

Randomized Trial

Analysis of Somatosensory Profiles Using Quantitative Sensory Testing During Tonic and BurstDR Stimulation for the Treatment of Chronic Pain

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Background: In the presence of neuropathic pain, other sensory qualities, such as touch or pressure, which are a sign of nerve damage, are almost always affected. However, it is unclear to which extent spinal cord stimulation (SCS) influences these simultaneously damaged sensory pathways or possibly contributes to their regeneration.

Objectives: The aim of this study was to investigate the effects and possible differences of tonic and BurstDR (Abbott, Austin, TX) SCS on somatosensory profiles of patients with chronic neuropathic pain, using quantitative sensory testing (QST).

Study Design: A randomized, single-blinded, single-center study.

Setting: University medical center.

Methods: After a washout phase of 4 hours and having done the basic QST measurement, either tonic or BurstDR stimulation was performed for 30 minutes in a randomized fashion. Then, the second measurement was taken. The third measurement followed after using the remaining stimulation mode for 30 minutes. Mean values of all QST parameters were calculated and compared. We also computed Z-values using standard data.

Results: We examined 14 patients (9 women, 5 men, mean age 58.4 years) with previously implanted SCS systems for chronic neuropathic pain, using QST (7 tests, 13 parameters). The QST raw data showed a statistically significant improved vibration sensation ($A\beta$) ($P = 0.019$) and lower mechanical pain threshold ($A\delta$) ($P = 0.031$) when testing BurstDR in comparison to tonic SCS. We found a significant improvement in the vibration sensation and also $A\beta$ fiber function during BurstDR when we used the Z-value analysis ($P = 0.023$). With regard to Z-values, BurstDR seemed to be superior regarding the normalization tendency of the $A\delta$ fiber function in the mechanical pain threshold ($P = 0.082$), and tonic SCS seemed superior regarding heat detection threshold (C) and cold pain threshold (C and $A\delta$) ($P = 0.093$).

Limitations: The study is limited by its small number of cases.

Conclusions: In this study, it could be shown that, in some QST parameters and tested fiber functions, normalization tendencies were recognizable by using BurstDR or tonic SCS. However, BurstDR SCS seemed to be superior to tonic stimulation in this regard.

Key words: Quantitative sensory testing, spinal cord stimulation, neuropathic pain, BurstDR stimulation, tonic stimulation, Z-transformation

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In patients with chronic neuropathic pain, other sensory qualities, which are a sign of nerve damage, are almost always affected (1,2). However, up till now it is unclear to which extent spinal cord stimulation (SCS) influences these simultaneously damaged sensory pathways or possibly contributes to their regeneration. So far, SCS has revealed a decrease in pain in other studies (3,4,5), but there are hardly any studies (6,7) that focus on whether SCS also improves other damaged nerve fiber functions. Quantitative sensory testing (QST) shows some differences in comparison to other established examination methods, such as classical electrophysiology, laser-evoked potentials, and the clinical bedside examination. The given possibility of a differential examination of the thick and the thin nerve fibers is a significant advantage of QST. And likewise, is its detection of both the sensory functional losses and the functional gains (8,9,10).

The aim of this study was to collect a complete somatosensory profile by using QST in patients who had implanted SCS probes in situ (9). We wanted to investigate whether SCS may not only relieve pain, but also act on damaged sensory fibers and partially restore their function. It was also interesting to establish whether there is a difference between tonic and BurstDR stimulation in this regard. The case that SCS could additionally also affect impaired sensory fibers positively is of great clinical importance.

We had the following hypotheses:

1. There is a difference in QST between tonic SCS ON and OFF and likewise between BurstDR SCS ON and OFF.
2. There is a difference in QST between tonic SCS ON and OFF and a control group.
3. There is a difference in QST between BurstDR SCS ON and OFF and a control group.

METHODS

Our aim was to examine the change of the sensory qualities in chronic, neuropathic pain patients using QST under 2 different modes of SCS. This is a randomized, single-blinded, single-center study. The study has been approved by the local ethic committee of the University of Tuebingen (Nr.796/2017BO1).

Inclusion Criteria

The inclusion criteria in this study were the following: unilateral, chronic limb pain that has been treated successfully with SCS. The minimum age was of 18 years, the patient had to be able to give con-

sent, and the patient also had to have a capacity to concentrate.

Mode of Stimulation

We used 2 different modes of stimulation: BurstDR stimulation, which does not cause paresthesias and applies trains of 5 stimuli at a frequency of 500 Hz, and tonic stimulation, which is used at a frequency of 50 Hz. As control, sham stimulation (OFF) was used.

QST Examination

Each of the 14 patients was examined individually. The current SCS was switched off for 4 hours before the start of the QST examination. The patient was also advised that if complications, such as unexpected severe pain, should arise, they could take their usual pain medication in order to relieve the pain.

The sequence of the stimulation (BurstDR or tonic) was randomized and the examiner who did the later analysis was blindfolded for this purpose.

The main pain area was marked with a colored skin-compatible pen. This marking ensured that the identical area was examined in all 3 test runs. The patient was asked to position themselves in order that the skin area to be examined was located vertically.

It took on average 4 hours, per patient, in order to complete the 3 QST measurements, to apply the different stimulation methods, and to fit in the breaks required for the adaptation to the next mode of stimulation (Fig. 1).

All of the following 13 tests were performed during the QST measurements: the cold detection threshold (CDT), the warm detection threshold (WDT), the thermal sensory limen, cold pain threshold (CPT), the heat pain threshold (HPT), the mechanical pain threshold (MPT), the mechanical pain sensitivity (MPS), the windup ratio, the mechanical detection threshold (MDT), the vibration detection threshold (VDT), the dynamic mechanical allodynia (DMA), the pressure pain threshold, and the paradoxical heat sensations.

Before each QST examination and after each set of stimulation, the patient was asked additionally about her/his current pain level, which they should indicate using the Numeric Rating Scale (NRS-11).

Statistical Evaluation

Processing / Evaluation of the Data

The results of the individual patients were collected from the obtained raw data as mean values \pm a standard deviation for each test. The statistical analysis of the

data was carried out by using the program SPSS Statistics 25.0.0.1 (IBM Corporation, Armonk, NY). The data were assessed for a normal distribution using the Shapiro-Wilk test. The Wilcoxon test was used to compare BurstDR with tonic stimulation and also for the comparison of the ON and OFF stimulation. *P* values ≤ 0.1 were considered as a trend and values of < 0.05 were regarded as significant.

Z-Transformation and Norm-Data

The study has been carried out according to the QST protocol of Rolke et al (11,12), which has been revised by Magerl et al (13).

Since we had decided upon the examination of only the most severely affected pain area of the patient, we used the data from the standard database for our evaluation,

which is divided according to age, gender, and the test location. The Z-transformation enabled a simple comparison of the somatosensory profile of an individual patient compared to those of healthy patients, which served as the reference values.

Positive Z-values indicated a gain in function (Fig. 2),

Fig. 1. The study protocol is presented. After a washout phase of 4 hours (SCS stimulation OFF), the first QST measurement (duration of 30-45 minutes) was performed with stimulation OFF. Then, the stimulation was started randomly (either BurstDR or tonic stimulation). The duration of the stimulation was 30 minutes. Then, while the stimulation was still ON, the next QST measurement was taken. This was followed by a washout phase of 30 minutes. Then, the second mode of stimulation was started and, after a duration of 30 minutes, the last QST measurement was carried out with the stimulation still switched ON.

SCS, spinal cord stimulation; QST, quantitative sensory testing.

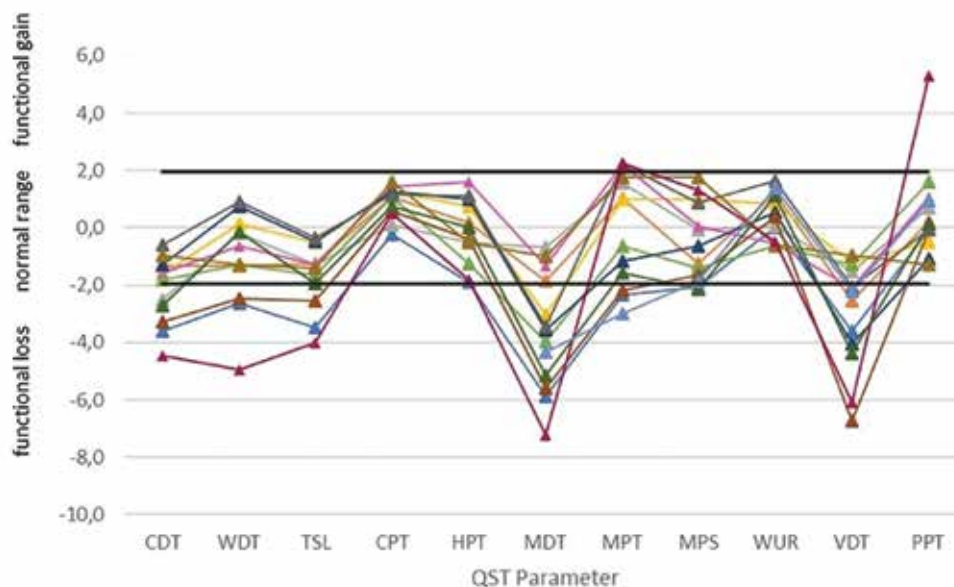
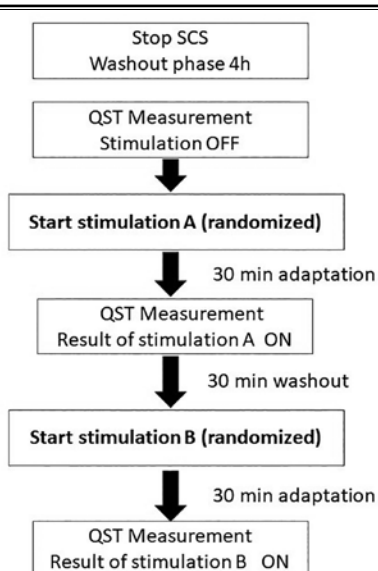


Fig. 2. A line graph shows the results of the Z-transformations with regards to all of the QST tests of all patients when BurstDR stimulation was used. Tests which had negative Z-values could be interpreted as a loss of function (CDT, MDT, VDT), while positive Z-values indicated a functional gain when compared to the norm-collective.

QST, quantitative sensory testing; CDT, cold pain threshold; MDT, mechanical detection threshold; VDT, vibration detection threshold.

which means that a patient is more sensitive to a certain stimulus than a comparable control group, whereas, negative Z-values indicated a loss of function (Fig. 2). Magerl et al (13) explicitly mention that the reference data of 180 healthy patients, divided into age, gender, and location, may be used by other examiners for a comparison with their own recorded values. In an unpublished pilot study that we previously conducted on 5 healthy patients, we found an average of all Z-values at -0.23 and a standard deviation of 0.29. Thus, the average Z-value we collected was within the defined range of Magerl et al (13) and we could use the standard database for our evaluation.

RESULTS

In this study, we examined 14 patients suffering from chronic neuropathic pain in one extremity. A total of 9 women and 5 men took part in the study (mean age 58.4 years). The demographic details of the patients are listed in Table 1.

Failed back surgery syndrome (n = 8) and chronic regional pain syndrome (CRPS) (n = 6) were the main indications for implanting an SCS electrode.

All of the patients underwent their surgeries at the Tuebingen University Hospital between the years 2008 and 2016.

The Wilcoxon test was used for all the following statistical calculations in order to compare BurstDR

with tonic stimulation and for the comparison of the ON and OFF stimulations.

Numeric Rating Scale

The mean value of the pain rating on the NRS-11 after the 4-hour washout phase prior to the first QST measurement was 5.1. The mean value of the NRS-11 after BurstDR stimulation was 5.0 and the mean value of the NRS-11 after tonic SCS was 4.7. There were, however, no statistically significant differences between the 2 modes of stimulation regarding the NRS-11 in all tests.

Comparison of the QST Parameters (Mean Values of the Raw Data) Using BurstDR SCS ON and OFF

When BurstDR was OFF, the patients had a higher tactile detection threshold, i.e., only stronger von Frey filaments were felt. Under BurstDR SCS, the tactile detection threshold reached the values of the healthy norm-collective, i.e., weaker stimuli were perceived ($P = 0.09$). BurstDR SCS thus showed a tendency toward normalization of the A β fiber function.

Comparison of the QST Parameters (Mean Values of the Raw Data) Using Tonic SCS ON and OFF

When tonic SCS was OFF, patients were more sensitive to cold pain, while tonic SCS evoked a lower temperature tolerance before the patient indicated a feeling of cold pain ($P = 0.08$). Tonic SCS tended to

Table 1. Demographic data.

No	Gender	Age (y)	Area of Pain	Duration of SCS Up to the Current Study	Indication for SCS	Type of Stimulation Used So Far	Type of Electrode Implanted
1	Woman	49	Left Leg (S1)	6 years	FBSS	Tonic	Octrode
2	Man	36	Left Arm and Hand	3.5 years	CRPS	BurstDR	Penta
3	Man	57	Left Leg	1.5 years	CRPS	BurstDR	Octrode
4	Woman	60	Left Leg	4 years	FBSS	BurstDR	Octrode
5	Woman	74	Right Thigh	8 years	FBSS	Tonic/BurstDR	Octrode
6	Woman	89	Right Foot	2 years	CRPS	Tonic/BurstDR	Octrode
7	Woman	33	Right Forearm	1.3 years	CRPS	BurstDR	Octrode
8	Woman	67	Left Leg	1 year	CRPS	BurstDR	Octrode
9	Man	64	Left Leg	5 months	FBSS	BurstDR	Octrode
10	Woman	50	Right Leg (L5)	3 years	FBSS	BurstDR/Tonic	Octrode
11	Man	53	Left Leg (L4)	2.5 years	FBSS	BurstDR/Tonic	Octrode
12	Man	68	Right Leg	6 years	FBSS	Tonic	Octrode
13	Woman	53	Right Arm and Hand	3.5 years	CRPS	BurstDR/Tonic	Octrode
14	Woman	65	Right Leg	8 months	FBSS	BurstDR/Tonic	Octrode

Abbreviations: SCS, spinal cord stimulation; FBSS, failed back surgery syndrome; CRPS, chronic regional pain syndrome.

normalize the cold pain values, and thus normalized the C and A δ fiber functions. With tonic SCS OFF, the patient could only feel stronger von Frey filaments. Under tonic SCS, von Frey filaments with lower strength were felt and the patients' tactile detection threshold reached the values of the healthy norm-collective ($P = 0.075$).

Comparison of the QST Parameters (Mean Values of the Raw Data) Using BurstDR SCS ON and Tonic SCS ON

Significant statistical changes were found when the 2 stimulation methods were compared. At the time when the BurstDR SCS was ON, the MPT was significantly lower and closer to the values of the norm-collective than at the time of the tonic SCS ON ($P = 0.019$). With BurstDR SCS ON, the patients were more sensitive to the needle stimuli and the MPT reached the norm-data ($P = 0.002$). The vibration detection threshold was significantly lower during BurstDR SCS ON than during tonic SCS ON ($P = 0.031$), i.e., patients were more sensitive to vibration perception with BurstDR SCS ON.

Comparison of the QST Parameters (Patient Compared to a Standard Group) Using Tonic SCS ON and OFF

The values during tonic stimulation ON and OFF were each compared to the standard values using the Z-transformation.

During tonic SCS ON, the Z-value of WDT reached zero. This indicated a tendency toward normalization of the C-fiber function under tonic SCS when compared to the test without SCS ($P = 0.084$). Tonic SCS ON showed an approximation of the CPT Z-value dropping to zero, and thus a tendency toward the normalization of the C and the A δ fiber functions when compared to the test results without SCS ($P = 0.093$). During tonic SCS, the VDT Z-value deviated further away from zero than at the time of testing without SCS ($P = 0.082$).

Comparison of the QST Parameters (Patient Compared to a Standard Group) Using BurstDR SCS ON and Tonic SCS ON

The values during BurstDR SCS ON and OFF were each compared to the standard values using the Z-transformation.

The tendency toward the normalization of the A δ fiber function was more pronounced using BurstDR SCS ON than with tonic SCS ON ($P = 0.082$). A significant difference in the Z-values could be demonstrated for the

VDT when compared to the measurement of BurstDR and tonic SCS ($P = 0.023$).

Z-Transformed Values

The Z-transformation was carried out using Excel 2016 with the method described above, including the standard database. Because the QST results in the different tests were similar to a large extent despite the different stimulation methods and the informative value of the statistical tests was limited due to the small number of cases, we decided on the adjustments of the Z profiles of the individual patients to an approximation of the Z-value toward zero, in order to examine each test period. All values beyond 2 standard deviations (beyond the 2 horizontal, black lines) were considered pathological because they were beyond the 95% confidence interval of the healthy norm-collective. A normalization of the nerve fiber function could be seen when the Z-value approached zero. On the contrary, moving the Z-value from zero into a more positive range was regarded as an over-function, and moving it into a more negative range, as a further loss of function.

At the time of testing, when using BurstDR SCS, some of the patients we examined showed above all that the CDT, MDT, and VDT had negative Z-values, which could be interpreted as a pathological loss of function when compared to the norm-collective (Fig. 2). At the time of the test under tonic SCS, some of the patients we examined showed above all that the CDT, MDT, and VDT had negative Z-values, which indicated a pathological loss of the A δ and A β fiber functions when compared to the norm-collective (Fig. 3). In a patient, who serves as an example, the parameters HPT, MDT, and VDT showed an approach toward zero, and thus a tendency toward the normalization of the nerve fiber function under active SCS (Fig. 4).

DISCUSSION

The aim of this study was to investigate the effects of different neuromodulation methods on the somatosensory profiles of patients with chronic neuropathic pain.

Under BurstDR SCS, the tactile detection threshold reached the values of the healthy norm-collective (hypothesis 1 confirmed). When tonic SCS was OFF, patients were more sensitive to cold pain, while tonic SCS evoked a lower temperature tolerance before the patient indicated a feeling of cold pain (hypothesis 1 confirmed). At the time the BurstDR SCS was ON, the

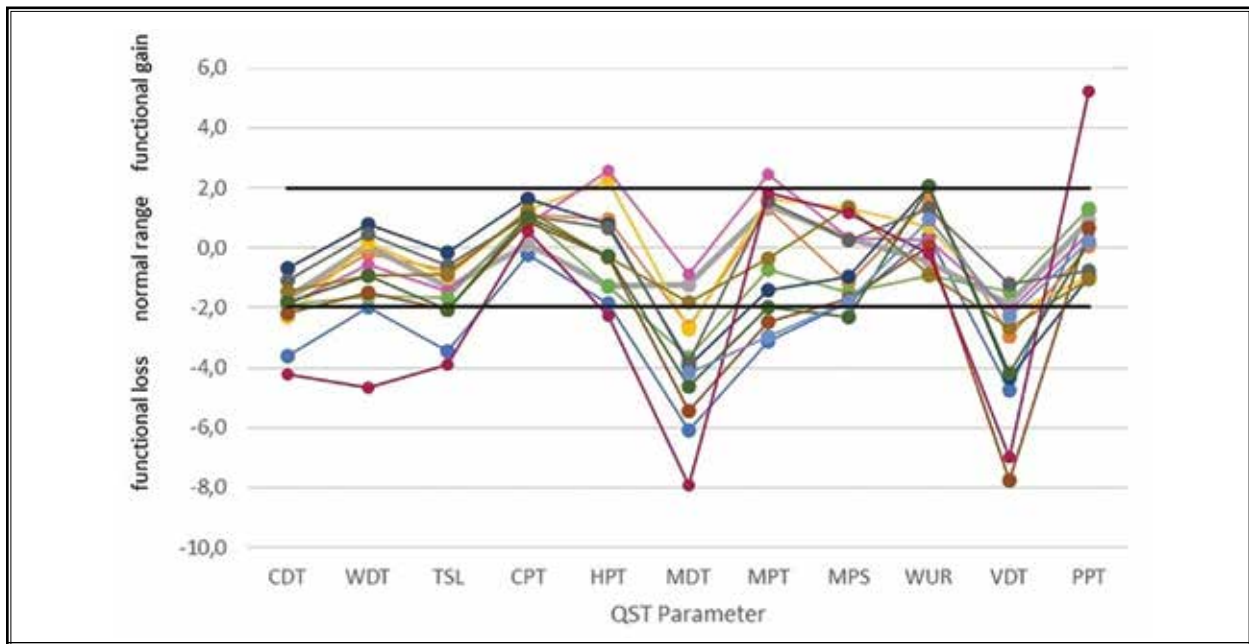


Fig. 3. A line graph represents the results of the Z-transformations with regard to all of the QST patients using tonic stimulation. Some of the patients examined showed negative Z-values (CDT, MDT, and VDT), which indicated a pathological loss of the $A\delta$ and $A\beta$ fiber functions, when compared to the norm-collective.
 QST, quantitative sensory testing; CDT, cold pain threshold; MDT, mechanical detection threshold; VDT, vibration detection threshold.

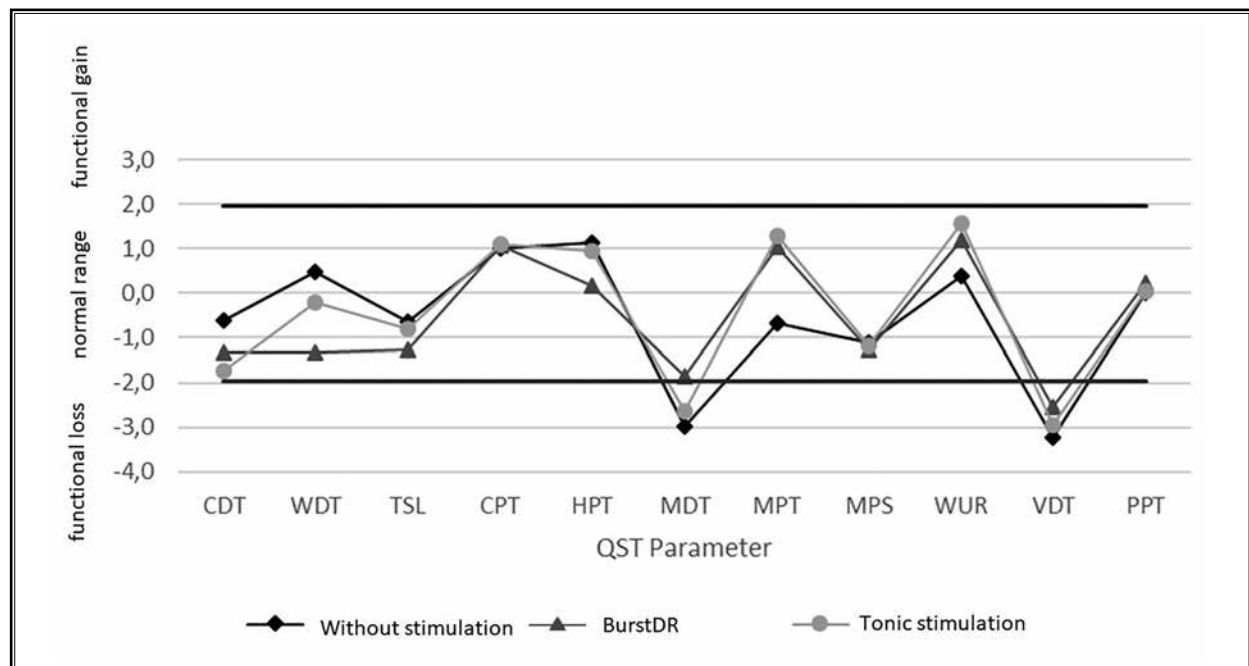


Fig. 4. A line graph presents the results of the Z-transformations of all the QST parameters of a single patient. The parameters HPT, MDT, and VDT showed values approaching zero, thus a tendency toward normalization of the nerve fiber function, under active SCS, in comparison to the test period with stimulation OFF.
 QST, quantitative sensory testing; HPT, heat pain threshold; MDT, mechanical detection threshold; VDT, vibration detection threshold; SCS, spinal cord stimulation.

MPT was significantly lower and closer to the values of the norm-collective than at the time of the tonic SCS ON (hypothesis 2 confirmed). During tonic SCS ON, the Z-value of WDT reached zero. This indicated a tendency toward normalization of the C-fiber function under tonic SCS when compared to the test without SCS (hypothesis 2 confirmed). The tendency toward the normalization of the A δ fiber function was more pronounced using BurstDR SCS ON than with tonic SCS ON (hypothesis 3 confirmed). According to our results, BurstDR appeared to be superior to tonic stimulation in improving impaired sensory fibers. However, a significant difference of statistical value could only be determined for the MPT and the VDT.

Few studies have looked at somatosensory changes while using SCS (6,14,18). The goal of most of these studies was the identification of factors, which predict the long-term therapeutic success of SCS. Some of these studies will be discussed below and then compared to our results.

Kemler et al (6) concluded that the only long-term effect of SCS is a minimal reduction in mechanical-static and dynamic-static hyperalgesia and that no effects on the thermal thresholds could be determined.

Our results showed that the ratings for the MPS and DMA of the patients using SCS were reduced, which agrees with Kemler et al's (6) outcome.

A normalization of the threshold values of CDT, WDT, and MDT on the painful side using SCS has been reported (14). In the studies mentioned above (6,14), it seems to be a prominent feature that all of them noticed an improvement with regards to the vibration sensation during tonic SCS when compared to the test period without SCS. In our study, an improved vibration sensation was noticed under BurstDR SCS, but it was less prominent under tonic SCS. The patients in our study could choose between tonic SCS with the paresthesias or the BurstDR method without paresthesias. It could be that during tonic stimulation the paresthesias distracted the patients from detecting the vibration feeling, and thus there was no reduction in VDT during tonic SCS. Nathan et al (15) showed in their study that a patient's attention or distraction regarding the perception of pain thresholds can have a greater effect than the electrical stimulation alone. This observation could also match with our result, which showed that the MDT and MPT were less under tonic SCS when compared to BurstDR. When tactile detection and pain sensitivity are investigated, it is possible that unusual paraesthesias might lead to a

distraction from the patient's perception of the fine von Frey filaments or pinpricks.

In 2015, Campbell et al (16) examined pain patients using QST at 4 different points in time: before the implantation of a SCS electrode, immediately afterward, after 1 month, and 3 months later. He was able to demonstrate that the allodynia decreased moderately over time. Ahmed et al (17) reported that the increased somatosensory thresholds occurring during BurstDR SCS make the patient less sensitive to the perception of the temperature differences and this lead to a greater decrease in the pain perception. As there is no other study currently available, which has investigated the somatosensory changes under BurstDR SCS, it would be worthwhile to conduct a larger study in order to continue the investigation of the trends we have detected.

From a critical point of view, it can be assumed that a possible impact on the changes that we found could have resulted from the time period in which the SCS was deactivated before the tests, or from the adjustment period to the different stimulation methods between the respective QST measurements.

As far as we know, there are only a few studies available that have examined the effects of the period after tonic SCS (17-19). Wolter et al (18) concluded that a complete SCS effect lasts for an average of approximately 60 minutes after the stimulation has ended and the SCS partial effects last for approximately 90 minutes.

Ahmed et al (17) chose a period of 20 minutes after SCS deactivation and Meier et al (19) a 12-hour intervals.

However, the time intervals, which have been chosen differently in the literature, indicate that there is no consensus about the persistence of the effect after switching off the SCS. Another problem is the so-called carryover effect of BurstDR stimulation, which has as far as we know not been investigated as yet regarding QST measurements.

We chose to use the QST protocol according to Rolke et al (11,12). The QST protocol recommends the comparison of the affected area with an unaffected contralateral area as it is in the case of some of the studies discussed (14,18). Konopka et al (20) was able to show that bilateral sensory dysfunctions are the rule rather than the exception in patients with neuropathic pain. Because this knowledge in the literature questions the validity of such side comparisons, we did not investigate a control area in our study and we decided to rather compare the results obtained to values of a standard database.

CONCLUSIONS

We considered an explorative interpretation of our results due to the few cases in our study. Three QST measurements were taken on the same skin area over a short time period (approximately 4-5 hours on average). This could lead to an increasing sensitivity of the area under investigation, serving as a learning effect,

as well as getting the patient used to the repetitive stimuli. It cannot be ruled out that the close sequence of the 3 QST measurements had a significant impact on our study and that our results were influenced by it. However, the probability of an error could be reduced in the future by randomizing the test sequence.

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