Case Study

Local Anesthetic Sympathectomy Restores fMRI Cortical Maps in CRPS I after Upper Extremity Stellate Blockade: A Prospective Case Study

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Background: Patients with complex regional pain syndrome type I (CRPS I) show a cortical reorganization with contralateral shrinkage of cortical maps in S1. The relevance of pain and disuse for the development and the maintenance of this shrinkage is unclear.

Objective: Aim of the study was to assess whether short-term pain relief induces changes in the cortical representation of the affected hand in patients with CRPS type I.

Study Design: Case series analysis of prospectively collected data.

Methods: We enrolled a case series of 5 consecutive patients with CRPS type I (disease duration 3 – 36 months) of the non-dominant upper-limb and previously diagnosed sympathetically maintained pain (SMP) by reduction of the pain intensity of more than > 30% after prior diagnostic sympathetic block. We performed fMRI for analysis of the cortical representation of the affected hand immediately before as well as one hour after isolated sympathetic block of the stellate ganglion on the affected side. Statistics: Wilcoxon-Test, paired t-test, $P < 0.05$.

Results: Pain decrease after isolated sympathetic block (pain intensity on the numerical rating scale (0 – 10) before block: 6.8 ± 1.9, afterwards: 3.8 ± 1.3) was accompanied by an increase in the blood oxygenation level dependent (BOLD) response of cortical representational maps only of the affected hand which had been reduced before the block, despite the fact that clinical and neurophysiological assessment revealed no changes in the sensorimotor function.

Limitations: The interpretation of the present results is partly limited due to the small number of included patients and the missing control group with placebo injection.

Conclusions: The association between recovery of the cortical representation and pain relief supports the hypothesis that pain could be a relevant factor for changes of somatosensory cortical maps in CRPS, and that these are rapidly reversible.

Key words: Cortical reorganization, cortical plasticity, cortical maps, complex regional pain syndrome (CRPS), sympathetically maintained pain (SMP), sympathetic block (SB)

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Patients with complex regional pain syndrome type I (CRPS I) show extensive cortical reorganization in the sensory system characterized by shrinkage of cortical maps in the contralateral primary somatosensory cortex (S1) (1-3). The extent of this phenomenon correlates with the pain intensity, but is also accompanied by clinical signs of impaired sensory and motor function. Long-term rehabilitation programs, including both pain treatment and sensorimotor training, induce a recovery of the cortical representation both in CRPS I (1,2) and in phantom limb pain (4), demonstrating the

reversibility of these neuroplastic changes. Whether the shrinkage of cortical maps is primarily mediated by pain or disuse of the affected extremity is still unclear.

If the CRPS-associated cortical changes proved reversible after rapid pain relief, we could conclude that pain is a major factor for their generation and/or maintenance and that disuse might play only a minor role, since a rapid increase in limb use after short-term pain relief is unlikely. However, pain relief after sensory nerve block with local anesthetics is unsuitable to examine the above stated hypothesis, because the sensory nerve block itself can also modify the cortical responses to sensorimotor stimulation, as previously described in patients with phantom limb pain (5) as well as in healthy subjects (6). Furthermore, short-acting drugs relieving pain in CRPS are not available.

In contrast, in a subgroup of patients with CRPS I and sympathetically maintained pain (SMP) (7-9) isolated sympathetic blocks (SB) enable the investigation of the influence of rapid pain relief without generally impairing the sensory afferent fibers and motor efferent fibers. Therefore, we analyzed the influence of rapid pain relief on the cortical representation of the affected hand in patients with previously diagnosed SMP using functional magnetic resonance imaging (fMRI) before and after isolated SB.

Methods

Patients

After approval by the local ethics committee and written informed consent we examined a case series of 5 patients with CRPS I of the non-dominant hand (Edinburgh Handedness Inventory) and pain relief > 30% after prior diagnostic SB. All patients gave their consent to publish any patients' data in scientific journals. The clinical data are presented in Table 1. The sensory findings were assessed during a clinical examination as well

Table 1. *Clinical data.*

ID	Age (yrs)	Sex	Disease duration (mos)	Affected side	Initiating event	Sensory findings*	Vasomotor signs #	Sudomotor/ edema signs +	Motor/trophic signs	Current medication
1	52	F	36	left	soft tissue injury	dysesthesia after touch, pinprick hyperalgesia	no	no	decreased range of motion of the hand joints	oxicodon, gabapentin
2	44	M	5	left	hand phlegmon with multiple surgeries	dynamic mechanical allodynia, dysesthesia after touch	blue-reddish skin color	increased sweating, edema	decreased range of motion of the hand and arm joints, increased hair and nail growth	celecoxib, amitryptilin
3	36	F	3	left	radial fracture with consequent surgery	dysesthesia after touch, hyperalgesia to heat, pinprick and pressure	temperature asymmetry (affected hand colder)	increased sweating, edema	decreased range of motion of the hand and arm joints, increased hair and nail growth	buprenorphine, pregabalin, celecoxib, amitryptilin
4	47	M	4	left	metacarpal fracture with consequent surgery	paresthesia after touch, hyperalgesia to cold pressure and pinprick stimuli	temperature asymmetry (affected hand warmer)	increased sweating, edema	decreased range of motion of the hand and arm joints, increased hair growth	celecoxib, gabapentin
5	19	F	12	left	soft tissue injury with wrist distortion	hyperalgesia to heat, pinprick and pressure	temperature asymmetry (affected hand colder)	edema	decreased range of motion of the hand and arm joints	tilidin/naloxone, pregabalin, amitryptilin, ibuprofen

*The sensory findings were assessed during a clinical examination as well as during a standardized quantitative sensory testing according to the protocol of the German Research of Neuropathic Pain (DFNS) (12,13). # Temperature asymmetry was assessed using a temperature data logger svea * TDL (Medicommerz GmbH, Germany). + Increased sweating and edema were assessed during the clinical examination. F: female, M: male

as during a standardized quantitative sensory testing according to the protocol of the German Research of Neuropathic Pain (DFNS) (10,11). Temperature asymmetry was measured by bilateral temperature assessment using a temperature data logger svea ® TDL (Medicommerz GmbH), whereas a temperature side difference of more than 1.5°C was regarded as clinically relevant. Increased sweating and edema were assessed during the clinical examination. All patients fulfilled the Budapest criteria for CRPS I (for research purposes) (12) and displayed an increased bone metabolism in the affected hand according to triple-phase bone scintigraphy (13). Peripheral nerve lesions were excluded by electroneurographical and neurological examination, supported by unaffected thermal and tactile detection thresholds in the quantitative sensory testing according to the protocol of the German research Network on Neuropathic pain (10,11). Other exclusion criteria were severe edema or skin lesions of the affected hand that might require disproportionally high stimulation intensities.

Study Procedures

FMRI scans were performed one hour before and one hour after stellate ganglion block on the affected side. The unilateral anesthetic blocks of the lower cervical sympathetic ganglion (ganglion stellatum) were performed by the anterior paratracheal approach injecting 15 mL bupivacaine 0.5% according to the current practice in Germany using anatomic landmarks without computed tomography (CT), ultrasound, or fluoroscopic guidance (14-16). While the patient is lying in a supine position, the cricoid notch is identified with the tip of the index finger and moved laterally, retracting the carotid sheath and sternocleidomastoid muscle. The anterior transverse process of C6 is then identified and fixed with the palpating finger to insert a needle immediately medially to it, until reaching the transverse process of C6, and after a negative aspiration test, the local anesthetic is injected. The sympathetic block was defined as sufficient independent from the appearance of a Horner syndrome but by temperature increase of at least 2°C measured on the affected extremity, because a Horner syndrome indicates a sympathetic block of the nerve fibers for the face area, but not for the upper extremity. It has been shown that a Horner syndrome was present also in about half of the blockades without sufficient sympathetic block on the upper extremity (17,18).

The current pain intensity (numerical rating scale, NRS 0 – 10) and skin temperature were assessed before the first fMRI measurement and 45 minutes after the block. Before and after SB standard somatosensory evoked potentials (SSEP) using a non-painful electrical stimulation of the index finger (pulse duration: 0.1 ms, repetition rate: 3 Hz, stimulation intensity: 2.5 fold of the sensory threshold) were recorded to prove an unaffected afferent function. SSEP were recorded using an electrode over the contralateral SI, 2 cm posterior to C3 (CP3) according to the international 10 – 20 system and the International Federation of Clinical Neurophysiology (IFCN) standards (19). A reference electrode was placed over midfront (FZ) position. SSEP were bandpass filtered (100 – 2000 Hz) and recorded in epochs from 20 ms before to 200 ms after stimulus onset with a 32-channel amplifier (Brain AMP; Brain Products, Munich) and stored for off-line analysis. For each stimulation, 800 stimulus-related epochs were automatically corrected for baseline, DC-drifts, and ocular movement artifacts, and averaged (BrainVision Analyzer, Brain Products, Munich). Peak-to-peak amplitudes of the cortical N20 – P25 SEP components and latencies of the cortical N20 components were analyzed.

FMRI Data Acquisition

Sensory stimulation of the index finger was performed using a DIGITIMER stimulator, type DS7A (Digitimer Ltd., England) with ring-electrodes on the index finger tip (pulse duration: 0.1 ms, repetition rate: 3 Hz, stimulation intensity: 1.5 fold of the sensory threshold). FMRI scanning was performed in a Block design with a whole body 1.5T scanner (Magnetom Symphony, Siemens Medical Systems, Germany) equipped with a high-power gradient-system (30 mT/m/s; SR 125 T/m/s) using a standard imaging head coil. BOLD images were obtained with a single-shot SpinEcho-EPI sequence (TR 3000 ms, TE 60 ms, matrix 64 x 64, field of view (FOV) 224 mm, 5 mm slice thickness, 1 mm gap between slices, voxel size 3.5 x 3.5 x 4 mm). We acquired 16 transaxial slices, parallel to the AC-PC line, covering the whole brain. We performed fMRI scanning by using 13 rest blocks without electrical stimulation and 12 blocks of stimulation, each of which contained 20 scans, resulting in a total number of 510 scans. Patients were instructed to keep their eyes closed and to concentrate on stimulation during the whole session. Anatomical images were acquired with an isotropic T1-3 dGE (MPRAGE) sequence (TR 1790 ms, TE 388 ms, matrix 256 x 256, FOV 256 mm, 1 mm slice thickness, no gap, voxel size 1 x 1 x 1 mm) with 160 sagittally orientated slices covering the whole brain. Imaging data were analyzed with the

Statistical Parametric Mapping (SPM) software package, version 5 (UCL Wellcome Trust Centre for Neuroimaging, London, UK), running under the MATLAB R12 environment (Mathworks, Sherborn, MA). Single subject spatial preprocessing consisted of realignment of all images to the first volume, generation of a mean image that corrected for head movement artifacts, normalization into standard stereotaxic space at 2 x 2 x 2 mm with an EPI template provided by the Montreal Neurological Institute, and smoothing with a 6 mm (full-width half maximum) isotropic, three-dimensional Gaussian filter. In single-subject analyses, contrast images comparing activation during sensory stimulation to the rest phases were calculated for both scanning sessions (before and after the block). The resulting contrast images were then entered into a paired t-test to compare the activation patterns before and after the block (extent threshold k = 20 voxels; height threshold t = 1.89, $P < 0.005$ uncorrected). For further quantification, for each subject the pre- and post-BOLD mean signal intensity in SI during stimulation was extracted from a cluster-sized region of interest built from the activated SI cluster (20).

Statistical Analysis

Clinical and electrophysiological data obtained before and after SB were analyzed by the Wilcoxon-test ($P < 0.05$). Values are presented as means ± standard deviation.

Results

Clinical Effects of the Sympathetic Block

In all patients skin temperature increased and pain intensity decreased significantly after SB (Table 2). Clinical examination revealed no sensorimotor deficits after SB. The (electrical) sensory threshold as well as latencies and amplitudes of SSEP remained unchanged, pointing to an unaffected afferent pathway. There were also no further changes in the clinically assessed symptoms and signs during the observation period of approximately 2 hours after SB.

FMRI Parameters

Before SB, somatosensory cortex activation in response to stimulation was reduced in the hemisphere contralateral to the affected side compared to the non-affected side. Fig. 1 shows the result of a two-sample t-test of the whole group, demonstrating a significantly stronger activation in BA1 of the healthy side (t = 2.31, Z = 2.02, $P = 0.022$ FDR small volume correction, MNI coordinates, x, y, z: 56, -24, 52). A paired t-test between the condition after and before intervention revealed a significant increase of activation in right postcentral gyrus after SB, corresponding to BA2 (t = 5.67, Z = 2.82, $P = 0.048$ FDR small volume correction, MNI coordinates, x, y, z: 54, -20, 46; Fig. 2).

Discussion

Like phantom limb pain, CRPS I is accompanied by shrinkage of the sensory cortical representation of the affected limb (1-3). The underlying mechanisms are still unknown, although a crucial effect of pain upon this reorganization has been discussed (1). Our fMRI results support the hypothesis that pain plays a major role in the generation and/or maintenance of the CRPS-associated cortical changes. Remarkably, the cortical shrinkage was reversible within one hour after decrease of pain intensity despite disease histories of up to one year.

It has been reported that sensory deafferentation can induce a rapid change in somatosensory cortical maps within a few minutes in amputees with phantom limb pain after ipsilateral plexus anesthesia and coincident pain reduction (5). Similarly, experimental

Table 2. *Changes of pain intensity and skin temperature after isolated sympathetic block.*

Patient	Pain intensity before sympathetic block (NRS 0 – 10)	Pain intensity after sympathetic block (NRS 0 – 10)	Skin temperature before sympathetic block (°C)	Skin temperature after sympathetic block (°C)
1	9.0	3.0	31.4	34.8
2	7.0	5.0	28.1	31.2
3	4.0	2.0	29.1	32.9
4	6.0	4.0	30.3	34.8
5	8.0	5.0	25.9	29,1
mean ± SD	6.8 ± 1.9	3.8 ± 1.3	29.0 ± 2.1°C	32.6 ± 2.4°C

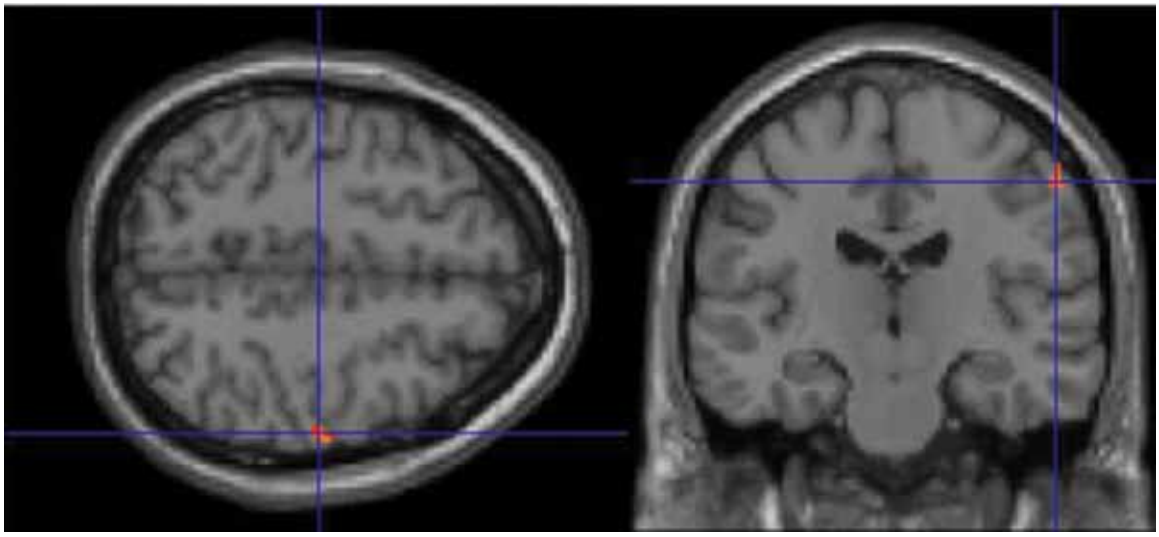

Fig. 1. *fMRI before sympathetic block – somatosensory cortex activation after stimulation of the hemisphere contralateral to the affected side (right S1 cortex) compared to the non-affected side (left S1 cortex). Stronger sensory activation of the healthy unaffected side compared to the affected side in patients with CRPS before the sympathetic block (two-sample t-test: t = 2.31, Z = 2.02, P = 0.022 FDR small volume correction, MNI coordinates, x, y, z: 56, -24, 52).*

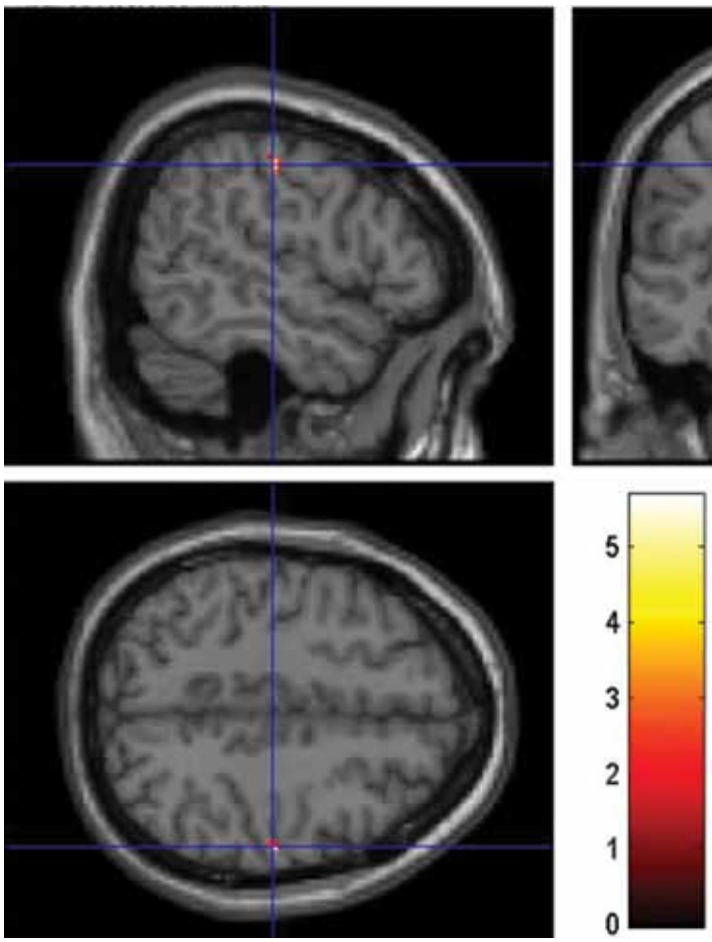

Fig. 2. *fMRI changes after sympathetic –block – somatosensory cortex activation after stimulation of the hemisphere contralateral to the affected side (right S1 cortex) at baseline and following sympathetic block on the affected extremity. Normalization of sensory activation in the group of patients with CRPS on the left hand after sympathetic block (paired t-test: t = 5.67, Z = 2.82, P = 0.048 FDR small volume correction, MNI coordinates, x, y, z: 54, -20, 46).*

regional anesthesia in healthy controls induced both an increase of cortical SEPs (21) as well as an enlargement of somatosensory cortical maps and disinhibition in paired-pulse transcranial magnetic stimulation protocols (22). Nevertheless, in theory, effects of anesthesia on cortical activity may not be comparable to effects of analgesia, i.e., selective decreases in nociceptive input may produce different effects than complete deafferentiation achieved by regional anesthesia as described in the above mentioned studies (5,21,22). We now demonstrate for the first time that also a relevant pain reduction induced by an isolated sympathetic block without clinical or neurophysiological somatosensory deficits can cause a rapid recovery of the previously shrunken somatosensory cortical maps in patients with CRPS I, though pain did not resolve completely after sympathetic block in any of the 5 patients.

The role of S1 as a part of the cortical network involved in pain processing has been discussed, due to the cognitive modulation of pain, and the inhibitory effects of noxious stimuli (23). It could be hypothesized that the sympathetic block leads to a reduction of pain afferents to S1. During acute pain, these afferents induce an intracortical inhibition (particularly in area 3b) (24) which was found to be reversible after pain reduction induced by the sympathetic block in our study. This mechanism could explain the recovery of cortical representation in S1 after rapid pain relief in our patients.

On the other hand, a recent study showed cortical reorganization in patients wearing a cast of the upper limb, indicating that disuse plays a role as well, at least in non-painful syndromes (20). However, casting the affected limb in patients with CRPS in order to ensure that the affected extremity is not being moved would be medically and ethically not justifiable. Moreover, use of the affected limb is not expected to recover within a short time in CRPS I, because patients with CRPS I also suffer from a dysfunction of the hand joints and muscles. Therefore, we would assume that the observed cortical changes occur as a result of the pain relief and that disuse plays only a minor role compared to the pain influence, especially as we studied only patients with CRPS I on the non-dominant hand.

Interpretation of the data could be tempered by the limitations of the present study, including the lack of a control groups. For ethical reasons, considering the invasive intervention, we did not perform placebo injection in patients with diagnosed sympathetically maintained pain and did not include an active treatment group of patients without pain relief after previous sympathetic blocks. Moreover, in contrast to lumbar facet blocks, it is nearly impossible to perform a double-blind approach when injecting sympathetic ganglia with saline vs. local anesthetics, as in case of successful sympathetic block clear autonomic signs like skin temperature increase and Horner's syndrome occur. One study examined 7 patients with SMP by fMRI (25). The authors applied a painful thermal stimulus on the chronically painful hand and demonstrated widely spread prefrontal hyperactivity, increased anterior cingulate activity, and decreased activity in the thalamus contralateral to the body side suffering from SMP, but was unrelated to sensorimotor activity. Interestingly, this activity dramatically decreased when the same stimulus was applied shortly after the sympathetic block that produces pain relief. Importantly, ineffective sympathetic blocks, i.e., blocks that did not diminish the SMP pain, did not change the cortical responses to the painful thermal stimulus. Thus, one could speculate that in our case saline injections, which do not diminish patients' pain, would have not induced a normalization of the cortical maps, unless a placebo-induced analgesia was achieved. Anyway, we cannot also exclude completely that disuse is an additional factor and that patients' expectations have at least partly influenced the cortical processing and modified the neuronal activity in the present study. Also, we cannot exclude that the patients' perception of ability to move under the influence of reduced pain might not also play a role for the observed cortical reorganization after the sympathetic block. For logistic reasons we were not able to perform a third control scan after pain had returned to its original intensity to determine whether the fMRI pattern seen at baseline was rapidly established, because the duration of pain relief after sympathetic blocks in patients with CRPS and SMP was shown to be interindividually highly variable, ranging from 18 hours up to 6 days (9).

Another concomitant fact could be the absence of local anesthetic plasma concentration measurement to exclude subclinical systemic effects of the local anesthetic agent. We performed SB according to the current practice in Germany injecting 15 mL of bupivacaine and the interventions were performed by experienced anesthetists. We have excluded any accidental afferent sensory block by thorough clinical examination after the blockade. A previous study of our group underlined the importance of that, as some accidental sensory blocks have been observed even after CT-guided lumbar and thoracic sympathetic blocks (15). Patients with CRPS are

characterized predominantly by a gain of sensory function, i.e., hyperalgesia to different stimuli, dysaesthesia and allodynia, whereas pre-existing negative symptoms (hypoesthesia) were not present in our patients' sample (see Table 1). Thus, a sensory afferent block after the intervention would have been detected in the clinical examination.

Indeed, the phenomenon of pain relief after sympathetic blockade itself has also been a subject for controversy for many years. Based on animal models, interactions between the sympathetic nervous system and the primary afferent neurons have been hypothesized to occur after nerve injury both within the dorsal root ganglion as well as in the peripheral nervous system (26,27). Baron et al (7) demonstrated the influence of experimentally increased or decreased sympathetic activity on ongoing pain and hyperalgesia, and the anti-hyperalgesic effects of sympathetic blocks in a subgroup of patients with CRPS and SMP. The present fMRI findings are in line with this. However, the clinical value of this phenomenon is still unclear, in view of only one placebo-controlled study (9).

Conclusion

In conclusion, the results of our study indicate the important role of ongoing pain as a trigger for the cortical reorganization in CRPS and provide a rationale for the effect of sympathetic block in defined patients with CRPS and SMP.

Conflicts of Interest

There were no financial relationships that might have led to a conflict of interest. CM, EK, MT, and AW are members of the German Research Network on Neuropathic pain (BMBF, grants 01EM0107 & 01EM0502). CM and AW are members of the Europain Collaboration, which has received support from the Innovative Medicines Initiative Joint Undertaking, under grant agreement no. 115007, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007 2013) and EFPIA companies (AstraZeneca, Pfizer, Esteve, UCB-Pharma, Sanofi Aventis, Grünenthal, Eli Lilly, und Boehringer Ingelheim) in kind contribution. CM has received research grants from Pfizer, MSD, Mundipharma, Grünenthal, Astellas, and Lilly; he has also received consultant and/or speaker fees from Astellas, Sanofi Aventis, Wyeth, Pfizer, Mundipharma, and Eli Lilly. EK has been a member of the IMI Europain (see above), she was also supported by intramural fundings of the Ruhr University Bochum (FoRUM: grant number K046-10, Heinemann Award 2013) and has received a travel grand from Mundipharma, speaker fees from Grunenthal and Pfizer as well as consultant fees from PainCert GmbH. PS was supported by intramural funding of the Ruhr-University Bochum (FoRUM grant R 2006). MT has received consultant and/or speaker fees from GSK and Pfizer.

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