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The link between Spinal Cord Stimulation and the parasympathetic nervous system in patients with Failed Back Surgery Syndrome

Running title: SCS and autonomic parameters

Lisa Goudman¹⁻⁴ MSc. PhD, Ann De Smedt^{2,4-5} MD. PhD, Frédéric Louis⁶ MD., Virginie Stalmans⁶, Bengt Linderöth⁷ MD. PhD, Philippe Rigoard⁸⁻¹⁰ MD. PhD, Maarten Moens^{1-2,4,11} MD. PhD

1. Department of neurosurgery, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Jette, Belgium.
2. Center for Neurosciences (C4N), Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Jette, Belgium.
3. Pain in Motion International Research Group, Laarbeeklaan 103, 1090 Jette, Belgium.
4. STIMULUS consortium (reSearch and Teaching neuroModULation Uz bruSsel), Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
5. Department of Physical Medicine and Rehabilitation, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
6. Clinique de la douleur, Clinique Sainte-Elisabeth-CHC, Rue du Naimeux 17, 4802 Verviers, Belgium.
7. Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.
8. Spine & Neuromodulation Functional Unit, Poitiers University Hospital, Poitiers, France.
9. Institut Pprime UPR 3346, CNRS, ISAE-ENSMA, University of Poitiers, Poitiers, France.
10. PRISMATICS Lab (Predictive Research in Spine/Neuromodulation Management and Thoracic Innovation/Cardiac Surgery), Poitiers University Hospital, Poitiers, France.
11. Department of Radiology, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Jette, Belgium.

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Conceptualization: LG,ADS,MM

Data collection: LG,FL,VS,MM

Formal analysis: LG,ADS,MM

Investigation: LG,ADS,MM

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Address of correspondence: Maarten Moens, Department of Neurosurgery, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Jette, Belgium. Tel: 003224775514; Fax: 003224775570; Email: maarten.moens@uzbrussel.be

Abstract

Objectives

In patients with chronic pain, a relative lower parasympathetic activity is suggested based on heart rate variability measurements. It is hypothesised that Spinal Cord Stimulation (SCS) is able to influence the autonomic nervous system. The aim of this study is to further explore the influence of SCS on the autonomic nervous system by evaluating whether SCS is able to influence skin conductance, blood volume pulse, heart rate and respiration rate.

Materials and Methods

Twenty-eight patients with Failed Back Surgery Syndrome (FBSS), who are treated with SCS, took part in this multicenter study. Skin conductance and cardiorespiratory parameters (blood volume pulse, heart rate and respiration rate) were measured during on and off states of SCS. Paired statistics were performed on a 5-minute recording segment for all parameters.

Results

SCS significantly decreased back and leg pain intensity scores in patients with FBSS. Skin conductance level and blood volume pulse were not altered between on and off states of SCS. Heart rate and respiration rate significantly decreased when SCS was activated.

Conclusions

Parameters that are regulated by the sympathetic nervous system were not significantly different between SCS on and off states, leading to the hypothesis that SCS is capable of restoring the dysregulation of the autonomic nervous system by primarily increasing the activity of the parasympathetic system, in patients with FBSS.

Key words: Chronic pain; Autonomic Nervous System; neuromodulation; skin conductance; respiration; heart rate

Introduction

Spinal Cord Stimulation (SCS) is a minimal invasive treatment for patients with therapy-refractory Failed Back Surgery Syndrome (FBSS) that is partly relying on the Gate Control Theory of Melzack and Wall^{1,2}. It involves the implantation of an epidural electrode, which is connected with a subcutaneous implanted pulse generator³. Electrical pulses at different frequencies can be generated and are delivered to the spinal cord to elicit paresthesia in the painful area⁴. The goal of this therapy is to make chronic pain tolerable, with proven benefits on functionality and health related quality of life among other effects^{5,6}.

Failed Back Surgery Syndrome (FBSS) is characterized by persisting back and/or leg pain of unknown origin either persisting despite surgical intervention or appearing after surgical intervention for spinal pain originally in the same topographical location⁷. Due to the presence of prolonged pain (i.e. chronic pain), changes in the balance of the autonomic nervous system can be observed in patients with chronic pain^{8,9}. The imbalance results in a reduction in the activity of the inhibitory parasympathetic system, investigated by indirect heart rate variability (HRV) measurements⁸. In a chronic low back pain population, reduced heart rate variability and increased heart rate were previously described¹⁰. It is also known that heart rate variability can evaluate the role of the autonomic nervous system in chronic diseases and can furthermore also serve as outcome parameter to evaluate therapeutic effects in chronic pain states¹¹⁻¹³.

Besides heart rate and heart rate variability, skin conductance and respiration rate are also influenced by the autonomic nervous system. The first parameter, skin conductance level (SCL), is thought to reflect general changes in autonomic arousal¹⁴ but previous research demonstrated inconsistent results concerning skin conductance in chronic pain patients^{15,16}. For the second parameter, i.e. respiration rate, a multidisciplinary chronic pain rehabilitation was able to significantly decrease the respiration rate both within and across training sessions in older chronic pain patients¹⁷. In chronic low back pain patients, practicing yoga for 3 months can increase the parasympathetic function¹⁸.

It has already been demonstrated that patients with FBSS have a relative weaker parasympathetic tone, measured with HRV¹⁹. This imbalance is restored when patients are treated with SCS¹⁹. Some pilot data was already reported in 1985 in several animal

experiments^{20, 21}. In patients with chronic refractory angina, a reduction of the low frequency/high frequency (LF/HF) ratio based on heart rate variability measurements was found when SCS was turned off^{22, 23}.

The aim of this study is to further elucidate the influence of SCS on the autonomic nervous system in patients with FBSS. In line with previous conclusions that were based on heart rate variability, we hypothesize a dominance of sympathetic activity without SCS, observable by an increased skin conductance level, heart rate and respiration rate. The objectives of this study are twofold:

1. To evaluate the influence of SCS on skin conductance in patients with FBSS
2. To evaluate the influence of SCS on cardiorespiratory parameters (respiratory rate, blood volume pulse and heart rate) in patients with FBSS

Methods

Participants

Patients with FBSS (at least 18 years old) who are treated with SCS at the department of Neurosurgery of Universitair Ziekenhuis Brussel or at the pain clinic of Clinique Sainte-Elisabeth-CHC were invited to participate in this study. Selection of patients was based on those FBSS patients who were scheduled for a 6 month SCS follow-up visit for routine clinical care. All patients that were scheduled for a follow-up, and who were eligible for study participation, were invited to take part in this study. Patients were not allowed to take part in the study if they had impaired skin integrity at the fingers or if they were previously diagnosed with major psychiatric problems.

The study protocol was approved by the central ethics committee of Universitair Ziekenhuis Brussel and the local ethics committee of Clinique Sainte-Elisabeth-CHC (B.U.N. 143201939519) whereby approval for the conduct of this study in both study centers was obtained on September 11, 2019. The study was registered on clinicaltrials.gov (NCT04121104). All patients provided written informed consent before participation. The study was conducted according to the revised Declaration of Helsinki (1998).

Study protocol

This multicenter study consisted of a single outpatient visit. Patients were asked to switch off their SCS at least 12 hours before the study visit. All patients were verbally asked to confirm that they switched off SCS 12 hours before the study visit. This statement was also controlled by evaluating whether SCS was effectively switched off (which was the case for all patients). The duration that the system was switched off, could not be verified. Patients were also asked to refrain from alcohol, tobacco and caffeine 12 hours before the study visit. Before the study visit, all patients were asked to wait in the waiting room for at least 10 minutes to ensure patients were not feeling agitated (e.g. due to walking to the hospital). More time was added in case patients did not feel calm yet. During the study visit, a 5-minute recording was made of the respiration, blood volume pulse and skin conductance level. Afterwards, patients were asked to provide a pain intensity score. After having filled in the questionnaire, the neurostimulator was switched on again. After a resting period of 30 minutes, a similar 5-minute recording took place and patients again rated their pain intensity. Due to the pain relieving effect of SCS that patients felt, we were not able to blind patients. There was no restriction regarding the use of prescribed medication, including analgesics.

Questionnaires

The visual analogue scale (VAS) was used to assess the pain intensity. Pain intensity scores were provided separately for back and leg pain. The VAS ranged from no pain to maximal pain and is expressed in cm from 0 to 10. Patients completed this pain intensity score twice; once after the 5-minute recording when SCS was switched off and once after the recording when SCS was activated. The VAS pain score is a reliable and valid tool that is sensitive to change ²⁴⁻²⁶.

The Medication Quantification Scale III (MQS) was used to quantify and monitor medication used to treat a variety of pain conditions ²⁷. The MQS was designed as a methodology to quantify different drug regimens. This tool uses a numerical representation of the negative impact each medication has in treating a patient's pain ²⁸.

Autonomic nervous system parameters

Continuous 5-minute recordings of skin conductance, blood volume pulse, heart rate and respiration were made by using the NeXus 10 MK-II (Mind Media BV; Herten, the

Netherlands). Processing was performed by BioTrace+ software version V2018A (Mind Media BV). Recordings were made with a blood volume pulse sensor, two skin conductance sensors and a respiration sensor which were attached to respectively the middle finger, the index and fourth finger and around the belly. The skin conductance sensor uses two Ag-AgCl electrodes that are secured by Velcro straps to the tip of the fingers. The electrodes are sensitive to small changes in skin conductance up to 1/1000 microsiemens. For blood volume pulse, fingertip photoplethysmography was applied to measure heart rate and monitor relative blood volume. An independent researcher collected all the autonomic nervous system parameters in all patients. BioTrace+ software was used to analyse data. All 5-minute recordings were visually screened for data collection errors. Suspicious fragments were removed before obtaining summary statistics over the 5-minute fragments. As such, all values that are presented in the manuscript are presenting an average over the 5-minute recorded fragment.

Sample size calculation

Sample size calculation was performed using G*Power 3.1.3 (Düsseldorf, Germany) based on the skin conductance level in chronic low back pain patients during rest versus auditory stimulation ²⁹. Mean skin conductance level (μs) values of 6.35 and 7.2 for rest and stimulation, respectively, with a standard deviation of 1.1 were used in the current calculation. The minimal total sample size should reach 16 patients, based on two-tailed testing to detect differences between matched pairs for skin conductance levels with $\alpha = 0.05$ and a desired power of 0.80.

Statistical analysis

All analyses were performed in R Studio version 1.2.5019 (R version 3.6). Normality was evaluated with the Shapiro Wilk test and QQ-plots and equality of variances by Levene's tests. Tukey Fences were applied to determine outliers whereby the fences were calculated as follows: $[Q1 - 1.5 * IQR ; Q3 + 1.5 * IQR]$. Outliers were identified as values located outside the fences ^{30, 31}. Descriptive statistics are provided as mean (\pm SD) or as median (interquartile range). Skin conductance, respiration, heart rate and blood volume pulse between the on and off states were compared with paired t-tests or Wilcoxon signed-rank tests. Effect sizes were calculated as well. A simple regression model was built with pain intensity scores as independent variable and the on and off state of SCS and pain location (low back or leg) as

explanatory variables. P values of 0.05 or less were considered statistically significant. There was no imputation for missing data. For each outcome measurement, only complete pairs were used in the analysis. Finally, Spearman rank correlations were calculated between changes in pain intensity and changes in SCL, HR, BVP and RR with a Bonferroni correction to account for multiplicity.

Results

In total 28 patients were included in the study. Patient recruitment started on 03/11/2019 and lasted until 24/1/2020. Due to data collection errors and the previously described outlier policy, 26 pairs of observations were available for SCL, 26 for respiration rate and 27 for heart rate. For one patient, VAS scores were missing when SCS was activated. Figure 1 is presenting the study flow chart.

Descriptive statistics

Nine males and 19 females participated in this study with an average age of 59 ± 13.12 years (Table 1). The median duration that patients were implanted with SCS was 31.82 (Q1-Q3: 13.22 - 76.25) months. All patients received SCS at level (T8)-T9-T10-(T11) and were implanted with either a Senza rechargeable system (Nevro Corp., Redwood City, CA, USA) with 2*8 contacts or a Restore Sensor™ SureScan system connected with a Specify™ 5-6-5 SureScan MRI surgical lead (IPG RestoreSensor, Medtronic, Inc., Minneapolis, MN, USA). SCS was delivered with a median charge per pulse of 2.16 (Q1-Q3: 0.8 – 3.42) μC , median charge per seconds of 260 (Q1-Q3: 58.5 – 444.6) $\mu\text{C}/\text{sec}$ and a median duty cycle of 5.85 (Q1-Q3: 2.32 – 5.85) %.

The median score on the MQS-III was 7.4 (Q1-Q3: 1.42 – 19.97). A simple regression model for pain intensity scores revealed a significant effect of condition (type III test: $F=37.59$, $p<0.001$) on pain intensity. The expected pain intensity score for a patient with FBSS when SCS is deactivated is 6.22 (95% CI from 5.55 to 6.89). When SCS is activated, the expected pain intensity score is 2.94 lower (95% CI from 1.99 to 3.88) (Figure 2).

Autonomic nervous system parameters

The median skin conductance level did not significantly differ between SCS on and off states ($V=216$, $p=0.15$). A summary of all outcome variables can be found in Table 2. Blood volume pulse during SCS on states was not different from blood volume pulse during SCS off states ($t(26)=0.19$). In Figure 3, data of individual patients is presented for HR and RR. Median heart rate when SCS was switched off was significantly higher than during SCS ($V=339$, $p=0.0001$) (Figure 3A). Respiratory rate was significantly lower when SCS was functioning ($V=257$, $p=0.038$) (Figure 3B). Post-hoc non-parametric bootstrap hypothesis testing with 5000 resamples was performed to obtain the distribution and 95% confidence interval of bootstrap replicates for the test statistic under the null hypothesis (Figure 4). This clearly indicates that the obtained test statistic is not in the neighbourhood of the test statistic under the null hypothesis, wherefore we can reject the null hypothesis that HR and RR respectively do not differ between SCS on and off states.

No significant correlations were found between changes in pain intensity and changes in HR, RR, SCL or BVP.

Discussion

The aim of this study was to evaluate the influence of SCS on skin conductance and cardiorespiratory parameters in patients with FBSS. In this study, skin conductance level and blood volume pulse were not altered between on and off states of SCS. Heart rate and respiration rate significantly decreased when SCS was activated, leading to the hypothesis that SCS is able to induce an influence on the autonomic nervous system, in patients with FBSS.

Subjective versus objective tools

Patient reported outcome measures (PROMs) and preferentially pain intensity scores, are still the most prominent outcome measures within the field of neuromodulation³². These outcome measurements are very useful to evaluate the clinical outcome of SCS, however they might only provide an evaluation of the '*perceived capacity*'³³. Furthermore, they might be unreliable, affected by observational bias and highly influenceable by the specificity of the pain diagnosis³⁴⁻³⁶. To conduct a holistic evaluation of a chronic pain patient, the '*actual ability*' should be evaluated as well^{33, 36} with a wide variety of possible tools such as

neurophysiological measures, neuroimaging tools or quantitative sensory testing³⁷. Objective tools are not observer-independent and are ultimately suited to further explore potential therapeutic mechanisms of SCS³⁴. The exact distinction between a subjective and objective tool might be difficult however the use of a machine measurement versus an observation based on human perception may guide the distinction³⁸. The use of both self-reported and objective criteria is useful for diagnosing patients, but also in the process of evaluating treatment effects.

SCS and autonomic nervous system

The exact mechanisms of action of SCS are largely unravelled, however some aspects remain uncertain. One of the mechanisms that is not yet clearly explored is whether SCS is able to influence the autonomic nervous system. Literature already revealed that peripheral and central systems regulating cardiovascular function and pain modulatory systems are interacting with each other through the nucleus tractus solitarius (NTS) by vagal-nociceptive interactions^{39, 40}. The NTS is allocated as the initial relay for vagally mediated nociceptive effects³⁹. Besides the input from the vagal afferent, the NTS is also receiving information from the ascending and descending nociceptive pathways⁴¹, enabling shared output mechanisms on both pain thresholds and autonomic outflow^{41, 42}. As an example, patients with chronic low back pain demonstrated reduced heart rate variability and increased heart rate, indicative for an autonomic dysregulation in this population¹⁰.

Building on those findings, this study further investigated whether a treatment (SCS) could influence the dysregulation of the autonomic nervous system. Our research consortium previously assessed this research question with heart rate variability as biomarker for the functioning of the autonomic nervous system^{19, 43}. When SCS was switched off, patients with FBSS presented relatively weaker parasympathetic activity compared to when SCS was activated. Nevertheless, this study was limited to heart rate variability (an indirect measurement tool for autonomic function), wherefore a thorough evaluation with skin conductance, blood volume pulse and respiration rate could enable us to further substantiate the previously stated hypothesis.

Skin conductance can be considered as a sign of internal stress since sweat glands are innervated by the sympathetic nervous system, resulting in an increase of skin conductance

under stressful or painful conditions ⁴⁴. Previously, the dysregulation of the sympathetic nervous system with abnormalities in sympathetic skin response in patients with FBSS was already demonstrated ⁴⁵. This dysregulation could be compared to the situation in which SCS was switched off during this study. Due to the significant decrease in pain intensity scores when SCS was switched on, a decrease in skin conductance level was expected. Although we measured a decrease in skin conductance, this effect was not statistically significant. A possible explanation for these negative results could possibly be found in the study design. Skin conductance was measured during a 5-minute recording with two sensors at the hand. All patients in this study were experiencing pain in the lower back and lower limbs wherefore the hand can be allocated as a remote body location. Perhaps different conclusions might be drawn when conductance is evaluated at symptomatic regions. Therefore, a possible direction for future research is to perform an assessment of sudomotor function at the symptomatic regions ⁴⁶ to further unravel the influence of SCS on the autonomic system.

Nevertheless, it might also be possible that SCS is not able to influence the sympathetic component of the autonomic nervous system. This would entail an upregulation of the parasympathetic system with a relative stable sympathetic activation. Electrodermal activity, the umbrella term for autonomic changes in the electrical properties of the skin, is an autonomic psychophysiological variable which is not contaminated by parasympathetic activity and solely influenced by sympathetic influences ^{14, 47, 48}. Based on this hypothesis, a marker which is only influenced by the sympathetic influence, would not reveal any treatment effects. This hypothesis could be further enforced by the negative results concerning blood volume pulse. The blood volume pulse is measured with a photoplethysmographic sensor that monitors the volume in arteries and capillaries. The sympathetic nervous system is responsible for regulating vasomotor activity (i.e. controlling blood vessel diameter) ^{49, 50}. As such, changes in blood volume pulse solely reflect alterations in sympathetic activation, whereby no differences between the SCS on and SCS off states were found in this study. Future studies are needed to refute or confirm the stated hypothesis.

Studies exploring the role of the autonomic nervous system in chronic pain conditions often use HRV recordings ^{51, 52} with distinct oscillations that can be subdivided into two primary components; high and low frequency oscillations. High frequency oscillations can be denoted as vagally mediated, while the idea that low frequency oscillations represent a combination

of sympathetic and vagal activity has been challenged ⁵³. Low frequency power could be denoted as a measure of modulation of cardiac autonomic outflow by baroreflexes and not a measure of cardiac sympathetic tone ^{54, 55}. Instead of relying on indirect, non-invasive measurement tools, microneurography is a more direct, invasive technique to evaluate potential reductions in sympathetic cardiovascular drive ^{56, 57}. Future studies could evaluate the sympathetic nerve activity with a direct measure to fully elucidate whether SCS is able to influence the sympathetic system.

Besides limb and trunk sensorimotor deficits, patients with spinal cord injury could present with an impaired autonomic neurocircuitry resulting in problems with respiration and coughing. In patients with spinal cord injury, SCS can recover the neurologic function of patients, including an improvement in motor control, cough and breathing ⁵⁸. In this study, it was demonstrated that SCS can also influence respiration parameters namely respiration rate in patients with FBSS, who do not have an impaired neurologic function for breathing. Additionally, in patients with chronic low back pain, increased heart rate was previously described ¹⁰. Our study revealed a decrease in heart rate when SCS was switched on, suggestive for an involvement of the autonomic system when SCS is activated. The observation that both heart rate and respiration rate show a similar behaviour is not surprising. Cardiorespiratory coupling is the temporal coherence of the respiratory system and cardiac rhythms, which is widely accepted ⁵⁹. The direction of the cardiorespiratory interaction ⁶⁰, however, is less clear since both a respiration-to-heart rate ^{61, 62}, a heart rate-to-respiration ⁶³ or a bidirectional interaction between both systems ⁶⁴ has been described. Combining these findings, it might be suggested that SCS is able to alter cardiovascular parameters by influencing the autonomic nervous system, and more specifically the parasympathetic activity.

Despite the significant results obtained in this study, at first sight, median values for RR and HR between the SCS on and off states seemed very similar. To gain more insight in the underlying phenomena, results were visualized with spaghetti plots to better reflect the design of this study (paired observations). Additionally, bootstrap replicates of the test statistic were calculated. Afterwards, it became clear that the distribution of the obtained observations during SCS on and SCS off states should definitely be taken into account. Only focusing on the median value might obscure the true underlying results.

Limitations

We report the largest study investigating the effect of SCS on several parameters of the autonomic nervous system in a population of patients with FBSS. Nevertheless, we need to acknowledge that the sample size is insufficient to evaluate the effect of confounders or mediators on the relation between SCS and HRV parameters. Patients were not instructed to omit the use of analgesics due to ethical reasons. Potential influencing factors that could have influenced the results in this study are medication use and different SCS stimulation types. Additionally, measurements were first obtained during SCS off states, and afterwards during SCS on states. Based on clinical experience, the effects of SCS disappear slowly (i.e. slow levelling-off), while activating SCS has almost an instant effect. Therefore, patients were instructed to switch off their SCS 12 hours before the start of the study. Exact wash-in and wash-out periods of SCS remain to be elucidated. The currently used time periods are in line with other reports in literature ^{19, 65, 66}. Since several SCS stimulation paradigms were used (suprathreshold and subthreshold paradigms) and due to the longer wash-out period compared to the wash-in period, patients could not be blinded to the stimulation condition. To limit the influence of the lack of blinding, objective (i.e. no self-reported) outcome parameters were used whereby the main outcome variable of this study (i.e. skin conductance) was measured with the NeXus 10 MK-II, a measurement device that provides objective, independent outcome parameters and is considered the gold standard photoplethysmography device ⁶⁷. Finally, with the current design, conclusions on alterations in pain intensity, cardiorespiratory parameters and skin conductance based on experimental manipulation of the SCS condition can only be drawn for the time period after SCS implantation. Generalisations towards the pre-implantation state are not possible and should be evaluated with prospective cohort studies.

Suggestions for further research

Determining the exact wash-in and wash-out periods of SCS would be highly beneficial for all SCS trials that are experimentally influencing SCS conditions. Besides the use of neuroimaging tools, one could also evaluate changes in autonomic nervous system functioning by exploring heart rate variability with an ecological momentary assessment using repeated real-time sampling to gain insight in the duration of wash-in and wash-out periods and carry-over

effects. Additionally, another direction for further research is to directly evaluate the influence of SCS on sympathetic nerve activity by microneurography.

Conclusions

SCS seems to be capable of altering the functioning of the parasympathetic autonomic nervous system in patients with FBSS. The decreased heart rate and respiratory rate during SCS and the non-significant changes in blood volume pulse and skin conductance level when SCS is activated, lead to the hypothesis that the dysregulation of the autonomic nervous system is primarily restored by an upregulation of the parasympathetic system instead of reducing the dominance of the sympathetic system.

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Conflict of interest: Bengt Linderöth serves as a consultant to Medtronic, St Jude/Abbott, Boston Sci and Elekta AB. Philippe Rigoard serves as a consultant for Medtronic Inc. He received honoraria for medical training from St. Jude Medical and research grants from St. Jude Medical, Medtronic Inc. and Boston Scientific. Maarten Moens has received speaker fees from Medtronic and Nevro. There are no other conflict of interests to declare.

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Tables

Patient	Center	Sex	Age (years)	MQS	SCS duration (months)
1	A	M	42	27.2	15
2	A	M	52	6.8	71
3	A	F	74	0	59
4	A	F	65	0	141
5	A	F	75	1.9	208
6	A	F	59	44.6	10
7	A	F	70	5.7	130
8	A	M	41	0	8
9	A	F	69	2.8	19
10	A	M	41	6.8	11
11	A	M	47	10.7	92
12	A	F	48	19.7	14
13	A	F	60	13.6	146
14	A	F	54	11.5	141
15	A	F	61	0	93
16	A	F	52	0	25
17	B	M	63	0	60
18	B	M	32	8	2
19	B	F	60	6.8	2
20	B	M	71	22.6	34
21	B	F	46	28.9	60
22	B	F	71	20.8	10
23	B	F	81	1.9	10
24	B	F	87	0	36
25	B	F	57	21.1	54
26	B	F	51	14	30
27	B	M	57	24	24
28	B	F	65	18.2	18

Table 1. Patient characteristics. Center A denotes Universitair Ziekenhuis Brussel, center B Clinique Sainte-Elisabeth-CHC. Abbreviations. F: female, M: male, MQS: Medication Quantification Scale III, SCS : spinal cord stimulation.

Parameter	SCS off	SCS on	Test statistic + p value	Difference with 95% CI for the difference	Effect size
Skin conductance level (μS)	1.330 [§] (Q1-Q3: 0.925 – 1.760)	1.310 [§] (Q1-Q3: 0.862 – 1.687)	V=216, p=0.15	0.11 [§] [-0.061 to 0.358]	r=0.272 (small)
	Center A: 1.39 (Q1-Q3 1.11 – 1.79)	Center A: 1.49 (Q1-Q3 0.97 – 1.69)			
	Center B: 0.94 (Q1-Q3 0.83 – 1.44)	Center B: 0.97 (Q1-Q3 0.67 – 1.63)			
Blood volume pulse (μV)	103.782 [§] (SD: \pm 63.787)	117.407 [§] (SD: \pm 74.262)	t(26)= -1.35, p=0.19	-15.339 [§] [-38.748 to 8.070]	d=0.259 (small)
	Center A: 96.448 (SD: \pm 71.634)	Center A: 115.901(SD: \pm 89.240)			
	Center B: 114.450 (SD: \pm 51.675)	Center B: 119.416 (SD: \pm 51.663)			
Heart rate (bpm) *	73.75 [§] (Q1-Q3: 65.79 – 84.22)	73.38 [§] (Q1-Q3: 63.01 – 78.45)	V=339, p=0.0001	4.35 [§] [2.395 to 6.000]	r=0.68 (strong)
	Center A: 74.11 (Q1-Q3 69.52 – 84.01)	Center A: 73.38 (Q1-Q3 64.90 – 75.95)			
	Center B: 72.72 (Q1-Q3 63.52 – 85.20)	Center B: 71.91 (Q1-Q3 61.89 – 81.53)			
Respiratory rate (bpm) *	16.87 [§] (Q1-Q3: 13.67 – 19.46)	14.60 [§] (Q1-Q3: 13.39 – 17.48)	V=257, p=0.038	0.975 [§] [0.032 to 2.576]	r=0.391 (intermediate)
	Center A: 16.25 (Q1-Q3 12.32 – 18.20)	Center A: 14.38 (Q1-Q3 13.12 – 16.51)			
	Center B: 18.05 (Q1-Q3 14.98 – 20.17)	Center B: 14.81 (Q1-Q3 13.78 – 17.64)			

Table 2. Summary of the calculated autonomic nervous system parameters during SCS on and off states. *: significant result. §: mean, §:median. For blood volume pulse, mean values with standard deviation are presented. For skin conductance level, heart rate and respiratory rate,

median values with first and third quartile are presented. Abbreviations. bpm: beats per minute, SCS: spinal cord stimulation, t: t test statistic, V: V test statistic.

Figures

Figure 1. Flow chart of the study. Abbreviations. HR: heart rate, RR: respiration rate, SCL: skin conductance level.

Figure 2. Boxplot of the pain intensity scores during SCS off and SCS on states for back (left) and leg pain (right). Brown and green boxes are representing respectively pain intensity scores during SCS off and SCS on states. Abbreviations. OFF: SCS switched off, ON: SCS switched on, SCS: spinal cord stimulation, VAS: visual analogue scale.

Figure 3. Spaghetti plots of significant results of SCS on heart rate (A) and respiratory rate (B). Each colour is presenting an individual patient. Abbreviations. Bpm: beats per minute, HR: heart rate, OFF: SCS switched off, ON: SCS switched on, RR: respiration rate, SCS: spinal cord stimulation.

Figure 4. Distribution of the bootstrap replicates (Wilcoxon test statistics) for HR (left) and RR (right) obtained with non-parametric bootstrap. The 95% confidence intervals for the bootstrap samples are plotted in blue. The observed test statistic is indicated in red. Abbreviations. HR: heart rate, RR: respiration rate.