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Research Article

Quantitative Sensory Testing (QST) in Patients with Burst and High Frequency Spinal Cord Stimulation (SCS), Follow-up Study

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Summary

Background: Spinal Cord Stimulation (SCS) and Quantitative Sensory Testing (QST) are important tools for healthcare providers in the treatment of chronic pain. Both SCS and QST play crucial roles in providing quality care for patients with chronic pain. SCS after implantation is rated as "successful" when it achieves ≥50% pain relief. Although in this population, burst or High-Frequency (HF) stimulation was considered "successful", some patients reported a change or a reduction in its effect, especially after switching to nonperceptible (burst, HF) stimulation. Our primary goal was to examine with Quantitative Sensory Testing (QST) the connection between initial SCS outcomes and long-term pain relief. Specifically, we wanted to understand how pausing stimulation affects pain perception. Do patients become accustomed to stimulation, and which neural phases respond quickly to changes in stimulation? **Materials and Methods:** Monocentric, non-randomised, follow-up observation of routine, standardised therapeutic measurements in 32 patients with either low back pain, radiculopathy or pseudo-radiculopathy, who received an SCS unit and who had been treated successfully with HF or burst stimulation for one to three years. QST was first performed with the SCS system switched on, stimulating the painful area. Afterwards, stimulation was paused for 24 h, as, according to the SCS manufacturers, the residual effect should have vanished after this lapse of time. We employed the Visual Analogue Scale (VAS) and the abbreviated version of the PainDetect™ neuropathic pain questionnaire for both assessments – prior to and following the intervention.

Results: All patients, including 20 women (63%) aged between 32 and 83 years, completed the trial. Temperature sensitivity as well as pain perception were not significantly altered after paused stimulation: Cold Detection (CDT; P=0.61), Warm Detection (WDT; P=0.66), Cold Pain Threshold (CPT; P=0.56), Heat Pain Threshold (HPT; P=0.16). SCS stimulates afferent nerve fibres, flooding the Aβ fibres with tactile input, thus activating the GATE neurone and alleviating pain by inhibiting the spinothalamic neuron. Conversely, stopping the stimulation for only 24 hours quickly deactivates the pain inhibitory neurones. This was demonstrated in our study by a significant pain sensitivity to pinprick and pressure and clear signs of allodynia. No significant difference was shown in wind-up and vibration swell. **Conclusions:** Paused SCS implies that different peripheral fibre classes (e.g., alpha-δ and A-β) induce pain sensitisation whose spatial spread and secondary hyperalgesia result in increased sensitivity to pinprick, pressure, vibration, and touch. Nociceptive alpha-δ and A-β afferents, which mediate pain sensitisation, are deactivated by spinal cord stimulation in prolonged chronic pain but are easily and rapidly reactivated when stimulation is turned off. C-fibres' homo- and heterotopic long-term pain potentiation can be assessed by temperature perception during QST. In contrast to the observed quick deactivation of pain inhibitory neurones after paused SCS, C-fibres are not rapidly reactivated. We assume that different mechanisms are involved in this pathway.

Keywords: Paused spinal cord stimulation; Rapid deactivation of pain-inhibitory neurones; Absent reactivation of C-fibres; Chronic pain; Neuropathic pain; Quantitative sensory testing

Introduction

Spinal cord stimulation (SCS) was developed as a treatment modality for medically intractable neuropathic pain. The concept was based on the pain gate mechanism, which postulated that stimulation of large A-b fibres suppresses pain transmission via the small unmyelinated C and small delta fibres.

Quantitative Sensory Testing (QST) is a psychophysical method that assesses the functional status of the somatosensory system. QST evaluates specific somatosensory modalities, including all types of afferent nerve fibres, by applying quantitative and graded stimuli using specific testing algorithms. QST may quantify sensory deficits, loss of nociception (hypoalgesia), and evoked pains such as allodynia, hyperalgesia, or enhanced temporal summation. Patients who received spinal cord stimulation (SCS) in our clinic usually have to undergo QST after implantation, with ≥50% pain relief being rated as "successful". In the selected population with "successful" pain relief, patients nevertheless reported a reduction of the positive effect, especially after switching to no sensory (burst, HF) stimulation.

The primary objective of this study was to examine the associations between early and long-term SCS pain outcomes. We investigated whether the pain gate theory applies here by finding out which nerve phases respond quickly to the cessation of stimulation and subsequent activation.

Methods

In this study, pain and sensation thresholds were determined by QST evaluation of both the stimulated and a non-stimulated control area during routine outpatient controls. Afterwards, the SCS system was paused for 24 hours, and a new QST measurement was performed on both areas again. Subsequently, the measured values were statistically analysed.

This single-centre, non-randomised study was conducted at the outpatient clinic of the Division of Special Anaesthesia and Pain Therapy at the Medical University of Vienna, where patients were recruited. The study protocol was approved by the ethics committee of the Medical University of Vienna (Registration Number: 1069/2019).

All patients gave written informed consent before the start of the trial.

The following inclusion criteria were applied: patients with neuropathic low back pain, radiculopathy, or pseudo radiculopathy are being treated at our division with the help of High Frequency (HF) or burst stimulation via the Spinal Cord Stimulation (SCS) unit for a duration of 1 to 3 years.

Exclusion criteria were pregnant or breastfeeding women, language barriers, patients being simultaneously enrolled in another study with devices or drug administration or patients intending to participate in such a study during follow-up, as well as patients with <30% pain reduction by SCS.

Sensory perception thresholds were determined during and again after SCS. For the patient's subjective pain assessment, we used the Visual Analogue Scale (VAS) and the short version of the PainDetect™ neuropathic pain questionnaire prior to QST.

The QST is a standardised clinical examination of somatosensory nerve pathways. Increased function (e.g., hyperalgesia and allodynia) and loss of function (e.g., hypaesthesia) can be diagnosed and quantified. For this purpose, we use the test battery of the German Network, which has been standardised for years.

The test was performed twice, first with the SCS system on and the painful area being stimulated, and then after 24 hours of paused stimulation, when, according to the technical manuals of the manufacturers, the residual effects should have completely vanished.

QST, as outlined by the German Research Network on Neuropathic Pain (DFNS) protocol, encompasses evaluation across the following 13 parameters: cold and heat detection threshold (CDT, WDT), thermal sensory calcium, paradoxical heat sensations (PHS), cold and heat pain thresholds (CPS, HPS), mechanical pain threshold and mechanical pain sensitivity (MPT, MPS), dynamic mechanical allodynia (DMA), pressure pain threshold (PPT), wind-up ratio, tactile (mechanical) detection threshold, and vibration detection threshold.

The primary outcome parameters aim to highlight a discernible difference between active and after-paused Spinal Cord Stimulation (SCS), where the latter represents the switched-off state. This comparison utilises sensitivity data obtained through Quantitative Sensory Testing (QST) (10).

Statistical analysis

The statistical analysis was performed for the number of 32 patients who had a measured value under active and after paused stimulation. Except for the number of paradoxical heat sensations during the TSL procedure, cold pain thresholds, heat pain thresholds, and vibration detection thresholds, all data were found to be approximately normally distributed in log space. To ensure the suitability for statistical analysis, these variables were logarithmically transformed prior to examination (9). The EQUISTA program was used to analyse the QST values. As a member of the German Research Network, the normal values as considered by DFNS (9) are available to us for research purposes. Using EQUISTA Software, the QST data of the patients were summarised and compared with the mean values of age- and

sex-matched healthy controls. Thereby, all patient data was z-transformed prior to statistical analysis, using the formula Z-score = (patient value - mean of controls) / standard deviation of controls. This normalisation process enables a comparative assessment of individual patient results against the control group. For descriptive purposes, individual patient data under both conditions are displayed graphically. The paired t-test was used for the comparison of values between the two conditions. Statistical analysis was performed using R version 4.0.0. Two-sided significance tests were applied. Due to the exploratory character of the study, no adjustment for multiple testing was applied.

Results

Between 05.2019 and 07.2021, 32 patients were included in the trial (20 females and 12 males) who were 32-83 years of age. Sixteen patients had SCS system implants from Nevro Corp. that employs high-frequency stimulation, while eight patients previously received an SCS system from Abbott Laboratories and another eight from Boston Scientific, both using burst stimulation.

90% of the study population with SCS therapy for pain in the area of the spine, with stimulation switched off, showed, according to results, an increase for neuropathic pain components or central sensitisation, especially allodynia. In 96% of patients, an increase in the total score of Paindetect Tests of 10 to 30% was observed. The mean pain intensity increase was VAS 4.5 (range 0-10). 33% showed one severe pain-related functional restriction during the stimulation pause, and 67% had clinically relevant sleep disturbance overnight when stimulation was paused. Burst stimulation offers promise for nonresponders, with 62.5% showing positive results. Initial responders also benefited from burst stimulation.

In the QST-assessed study metrics, temperature sensitivity and pain perception were not significantly altered with paused stimulation CDT (P=0.61), WDT (P=0.66), CPT (P=0.56), or HPT (P=0.16) (Figures 1-4).

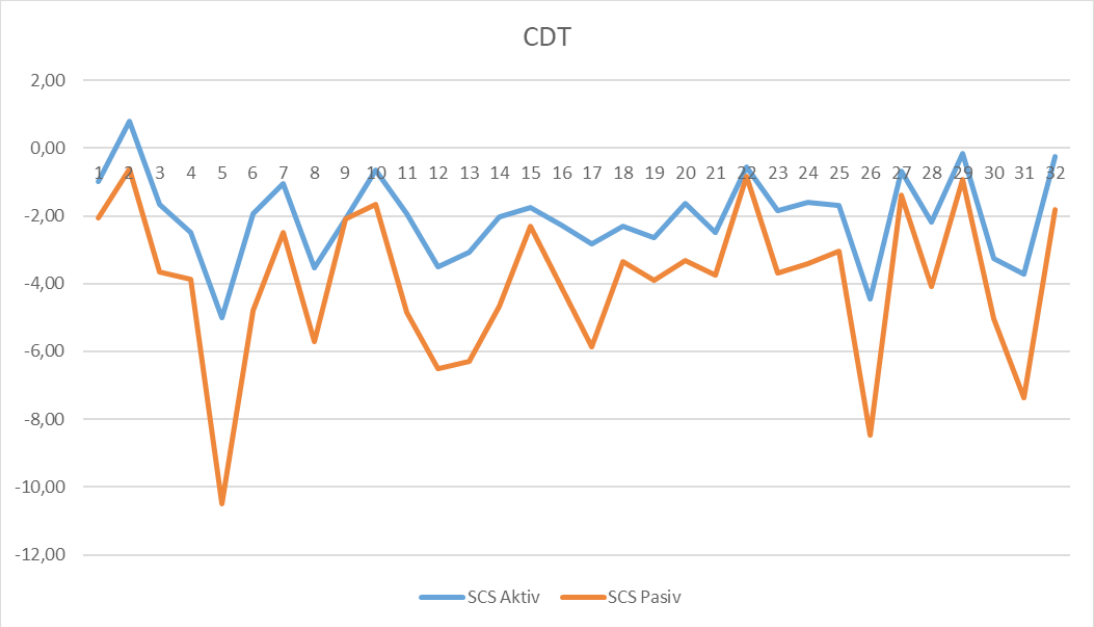

Figure 1: CDT (P=0, 61) QST Cold detection threshold: Graphical representation of the CDT on the affected side with active (blue) and after paused (orange) SC Stimulation.

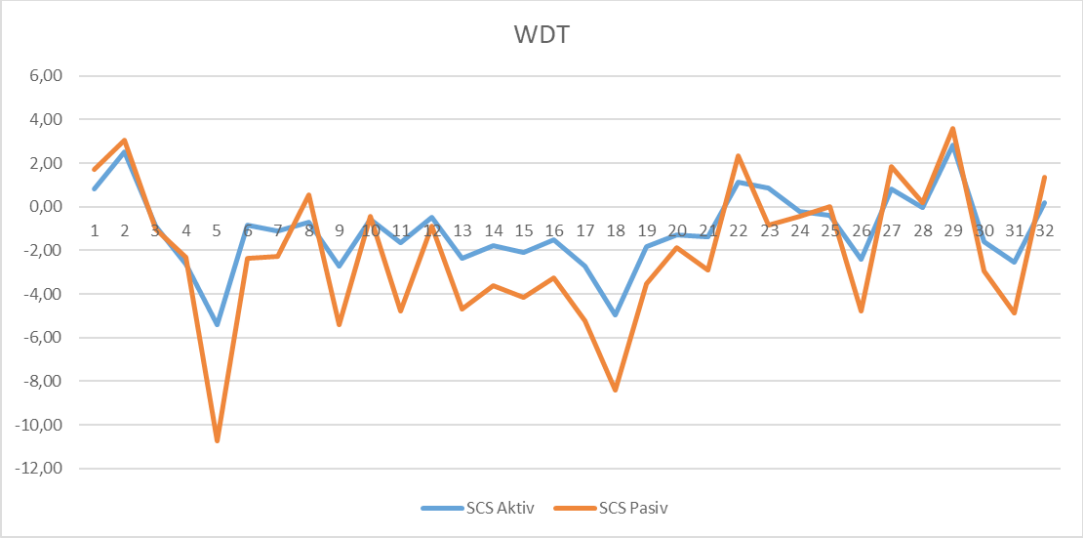

Figure 2: WDT (P=0, 66) QST warm detection threshold: Graphical representation of the WDT on the affected side with active (blue) and after paused (orange) SCS.

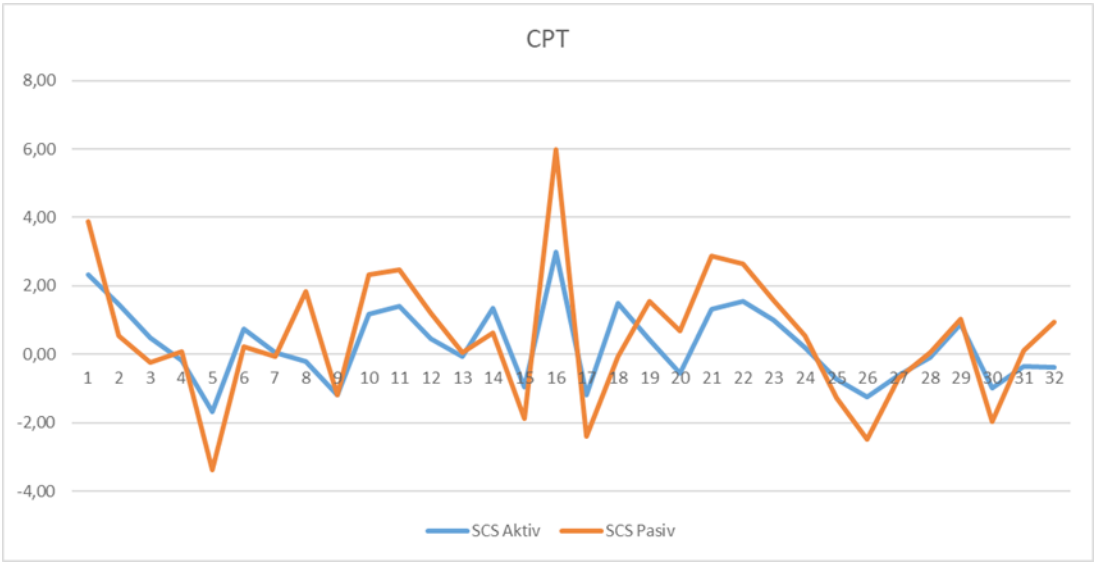

Figure 3: CPT (P=NS) QST cold pain threshold: Graphical representation of the CPT on the affected side with active (blue) and after paused (orange) SCS.

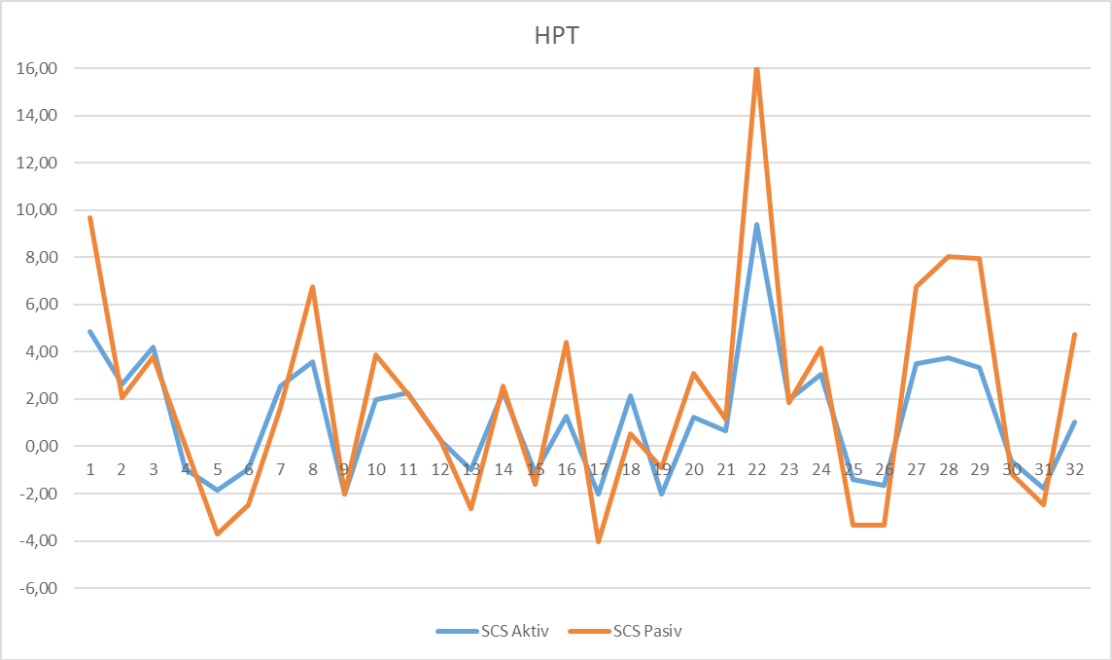

Figure 4: HPT (P=NS) QST heat pain threshold: Graphical representation of the HPT on the affected side with active (blue) and after paused (orange) SCS.

When stimulation was paused, deactivation of the pain inhibitory neurones occurred quickly. We observed a significant pain sensitivity on pinprick, pressure algometer and clear allodynia signs. In comparing QST during and after SCS, significant differences were found for MDT (mechanical detection threshold) (p=0.0129), MPT (mechanical pain threshold) (p=0.0002), MPS (mechanical pain sensitivity) (p=0.0048), and PPT (pressure pain threshold) (p=0.0447) (Figures 5-8) No significant differences were shown by C and A δ fibres controlled wind-up WUR (wind-up ratio) (p=0.5515) and vibration swell VDT (vibration detection threshold) (p=0.857) (Figures 9,10).

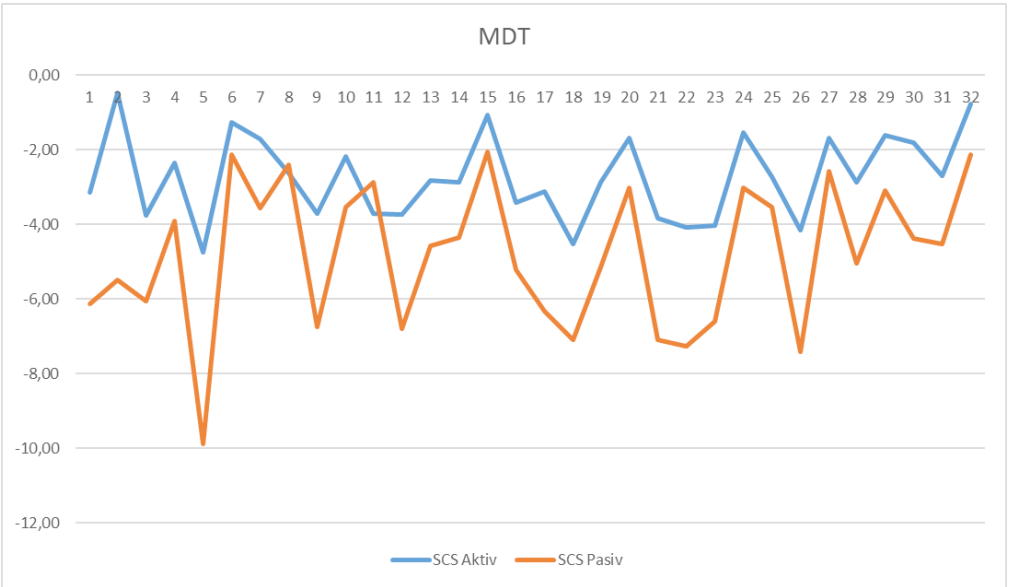

Figure 5: MDT (p=0.0129) QST Mechanical detection threshold: Graphical representation of the MDT on the affected side with active (blue) and after paused (orange) SCS.

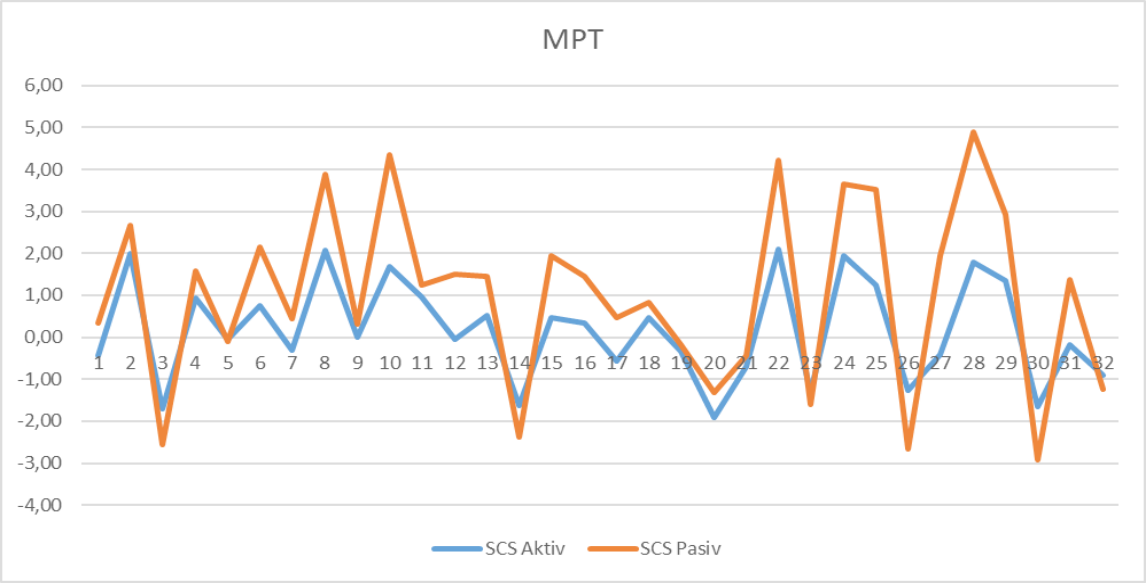

Figure 6: MPT (p=0, 0002) QST Mechanical pain threshold: Graphical representation of the MPT on the affected side with active (blue) and after paused (orange) SC Stimulation.

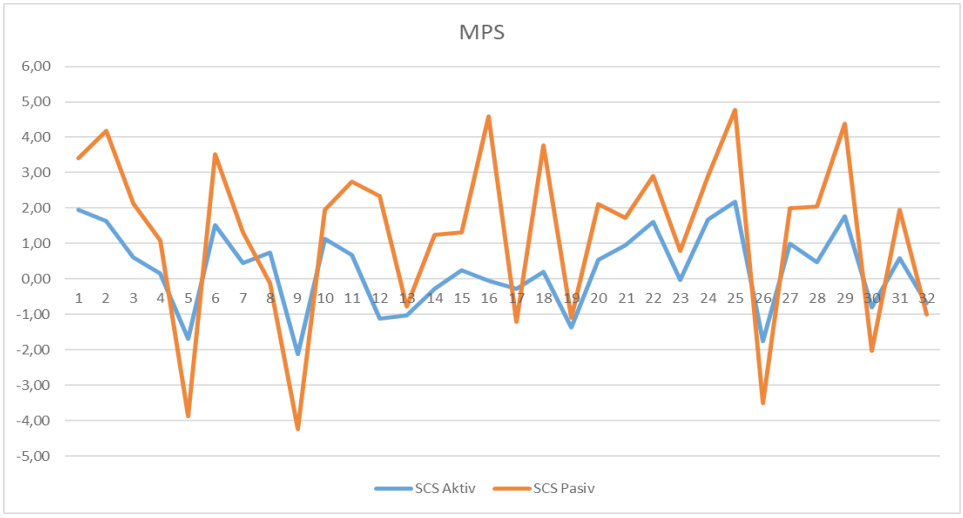

Figure 7: MPS (p=0, 0048) QST Mechanical pain sensitivity: Graphical representation of the MPS on the affected side with active (blue) and after paused (orange) SC Stimulation.

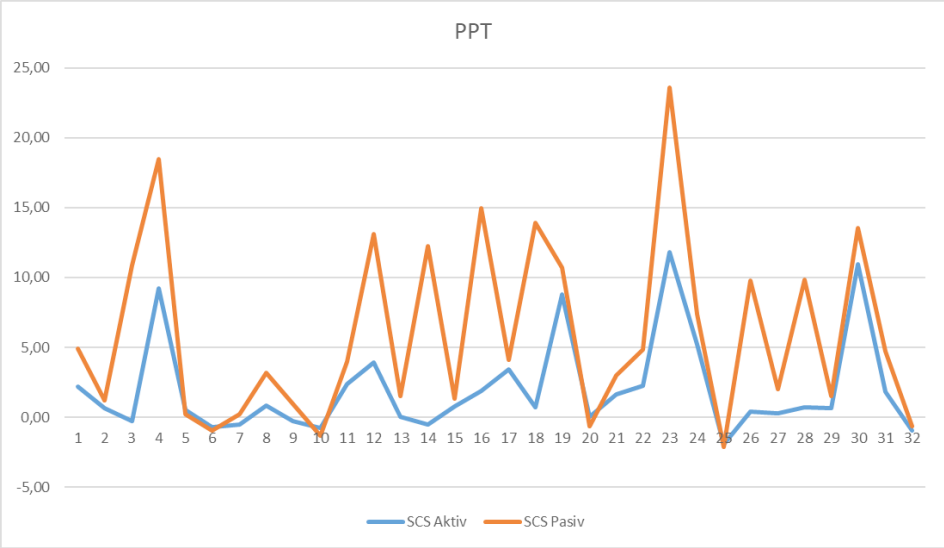

Figure 8: PPT (p=0, 06) QST Pressure pain threshold: Graphical representation of the PPT on the affected side with active (blue) and after paused (orange) SC Stimulation.

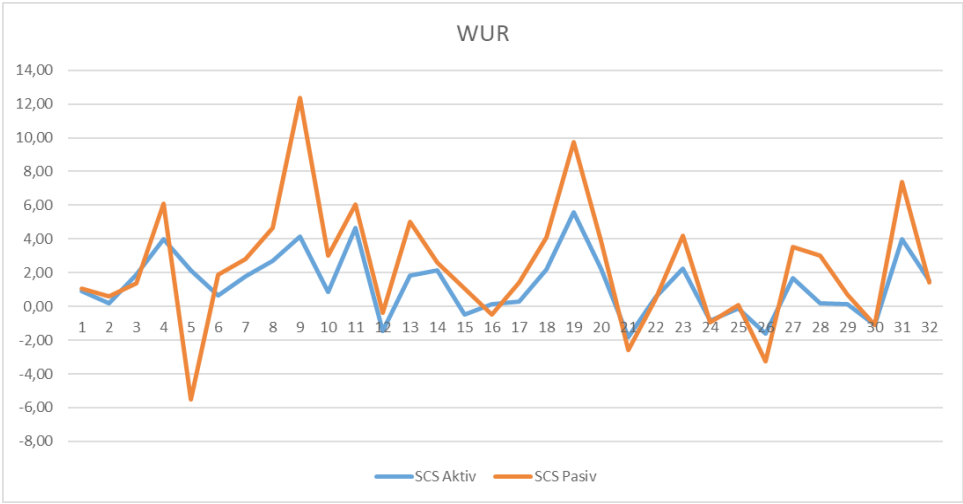

Figure 9: WUR (p=0, 5515) QST Wind-up ratio: Graphical representation of the WUR on the affected side with active (blue) and after paused (orange) SC Stimulation.

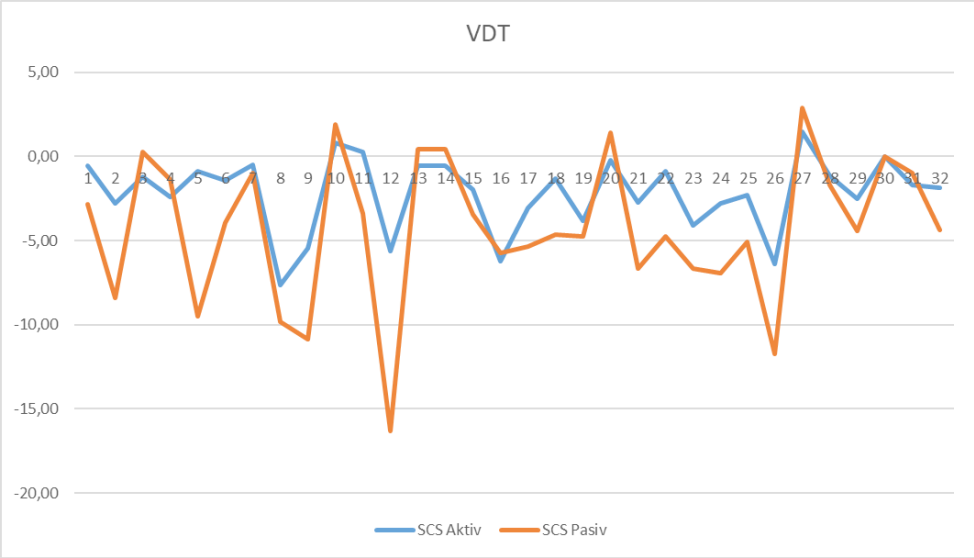

Figure 10: VDT (p=0,857) QST Vibration detection threshold: Graphical representation of the VDT on the affected side with active (blue) and after paused (orange) SC Stimulation.

Discussion

Our study, focusing on high-frequency and burst Spinal Cord Stimulation (SCS) effects, provides valuable insights into the management of neuropathic pain. The study primarily investigates the effects of high-frequency and burst SCS on pain thresholds, sensory perception, and nerve pathway activation during routine outpatient controls.

Our study reveals that high-frequency and burst SCS result in increased pain sensitivity after the 24-hour pause in stimulation. This phenomenon suggests that SCS stimulates afferent nerve fibres, particularly Aβ-fibres, flooding them with tactile input. This activation of the GATE (Gate Control Theory proposed by Ronald Melzack and Patrick Wall in 1965) neurone is thought to relieve pain by inhibiting spinothalamic neurones. In summary, spinal cord stimulation rapidly stimulates all afferent neurones, with A fibres playing a significant role in the induction of heterotopic pain potentiation.

However, our findings also indicate that temperature sensitivity and temperature-dependent pain perception remain largely unaffected during the paused stimulation. Sensory fibres exhibit varied responses to thermal stimuli, classified based on their temperature thresholds. C and Aδ1 fibres respond at temperatures >43°C, while the rarer Aβ fibres respond only at temperatures >52°C (Adriaensen et al., 1983). The lack of significant changes in temperature perception when SCS is turned off suggests that C and Aδ fibres, as the main inducers involving the TRPV1 receptor, affect homotopic and heterotopic long-term potentiation. Other mechanisms may also contribute to the assessment of temperature perception during QST examinations, indicating that these fibres are not rapidly reactivated when stimulation is turned off.

In contrast, A-fibres, responsible for pinprick pain and hyperalgesia, appear to be rapidly reactivated when stimulation is paused. Our results demonstrate that different peripheral fibre classes, including alpha-δ and A-ß fibres, induce pain sensitisation, resulting in increased sensitivity to pinprick, pressure, vibration, and touch (Rasche et al., 2005; Schlaier et al., 2007). Nociceptive alpha-δ and A-ß afferents, which induce pain sensitisation, are deactivated by spinal cord stimulation in prolonged chronic pain but easily and quickly reactivate and mediate pain after terminated stimulation.

These findings suggest the involvement of specific nerve fibre classes, such as Aδ and A-ß fibres, in pain sensitisation and hyperalgesia. The use of quantitative sensory testing in our study provides valuable information on the effects of SCS on different sensory pathways and pain perception. On the other hand, (1) conducted a comparative study to investigate the effects of two SCS paradigms, tonic and burst, in patients with neuropathic pain and failed back surgery syndrome. Their study revealed that burst stimulation is significantly more effective in pain suppression than tonic stimulation. Burst stimulation shows promise in rescuing nonresponders to tonic stimulation, with 62.5% of these patients responding positively to burst stimulation. Moreover, patients who initially responded to tonic stimulation experienced further improvement with burst stimulation. These findings suggest that burst stimulation can offer additional pain relief and represents a promising alternative for patients who do not achieve satisfactory

outcomes with conventional tonic stimulation.

Together, our study and the work by Kinfe et al. (2016) shed light on the potential benefits and mechanisms of different SCS approaches for managing neuropathic pain. High-frequency SCS, as studied in our investigation, provides a detailed understanding of its effects on nerve pathways and sensory perception, supporting the notion that SCS can modulate pain by targeting specific nerve fibres. Research by Dirk De Ridder. ("Burst spinal stimulation for limb and back pain." World Neurosurgery doi:10.1016/j.wneu.2013.01.040.) Comparing 500 Hz tonic mode to 500 Hz burst mode, without QST examination, shows that 500 Hz burst mode is superior to tonic mode. It is also possible that 500 Hz has a selective effect on A-b fibres, similarly to what has been described for 2000 Hz, and thereby has a maximum effect on the pain gate mechanism. Our study, with QST examination data, shows the same results.

The findings from both our study and the work by Kinfe et al. (2016) have significant clinical implications. They suggest that the choice of SCS paradigm, whether high-frequency or burst stimulation, can have a profound impact on pain relief and treatment success. For patients who have undergone conventional tonic stimulation and experience limited pain relief, switching to burst stimulation may offer new hope for improved outcomes. Additionally, the insights gained from our study on the mechanisms of SCS on nerve pathways can inform personalised treatment approaches and optimise stimulation settings based on individual pain profiles.

Despite the valuable insights from both studies, some limitations need to be acknowledged. Our study and the study by Kinfe et al. (2016) are retrospective and lack placebo-controlled designs, which may influence the interpretation of the results. Future studies with larger patient cohorts, randomised designs, and longer follow-up periods would strengthen the evidence and provide more robust conclusions. Moreover, the mechanisms underlying the pain relief effects of burst stimulation warrant further investigation to better understand its potential benefits in various pain conditions.

Limitation

The study was planned with randomisation, but during preparation of the protocol and recruitment, it was clear that the patients, who have been successfully treated with spinal cord stimulation for 1-3 years, know the stimulation system and all the conditions very well and have the ability to adjust the strength of the programmes themselves. Accordingly, they can also check whether the stimulation is active or the system is paused. Removing the stimulation during follow-up was also ethically incorrect, so patients knew about pausing the stimulation. We felt that this could also cause a subjective overestimation in the secondary outcome measures (e.g., VAS and PainDetect™).

Conducting our research during the challenging circumstances of the COVID-19 pandemic, we operated with heightened responsibility. Testing patients required additional precautions, and in the event of COVID-19 infections, we prioritised their recovery. To ensure a comprehensive study, the research period was extended by one year, allowing sufficient time to study all recruited patients amidst the challenges posed by the pandemic.

To assess a measurable difference in QST data between ongoing SCS therapy and after a 24hour break in SCS, which is reflected in a change in the sensation and pain threshold for heat, cold and/or mechanical stimuli (primary hypothesis), a comprehensive QST protocol set of the DFNS was included in this study. 60-minute examinations practically twice in 24 hours were extremely time-consuming and strenuous for us and for patients.

From our perspective, despite the subjectivising nature of the data, it is important to continue testing patients so that we as clinicians can further identify, improve, and adapt the best treatment for these patients. Therefore, we recommend that future research should include standardised QST for diagnosis and use QST testing for follow-up, for adaptation of medication and especially for neuromodulation to improve outcomes and treatment planning.

Conclusion

Comparative analysis of thresholds when SCS is turned on or turned off revealed that SCS generally leads to increased pain tolerance and improved pain management compared to absent SCS. Considering the advantages associated with SCS, including increased pain tolerance and reduced sensitivity to mechanical and pressure-induced pain, active SCS stands as a more beneficial option for patients seeking effective chronic pain management.

Our study's analysis of the effects of high-frequency and burst SCS on sensory pathways, combined with similar work by colleagues on the comparative evaluation of burst and tonic stimulation, supports the neurophysiological theory of neuromodulation:

SCS works by stimulating afferent nerve fibres, particularly Aβ fibres. This creates a tactile input flood, which inhibits spinothalamic neurones and reduces pain.

When stimulation is paused for just 24 hours, pain-inhibiting neurones deactivate quickly, and this leads to:

- Increased pain sensitivity to pinprick and pressure.
- Clear signs of allodynia.
- No major changes in wind-up pain or vibration perception.

Pausing SCS reactivates peripheral fibres with the following sensitisation mechanisms: Aδ- and Aβ-fibres are responsible for secondary hyperalgesia, increasing sensitivity to pinprick, pressure, vibration, and touch.

C-fibres associated with TRPV1 receptors contribute to long-term pain modulation and appear not to respond as quickly to changes in stimulation, even when patients change the stimulation intensity, and also do not reactivate as quickly as the other fibres.

To determine how long the deactivation and reactivation of the C-fibres lasts and how their stimulation can be adjusted, a further study with longer stimulation deactivation is needed, although it is difficult to obtain patient consent to a longer period of stimulation deactivation, because active SCS stands as a more beneficial option for patients seeking effective chronic pain management.

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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.

Conflict of Interest: All authors declare no conflicts of interest.

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