smaller representation of the CRPS-affected hand on the primary somatosensory cortex (S1) compared to the unaffected hand after painless stimulation.¹¹⁻¹⁵ None of the above mentioned studies described changes in the ipsilateral hemisphere. Thus, the disinhibition in the hemisphere contralateral to the clinically unaffected side as found in our study is rather difficult to explain. As all our subjects and patients stated that stimulation was painless to them, the phenomenon of bilateral disinhibition in patients with CRPS should not be mediated by nociceptive A δ or C-fiber stimulation. Additionally, the N20-P25 potential component which we analyzed in our study occurs after stimulation of mechano-receptive A β fibers. Thus, it is unlikely that the observed discrepancies are mediated by differences in processing of nociceptive vs innocuous stimuli. We rather propose that we here can observe 2 different aspects of somatosensory cortical changes in patients with CRPS: the size of cortical representations and the excitability of cortical neurons. However, the size of representation might not necessarily reflect the excitability level of cortical neurons, leading to the discrepancies we observed.

Interestingly, a bilaterally reduced PPS was also found in the motor cortex of patients with focal task-specific dystonia.²⁸ This was attributed to a bilaterally disturbed motor cortex input from the basal ganglia.²⁹ Thus, it might be possible that basal ganglia involvement causes the observed disinhibition in the somatosensory cortex, as it is closely linked to the motor system via cortical horizontal connections. However, this basal ganglia involvement might often be subclinical because dystonia was rarely observed in our patients.

More interestingly, CRPS symptoms were reported not only to spread from the affected hand to the ipsilateral unaffected foot but also to the contralateral hand, or to show an initial bilateral distribution.^{5,30,31} A recent study describes bilaterally decreased pain thresholds in patients with CRPS.¹⁶ In another study, originally unilateral pain of a patient with chronic CRPS spread to the opposite side, and this was accompanied by the appearance of an abnormal ipsilateral response in S1.³¹ Taken together, these findings illustrate a variety of abnormal

features that occur in a part of the body with no known CRPS pathology, strongly suggesting that CRPS does not affect only one extremity but rather is a disease of the whole nervous system. Perhaps the results of our study are a consequence of CRPS spreading into the unaffected limb such that early subclinical symptoms within this arm were responsible.^{5,32} Although this might be a reasonable explanation, other studies found such a spreading of CRPS symptoms into another limb in only 4%³² to 10%⁵ of cases. Therefore, such an uncommon incidence may not fully account for the significant disinhibition of the somatosensory cortex contralateral to the unaffected limb within this CRPS study sample. Alternatively, the bilateral disinhibition could indicate a pre-existent increased susceptibility to a development of CRPS.

Generally, in all studies using paired-pulse techniques, changes of the amplitude ratio between the first and second response (i.e., a reduction of PPS) can be either achieved by changes of the second response or by changes of the first response. In our study, we neither found significant differences of the pure first amplitudes (A1) nor of the second amplitudes (A2s) comparing CRPS and control patients. Compared to healthy subjects, we found a trend toward reduced A1 responses only for the affected side of patients with CRPS. Taken together, we cannot state which amplitude is responsible for our observations of altered A2s/A1 ratios.

A possible limitation of the study might be that in healthy subjects only the dominant hand was measured. As we found no side effects of PPS in healthy subjects (data not shown) in prior studies, we decided to compare the patients' data only to the dominant side of healthy subjects. Another fact that should be discussed here is that all control patients were female. As it was rather difficult to find non-neuropathic controls for this study, we could not match the control patients group to the CRPS group. In former studies with healthy subjects we found no sex differences for the method of PPS measurement in the somatosensory system (data not shown). Thus, we considered it feasible to compare our CRPS data with a female control group.

Taken together, our present findings and the results of a previous study in the motor system¹⁷ suggest bilaterally disturbed inhibition in the central motor-sensory network of patients with CRPS I. Two possible mechanisms are conceivable: the observed phenomenon could be 1) a symptomatic change occurring in the disease process or 2) a predisposition to disease development. Based on the fact that disease duration does not influence bilateral disinhibition, we rather propose bilateral cortical excit-

ability changes to be a predispositional factor for the development of CRPS. This means that in those people with disturbed sensory-motor inhibition the risk for development of CRPS after a minor trauma may be heightened. Follow-up studies will provide new insights into the causality of the phenomena we observed. Given that plastic changes within the S1 cortex contralateral to the affected hand were reversed following successful treatment and recovery from CRPS,^{12,14} an interesting question will be whether such a reversal can also occur with regard to changes in cortical excitability. If bilateral disinhibition is a phenomenon developing during the course of the disease, it should diminish with successful treatment and recovery. As already described for the motor cortex,¹⁷ bilateral somatosensory cortex disinhibition cannot be used as a specific neurophysiologic marker for CRPS I in individual patients, because there is considerable individual overlap between patients and control subjects. However, the results of the present study highlight a bilateral central nervous involvement in the pathogenesis of CRPS, which should be considered in the development of new therapeutic approaches.

AUTHOR CONTRIBUTIONS

M. Lenz performed the experiments, analyzed and interpreted the data, provided figures, and wrote the paper. O. Höffken designed techniques and methods and analyzed and interpreted the data. P. Stude designed techniques and methods and performed the experiments. S. Lissek analyzed and interpreted the data and revised the manuscript for content. P. Schwenkreis contributed statistical analyses and revised the manuscript for content. A. Reinersmann coordinated and performed the experiments and analyzed the data. J. Frettlöh coordinated and performed the experiments and analyzed the data. H. Richter contributed analysis tools, conducted statistical analyses, and provided figures. M. Tegenthoff designed, coordinated, and supervised the study, obtained funding, contributed techniques and methods, and wrote the paper. C. Maier designed, coordinated, and supervised the study, obtained funding, contributed techniques and methods, and wrote the paper.

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DISCLOSURE

M. Lenz, Dr. Höffken, Dr. Stude, and Dr. Lissek report no disclosures. Dr. Schwenkreis has received speaker honoraria from Bayer Vital GmbH, Biogen Idec, Merck Serono, UCB, and Pfizer Inc, and received research support from Merck Serono. A. Reinersmann, Dr. Frettlöh, and H. Richter report no disclosures. Dr. Tegenthoff receives research support from DFG, BMBF, and DGVU. Dr. Maier receives research support from the Innovative Medicine Initiative (IMI) of the EU, BMBF, and DGVU.

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