Effect of Spinal Cord Stimulation on Sensory Characteristics
A Randomized, Blinded Crossover Study

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Objectives: Spinal cord stimulation (SCS) is increasingly used to treat various chronic pain conditions. One undetermined issue is to what extent SCS alters the processing of sensory information from the periphery, including those stimuli that are mediated by small-fiber populations. We aimed to investigate these possible changes using quantitative sensory testing (QST).

Methods: Fourteen patients in long-term SCS treatment for complex regional pain syndrome (n = 5) or pain following peripheral nerve injury (n = 9) were examined with QST. All patients answered questionnaires about their pain and underwent QST while the SCS treatment was activated and deactivated (12 h interval between the sessions) in a randomized, double-blinded crossover setting. Both the painful side and the corresponding contralateral side were examined.

Results: Thermal and mechanical thresholds were similar during SCS activation and deactivation. The same result was found for intensity of pain and areas with painful symptoms even though all patients had documented long-term benefit of the treatment.

Discussion: The results support existing evidence suggesting that SCS does not change sensory characteristics, which is important information for both patients and clinicians. Changes in pain intensity after deactivation of SCS may be different in short-term and long-term SCS treatment.

Key Words: SCS, spinal cord stimulation, quantitative sensory testing, neuropathic pain, safety

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K.M. designed the study with advice from all coauthors, examined and included the patients, conducted the quantitative sensory testing, and prepared the first draft of the manuscript. T.S.J. provided the original idea for the study as well as clinical and scientific advice. L.N. provided clinical and scientific advice and technical assistance. J.C.S. provided clinical and scientific advice. All authors revised, contributed to, and approved the final manuscript.

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S pinal cord stimulation (SCS) is a surgical treatment for chronic pain, which is increasingly used for a variety of conditions such as pain due to failed back surgery syndrome,1,2 complex regional pain syndrome (CRPS),3,4 and peripheral nerve damage.5 The success rate varies depending on the underlying etiology of pain, but in many cases patients report a significant pain relief. However, despite extensive research especially in recent years, our understanding of the exact mechanisms of action remains incomplete; in particular, there are very limited data about the potential mechanisms in humans.

SCS is originally based on the theoretical framework laid out in 1965 in the Gate Control Theory of Pain,6 according to which selective activation of large myelinated A-fibers reduces spinal cord nociceptive transmission by inhibiting activity transmitted in small myelinated and unmyelinated fiber populations. Other suggested mechanisms include activation of a spinal-brainstem-spinal feedback loop inhibiting noxious signaling neurons in the spinal cord,7 an antidromic activation of fiber systems from electrodes placed rostrally to the involved spinal segment,8 and spinal release of inhibitory neurotransmitters such as GABA and acetycholine.9

An undetermined issue is whether SCS can alter the processing of sensory information from the periphery, including those stimuli that are mediated by small-fiber populations. One way to assess this issue is to use quantitative sensory testing (QST), a method where different sensory modalities are applied to body parts, and the sensory perception of these stimuli is determined in a semi-quantitative manner.10–12

Patients with neuropathic pain have abnormal pain and sensory thresholds, ranging from hypoesthesia to hyperalgesia and allodynia. A return to physiological values of the sensory characteristics would represent a beneficial effect of the treatment. Conversely, if SCS treatment causes sensory characteristics to deviate further from those on the unaffected side of the body, this change could potentially result in negative side effects, such as a decreased sense of balance, lowered grip stability, or added risk of mechanical or thermal injury.

QST has only been used in a few of the studies that have examined the effect of SCS treatment.13–17 Because of differences in diagnoses, QST protocol, and experimental setup, the results from these studies are difficult to compare. Here we report the results from a randomized, controlled, crossover study in which QST, including measurements of mechanical and thermal thresholds and areas of spontaneous and evoked pain, was carried out in 14 neuropathic pain patients with the stimulator activated and deactivated. This was done to gain insight into whether SCS activation results in a return to physiological values of sensory
characters, expressed as a decrease in the difference between the QST results obtained from the affected side and from the corresponding contralateral side.

MATERIALS AND METHODS

Patients

Fifteen patients were included in the study and were recruited from the population of patients in permanent treatment with SCS at Aarhus University Hospital. Inclusion criteria were the following: unilateral pain either because of CRPS or peripheral nerve injury, uncomplicated SCS treatment with only unilaterally perceived effect for at least 3 months before the study and an initially reported beneficial effect, no change of SCS treatment parameters (except amplitude adjustments) for 7 days before the study, age 18 years and above, ability to understand the study design, and signed informed consent. One patient (ID 13) was excluded from the study because of displacement of the lead to the anterior part of the spinal cord (as documented by subsequent x-ray examination).

A total of 14 patients (9 female and 5 male; median age, 53 y; interquartile range [IQR], 45 to 59) completed the study. Five patients had CRPS and 9 patients had chronic pain after a peripheral nerve injury. Ten patients used analgesic medication as a supplement to their SCS treatment. The median interval from onset of pain until SCS treatment was 79 months (IQR, 41 to 118), and the median interval from the last SCS procedure to study participation was 19 months (IQR, 6 to 28). Detailed patient characteristics are shown in Table 1 and Figure 1.

All patients had been implanted with a percutaneous lead (patient 6 had 2 leads implanted on the same side) placed lateral to the midline by an experienced implanter (K.M. or J.C.S.). The equipment was standard SCS implants manufactured by St Jude Medical, St Paul, Minnesota. Patients 1 to 4, 6, 8, 10, and 11 were implanted with Octrodes, the rest of the patients with SS-series Lamitrodes.

To document the beneficial effect of the SCS treatment, all patients were asked to complete a standard SF-36 health survey questionnaire and to record their intensity of pain before implantation and at inclusion in the study. The SF-36 Health Survey questionnaire is a well-validated tool for evaluating health-related quality of life. The questionnaire is divided into 8 domains, 4 of which relate to physical well-being and 4 to mental well-being. Intensity of pain was recorded for 7 consecutive days using a conventional 11-point numerical rating scale (NRS) with “0” representing no pain, and “10” the worst pain imaginable. For data analysis a mean of the 7 days was calculated. Table 2 shows that the SCS treatment reduced the median intensity of pain from 6.9 (IQR, 5.1 to 8.7) to 4.4 (IQR, 4.0 to 6.0) ($P = 0.003$). For all domains of the SF-36 questionnaire, there was a numerical increase in score; the change was statistically significant in 3 domains (vitality, mental health, and bodily pain).

The study was approved by the Ethics Committee of Central Denmark Region (project ID: M-20100078) and registered at clinicaltrials.gov (project ID: NCT01261468). The study was carried out in accordance with the Declaration of Helsinki.

Experimental Setup

Patients were asked to leave their stimulator constantly activated at their usual settings for at least 24 hours before the examination. In the morning on the first day of

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Nerve Injury/Trauma</th>
<th>Painful Area</th>
<th>Duration of Pain Before SCS (mo)</th>
<th>Interval From SCS to QST (mo)</th>
<th>Daily Analgesic Treatment (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M 61</td>
<td>Branches from median and ulnar nerve</td>
<td>L index, finger, R forearm</td>
<td>32</td>
<td>31</td>
<td>Pregabalin 450</td>
<td></td>
</tr>
<tr>
<td>2 F 58</td>
<td>Lateral antebrachial cutaneous nerve</td>
<td>CRPS I followed by lower limb amputation</td>
<td>27</td>
<td>55</td>
<td>Oxydodone 40, tramadol 200, oxcarbazepine 900, nortriptyline 10</td>
<td></td>
</tr>
<tr>
<td>3 M 52</td>
<td>CRPS I</td>
<td>L leg</td>
<td>102</td>
<td>55</td>
<td>Oxycodone 45, paracetamol 500</td>
<td></td>
</tr>
<tr>
<td>4 M 67</td>
<td>CRPS I after fracture</td>
<td>L hand</td>
<td>38</td>
<td>15</td>
<td>Morphine 30, pregabalin 975</td>
<td></td>
</tr>
<tr>
<td>5 F 41</td>
<td>Intercostal and intercostobrachial nerve</td>
<td>L lower leg, L arm and trunk</td>
<td>95</td>
<td>45</td>
<td>Oxycodone 45, paracetamol 500</td>
<td></td>
</tr>
<tr>
<td>6 F 45</td>
<td>CRPS I after twisted ankle</td>
<td>L foot</td>
<td>63</td>
<td>25</td>
<td>Morphine 300, pregabalin 450, ibuprofen 1200, paracetamol 3000</td>
<td></td>
</tr>
<tr>
<td>7 M 46</td>
<td>CRPS II after amputation</td>
<td>L forearm</td>
<td>122</td>
<td>5</td>
<td>Methadone 50</td>
<td></td>
</tr>
<tr>
<td>8 M 54</td>
<td>CRPS I after dislocated ankle</td>
<td>L lower leg</td>
<td>56</td>
<td>3</td>
<td>Codeine 15, gabapentin 900, duloxetine 60, acetylsalicylic acid 750</td>
<td></td>
</tr>
<tr>
<td>10 F 45</td>
<td>Intercostobrachial nerve</td>
<td>R upper arm</td>
<td>41</td>
<td>27</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>11 M 65</td>
<td>Stump pain following traumatic amputation</td>
<td>L hip region</td>
<td>157</td>
<td>23</td>
<td>Tramadol 600, lamotrigine 100</td>
<td></td>
</tr>
<tr>
<td>12 M 34</td>
<td>Peroneal and saphenous nerve</td>
<td>R foot</td>
<td>155</td>
<td>8</td>
<td>Morphine 90</td>
<td></td>
</tr>
<tr>
<td>14 F 59</td>
<td>Peroneal nerve</td>
<td>L. heel</td>
<td>58</td>
<td>5</td>
<td>Duloxetine 60</td>
<td></td>
</tr>
<tr>
<td>15 F 32</td>
<td>Stump pain following lower limb amputation</td>
<td>R lower leg</td>
<td>117</td>
<td>5</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

CRPS indicates complex regional pain syndrome; QST, quantitative sensory testing; SCS, spinal cord stimulation.
examination, the examiner (K.M.) conducted a semi-
structured interview to collect information about medical
history and treatment. After that the first QST (Reference,
REF) was performed with the SCS treatment activated.
Immediately after completion of QST REF, patients were
randomized either to have their SCS system deactivated or
to keep their present stimulation.

SCS settings were adjusted by an assistant and were
blinded to both the patient and the examiner. Assignment
to activation status was random; the randomization was

FIGURE 1. Localization of spontaneous pain in 14 patients with neuropathic pain.
TABLE 2. Pain and Quality of Life Before and After SCS Implantation

<table>
<thead>
<tr>
<th></th>
<th>Pain (NRS)</th>
<th>Physical Function</th>
<th>General Health</th>
<th>Vitality</th>
<th>Mental Health</th>
<th>Role Physical</th>
<th>Role Emotional</th>
<th>Social Function</th>
<th>Bodily Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before SCS</td>
<td>6.9 (5.1-8.7)</td>
<td>39 (15-70)</td>
<td>49 (40-62)</td>
<td>25 (15-50)</td>
<td>58 (40-76)</td>
<td>13 (0-100)</td>
<td>0 (0-100)</td>
<td>50 (25-88)</td>
<td>22 (0-41)</td>
</tr>
<tr>
<td>At study inclusion</td>
<td>4.4 (4.0-6.0)</td>
<td>51 (20-75)</td>
<td>47 (35-62)</td>
<td>58 (25-70)</td>
<td>76 (64-92)</td>
<td>63 (0-100)</td>
<td>83 (0-100)</td>
<td>75 (50-100)</td>
<td>41 (41-51)</td>
</tr>
<tr>
<td>P</td>
<td>0.003</td>
<td>0.218</td>
<td>0.974</td>
<td>0.041</td>
<td>0.023</td>
<td>0.149</td>
<td>0.079</td>
<td>0.058</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Results are presented as median (interquartile range) (n = 14). Wilcoxon signed-rank test was used for comparison. Bold values indicate statistical significance.

NRS indicates numerical rating scale; SCS, spinal cord stimulation.

done in blocks of 4 using an automated number generator (http://www.randomizer.org). After an interval of 10 to 12 hours, the second QST was performed (QST A) in the same way as QST REF. Immediately after completion of QST A, the SCS settings were reversed by an assistant so that patients with active SCS treatment had the system disabled and vice versa. The procedure was still blinded to the patients and the examiner. After a second 10 to 12 hours interval, the patients were examined for the third time in the morning of day 2 with QST (QST B), follow-up information was gathered, and the patients could restore SCS activation if necessary. The sequence is illustrated in Figure 2.

The patients were asked to continue their usual analgesic medication. They were requested to use only paracetamol (acetaminophene) as rescue medication instead of opioids during the examination period.

QST

All experiments were conducted in the same room kept at a constant temperature of 21 to 23°C. Patients were examined lying in a supine or reclining position in a hospital bed. If patients had positional variation of stimulation intensity, they were asked to position their body at QST REF so they had a clear, comfortable sensation in the examined area without having to change stimulation settings. QST A and QST B were then performed with the patient in the same position as for QST REF.

QST was carried out in the area of both maximum pain intensity and clearly felt paresthesia during active SCS treatment (affected area, AA), and outside scar tissue. If severe hyperalgesia or allodynia prevented examining the area, an adjacent, less sensitive area was selected.

The selected site was marked with a permanent pen. The corresponding contralateral site served as control area (CA). The patients were carefully introduced to each part of the QST. The control area was always examined first. All QST examinations were carried out by the same examiner (K.M.).

Mechanical Thresholds

Mechanical thresholds were examined as described previously. Briefly, with the patient’s eyes closed, TouchTest monofilaments of increasing force (set of 20 filaments from 0.0045 to 446.7 g) were applied to the test area with enough force to bend the monofilament. Tactile detection threshold (TDT) was defined as the smallest monofilament size where the patient noticed a sense of touch upon application. Tactile pain threshold (TPT) was defined as the smallest monofilament size where stimulation evoked a sensation of pain.

Pressure pain threshold (PPT) and pressure tolerance threshold (PTT) were determined using a hand-held electronic pressure algometer with a circular probe with a surface area of 1 cm² (Algometer, Somedic). The probe was applied with an ascending force of 30 kPa/s (upper cutoff limit 700 kPa), and patients activated a push-button when the pressure was perceived as painful. PPT was determined as the mean of the 3 measurements. PTT was determined by applying force until the patient perceived the pressure pain as intolerable.

Vibration detection threshold (VDT) was examined with a vibrator (Vibrometer, Somedic) with a circular probe of 1 cm². With a constant force of 650 g and at a frequency of 120 Hz, the vibration amplitude was gradually increased by the examiner until the patient registered the sensation as vibration. The amplitude was then increased slightly and then gradually decreased until the patient no longer felt the vibration. VDT (in μm) was determined as the mean of 3 consecutive measurements. The vibrator’s upper limit was 40 μm.

Thermal Thresholds

Thermal thresholds were measured using a computer-controlled thermode with a surface area of 9 cm² connected to a patient-activated push-button (TSA-II NeuroSensory Analyzer; Medoc, Ramat Yishai, Israel). Baseline was set at 32°C, and the temperature was decreased at a constant rate of 1°C/s until patients perceived the thermode as cold. Three consecutive measurements were performed with the thermode returning to baseline temperature each time. Cold detection threshold (CDT) was determined as the mean of the 3 measurements. Heat detection threshold (HDT), cold pain threshold (CPT), and heat pain threshold (HPT) were determined in a similar manner, and in that order. To avoid
thermal injury, a lower cutoff value of 0°C and an upper cutoff value of 50°C were decided.

**Wind-Up-Like Pain**

A 75.86 g TouchTest monofilament was repeatedly applied to the test area with a frequency of 2 Hz for 30 seconds. Patients were requested to rate their pain on the NRS immediately before and after the procedure. Wind-up pain score was determined as the difference in pain after and before stimulation. If the patient found the procedure intolerable, it was stopped immediately, and the pain score was noted along with the number of pinpricks.

**Pain Intensity and Areas of Painful Symptoms**

Immediately before each QST examination, the patient was requested to rate their present pain (NRS) as well as their average pain in the last 10 hours. They were also asked to state whether they believed their stimulator was turned on or off. The pain scores and the reply to the question about stimulator setting were hidden to the examiner at QST A and B.

Patients were then asked to outline their areas of spontaneous pain. A pain drawing based on the patients’ instructions was created. The areas of hyperalgesia and allodynia were assessed as described previously.21 Pinprick hyperalgesia was assessed by applying a 75.86 g monofilament (TouchTest; North Coast Medical, San Jose, CA) to the skin from outside the affected area along 6 to 8 different lines converging toward the painful area. Brush-evoked allodynia was determined in the same manner using a brush (SENSELab Brush-05; Somedic AB, Hörby, Sweden). For pinprick hyperalgesia, patients were asked if and when the sensation of pinprick became more painful. For brush-evoked pain, patients were asked if and when the sensation of touch changed to a sensation of pain. The areas of hyperalgesia and allodynia were marked on separate sets of drawings.

Relevant body parts were selected and enlarged to size A3 (297 × 420 mm). Upon completion of all 3 QST sessions, drawings were manually digitized using a pen tablet (Intuos2; Wacom, Kazo-shi, Japan) and converted to cm² using image analyzing software (Quantify One; KLONK, Slagelse, Denmark).

**Statistical Analysis**

All data were entered into a database created using Access 2010 (Microsoft Corporation, Redmond, WA), and the output was transformed using Stat/Transfer 10 (Circle Systems, Seattle, WA). All statistical analysis was performed using Stata IC 11.0 (StatCorp LP, TX). Data from the completed SF-36 forms were analyzed using the tool sf36.ado v2.2.2.22

Data are presented as median (IQR). Wilcoxon signed-rank test for paired, nonparametric data was used for comparisons. P-values < 0.05 were considered significant. For all QST data, the absolute differences between the affected area and the control area were calculated, Δ(CA-AA), and the resulting Δ-values were compared. A certain variability in the results of repeated testing can be expected.23 To supplement the assessment of changes between the affected area and the control area, we investigated the unilateral changes between sessions to assess the variability in test outcomes. The changes between the 3 QST sessions (Δ[ON-REF], Δ[OFF-REF], and Δ[ON-OFF], respectively) for the affected area was plotted in a scatter plot as a function of the corresponding Δ-values for the control area (Online supplementary material, QST analysis 1 to 3, Supplemental Digital Content 1, http://links.lww.com/CJP/A125). Each numbered dot represents the patient IDs in Table 1.

**RESULTS**

**QST**

The QST data are shown in Table 3. Reference scores are listed for the control area and the affected area. The differences between sides are listed as Δ(CA-AA). For QST ON and QST OFF, only the Δ-values are listed. Statistical comparisons were performed for Δ-values for each QST. A summary of the results are listed below.

When the replies to the question about stimulator setting at various stage of the examination sequence were compared with the records, it showed that all patients, except 1 (ID 9), were able to identify during the study if their stimulator was turned ON or OFF, indicating that the study de facto was a single-blinded study.

**Mechanical Thresholds**

Generally there was no significant difference seen with changed stimulator status. Tactile pain threshold showed a consistently lower value on the affected side; however, this value tended to diminish at QST A and QST B, independent of stimulator settings.

No significant difference was found between the QSTs for PPT and the PTT. Both thresholds were lower on the affected side compared with the control side for all QSTs. Except for 1 patient (ID 14) with high vibration thresholds on both sides, there was no significant overall change between the sessions, and no major difference between the affected area and the control area at any of the QST sessions.

**Thermal Thresholds**

Differences in detection thresholds between the control area and the affected area showed a very high inter-individual variation. No significant differences were found between the 3 QST sessions for CDT or HDT. No significant differences were found between the 3 QST sessions for CPT. A better tolerance for cold pain was found on the control area for the reference QST; this difference was less clear at the subsequent QSTs. HPT showed a statistically significant, but numerically small difference between sides when the reference QST was compared with SCS OFF and when SCS ON was compared with SCS OFF.

**Wind-Up-Like Pain**

There was no significant difference between QSTs. The increase in pain was generally higher on the affected side than on the control side (expressed by a negative value when the difference in pain increase between the 2 sides was computed). If only the affected side was considered, there was a mean increase in pain score of 2.0 (IQR, 1 to 3), 1.0 (IQR, 1 to 2), and 1.0 (IQR, 0 to 3) for wind-up at reference QST, SCS ON, and SCS OFF, respectively (no significant difference; data not shown). The number of pinpricks the patients could tolerate was on average higher on the control side than on the affected side. No statistical difference was found between the QST sessions.
TABLE 3: Results From Quantitative Sensory Testing

<table>
<thead>
<tr>
<th>Test Modality</th>
<th>Reference (REF)</th>
<th>ON</th>
<th>OFF</th>
<th>P (Comparison of Δ-values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tactile detection threshold</td>
<td>14 0.7 (0.4-1.2)</td>
<td>0.4 (0.4-1.2)</td>
<td>0 (0.1 to 0.3)</td>
<td>0.23 0.64 0.11</td>
</tr>
<tr>
<td>Tactile pain threshold</td>
<td>14 281.8 (125.9-446.7)</td>
<td>5.5 (3.6-75.9)</td>
<td>276.3 (26.8-320.8)</td>
<td>0.04 0.57 0.14</td>
</tr>
<tr>
<td>Pressure pain threshold</td>
<td>14 293.2 (239.2-553.3)</td>
<td>184.0 (99.0-259.3)</td>
<td>116.8 (64.3-192.0)</td>
<td>0.14 0.30 0.73</td>
</tr>
<tr>
<td>Pressure pain tolerance threshold</td>
<td>14 575.0 (286.0-700.0)</td>
<td>277.0 (200.0-623.0)</td>
<td>81.5 (38.0-263.0)</td>
<td>0.80 0.75 0.40</td>
</tr>
<tr>
<td>Vibration detection threshold</td>
<td>10 2.9 (1.1-7.9)</td>
<td>2.3 (1.5-4.5)</td>
<td>-0.3 (-1.2 to 1.1)</td>
<td>0.59 0.48 0.53</td>
</tr>
<tr>
<td>Cold detection threshold</td>
<td>13 28.8 (25.3-29.6)</td>
<td>26.9 (22.9-28.6)</td>
<td>1 (-1.3 to 5.2)</td>
<td>0.53 0.26 0.65</td>
</tr>
<tr>
<td>Heat detection threshold</td>
<td>13 35.8 (34.4-39.9)</td>
<td>38.9 (35.1-42.3)</td>
<td>-0.5 (-5.4 to 2.3)</td>
<td>0.83 0.15 0.12</td>
</tr>
<tr>
<td>Cold pain threshold</td>
<td>13 11.9 (0.0-20.0)</td>
<td>19.3 (15.2-26.5)</td>
<td>-10.4 (-14.0 to 0.0)</td>
<td>0.28 0.35 0.81</td>
</tr>
<tr>
<td>Heat pain threshold</td>
<td>13 44.7 (38.9-47.0)</td>
<td>43.4 (41.5-46.2)</td>
<td>0.2 (-1.0 to 2.4)</td>
<td>0.51 0.01 0.01</td>
</tr>
<tr>
<td>Wind-up-like pain</td>
<td>14 0.0 (0.0-2.0)</td>
<td>2.0 (1.0-3.0)</td>
<td>-1.0 (-3.0 to 0.0)</td>
<td>0.52 0.72 0.68</td>
</tr>
<tr>
<td>Wind-up-like pain, pinpricks</td>
<td>14 60.0 (60.0-60.0)</td>
<td>60.0 (23.0-60.0)</td>
<td>0.0 (0.0-30.0)</td>
<td>0.18 0.43 0.26</td>
</tr>
</tbody>
</table>

Median (interquartile range) is shown for reference data for control area and affected area, and for the difference between them (Δ-value). For SCS ON and SCS OFF, only the Δ-values are shown. For 4 patients, a few sensory modalities could not be determined for technical reasons.

Wilcoxon signed-rank test was used for comparison. Bold values indicate statistical significance.

AA indicates affected area; CA, control area; REF, reference; SCS, spinal cord stimulation.

Analysis of Unilateral Changes

The scatter plots of unilateral changes of thresholds for the control area as function of corresponding changes on the affected area for all QST sessions (Online supplementary material, Supplemental Digital Content 1, http://links.lww.com/CJP/A125) showed a highly variable, non-systematic pattern. This indicates that both variation between QST sessions and interindividual variation seems to be very high on both the control side and the affected side.

Pain Intensity and Areas of Painful Symptoms

The results are presented in Table 4. Median pain scores were similar during SCS activated (4.5 [IQR, 3 to 6]) and SCS deactivated (4.5 [IQR, 3 to 8]) (Table 3 and Fig. 3). A similar pattern emerged for average pain intensity for the last 10 hours before QST.

TABLE 4. Pain Intensity and Areas of Spontaneous Pain, Pinprick Hyperalgesia, and Brush Allodynia

<table>
<thead>
<tr>
<th>SCS Setting</th>
<th>REF</th>
<th>ON</th>
<th>OFF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present pain intensity*</td>
<td>3.8 (3-6)</td>
<td>4.5 (3-6)</td>
<td>4.5 (3-8)</td>
<td>0.461 0.137 0.190</td>
</tr>
<tr>
<td>Pain intensity, last 10 h*</td>
<td>4 (2.5-6)</td>
<td>5 (3-7)</td>
<td>5.5 (4-7)</td>
<td>0.771 0.111 0.539</td>
</tr>
<tr>
<td>Area of spontaneous pain (cm²)†</td>
<td>217 (64-408)</td>
<td>186 (64-388)</td>
<td>209 (35-475)</td>
<td>0.441 0.700 0.484</td>
</tr>
<tr>
<td>Area of pinprick hyperalgesia (cm²)†</td>
<td>278 (101-899)</td>
<td>337 (178-783)</td>
<td>253 (129-1026)</td>
<td>0.051 0.075 0.051</td>
</tr>
<tr>
<td>Area of brush allodynia (cm²)†</td>
<td>329 (161-967)</td>
<td>225 (122-788)</td>
<td>310 (65-1039)</td>
<td>0.023 0.061 0.037</td>
</tr>
</tbody>
</table>

Results are presented as median (interquartile range). Wilcoxon signed-rank test was used for comparison. Bold values indicate statistical significance.

* n = 14.
† n = 11 (area data could not be determined for technical reasons).

DISCUSSION

Effect of SCS on Sensory Thresholds

We hypothesized that SCS would result in return to physiological values of sensory thresholds, expressed as a decreased difference between the affected side and the control side, Δ(CA-AA). This was not the case, apart from the HPT that showed a clearly significant difference for
both SCS ON versus SCS OFF, and for reference QST versus SCS OFF. However, the numerical difference was small, and the clinical implication is unclear.

Other studies examining SCS patients with QST have mainly focused on predictors for SCS treatment success.13-15 Rasche et al16 described examination with QST during the SCS trial phase in 7 patients with radicular pain after spine surgery, and with comparisons with a contralateral control area. QST was performed first with deactivated SCS stimulation and then 30 to 60 minutes later with active stimulation. Statistically significant different but numerically modest differences in CDT, HDT, and TDT were found. Kemler et al.17 performing repeated QSTs in 24 CRPS patients over 12 months of SCS treatment, found only a minimal reduction in mechanical hyperalgesia as examined with application of soft manual pressure or stroke with a brush. Differences in indications and duration of follow-up may play a role for the different results obtained in these 2 studies.

A recent study with SCS treatment in rats after spinal nerve ligation,24 suggested that attenuation of mechanical hypersensitivity is a gradual process and pointed to a possible 2-component mechanism of action: an immediate action and a longer lasting carry-over effect. Such a mechanism may serve to explain why we in our setting did not detect any significant changes in sensory characteristics.

QST Changes on the Control Area

Three full QSTs performed within 26 hours will in many cases cause marked tenderness at the examined area. Participation in repeated QSTs also seems to affect patients’ thresholds. Previous studies have shown a learning effect and a habituation to repetitive stimulation, and we cannot exclude that this may have played a role in the present study.25

A recent study investigating sensory perception on the nonpainful side in 81 patients with unilateral neuropathic pain (mainly after peripheral nerve injury) documented that the patients had sensory abnormalities compared with pain-free control participants,26 underlining the complexity in assessing sensory function in chronic neuropathic pain patients.

In addition, it cannot be excluded that SCS stimulation had an effect on the control side even though the patients claimed to have only unilateral effect. The electrical field around the SCS lead is aimed at the dorsal column. However, due to conductance in the cerebrospinal fluid, the current also affects structures more distant from the zone of contact of the lead, including the dorsal nerve root, notable for its low threshold.27 It cannot be entirely excluded that a nonperceptible (subthreshold) effect on the control side did somehow affect the outcome, an effect also suggested by Rasche et al.16 The variation in the plots in the various QST analyses (online supplementary material, Supplemental Digital Content 1, http://links.lww.com/CJP/A125), however, does not point to a clear effect on the control side either.

These factors combined indicate that not only QST parameters at the pain-affected area change with SCS status, but the control area might also change. This may either be caused by unexpected bilateral stimulation effect, or be caused by variation seen in repeated QSTs.

Effect of SCS on Pain Intensity

This randomized, controlled study of SCS in patients with well-characterized neuropathic pain due to peripheral nerve injury or CRPS did not show any change in perceived pain or in detection of pain thresholds when SCS was activated versus when SCS was deactivated. Although patients generally proved to be aware of the stimulator ON/OFF setting, only half of the patients reported a reduction of pain during stimulation; the remaining patients either had no change or even an increase in their perceived pain during stimulation. This is surprising, considering that the study patients generally reported a significant pain relief from the treatment. The reason for this discrepancy between the reported overall pain relief and changes in pain relief in the present controlled session is not clear.

This study was, however, not powered to determine an effect of SCS on pain and detection thresholds, so we cannot rule out that an effect would have been seen on any of these parameters if a larger patient material had been examined. However, it should be noted that there was no clear indication in the present study that we might have overlooked an effect.

Effect of SCS on Areas of Spontaneous Pain, Hyperalgesia, and Allodynia

We hypothesized that SCS status would alter symptom distributions. Data from an open study performed in our laboratory on the effect of SCS in patients with neuropathic pain have shown that long-lasting SCS seems to reduce areas of spontaneous pain when compared with areas of spontaneous pain before initiation of SCS treatment.28 It is not clear whether the statistically significant smaller area of brush allodynia with SCS ON represent a true value as a similar significant difference was seen between SCS ON and reference value (where SCS was also activated).

Study Design

Three major considerations in the study design merit further discussion.

Reference Setting and Interval Between Examinations

A paradigm of 12-hour SCS activated versus 12-hour SCS deactivated may have been insufficient to alter thresholds to sensory stimulation or pain perception. It is a well-known clinical observation that when activating or

![FIGURE 3. Changes in present pain on a 0 to 10 numerical ranking scale between examination sessions with spinal cord stimulation system (SCS) turned on and off.](image-url)
Effect of SCS on Sensory Characteristics

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REFERENCES


CONCLUSIONS

This study examined patients in permanent SCS treatment using QST with stimulation activated versus deactivated in a randomized, blinded crossover manner. There was no significant change in sensory perception as expressed by sensory detection and pain thresholds. Combined with the existing evidence on QST changes after SCS treatment, data seem to suggest that active SCS treatment does not change sensory perception. In addition, there was no significant change in pain intensity, suggesting a chronic effect of SCS in long-term implanted patients rather than acute changes.


