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Allodynia, Hyperalgesia, (Quantitative) Sensory Testing and Conditioned Pain Modulation in Patients With Complex Regional Pain Syndrome Before and After Spinal Cord Stimulation Therapy

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ABSTRACT

Objectives: Complex regional pain syndrome (CRPS) is a chronic debilitating disease characterized by sensory abnormalities. Spinal cord stimulation (SCS) is an effective therapy for CRPS, but few studies have investigated the effects of SCS therapy on sensory characteristics. Therefore, this study investigated the effect of SCS on allodynia, hyperalgesia, electrical quantitative sensory testing (QST) parameters, and conditioned pain modulation (CPM) effect.

Materials and Methods: This study is part of a multicenter randomized controlled trial (ISRCTN 36655259). Patients with CRPS in one extremity and eligible for SCS were included. The outcome parameters allodynia (symptom and sign), hyperalgesia (symptom), sensory thresholds with QST, CPM effect, and pain scores were tested before and after three months of SCS (40-Hz tonic SCS). Both the CRPS-affected extremity and the contralateral, clinically unaffected extremity were used to test three sensory thresholds with electrical QST: current perception threshold (CPT), pain perception threshold (PPT), and pain tolerance threshold (PTT). The PTT also was used as a test stimulus for the CPM paradigm both before and after the conditioning ice-water test. Nonparametric testing was used for all statistical analyses.

Results: In total, 31 patients were included for analysis. Pain, allodynia (sign and symptom), and hyperalgesia (symptom) were all significantly reduced after SCS therapy. On the unaffected side, none of the QST thresholds (CPT, PPT, and PTT) was significantly altered after SCS therapy. However, the CPT on the CRPS-affected side was significantly increased after SCS therapy. A CPM effect was present both before and after SCS.

Conclusions: Standard 40-Hz tonic SCS significantly reduces pain, hyperalgesia, and allodynia in patients with CRPS. These findings suggest that SCS therapy should not be withheld from patients who suffer from allodynia and hyperalgesia, which contradicts previous findings derived from retrospective analysis and animal research.
ISRCTN Registry: The ISRCTN registration number for the study is ISRCTN 36655259.

Keywords: Complex regional pain syndrome, conditioned pain modulation, neuropathic pain, quantitative sensory testing, spinal cord stimulation

Conflict of Interest: Frank J.P.M. Huygen is on the advisory board of Abbott, Saluda Medical, and Pfizer. The remaining authors reported no conflict of interest.

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INTRODUCTION

Complex regional pain syndrome (CRPS) is a chronic debilitating disease characterized by a collection of locally appearing painful conditions after trauma, which chiefly occurs distally and exceeds the expected clinical course of the original trauma in both intensity and duration. It is often accompanied by several other abnormalities in the sensory, vasomotor, sudomotor, and trophic domains. The pathophysiology of CRPS is multifaceted and still not fully elucidated. An altered immune response based on genetic or immune-derived factors likely plays a role in the initiation of the disease.[1] The pathophysiological mechanisms that lead to the various clinical phenotypes of CRPS are 1) afferent mechanisms such as inflammation; 2) efferent mechanisms such as sensory, motor, and autonomic disturbances; and 3) central mechanisms such as cortical reorganization and psychologic factors.[2–8] Clinical presentations of the sensory disturbances in CRPS are allodynia and hyperalgesia.

CRPS has a favorable natural course in most patients, and it is treated with activation and mobilization, along with conventional medical treatment (antiinflammatory drugs, vasodilators, (co)analgesics, and spasmolytics) and psychologic interventions if indicated. The various clinical phenotypes of CRPS must be considered when tailoring individual treatments. Spinal cord stimulation (SCS) therapy is often considered as a last resort to alleviate chronic intractable nociplastic/neuropathic pain in patients with CRPS and other neuropathic pain conditions, such as diabetic polyneuropathy and persistent spinal pain syndrome type 1 and type 2 (previously called failed back surgery syndrome [FBSS]).[9–15]

The materials and techniques for SCS have greatly improved in the last decade and are now successfully used for patients with CRPS. Until recently, the most widely used and studied paradigm for SCS is with standard frequencies ranging between 40 and 100 Hz, which typically induces paresthesia in the CRPS-affected extremity when the dorsal column is stimulated.[16–18] The classical proposed mechanism of action of standard-frequency SCS is through interfering with the input of the various sensory afferent fibers (Aβ, Aδ, and C fibers) at the dorsal horn of the spinal cord, which alters the gate control input.[14] Recent studies also have identified spinal and supraspinal mechanisms of action in SCS.[19,20]

During the last decade, other stimulation modalities such as high-frequency SCS and burst SCS have become available to further optimize the treatment of patients with nociplastic/neuropathic pain. Although sensory disturbances are often prominent, only a few studies have investigated the effects of SCS on the sensory characteristics of allodynia and hyperalgesia, and on sensory threshold testing.[19,21]

Sensory abnormalities such as allodynia and hyperalgesia constitute one of the hallmark changes in CRPS.[22,23] The International Association for the Study of Pain (IASP) defines allodynia as "pain due to a stimulus that does not normally provoke pain" and hyperalgesia as "increased pain from a stimulus that normally provokes pain."[24] Allodynia is a sensory characteristic of special interest because a retrospective analysis by van Eijs et al[25] found that brush-evoked allodynia may be a negative prognostic factor for the outcome of SCS after one year. Furthermore, animal research suggests an inverse relationship between the severity of allodynia and outcome of SCS.[26–29]

Diagnosing and quantifying the sensory abnormalities of CRPS is a partially subjective process that involves documenting what patients report and what physicians observe during physical examination. Several attempts have been made to incorporate a more quantitative method to diagnose and monitor therapeutic effects.

Quantitative sensory testing (QST) is a collective term that refers to various domains and approaches of sensory threshold testing: mechanical, pressure, vibration, electrical, and thermal. It usually relies on documenting various detection and tolerance thresholds for a specific QST paradigm.[30–32] These thresholds can provide more insight into how pain is processed and which nerve fibers are implicated in the (patho)physiology. Allodynia and hyperalgesia could potentially be quantified with QST and used to monitor therapeutic efficacy over time.[25,33]

Conditioned pain modulation (CPM) is a psychophysical measure used to test the behavioral aspects of endogenous inhibitory pain pathways by applying a painful conditioning stimulus.[34–36] CPM also is referred to as the pain-inhibiting-pain phenomenon. Studies suggest that it is a potential biomarker for predicting the efficacy of a therapeutic intervention and a potential predictor of trial SCS failure and early SCS therapy failure.[34–36]

Aim

This study aims to investigate the effects of SCS on various sensory characteristics such as allodynia and hyperalgesia, QST, and CPM parameters in patients with CRPS. The study attempts to answer the following questions: 1) Are the sensory characteristics of allodynia and hyperalgesia in patients with CRPS altered by standard-frequency (40-Hz) SCS? 2) Can allodynia and hyperalgesia be quantified by QST parameters, and are these parameters altered by SCS? 3) Is CPM altered by SCS?

MATERIALS AND METHODS

Study Design

The results presented in this article are part of a larger, multicenter, randomized, double-blind, placebo-controlled trial (RCT) that investigated the effects of SCS with various frequencies and waveforms in patients with CRPS, along with their preferred stimulation modality.[37] A previously published article provides an overview of the entire study design, all outcome parameters, and the full inclusion and exclusion criteria.[38] Ethical approval was granted by the Erasmus MC Medical Ethics Committee in 2011; the RCT was registered in the Current Controlled Trials register (ISRCTN 36655259), and written informed consent was obtained before trial enrollment.

All patients who enrolled in this study had CRPS in one extremity (upper or lower), disease duration of at least one year, insufficient pain reduction with conventional therapy, and a pain score ≥ 5 on the numerical rating scale (NRS) and were eligible for SCS in accordance with the national guidelines.

Clinical sensory characteristics, electrical QST, and CPM were assessed at baseline pre-SCS assessment (T0) and three months after standard-frequency (40-Hz) SCS (T1). All patients were implanted with a cylindrical percutaneous Octrode™ lead (St Jude Medical, Plano, TX, currently Abbott, Plano, TX) and received a permanent Eon™ rechargeable internal pulse generator if trial stimulation was successful.

Sensory Characteristics, QST, and CPM

The clinical sensory characteristics used in this study were the presence of allodynia and/or hyperalgesia, both symptoms (reported by the patients) and signs (according to the physician

during physical examination with the use of a standard paint brush).

The electrical QST tests and CPM paradigm used in this study are based on the investigative protocol that was used by the pain department at Radboud University in Nijmegen, The Netherlands.[39,40] All QST and CPM tests were performed in a standardized order that depended on which extremity was affected by CRPS, as shown in Supplementary Data File 1. The three electrical sensory thresholds recorded with QST were 1) current perception threshold (CPT), 2) pain perception threshold (PPT), and 3) pain tolerance threshold (PTT). Each threshold was determined three times, and the median value of these three values was used for further analysis. The PPT and PTT values were used to assess allodynia and hyperalgesia, respectively. Furthermore, the pain intensity of the PTT stimulus was rated by the patient on the NRS (ranging from 0 [no pain] to 10 [worst pain imaginable]). All thresholds were first tested on the clinically unaffected side (henceforth designated as the "healthy" side for practical purposes) before testing thresholds on the CRPS-affected side.

Ratios were used to further explore the relationship of the threshold between the CRPS and the healthy control side.[41] The advantage of using a ratio is that it eliminates the intersubject differences in absolute CPT, PPT, and PTT. The ratios of each QST threshold were calculated for all patients using the formula (Electrical QST threshold$_{CRPS}$ side) / (electrical QST threshold$_{healthy}$ side). This yielded the following ratios: CPT ratio, PPT ratio, and PTT ratio.

The amplitude of PTT was selected as the reference test stimulus for the CPM test, whereas an ice-water bucket was used as the conditioning stimulus. The extremity that was submerged depended on the location of CRPS (Supplementary Data File 1). The PTT measurements before and after the ice-water test (PTT_{before} and PTT_{after}) were compared. The appropriate extremity was submerged into the ice water, and patients were instructed to withdraw the extremity if the pain from the ice water became unbearable or when 3 minutes had passed. Three consecutive PTT_{after} measurements were taken immediately after the removal of the extremity from the ice water. Furthermore, the duration for which the extremity was kept submerged in the ice water was recorded, and patients rated the pain owing to the ice water, PTT_{before}, and PTT_{after} on the NRS.

Statistical Analysis

Sample size was calculated on the basis of the primary end point of the main RCT and not on the basis of measurements of sensory characteristics.[38] The sensory data collected in this study were analyzed on all patients who completed the T0 and T1 assessment. All statistical analyses were performed using the SPSS (version 26; IBM, Armonk, NY). Most data were not normally distributed; therefore, nonparametric testing was used to analyze the results. The paired nature of the comparisons (T0 vs T1 and healthy extremity vs CRPS extremity) was accounted for in the analyses. For continuous data, Wilcoxon signed-rank tests were used, and McNemar tests for binary data. In cases where data were used for multiple tests (comparisons between time points and extremities), Bonferroni corrections were applied. Missing data were not extrapolated because the effects of SCS on the electrical thresholds are uncertain, and this study intends to uncover just that. The significance level for all tests was set at an α of 0.05 (unless otherwise stated to account for multiple testing), and all tests were two sided. Post hoc testing was performed on the QST ratios.

RESULTS

Between August 2011 and June 2015, a total of 43 patients were included in the RCT, and the analyses for this study were performed on 31 patients who had completed the T1 assessment. There were no missing data in these 31 patients. Figure 1 details the flowchart of this study, and the baseline characteristics of the included patients are presented in Table 1. As shown in Table 2, the pain intensity that patients reported for their CRPS was significantly reduced after SCS therapy (a median NRS score of 7 [5–8] at T0 and a NRS score of 2 [1–3] at T1, p value < 0.0001).

Allodynia and Hyperalgesia Sign and Symptom

At baseline, the allodynia symptom was present in 74.2% and the allodynia sign in 51.6% of the patients, whereas hyperalgesia was present in all patients. As illustrated in Table 3, allodynia (sign and symptom) and hyperalgesia (symptom) on the CRPS-affected extremity were significantly reduced after three months of SCS ($p = 0.002$, $p = 0.008$, and $p = 0.016$, respectively).

CPT, PPT, and PTT

The electrical QST thresholds were not significantly different between the CRPS-affected side and contralateral healthy side at both T0 and T1, with an adjusted α of 0.025 (Table 4; Fig. 2). On the healthy side, none of the QST thresholds (CPT, PPT, and PTT) was significantly altered after SCS (adjusted α of 0.025). However, on the CRPS-affected side, the CPT was significantly higher after SCS ($p = 0.018$), but there was no change in PPT ($p = 0.489$) and PTT ($p = 0.102$) after SCS (all with an adjusted α of 0.025). The patient-reported pain scores for PTT (Table 2) were significantly higher at both T0 and T1 on the CRPS-affected side than on the healthy side. As shown in Table 5, none of the ratios was significantly altered after SCS.

Conditioned Pain Modulation

The PTT values before and after the ice-water test (PTT_{before} and PTT_{after}) showed that a significant CPM effect could be elicited both before and after SCS, as illustrated in Table 6. The duration of submergence of the extremity in ice water was not significantly different between T0 and T1.

A protocol deviation occurred during the PTT test at T0 in three patients because the maximum allowable current administration of 50 mA had been reached. This was solved by choosing another location, that is, another extremity not affected by CRPS, to determine the PTT_{before} and PTT_{after} values. This location also was used during the T1 assessment to ensure consistency. These protocol deviations did not alter the CPM outcome, and the above-mentioned CPM results are still upheld when these three cases are excluded from the statistical analyses (results not shown). The pain score before and after the ice-water test (NRS PTT_{before} and NRS PTT_{after}) and the pain score of ice water (NRS ice water) did not significantly differ between T0 and T1.

DISCUSSION

Main Outcomes

SCS can reduce CRPS pain, as reported previously.[37] Pain scores improved significantly after three months of SCS, with an overall pain reduction of 71% in the 31 patients included in this study. Moreover, allodynia (sign and symptom) and hyperalgesia were

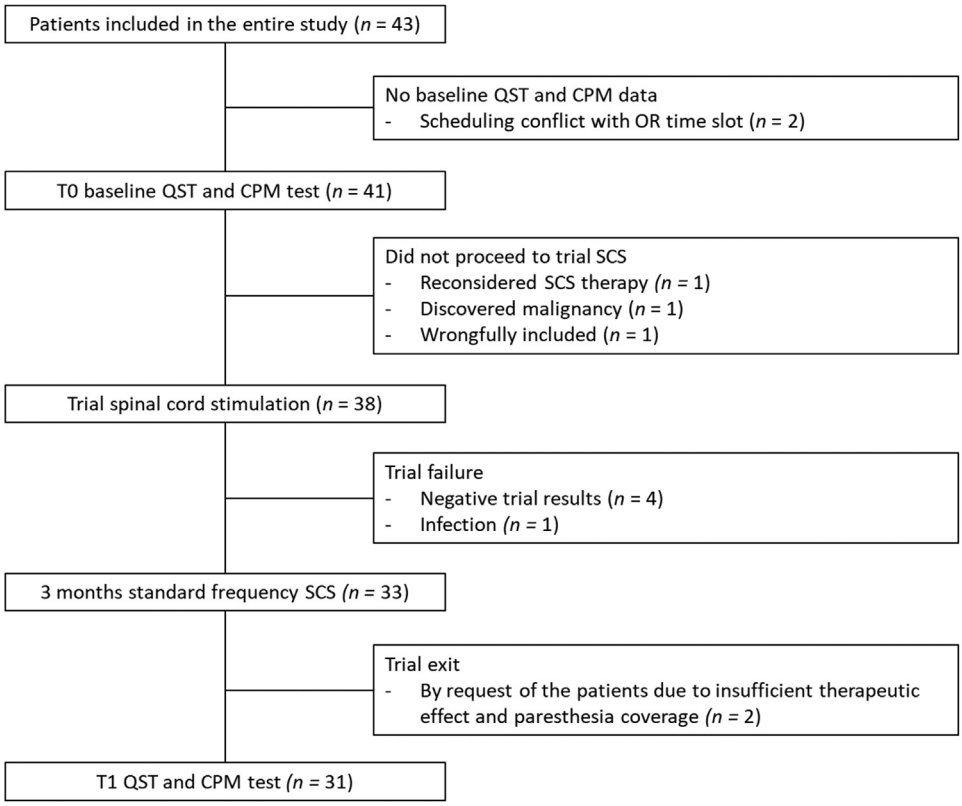

Figure 1. Consolidated Standards of Reporting Trials flowchart.

ameliorated by SCS therapy; the CPT value increased in the CRPS-affected extremity after SCS; and a CPM effect was observed both before and after SCS.

Mechanisms of Action of Standard-Frequency SCS

The current concept of the mechanisms of action of standard-frequency SCS includes activation of segmental and supraspinal mechanisms that (partially) restores the signaling imbalance at the dorsal horn.[19,21] It also activates the descending antinociceptive system (DAS) after orthodromic stimulation caused by the electric field, which activates the supraspinal areas in the brain such as the rostral ventromedial medulla, periaqueductal gray, and locus coeruleus. The DAS in turn modulates the dorsal horn and projection neurons. In addition, antidromic Aβ fiber stimulation can activate the inhibitory interneurons of the dorsal horn and consequently influences the projection neurons. These mechanisms of action of SCS are thought to be involved in the reduction of allodynia and hyperalgesia.[19,21]

Table 1. Baseline Demographic Data.

Demographic and clinical data of the participants (n = 31)		
Sex (n)	Men	27
	Women	4
Age (y)*		43 ± 13
BMI (kg/m^2)*		29 ± 5.8
Ethnicity (n)	Caucasian	30
	Asian	1
CRPS-affected extremity (n)	Upper	12
	Lower	19
CRPS duration (y)†		2 (1–5)

BMI, body mass index.
*Mean and SD.
†Median and interquartile range.

Table 2. Patient-Reported Pain Scores: CRPS Pain, PTT Pain, and CPM Pain.

A)	Pain scores*	
	T0	T1
NRS score of CRPS pain on the day of testing	7 (5–8)	2 (1–3)
NRS PTT healthy	8 (7–9)	8 (6–9)
NRS PTT CRPS	8 (7–9)	8 (7–9)
NRS PTT before CPM test	8 (7–9)	8 (7–9)
NRS PTT after CPM test	8 (7–9)	8 (7–9)
NRS score of the conditioning ice-water test	9 (8–10)	9 (8–10)

B)	Test statistics†	
	Z	p Value
NRS score on the day of testing T0 vs T1	−4.446	0.000
NRS PTT healthy vs CRPS at T0	−2.265	0.024
NRS PTT healthy vs CRPS at T1	−3.441	0.001
NRS PTT before vs after CPM at T0	−1.428	0.153
NRS PTT before vs after CPM at T1	−0.577	0.564
NRS score of the ice-water test at T0 vs T1	−0.073	0.942

*Median and interquartile range.
†Wilcoxon signed-rank test.

Table 3. Signs and Symptoms of Allodynia and Hyperalgesia.

T0 vs T1	No. of patients with symptom/sign present at T0 (%)	No. of patients with symptom/sign present at T1 (%)	*p* Value*
Allodynia symptom	23 (74.2%)	13 (41.9%)	0.002†
Allodynia sign	16 (51.6%)	8 (25.81%)	0.008†
Hyperalgesia symptom	31 (100%)	24 (77.4%)	0.016†

*McNemar test.
†Binomial distribution used.

Allodynia and Hyperalgesia

Both allodynia and hyperalgesia are characteristic findings in patients with CRPS.[2,22] In this study, allodynia, as both symptom and sign, was significantly reduced after SCS (Table 2). The PPT value obtained from the QST tests could theoretically be a surrogate marker for allodynia. One would expect the PPT value of the CRPS-affected extremity to be lower than the contralateral, healthy extremity. At T0, the median PPT value was lower on the CRPS-affected side (6.0 mA) than on the healthy side (6.3 mA), whereas at T1, the median PPT was higher on the CRPS-affected side (7.1 mA) than on the healthy side (6.3 mA); however, these differences at T0 and T1 were not statistically significant (Table 4; Fig. 2).

Table 4. QST Thresholds: CPT, PPT, and PTT.

A)	QST thresholds (mA)*	
	Healthy	CRPS
CPT at T0	3.6 (2.3–5.8)	3.2 (2.2–5.2)
PPT at T0	6.3 (4.5–9.9)	6.0 (3.8–9.0)
PTT at T0	9.4 (7.4–15.1)	8.6 (6.2–14.2)
CPT at T1	3.7 (2.2–5.1)	4.2 (2.4–5.7)
PPT at T1	6.3 (4.8–11.4)	7.1 (4.2–9.8)
PTT at T1	10.1 (7.5–17.8)	11.7 (6.5–17.8)

B)	Test statistics†	
	Z	*p* Value‡
CPT healthy vs CRPS at T0	−0.604	0.546
CPT healthy vs CRPS at T1	−1.039	0.299
PPT healthy vs CRPS at T0	−0.735	0.462
PPT healthy vs CRPS at T1	−0.157	0.875
PTT healthy vs CRPS at T0	−0.504	0.614
PTT healthy vs CRPS at T1	−0.497	0.619

C)	Test statistics†	
	Z	*p* Value‡
CPT healthy T0 vs T1	−0.628	0.530
PPT healthy T0 vs T1	−0.671	0.502
PTT healthy T0 vs T1	−0.292	0.770
CPT CRPS T0 vs T1	−2.358	0.018
PPT CRPS T0 vs T1	−0.692	0.489
PTT CRPS T0 vs T1	−1.635	0.102

*Median and interquartile range.
†Wilcoxon signed-rank test.
‡Adjusted α level of 0.025; Bonferroni correction is applied because every outcome is used in two comparisons.

The PTT parameter of the QST was hypothesized to be a surrogate marker for hyperalgesia. At T0, the median PTT was lower on the CRPS-affected side (8.6 mA) than on the healthy side (9.4 mA), whereas at T1, the median PTT was higher on the CRPS-affected side (11.7 mA) than on the healthy side (10.1 mA); however, these differences at T0 and T1 were not statistically significant (Table 4; Fig. 2).

Thus, this study did not yield significant results to support the hypothesis that PPT and PTT may be used as a surrogate marker for allodynia and hyperalgesia, respectively. This is probably caused by the small number of patients included and a large variance in the results.

Previous research suggests an inverse relationship between allodynia severity and SCS outcomes, and that allodynia may even be an overall negative predictor of the success of SCS in CRPS.[25–29] Although the severity of allodynia was not classified in this study, the results (Table 3) indicate that allodynia and hyperalgesia were

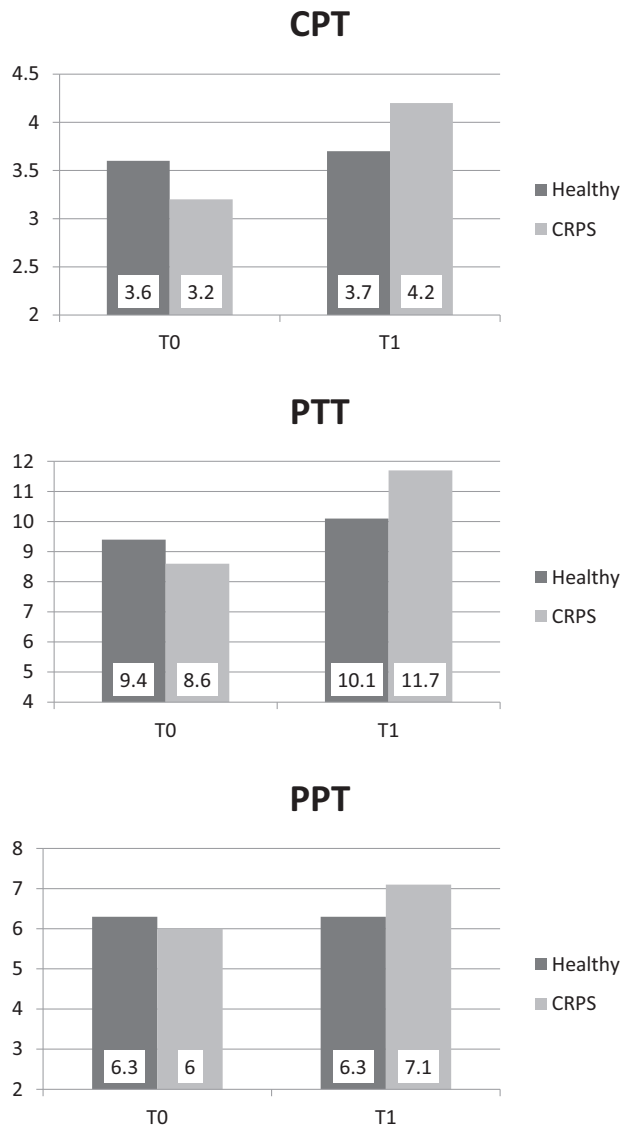

Figure 2. QST thresholds: CPT, PPT, and PTT. Graphical representation of the CPT, PPT and PTT (mA) on the CRPS-affected side and healthy side both at T0 and T1.

Table 5. Ratios of the QST Thresholds CPT, PPT, and PTT.

A)	Ratios of the QST thresholds*	
	T0	T1
CPT ratio	0.96 (0.79–1.19)	1.11 (0.80–1.35)
PPT ratio	0.86 (0.71–1.25)	0.93 (0.75–1.27)
PTT ratio	0.82 (0.67–1.67)	1.00 (0.79–1.41)

B)	Test statistics†	
	Z	*p* Value
CPT ratio T0 vs T1	−1.911	0.056
PPT ratio T0 vs T1	−0.020	0.984
PTT ratio T0 vs T1	−0.715	0.474

Formula for the ratio calculation: (Electrical QST threshold$_{CRPS\ side}$) / (electrical QST threshold$_{healthy\ side}$). This yielded the following ratios: CPT ratio, PPT ratio, and PTT ratio.
*Median and interquartile range.
†Wilcoxon signed-rank test.

significantly reduced after SCS therapy. Therefore, the findings of our prospective study suggest that SCS therapy should not be withheld from patients who suffer from allodynia and hyperalgesia.

Sensitization

The cause of allodynia and hyperalgesia is thought to be associated with alterations in chronic pain signaling, specifically central sensitization and peripheral sensitization. The IASP defines sensitization as "increased responsiveness of nociceptive neurons to their normal input and/or recruitment of a response to normally subthreshold inputs." Sensitization is classified into two types: 1) peripheral sensitization, defined as "increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields," and 2) central sensitization, defined as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input."[24]

Under normal circumstances, afferent Aβ and C fibers relay their input (nonnoxious and noxious, respectively) to the second-order projection neurons in the dorsal horn. Two types of second-order projection neurons are identified: wide-dynamic range neurons and nociceptive-specific neurons. In turn, the pain signals are processed in various regions of the brain, also referred to as the "pain matrix." Nerve injury or repeated peripheral C-fiber stimulation leads to central sensitization by various mechanisms.[19,33,42]

As mentioned before, the mechanisms of action of SCS are thought to be both segmental and supraspinal mechanisms, which lead to (partial) restoration of the signaling imbalance. It remains unclear how SCS influences the neural signaling in our patients with CRPS and how this can be encompassed with QST.

We also need to consider that the electric field generated by SCS at the dorsal column is not strictly confined to the affected side. It also may influence the healthy side, considering the close anatomical relationship of the dorsal column and the electric field generated through the epidural leads. Patients often report paresthesia on the healthy side.

Table 6. CPM Thresholds Before and After the Conditioning Ice-Water Test.

A)	T0	T1
PTT before (mA)*	9.2 (7.2–14.1)	10.1 (7.5–15.8)
PTT after (mA)*	11.7 (9.7–16.1)	12.8 (9.1–16.2)
Duration of submergence in ice water (s)*	31 (20–61)	30 (18–57)

B)	Test statistics†	
	Z	*p* Value
T0 CPM PTT$_{before}$ vs PTT$_{after}$	−4.195	0.000
T1 CPM PTT$_{before}$ vs PTT$_{after}$	−3.871	0.000
Duration of submergence in ice water (s) T0 vs T1	−0.377	0.706

*Median and interquartile range.
†Wilcoxon signed-rank test.

Quantitative Sensory Testing

QST can be used to explore the sensory characteristics of patients with chronic pain. The German Research Network on Neuropathic Pain (DFNS) has postulated a standardized method by using thermal and mechanical stimuli to quantify the sensory characteristics.[31,32,43] However, these tests are time consuming and were not incorporated into this study for practical reasons. Another QST method that is in use is electrical QST, where an electric stimulus is applied to the skin to test various thresholds such as detection threshold (DT), pain DT, and tolerance threshold (TT) in patients with chronic pain, along with the ratios of these thresholds.[41,44] We used the ratios method, provided by Olesen et al[41] and Bouwense et al,[44] as an alternative to standardize the data between the CRPS-affected extremity and the contralateral healthy control side.

In this study, all median electrical QST thresholds (CPT, PPT, and PTT) of the CRPS-affected extremity were lower than those of the healthy extremity at T0. At T1, however, all QST thresholds of the CRPS-affected extremity were higher than those of the healthy extremity. Although these differences were not statistically significant owing to the small sample size, this trend could still suggest that SCS modulates neural signaling, which results in slightly altered QST thresholds.

QST also has been used in several studies to quantify the sensory characteristics before and after SCS in patients with chronic pain, specifically CRPS.[45–53] Some studies concluded that SCS does not alter the sensory characteristics of patients with chronic pain, whereas others reported that SCS does influence the sensory characteristics. Nearly all studies that have investigated the effects of SCS and sensory characteristics by means of QST have the limitations of a small sample size, heterogeneity in the patient population (ie, diverse pain conditions investigated), and variation in the modalities used to investigate the QST thresholds (ie, thermal, electrical, or mechanical).

A systematic review by Bordeleau et al[54] provides a summary of the various QST paradigms used to measure the effects of SCS. The review showed that the DT measured with the Neurometer (which is similar to our CPT) at 5 and 250 Hz was unchanged by SCS in two studies, and DT at 2000 Hz increased in only one of these two studies. TT measured with the Neurometer (which is similar to our PTT) at 5, 250, and 2000 Hz remained unchanged after SCS in one study, increased in another study (at all frequencies), and increased in yet another study at all frequencies except the TT at 2000 Hz. The review concluded that SCS did not have a clinical influence on most QST parameters and that it can be safely used without interference from external stimuli.

Conditioned Pain Modulation

CPM is a measure used to investigate the efficacy of the descending pain pathways and can be used as a marker for activation of the endogenous pain pathways through descending inhibition.[55] Yarnitsky[36] have postulated that CPM becomes less efficient in individuals with a chronic pain condition. Furthermore, in their study, patients with chronic pain were fit into two profiles: 1) "antinociception," where the CPM was efficient, and 2) "pronociception," where the CPM was less efficient. Few studies have investigated the CPM profile in patients receiving SCS.

Ramaswamy et al[56] have studied the role of CPM in patients with FBSS before and after three months of receiving SCS. At baseline, 65% of the patients with FBSS had inefficient CPM; remarkably, after three months of SCS therapy, they turned into responders with efficient CPM.

In this study, we found an overall efficient CPM effect both before and after three months of SCS in patients with CRPS. The median pain scores for the CPM electrical test stimulus and ice-water test (conditioning stimulus) were not significantly different both before and after SCS. This finding indicates that the differences in thresholds are less likely to be influenced by a perceived difference in pain experience or duration of submergence of the extremity in ice water.

Caution must be exercised when drawing conclusions from CPM studies in general and studies that use CPM in combination with SCS because most studies are small, use diverse test or conditioning stimuli, and investigate different chronic pain conditions with various pathophysiological differences. CPM also may be influenced by several other factors such as age, sex, and ethnicity. Nearly all our patients with CRPS were women, which is consistent with other studies on CRPS where more women than men are affected.[55,57]

Limitations

Certain limitations should be considered when interpreting the results of this study. The main RCT was powered for the primary outcome parameter of pain, global perceived effect, and preferred SCS modality, but not for the secondary outcome parameters reported in this study, such as allodynia, hyperalgesia, QST, and CPM presented in this study. Although a trend toward a change in some sensory threshold parameters could be observed after SCS, it remains unclear whether this trend could reach statistical significance if the sample size of this study were larger.

For practical reasons, the comprehensive QST protocol set of the DFNS was not included as a secondary outcome measure in this study because it was extremely time consuming and exhausting for our patients to undergo all QST measurements, along with all other tests and questionnaires they were subjected to during the T0 and T1 assessment. We chose the electrical QST and CPM paradigm because it was at our disposal in our clinic, we had experience with this test, it was easy to use, and it has been used in previous studies.[39–41,44,54] Furthermore, no statements can be made on the effects of SCS on temporal summation because that is part of the German QST protocol set. The generalizability and comparability of our results are possibly affected by these choices. A strength of this study is that we included only patients with CRPS in a single extremity, unlike several other studies that reported findings obtained in considerably heterogeneous groups of patients with various pain conditions.

Another drawback is that this study was designed in 2010 on the basis of the QST and CPM evidence available at the time, and it took several years for the study to be completed. In the meantime, more studies have become available with results and suggestions on how to perform research regarding QST and CPM. New evidence on various SCS paradigms such as high-frequency SCS, burst SCS, high-density SCS, paresthesia-free SCS, and closed-loop SCS has since become available.

The emphasis of this study with QST and CPM was to investigate the pain processing in patients with CRPS before and after SCS therapy and less on diagnosing or identifying CRPS profiles/phenotypes in this study. Therefore, we must be cautious when interpreting the results of this study. Recent literature suggests that CRPS is not just a heterogenous disease and that several CRPS profiles/phenotypes can be distilled from this heterogenous group.[6,58–60] However, diagnosing CRPS and identifying subgroups or phenotypes based on the QST profiling is challenging based on recently published literature, but not impossible.[61,62] Still, it is important to continue to identify these subgroups so that we as clinicians can further identify, improve, and tailor the best treatment for these patients. Therefore, we recommend that future research should incorporate standardized QST to diagnose and profile patients with CRPS and to make the results more comparable with previously published studies.

CONCLUSIONS

This study aimed to investigate the effects of SCS on the sensory characteristics allodynia and hyperalgesia in CRPS and its effect on QST and CPM parameters. On the basis of our results, we conclude that 1) SCS significantly reduces CRPS pain; 2) SCS significantly diminishes the sensory characteristics allodynia (sign and symptom) and hyperalgesia (symptom) and thus should be offered to patients suffering from allodynia and hyperalgesia; 3) it remains unclear whether allodynia and hyperalgesia can be quantified by the QST parameters PPT and PTT, respectively, and whether these parameters can be used to monitor the effect of SCS over time; 4) the CPT of the CRPS-affected extremity increases as a result of SCS; and 5) on average, a CPM effect is observed both before and after SCS. In the future, adequately powered studies may answer the question whether SCS—including standard-frequency SCS, high-frequency SCS, burst SCS, high-density SCS, and closed-loop SCS—affects QST parameters and CPM.

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Authorship Statements

All authors contributed equally to the study design, execution, analyses, and manuscript writing. The final manuscript was read, corrected, and approved by all authors before submission.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2022.06.009.

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COMMENTS

A very well-designed structured and conducted trial. The findings would be of great interest to the general leadership and scholars in the area to probe expectedly sign objective assessment diagnostic tools to the outcome of neuromodulation and CRPS, which would provide a very well-needed piece of information.

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This article presents an interesting hypothesis, and one that bears further investigation.

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A clear, well-explained study looking at the novel question as to the effect of SCS on allodynia and hyperalgesia in patients with CRPS and attempts at quantifying these characteristics with QST. This study confirmed the known fact that SCS reduces pain in CRPS; it also showed that SCS diminishes allodynia and hyperalgesia in these patients, which confirms that SCS should be offered to these patients (which has not been shown in some previous studies). This study showed no changes in conditioned pain modulation before and after SCS.

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The authors are to be thanked for the publication of their older results, because efforts to use QST methods to confirm the diagnosis of CRPS have stagnated in recent years. Subanalysis of data from the larger (older) study can undoubtedly yield interesting results. One problem with the study is that the investigators spared the effort of a standardized QST (Rolke R, Baron R, Maier C, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. *Pain*. 2006;123:231–243) (Baron R, Maier C, Attal N, et al. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158:261–272). However, this disadvantage is compensated by the selected standardization procedure. For further studies, it also is recommended to use standardized QST measurements, for example those of the DFNS network for diagnosis and profiling of patients with CRPS. This would make the results more comparable with those of previous examinations.

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