Observational Study

# Event-Related Cortical Processing in Neuropathic Pain under Long-Term Spinal Cord Stimulation

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**Background:** Several mechanisms were suggested in the past to explain the beneficial effect of spinal cord stimulation (SCS) in patients suffering from neuropathic pain. Little is known about potential supraspinal mechanisms.

**Objective:** In this study cortical signaling of patients with neuropathic pain and successful long-term treatment with SCS was analyzed.

**Study Design:** Observational study.

**Setting:** University hospital, neurosurgical department, outpatient clinic for movement disorders and pain, institute for cognitive and clinical neuroscience.

**Methods:** Nine patients with neuropathic pain of a lower extremity with a lasting response to chronic SCS were included. Cortical activity was analyzed using event-related potentials of the electroencephalogram after non-painful and painful stimulation. Each patient was tested under the effect of long-term SCS and 24 hours after cessation of SCS. Cortical areas involved in the peaks of evoked potentials were localized using a source localization method based on a fixed dipole model.

**Results:** Detection threshold and intensity of non-painful stimulation did not differ significantly on both sides. Pain threshold was significantly lower on the neuropathic side under the effect of SCS ($P = 0.03$). Bilateral pain thresholds were significantly lower ($P = 0.03$ healthy side, $P = 0.003$ neuropathic side) in 5 patients with increased pain after cessation of SCS.

Under the effect of SCS cortical negativities (N1, N2, N3) and positivities (P1) demonstrated bilaterally comparable amplitudes. After cessation of SCS, decreased threshold for peripheral stimulation resulted in lowered negativities on both sides. The positivity P1 was differentially regulated and was reduced more contralateral to the unaffected side. N2 was localized at the sensory representation of the leg within the homunculus. The main vector of P1 was localized within the cingular cortex (CC) and moved more anteriorly under the effect of SCS.

**Limitations:** The exact time span that SCS continues to have an effect is not known. However, due to patient discomfort discontinuation of SCS therapy was not prolonged over a 24 hour period. Further limitations were the low number of patients who agreed to discontinue SCS therapy for research purposes.

**Conclusions:** Long-term SCS for treatment of neuropathic pain influenced both pain thresholds and cortical signalling. Source localization of P1 suggests involvement of regions involved in cognitive/associative processing of pain.

**Key words:** Event related cortical processing, neuropathic pain, spinal cord stimulation, SCS

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Spinal cord stimulation (SCS) is a valuable and clinically well-established tool for the treatment of neuropathic and ischemic pain (1-5). The mechanisms by which it modulates pain, however, are not yet fully understood. Initially, SCS was thought to simply provide a spinal inhibitory mechanism based on the gate control theory (6). Several findings from experimental studies, however, raised doubts about the simple mechanistic applicability of this hypothesis to SCS (7). The fact that pain relief exceeds the period of stimulation in SCS argues against a mechanism that simply "closes the gate" by electrical activation of inhibitory connections. Subsequently, a complex variety of mechanisms has been uncovered (8). Today, it is widely accepted that SCS-related pain relief is mediated via segmental and supraspinal mechanisms recruited by antidromic and orthodromic activation (9). Experimental work provided evidence for the relative importance of the 2 different pathways (10).

During the last decade, neuroplastic changes within central neuronal structures have received more attention in patients suffering from chronic pain. In postamputation neuropathic pain, for example, it was demonstrated that the extent of cortical representation of the lost extremity was negatively correlated with the intensity of pain (11). Furthermore, restitution of the representation by peripheral electrical stimulation or by a special exercise applying mirror training could improve phantom pain (12,13). Little is known about the influences of long-term SCS on supraspinal signaling and the results are partially conflicting. Previous studies reported reduced amplitudes of short-, mid-, and long-latency components of somatosensory evoked potentials (SEPs) during SCS (14-17). Newer studies reported more differentiated influences on neural activity of the human cortex with an increased cortical activation in functional imaging under the effect of SCS (18-23). In electrophysiological studies, a decrease of cortical potentials over SI and SII was reported during SCS whereas the potentials were increased over the midcingular area (24,25). Evoked potentials in these studies were the result of a nonpainful stimulation.

It was reported in the mid-seventies that pain-evoked potentials could be suppressed during stimulation in patients with chronic stimulation of the ganglion Gasseri for treatment of refractory trigeminal neuropathy. It was also shown that pain thresholds under stimulation were increased for electrical stimulation of the tooth pulp (26). Positron Emission Tomography (PET) studies showed that main differences were seen in the perigenual part of the anterior cingular cortex (ACC) when rCBF was compared to the stimulation-off situation and during chronic stimulation (27). The cingular cortex in general is thought to be involved in unpleasant painful sensations such as allodynia or other manifestations of neuropathic pain (28).

Here, we investigated cortical activity using event-related electroencephalography (EEG) after painful stimulation in patients with chronic SCS in both the on and off stimulation state.

## Methods

### Patients

Inclusion criteria were neuropathic pain confined to the lower extremities which had responded well to chronic SCS within a period of 2 years. Results had to have been stable for at least 6 months. Twenty-eight patients fulfilled the inclusion criteria. Seventeen patients refused to switch off the stimulator for at least 24 hours because of the risk of recurrent pain. Eleven patients signed informed consent and were selected to participate in the study. After day 1, one patient was excluded from the study because she complained of intense neuropathic pain comparable to the pre-operative state and opted to refrain from further investigation. A second patient was excluded because it was not possible to provoke painful stimulation despite maximally possible stimulation intensity on day 1.

Demographic data of the participating patients are summarized in Table 1. All patients had surgically placed quadripolar plate electrodes (Resume II, Medtronic, Minneapolis) at D11 to D9 connected to a pacemaker (Itrel II, Itrel III, or Restore, Medtronic, Minneapolis) in an upper abdominal quadrant. Clinical pain intensity was quantified using the Pain Intensity subscale of the German version of the West-Haven-Yale Multidimensional Pain Inventory (29). Response to chronic SCS was rated by each patient with a 6 step scale as follows: 1 = excellent, 2 = good, 3 = fair, 4 = minor, 5 = no improvement, and 6 = increase of pain under treatment. Only patients with at least fair improvement were included (ratings between 1 and 3). Participation in the study was voluntary, and patients were informed about the planned study during routine follow-up examinations. Informed consent was obtained on the first day of the study protocol. The study design was approved by the local ethics committee.

Table 1. *Demographic data of patients with neuropathic pain and SCS treatment who gave informed consent.*

| No | Age | Gender | Location of NeuP | Allodynia | Prior surgery | SCS System |
|---|---|---|---|---|---|---|
| 01 | 49 | M | lat lower leg, dorsal foot | dorsal foot | 2 x disc surgery L4/5 | Itrel II |
| 02 | 57 | F | lat. lower leg, lat. foot | lat. lower leg | 2 x disc surgery L5/S1 | Itrel III |
| 03 | 61 | M | lat. thigh, lat. lower leg, foot | foot | 2 x disc surgery L3/4, decompression spinal stenosis L3-5 | Itrel III |
| 04 | 39 | M | lat. lower leg, dorsal foot | n.a. | no prior surgery | Itrel III |
| 05 | 50 | M | lat thigh, ventro-lat lower leg | lat. lower leg | 3 x disc surgery L4/5 and L5/S1, decompression spinal stenosis L2-4 | Itrel III |
| 06 | 59 | F | lat. thigh. lat lower leg, foot | dorsal foot | 3 x disc surgery L4/5 and L5/S1 | Itrel II |
| 07 | 63 | F | lat. thigh lat lower leg | lat. thigh | decompression spinal stenosis L3-5 | Itrel III |
| 08 | 74 | F | ventro-lat thigh, ventro-lat lower leg | n.a. | disc surgery L4/5, decompression spinal stenosis L2/L3 and L4/5 | Itrel III |
| 09 | 50 | F | lat. thigh, lat. lower leg, dorsal foot | dorsal foot | 3 x disc surgery L4/L5 and L5/S1 | Itrel III |
| 10 | 56 | F | lat. thigh, | n.a. | 1 x disc surgery L3/L4, decompression spinal stenosis L2/3 and L4/L5 | Itrel III |
| 11 | 53 | F | lat. thigh, lat lower leg | n.a. | 1 x laserdiscectomy L4/5, 1 x disc surgery L4/5 | Itrel II |

## Stimulation Protocol and Pain Assessment

Each patient was tested twice within 2 days. The SCS-on condition was tested on the first day whereas the SCS-off condition was tested 24 hours after cessation of SCS. Prior to experimental peripheral stimulation, the neuropathic area was specified according to the quantitative somatosensory testing (QST) method. Usually, stimulation was applied within the neuropathic area over the thigh to provide a homogeneous test-field. Both SCS-on and SCS-off conditions included identification of thresholds, specification of intensities for non-painful and painful stimulation, and finally evaluation of the stimulation effect.

As artifacts impeded analysis of the EEG during SCS, the SCS-on situation was assessed immediately after turning off the stimulator.

For peripheral stimulation, an electrical stimulation modus was used allowing to activate both Aβ and A-fibers. A stripe electrode was placed over the area of neuropathic pain and a homologous contralateral site. Perception and pain thresholds were identified in 3 ascending and descending series. For non-painful stimulation, patients were asked to identify a stimulation intensity that corresponded to a moderate stimulation intensity of 5 on a scale reaching from 1 (just perceptible) to 10 (starting to be painful). The stimulation paradigm started with non-painful stimulation using 2000 unipolar rectangular impulses (Digitimer DS7A, Digitimer Ltd, Hertfordshire, England) with a pulse width of 200 µs. Groups of 100 stimuli were applied alternately over the neuropathic area and the corresponding area of the healthy leg. The interstimulus interval (ISI) was 200 ms. To further avoid habituation effects, this interval was randomly changed within a time period of 100 ms.

For painful stimulation, patients were also asked to identify a moderate pain intensity of 5 on a scale reaching from 1 (starting to be painful) to 10 (extremely painful). Only 250 bipolar stimuli were used in groups of 25 stimuli. Testing was also performed alternately in the neuropathic pain site and the corresponding contralateral control area. ISI was 2000 ms and was randomly changed within 1000 ms.

## Recording of Cortical Responses

Recordings were obtained in an electrically shielded room. The EEG was recorded from 58 scalp positions by Ag/AgCl-electrodes that were mounted on a cap according to the 10-20-system (Jaspers 1958) (reference: Cz, grounding: midline between Fpz and Fz). Data acquisition was achieved according to standard recordings of SEPs (AQUIRE, Neurosoft Version 4.0, sampling rate: 1000 Hz, signal amplification: 500-fold, bandpass filter: 0 – 200 Hz). The stimulus-related signal of a stimulus was recorded and simultaneously saved with the EEG recording. Finally, an electrooculogramm (horizontal and vertical) was recorded for artifact control.

At the end of the investigation, the distribution of the individual matrix of electrode positions was digitized by a three-dimensional infrared-based camera system (Optotrak, Northern Digital) that included nasion, left and right preauricular points, and Cz as

reference sites. For the overlay of the dipole localizations with the anatomical structures of the cortex, a standard magnetic resonance image (MRI) was employed since safety reasons precluded individual MRI scans.

### Preprocessing of Evoked Potentials

The recorded data were preprocessed with Brain Vision Analyzer 1.03 (Brain Products GmbH, Gilching, Germany). The raw signal was cut into time frames with a length of 250 ms for non-painful stimulation (2000 segments) and 450 ms for painful stimulation (250 segments) as follows: 50 ms before the stimulus and 200 ms and 400 ms, respectively, after the stimulus. The prestimulus period of 50 ms was used to adapt the offset of each channel. Each segment was manually controlled for artifacts due to eye-movements, muscle activation, $\alpha$-activity, or other technical artifacts.

### Latencies

During the recorded segments at least 3 negative waves (N1, N2, and N3) were found according to activation of SI (40 – 100 ms, N1 and N2) and of SII (110 – 150 ms, N3). A broad positive wave was seen with a peak at about 180 – 280 ms. A peak-to-peak analysis of amplitudes was performed.

### Source Localization

For the great average data equivalent dipoles were calculated for P1 at about 230 ms. Theoretical field distribution was compared to the measured field distribution by iterative optimization of the dipole location and orientation according to a fixed dipole model. This method results in a residual variance. The reciprocal value is a measure for the quality of the equation and is called goodness of fit (GoF). Equivalent dipole is described by 6 parameters which define the position (xp,yp,zp) in a three-dimensional Cartesian coordinate system and the direction (xd,yd,zd). The sum-vector is a measure for the amount of synchronously firing neurons at a defined time-point (30).

## Results

Although preoperatively present in all patients, only one patient complained of allodynia under chronic stimulation. In a second patient allodynia re-emerged on day 2. Quantification of pain 24 hours after cessation of SCS showed that pain increased only in 5 patients, whereas 4 patients reported no increase of pain on day 2 (Table 2).

Detection threshold and non-painful stimulation did not differ significantly between the neuropathic side and the contralateral side although there was a tendency towards higher stimulation intensity on the neuropathic side under SCS. Pain threshold was significantly lower on the neuropathic side under the effect of SCS ($P = 0.03$ Mann Whitney rank sum test) Comparing only the 5 patients with increased spontaneous pain after cessation of SCS (pat. 02, 03, 05, 09, 10) this difference was also significant ($P = 0.001$, Mann Whitney rank sum test). The latter group also tolerated significantly lower intensities for painful stimulation on both sides ($P = 0.03$ healthy side, $P = 0.003$ neuropathic side; Mann Whitney rank sum test) (Table 3).

Analysis of grand average curves under painful stimulation on day 1 revealed comparable amplitudes

Table 2. *Pain intensity according to the West-Haven-Yale-Multidimensional-Pain-Inventary (MPI-D).*

| Patient ID | Day 1 | Day 2 |
|---|---|---|
| 02 | 1.3 | 2.3 |
| 03 | 3.3 | 3.6 |
| 04 | 4 | 3.3 |
| 05 | 1.6 | 3.3 |
| 07 | 5.6 | 5 |
| 08 | 0 | 0 |
| 09 | 5.3 | 5.6 |
| 10 | 3.3 | 4 |
| 11 | 0.6 | 0.3 |

Table 3. *Thresholds and stimulation parameters of non-painful and painful stimulation in five patients with increased spontaneous pain after cessation of SCS. (Given are mean values and relative changes compared to the control side on day two with SCS off).*

| | Control | | | Neuropathy | | |
|---|---|---|---|---|---|---|
| | SCS on | SCS off | | SCS on | SCS off | |
| Perception Threshold | 5.02 (1.13) | 4.44 (1) | n.s. | 6.0 (1.35) | 4.72 (1.06) | n.s. |
| Non-Painful Stimulation | 8.4 (0.84) | 9.6 (1) | n.s. | 14.28 (1.43) | 8.81 (0.88) | n.s. |
| Pain Threshold | 14.88 (1.3) | 11.48 (1) | n.s. | 18.65 (1.62) | 10.66 (0.93) | $P < 0.001$ |
| Painful-Stimulation | 20.82 (1.65) | 12.69 (1) | $P = 0.028$ | 23.42 (1.85) | 12.58 (0.99) | $P < 0.003$ |

for N1, N2, and N3 as well as P1 over both cortices (Table 4). In accordance with decreased stimulation parameters after cessation of SCS on day 2, the amplitudes of the negative peaks (N1, N2, and N3) were reduced, too. However, the amplitude of P1 on the neuropathic side stayed high and differed about 1.1 μV on day 2 compared to the control side (Fig. 1). On day 2 all latencies on the control side were increased; whereas, they were decreased on the neuropathic side (Table 4).

The main source of cortical activity during P1 was localized within the mid cingular region. In the SCS-on condition the main vector of P1 representing the neuropathic side was localized within the cingulum slightly more anterior (Figs. 2a,b) (Table 5).

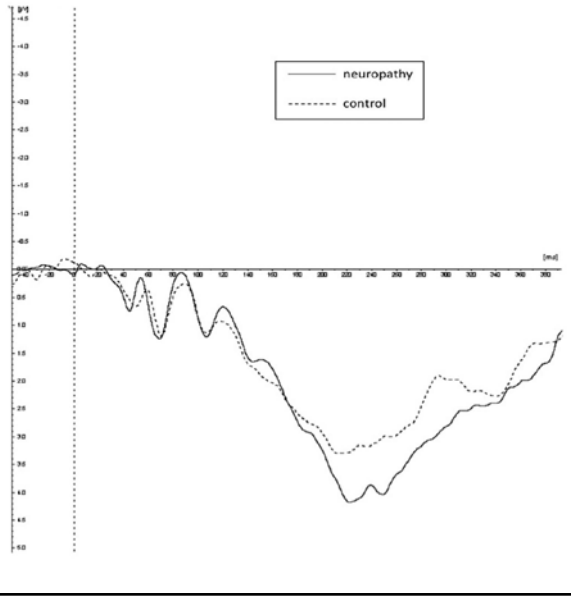


Fig. 1. *Grand average curves of pain evoked potentials after cessation of spinal cord stimulation on day 2 (Dotted line = control side, black line = neuropathic side).*

Table 4. *Latencies and amplitudes of N1, N2, N3, and P1 on day 1 (SCS-on) and day 2 (SCS-off) of 5 patients with increased spontaneous pain after cessation of SCS.*

| | Day 1 | | Day 2 | |
|---|---|---|---|---|
| | Control | Neuropathy | Control | Neuropathy |
| N1 | N50 | N50 | N58 | N45 |
| | -0.5 | -0.9 | -0.35 | -0.6 |
| N2 | N83 | N87 | N89 | N86 |
| | -1.25 | -1.3 | -0.95 | -1.15 |
| N3 | N116 | N126 | N120 | N120 |
| | -0.95 | -0.7 | -0.3 | -0.35 |
| P1 | P207 | P230 | P215 | P222 |
| | 4.4 | 4.4 | 2.3 | 3.5 |

## Discussion

In our patients with long-term SCS there was a significant decrease of pain threshold on the neuropathic side after cessation of SCS. As we tested our patients within the neuropathic area, this finding is in accordance with early findings of Krainick and Thoden (31). Furthermore, the intensity of painful stimulation significantly decreased with discontinuation of SCS not only on the side of neuropathic pain but also on the contralateral healthy side. The fact that pain tolerance was diminished on both sides most likely argues for a central effect of SCS. We saw neither a significant change of detection threshold nor of the intensity of nonpainful-stimulation between both sides although there was a tendency towards higher stimulation parameters on the neuropathic side under SCS. This difference, however, was diminished with discontinuation of SCS. More likely this finding is attributed to difficulties of patients to detect electrical stimuli under the effect of SCS than that it reveals a setting-independent sensory deficit of the neuropathic area.

Hypotheses on the antinociceptive effect of SCS reach from a block of peripheral pain pathways by induction of antidromic action potentials (32) to orthodromic activation of antinociceptive pathways of supraspinal systems (10,33). Not only electrical effects but also neurohumoral cascades are thought to be involved. Especially the inhibitory neurotransmitter gamma-amino-butyric-acid (GABA) seems to be regulated differentially by SCS. It was shown that GABA release was down-regulated in the periaqueductal grey matter (PAG) leading to disinhibition of antinociceptive pathways originating there (34). In contrast, animal studies using microdialytic techniques revealed up-regulation of GABA release within segments of the myelon which represented allodynic dermatomes in a nerve constriction injury model (35). Fast electrical effects and comparably slower neurohumoral effects might explain the clinical observation that early improvement of pain within seconds and minutes under SCS is followed by further amelioration during permanent stimulation within hours (7). Another explanation might point at slowly developing neuroplastic mechanisms in the cortex (25,36).

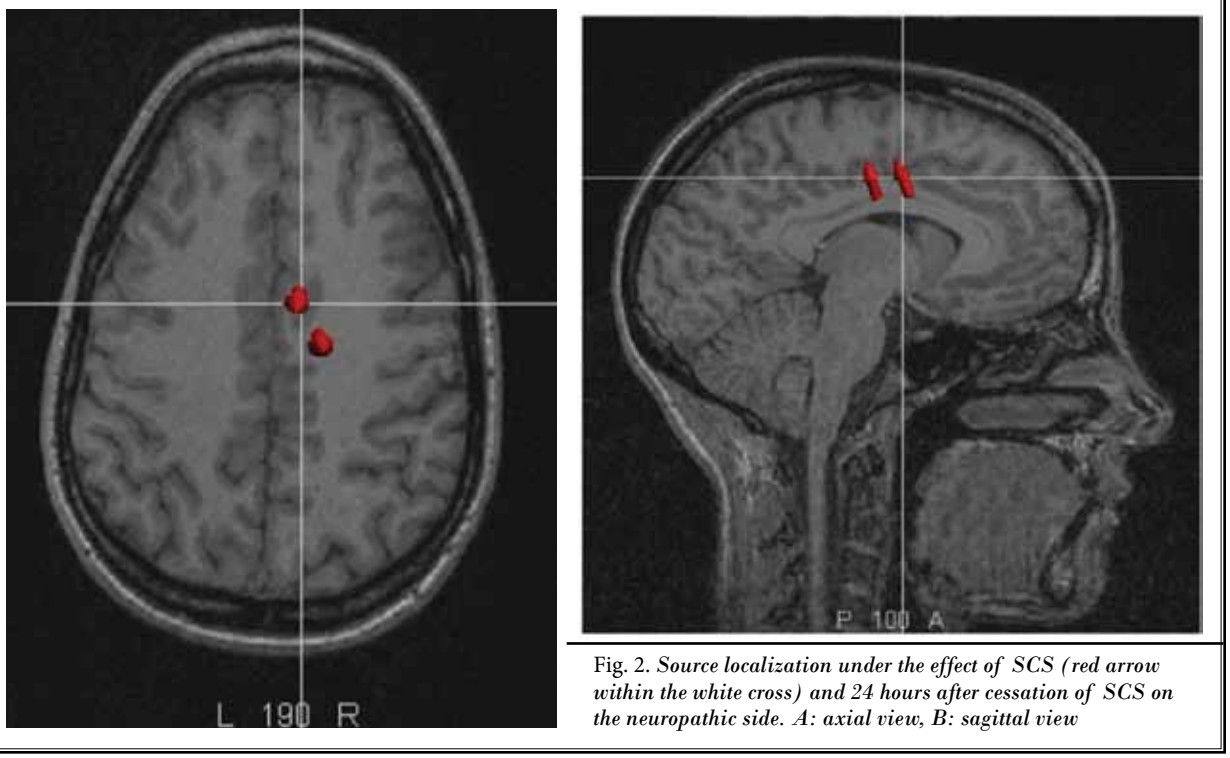


Fig. 2. *Source localization under the effect of SCS (red arrow within the white cross) and 24 hours after cessation of SCS on the neuropathic side. A: axial view, B: sagittal view*

Table 5. *Coordinates and direction of source vectors of P1 in a cartesian coordinate system (mA = Milliampere).*

| | Coordinates | | | Direction | | | Dipolmoment | Goodness of Fit |
|---|---|---|---|---|---|---|---|---|
| | X | Y | Z | Px | Py | Pz | Ma | |
| Control, Day 1 | 17 | 8.3 | 79 | -0.025 | -0.12 | 0.89 | 58 | 0.9547 |
| Control, Day 2 | 9.7 | -2.8 | 81 | 0.004 | -0.13 | 0.89 | 40 | 0.8978 |
| Neuropathy, Day1 | 28 | -4.96 | 76 | -0.19 | 0.089 | 0.98 | 56 | 0.773 |
| Neuropathy, Day 2 | 15 | -13 | 78 | -0.083 | -0.065 | 0.99 | 47 | 0.8996 |

It has been generally assumed that the complex experience of pain is processed in a network of different structures. The intensity and affective quality of perceived pain is the net result of interaction between ascending nociceptive inputs and antinociceptive controls (37). The sensory discriminative component of pain exhibits closer association with SI and SII. Accordingly, amplitudes of negativities N1 and N2 that correspond to the activity in SI and SII linearly reflect the intensity of the stimulus. As stimulus parameters were reduced in our patients after cessation of SCS, we saw a homogenous decrease of amplitudes of negativities. Obviously, the cortical response in somatosensory areas is closer related to the intensity of a stimulus than to the individual estimation of medium pain intensity at a constant level of 5 from 10 (the patients were asked to tolerate a pain intensity of 5 under painful stimulation on both days). In other words, the cortical activation in SI and SII changed according to the lowered stimulation intensities; whereas, the individual estimation of pain intensity was stable on both days. Thus, the individual estimate of pain intensity appears not to depend on the absolute value of the stimulus, but is rather determined by emotional and cognitive-associative factors that in-

fluence pain processing. Especially the anterior portion of the midcingular cortex is thought to be involved in these processes (38-41). One problem in interpretation of previous data is the varied nomenclature of the cingular cortex (CC) which has been used in different studies.

Anatomically, the CC is not a homogenuous structure. Initially, it was divided by Brodman into a precingular region (ACC including area 24, 25, 32, and 33) and a postcingular region (posterior cingular cortex [PCC] including area 23, 29, 30, and 31) (42). According to cytoarchitectural and functional aspects it was later subdivided into 4 subregions: i) the perigenual anterior cingular cortex (pACC, area 24, 32) which is involved in affect, including the subgenual subregion (SGSR, area 25) charged with visceromotor control; ii) the midcingular cortex (MCC, area 24, 32, 33) which is involved in response selection; iii) the PCC (area 23, 31) which plays a role in visuospatial processing; and finally, iiii) the retrosplenial cortex (RSC, area 29, 30) which is related to memory access (39). In recent publications the ACC was further subdivided into perigenual ACC and midcingular cortex (MCC) (28). The latter consists of 2 functionally and anatomically distinct compartments: anterior midcingular cortex (aMCC) which is more concerned with fear and affective processing and posterior midcingular cortex (pMCC) which is more concerned with executive functions (43). On the single cell level it has been demonstrated that the ACC has a significant role in pain sensation. Nociceptive cells without somatotopic order and with large receptive fields that can include the whole body were found in animal studies (44). Hutchison et al (45) also described similar cells in men. Most of the cells were activated, only a few were inhibited during the experience of a painful sensation. Direct stimulation of pain sensitive cells, however, did not elicit painful sensations (46). Obviously these cells do not simply mirror a painful event but interact within a network of neural cells that code for a complex experience of pain with its affective, attentional, motivational, and cognitive aspects. Therefore, another explanation suggests that the ACC is involved in descending modulation routines rather than in the simple perception of pain (46). We also have to consider, that a cortical response as detected by EEG techniques does not simply reflect the stimulus but rather represents the net sum of activated and inhibited cells.

Our EEG study revealed differential characteristics of the positivity of evoked potentials detected at about 230 ms. According to previous findings this positivity corresponds well to activation of the CC (47-49) which is supported by our data. The sources for later peaks (> 200 ms) of the EEG signal have been localized in the CC at the border of its anterior and posterior portion (50,51). Delineation of the anatomical substrate of the CC has been ambiguous, however, as outlined above. In functional imaging studies the ACC has been the most commonly activated region (52,53) with acute nociceptive activation localized in pMCC and throughtout aMCC (43). The ACC and the prefrontal cortex appear to subserve more specifically the affective, attentional, motivational, and cognitive aspects of pain, with cognitive aspects to be processed at the border towards the midcingular cortex according to the functional model of the CC described by Vogt et al (39). The dichotomic cortical processing of pain correspond well to the thalamic organization with sensory discriminative information passing the lateral nuclei i.e., the VPL/VPM nuclei, whereas affective motivational information polysynaptically reaches the medial and intralaminar nuclei (54). Recently, the latter were found to be involved in SCS-related pain relief (21). In line with these findings, the positivity at about 230 ms that represents activity of the cingular and the prefrontal cortex appears to be the net result of affective, attentional, motivational, and cognitive aspects of pain. The absolute value of the amplitude of P1, however, cannot be ascribed exclusively to any of these aspects.

Concerning the CC, we saw similar cortical responses on both sides under SCS which might reflect the study design as we asked the patients to identify an intensity of 5 on a scale between 0 – 10. It was suggested that the amplitudes of peaks are related more closely with the perceived pain intensity than with the strength of the stimulus (55). Interpreting the results along this line might indicate that SCS adjusted the cortical response for the neuropathic side to that of the unaffected side. Without SCS, net activation was accentuated contralateral to the neuropathic area. Whereas the amplitude contralateral to the neuropathic limb decreased by 20% it decreased by 48% contralateral to the unaffected side while stimulation intensity was reduced significantly on both sides by 46% and 40%, respectively. Together with the fact that stimulation intensity decreased on both sides and reached similar levels on both sides, there seems to be a change in the internal valuation system related to cognitive-associative processes. Remarkably, source analysis of P1 showed that the main activity contralateral to the neuropathic side was localized more anterior within the MCC under SCS; whereas, it was at a similar sagittal level after cessation of SCS on day 2 as compared to the unaffected side.

Involvement of cognitive-associative functions may explain the sagittal shift of the source vector under the effect of SCS as compared to the situation without SCS (Fig. 2) and also as compared to the healthy side. The more complex interaction with regard to the cortical response of the CC under painful stimulation, i.e., the positivity at about 230 ms, might reflect the fact that the functionality of the CC and the prefrontal cortex is not as straightforward as it seems to be within the somatosensory cortex.

Studies that examined the effects of distracting patients from pain showed enhanced activation of ACC during EEG (56). This exemplifies the importance of the ACC in attention and cognition and its influence on pain perception (37). It seems that in chronic pain states activation of primary pain encoding areas by experimental pain stimuli is decreased while it is increased in higher cortical areas. The preferential activation of the prefrontal cortex supports the hypothesis that chronic pain states have stronger cognitive, emotional, and introspective components (37,57). Chronic pain states may reflect a decreased sensory processing and enhanced emotional/cognitive processing (37). In our patients the amplitude of P1 remained high even after cessation of SCS. Under the effect of SCS, the amplitude of P1 was comparable on both sides. In other words, SCS may adjust functional activation to that of the healthy side.

One limitation of our study is the fact that we could not prolong the stimulation-off period for more than 24 hours, due to patient comfort. There is only little information available about the time span that SCS treatment continues to have an effect. It has been reported to range between one hour (7) and "some" hours (17). Information has been recruited mainly from studies that tested recurrence of pain after cessation of SCS in the early period of treatment. Yet, to the best of our knowledge, the time to recurrence of pain after controlled cessation of chronic long-term SCS has not been specified in detail.

## Conclusion

In our study, chronic long-term SCS influenced cortical signaling of pain. The shift of the main source vector of the late positivity to a more anterior position within the CC suggests involvement of cognitive-associative and motivational pain processing during chronic long-term SCS. In addition to spinal mechanisms, neuroplastic changes might be relevant to control neuropathic pain on the long-term.

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