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Examining the Duration of Carryover Effect in Patients With Chronic Pain Treated With Spinal Cord Stimulation (EChO Study): An Open, Interventional, Investigator-Initiated, International Multicenter Study

Kaare Meier, MD, PhD[1,2,3]; Cecile C. de Vos, MSc, PhD[4]; Martine Bordeleau, MSc, PhD[5]; Sharon van der Tuin, RN, MSc[6]; Bart Billet, MD[7]; Thomas Ruland, MD[8]; Morten Rune Blichfeldt-Eckhardt, MD, PhD[9]; Matthias Winkelmüller, MD[10]; Helga Angela Gulisano, MD, MPG[11]; Kliment Gatzinsky, MD, PhD[12]; Anne Lene Knudsen, RN, MSc[1]; Jens Christian Hedemann Sørensen, MD, PhD, DMSc[1,3]; Ioanna Milidou, MD, MSc, PhD[13,14]; Sylvine Carrondo Cottin, MSc, PhD[15]

ABSTRACT

Objectives: Spinal cord stimulation (SCS) is a surgical treatment for severe, chronic, neuropathic pain. It is based on one to two lead(s) implanted in the epidural space, stimulating the dorsal column. It has long been assumed that when deactivating SCS, there is a variable interval before the patient perceives the return of the pain, a phenomenon often termed echo or carryover effect. Although the carryover effect has been problematized as a source of error in crossover studies, no experimental investigation of the effect has been published. This open, prospective, international multicenter study aimed to systematically document, quantify, and investigate the carryover effect in SCS.

Materials and Methods: Eligible patients with a beneficial effect from their SCS treatment were instructed to deactivate their SCS device in a home setting and to reactivate it when their pain returned. The primary outcome was duration of carryover time defined as the time interval from deactivation to reactivation. Central clinical parameters (age, sex, indication for SCS, SCS treatment details, pain score) were registered and correlated with carryover time using nonparametric tests (Mann-Whitney/

Address correspondence to: Kaare Meier, MD, PhD, Department of Neurosurgery, Aarhus University Hospital, Palle Juul-Jensens Boulevard 165J, DK-8210 Denmark. Email: kaamei@rm.dk

[1] Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark;
[2] Department of Anesthesiology, Aarhus University Hospital, Aarhus, Denmark;
[3] Center for Experimental Neuroscience (CENSE), Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark;
[4] Center for Pain Medicine, Department of Anesthesiology, Erasmus University Medical Center, Rotterdam, The Netherlands;
[5] Research Centre on Aging, CIUSSS de l'Estrie-CHUS, Université de Sherbrooke, Sherbrooke, Quebec, Canada;
[6] Department of Neurosurgery, Medisch Spectrum Twente, Enschede, The Netherlands;
[7] Department of Anesthesiology, AZ Delta, Roeselare, Belgium;
[8] Neurocenter, Sunderby Hospital, Luleå, Sweden;
[9] Department of Neurosurgery, Odense University Hospital, Odense, Denmark;
[10] Department of Neurosurgery, Diakoniekrankenhaus Friederikenstift, Hannover, Germany;
[11] Department of Neurosurgery, Aalborg University Hospital, Aalborg, Denmark;
[12] Department of Neurosurgery, Sahlgrenska University Hospital, Göteborg, Sweden;
[13] Department of Pediatrics and Adolescent Medicine, Regional Hospital West Jutland, Herning, Denmark;
[14] Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark; and
[15] Department of Neuroscience, CHU de Québec–Université Laval, Quebec City, Canada

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Kruskal-Wallis) for categorical data and linear regression for continuous data.

Results: In total, 158 patients were included in the analyses. A median carryover time of five hours was found (interquartile range 2.5;21 hours). Back pain as primary indication for SCS, high-frequency stimulation, and higher pain score at the time of deactivation were correlated with longer carryover time.

Conclusions: This study confirms the existence of the carryover effect and indicates a remarkably high degree of interindividual variation. The results suggest that the magnitude of carryover may be correlated to the nature of the pain condition and possibly stimulation paradigms.

Clinical Trial Registration: The Clinicaltrials.gov registration number for the study is NCT03386058.

Keywords: Carryover, echo effect, neuropathic pain, SCS, spinal cord stimulation

INTRODUCTION

Spinal Cord Stimulation

Spinal cord stimulation (SCS) is a minimally invasive surgical treatment for severe, chronic, neuropathic pain that does not respond sufficiently to pharmacologic treatment. The treatment comprises one or two electrical leads implanted in the epidural space of the spinal cord, most commonly through a percutaneous approach, or alternatively through a surgical (hemi-) laminectomy. The implanted leads, connected to a subcutaneously implanted pulse generator (IPG, Fig. 1), typically have eight to 16 contacts that can be individually programmed to generate an electrical field, stimulating the dorsal column of the spinal cord.[1]

After surgery, the patients are given a control device that allows switching between various preconfigured settings of the SCS device (programs), adjusting the amplitude of the stimulation, and de/reactivating the device.

Originally based on the gate control theory of pain,[2] the exact mechanism of action is still not fully elucidated but appears to involve both segmental and supraspinal pathways.[3]

The most common indications for SCS include radicular pain and/or back pain after spine surgery, pain after peripheral nerve damage, complex regional pain syndrome (CRPS), and painful polyneuropathy but also are used for other chronic pain conditions.[4]

SCS: Waveforms

The electrical pulses for SCS have traditionally been delivered in the form of regular biphasic square-waves, usually with a frequency within the range of 40 to 100 Hz and a pulse width of 100 to 500μs (often termed tonic stimulation).[3]

During the last decade, new paresthesia-free stimulation paradigms have emerged, notably continuous 10-kHz high-frequency stimulation,[5] and burst stimulation, which is based on delivery of regular trains of four to six pulses;[6] 10 kHz and burst do not depend on eliciting paresthesias when the stimulation is active, as opposed to tonic stimulation, which is clearly perceptible by the patient.

Carryover or Echo Effect

On the basis of clinical observations, it has generally been assumed that when deactivating SCS, there is a variable interval before the patient perceives a clinical effect of the change, ie, return of pain. This phenomenon goes by different terms (carryover, echo, aftereffect, etc)[7] and is recently actively used in programming SCS devices relying on imperceptible burst stimulation to operate on automated ON/OFF cycles.[8]

On a more negative side, carryover has been problematized as a source of error in crossover studies in SCS,[7,9,10] and it may complicate programming and reprogramming of device settings given those depend on the patient's feedback on perceived stimulation. In their 1967 report on related therapy peripheral nerve stimulation (PNS), Wall and Sweet already noted that their patients seemed to benefit from a treatment effect for some time after stimulation was stopped;[11] despite this finding, to our knowledge, no systematic, experimental research has been published on the topic of carryover effects in invasive neuromodulation for chronic pain.

This open, prospective, international multicenter study aimed to systematically investigate and document the carryover effect in SCS.

MATERIALS AND METHODS

The study was registered at ClinicalTrials.org (NCT03386058) and was approved by the local ethical committees and data protection agencies at each participating center (for Denmark VEK 60629 and DT 2015-57-0002). The inclusion period was between April 2018 and March 2021.

Study Participants

Patients were invited to participate in the study if they were implanted with a full SCS system, were routinely followed up by one of the participating centers (Table 1), and met the inclusion criteria listed in Table 2.

Upon inclusion in the study, the recruiting healthcare professional registered the core clinical parameters, listed in Table 3.

Deactivation Protocol

Participants were instructed orally and in writing to deactivate their SCS device in their own home on a weekday between 08:00 AM and 11:00 AM after a period of ≥48 hours of continuous use when they had not experienced pain rated >7 on a conventional 0-to-10 numerical rating scale (NRS; 0 = no pain, 10 = worst pain imaginable). If the participants normally used various programs, they were asked to stay on one program for those 48 hours. Patient-controlled adjustments in stimulation amplitude were allowed, provided the amplitude was not set to 0.

Patients recorded parameters from Table 3 in a standard form during the trial. They were asked to reactivate their device on previous settings if their pain increased by ≥3 points on NRS. "Unbearable pain" or "other unpleasant sensations" also were

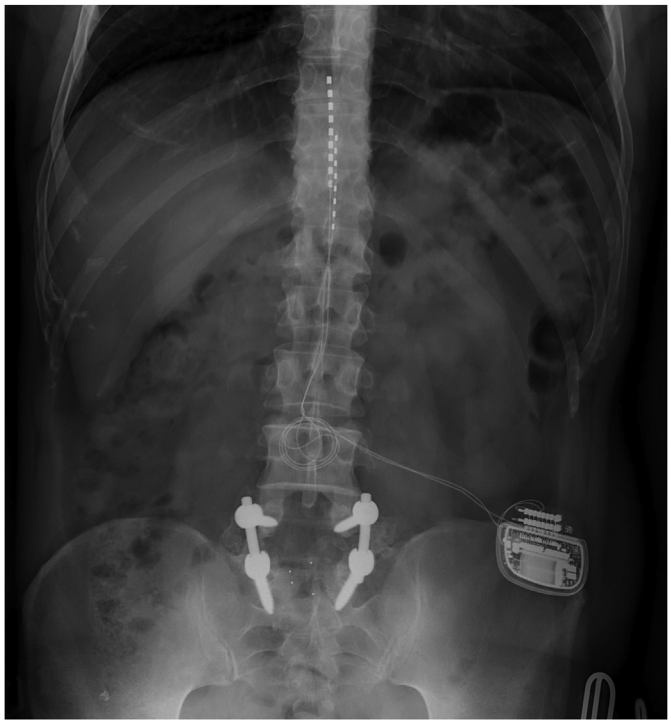

Figure 1. Anterior/posterior x-ray image of an implanted system for SCS. This system comprises two different leads (one conventional percutaneous lead and one hybrid lead) implanted in the epidural space with the most distal tip at the levels of vertebrae T10 and T11. An IPG is implanted in the upper buttock region. Picture from Aarhus University Hospital, Denmark.

allowed as reasons for reactivation, considered signs of remission of treatment effect, in addition to for ethical reasons.

The participants were asked to maintain their usual medication and level of physical activity in the study period. The study participants received both oral information and a detailed instruction letter on the deactivation procedure.

Participants who volunteered to do so were asked to repeat the process after at least a seven-day "washout" period after conclusion of the first round.

Data Analysis

Data were collected in Research Electronic Data Capture under the auspices of Aarhus University, Aarhus, Denmark.[12] Data analysis was carried out by authors IM and KM using Stata 16SE (StataCorp, College Station, TX).

The primary outcome was carryover time, defined as the time interval in hours from deactivation of the SCS device to reactivation. For patients experiencing a carryover time >120 hours, the carryover time was capped at 120 hours.

We investigated carryover time according to the following categorical parameters: sex, indication (primary cause of painful condition treated with SCS), pain score at the time of SCS device deactivation, pain type, stimulation paradigm (tonic, burst, or 10 kHz), and SCS lead location.

Burst SCS was originally devised by Dirk De Ridder[6] and later marketed by Abbott as BurstDR.

For this study, we have not distinguished between BurstDR and other similar waveforms marketed under various other burst labels, although a difference in mechanism of action has been claimed.[13]

The indications were categorized as listed in Table 4. Patients with both radicular pain and a secondary back pain component were grouped as radicular pain; a subsequent subgroup analysis was performed to compare patients with and without a secondary back pain component. SCS lead location was registered, as SCS convention dictates, as the vertebral level of the most distal (rostral) tip of the lead as seen on x-ray. The lead locations were grouped into three categories: cervical (C1–C7), high/midthoracic (T1–T9), and low (T10 and below). This division follows the most common guidelines for lead level for treating upper extremity, truncal, and lower extremity pain, respectively.[14] Patients with two leads located in two different subgroups were excluded from this analysis.

Furthermore, carryover time was investigated according to the following continuous parameters: age, symptom duration (defined as time in months from symptom debut to study participation), and SCS treatment duration (defined as time in months from first SCS implant to study participation).

Statistical Methods

For categorical parameters, the median, interquartile range (IQR), and tenth and 90th percentile of carryover time for each category were reported and graphically presented as scatterplots and bar charts. Nonparametric tests were used to test for differences in carryover time among the groups at a 0.05 significance level (Mann-Whitney for dichotomous parameters and Kruskal-Wallis for >two categories).

Table 1. Participating Centers, Listed Alphabetically.

Abbreviated name	Full institution name
Aalborg, Denmark	Aalborg University Hospital, Aalborg, Denmark
Aarhus, Denmark*	Aarhus University Hospital, Aarhus, Denmark
Enschede, The Netherlands*	Medisch Spectrum Twente, Enschede, The Netherlands
Göteborg, Sweden	Sahlgrenska University Hospital, Göteborg, Sweden
Hannover, Germany	Diakoniekrankenhaus Friederikenstift, Hannover, Germany
Odense, Denmark	Odense University Hospital, Odense, Denmark
Quebec City, Canada*	CHU de Québec – Université Laval, Quebec City, Canada
Roeselare, Belgium*	AZ Delta, Roeselare, Belgium
Rotterdam, The Netherlands*	Erasmus University Medical Center, Rotterdam, The Netherlands
Sunderby, Sweden	Sunderby Hospital, Luleå, Sweden

*Centers that have recruited >five patients included in the final analyses.

Table 2. Inclusion Criteria for Study Participation.

- patient age ≥18 y
- signed informed consent
- implanted with full SCS system for neuropathic pain
- SCS treatment duration ≥6 mo before inclusion
- no surgical SCS lead revision for the last 6 mo before inclusion
- maximum pain score ≤7 on a 0–10 NRS at the most painful area of pain treated with SCS during the last 48 hours before study-related deactivation of the device
- no changes in the programming patterns of the device (except patient-controlled changes in amplitude) for a minimum of 30 d before the study-related deactivation of the device
- SCS device not set to automated ON/OFF cycles
- no other ongoing neuromodulatory treatment (PNS, TENS, etc)
- no other neuromodulatory treatment with lasting effect (RFA, sympathectomy, infiltration anesthesia, nerve blockade) within the last 60 d
- no changes in medication within the last 30 d (rescue medication allowed)

RFA, radiofrequency ablation; TENS, transcutaneous electrical nerve stimulation.

Continuous parameters were described by their median, IQR, and range, and plotted to the carryover time (scatterplot) to graphically show possible associations. Furthermore, linear regression models of carryover time as a function of age, symptom duration, and treatment duration were fitted.

In the subgroup of patients who completed two rounds of deactivation, linear regression analysis was performed for the carryover time of the second to first deactivation.

RESULTS

Study Participants

Of 201 patients initially recruited to the study, 43 were excluded, leaving data from 158 patients for analysis (Fig. 2). The patients included in the analyses were recruited from ten different centers across six Western countries. Five centers recruited <five patients each, hence were grouped as "Other centers" (Table 4).

Seven patients (4.4%) reactivated their device owing to "other unpleasant sensations." Less than 5% of patients experienced a carryover time above the cap of 120 hours.

Deactivation of the SCS device is a common procedure performed at reprogramming sessions, SCS procedures (revisions, IPG replacements), and for safety reasons in relation to other procedures such as surgery or magnetic resonance imaging. Moreover, many SCS practitioners recommend "SCS holidays" to their patients, ie, intermittent periods of SCS deactivation to counteract habituation to the therapy. Despite this, and even though the study-related de/reactivation was left in the hands of the participants, the most common reason for refusal to participate among eligible patients was fear of the consequences of deactivation, eg, fear of the pain surge in the period of deactivation or not being able to regain their pain control.

Carryover Time

The median carryover time for all patients was five hours with an IQR of 2.5;21 hours. The 10% and 90% percentiles of the carryover time were 0.9 and 62.8 hours, respectively (Table 4 and Fig. 3).

The results from the analyses of the categorical parameters are summarized in Table 4 and in Figure 4a to g. Statistically significant differences were found within the indication groups. A subsequent Mann-Whitney test comparing each group with the rest found a statistically significant difference for the patients with CRPS (displaying the shortest carryover time) and the group with back pain (experienced the longest; Fig. 4b). The patients experiencing radicular pain, painful neuropathy, and peripheral nerve damage pain showed carryover times between these extremes. The subgroup analysis of patients with radicular pain with or without back pain did not show any difference between the subgroups.

The carryover time tended to be longer in the group of patients with a limited treatment effect as reflected in a higher pain score at the time of deactivation (Fig. 4c). Constant pain was associated with shorter carryover time (Fig. 4d).

Patients receiving 10-kHz high-frequency stimulation experienced statistically significant (intergroup Mann-Whitney test) longer carryover effects than did patients on tonic or burst

Table 3. Clinical and Patient-recorded Parameters.

Clinical parameters registered at enrollment

- Sex
- Age
- Indication for SCS treatment*
- Stimulation paradigm (tonic, burst, 10 kHz)
- Location of the SCS lead (vertebral level of SCS lead[s] tip)
- Symptom (pain) debut
- SCS therapy initiation date

Parameters registered by the patient during the trial

- Exact time of deactivation
- Pain score (NRS 0–10) at deactivation
- Primary pain experience (constant pain or predominantly pain spikes)
- Exact time of reactivation
- Reason for reactivation
- Pain score (NRS 0–10) at reactivation

CRPS, Complex Regional Pain Syndrome; HF10, 10-kHz high-frequency stimulation; NRS, Numerical Rating Scale; SCS, spinal cord stimulation.
*Back pain, radicular pain, radicular pain with a secondary component of back pain, peripheral nerve damage, CRPS 1 and 2, painful neuropathy, other.

Table 4. Carryover Time and Clinical Characteristics, Categorical Parameters.

Categorical parameter	*n*	Carryover time (h)			*p* Value*
		Median	IQR 25;75%	10th–90th percentile	
Total (1 round)	158	5.0	2.5–21.0	0.9–62.8	n/a
Total (2 round)	130	5.0	2.8–21.3	1.4–48.3	n/a
Sex					0.300
Women	68	5.4	3.0–25.4	1.4–67.0	
Men	90	5.0	2.2–20.0	0.8–55.0	
Primary indication for SCS therapy					0.006
Back pain	19	25.0	3.0–82.3	1.6–120	
Radicular pain	78	5.5	3.0–20.0	1.3–62.8	
Peripheral nerve damage	15	4.2	3.0–11.3	1.3–21.0	
CRPS	26	2.8	0.3–7.7	0.2–48.0	
Neuropathy	14	4.8	2.5–8.0	0.8–11.0	
Other†					n/a
Radicular pain with no back pain component	21	5.0	3.0–11.5	1.5–26.5	0.480
Radicular pain with back pain as secondary indication	55	7.0	3.0–21.0	1–62.8	0.480
Pain score at the time of deactivation					0.018
None/almost none (NRS 0–1)	26	5.3	3.1–10.5	1.5–67.0	
Low (NRS 2–4)	86	3.6	1.7–13.0	0.3–49.0	
Moderate (NRS 5–7)	46	10.6	3.0–27.5	1.6–96.5	
Pain type					0.09
Constant pain	121	4.5	2.3–17.3	0.9–48.3	
Predominantly spikes	28	11.4	3–29.8	0.8–60.0	
Stimulation paradigm					0.01
Burst	48	5.0	1.8–9.5	0.3–29.8	
10 kHz	13	22.8	6–97.5	2.7–120	
Tonic	97	4.5	2.5–24.0	0.9–50.0	
Lead location (tip)					0.25
Cervical (C1–C7)	24	3.6	1.3–12.3	0.3–24.5	
High/midthoracic (T1–T9)	83	5.3	2.7–22.8	1.3–97.5	
Low (T10 and below)	39	5.0	3.0–24	0.8–50.0	
Recruiting center					0.0008
Aarhus, DK	18	4.2	2–29.8	0.2–120	
Québec City, CA	28	26	5–48.3	1.1–98.0	
Enschede, NL	45	5.0	3–11.6	1.3–25.5	
Rotterdam, NL	27	3.0	0.9–5	0.3–22.8	
Roeselare, BE	19	7.9	2.3–47	0.8–120	
Other centers	20	4.1	3–7.8	2.1–20	

10 kHz, 10-kHz high-frequency stimulation; BE, Belgium; CA, Canada; DK, Denmark; NL, The Netherlands; n/a, not applicable.
*Nonparametric Mann-Whitney test for dichotomous parameters and Kruskal-Wallis test for >two categories.
†Excluded from subgroup analysis owing to small group.

stimulation (Fig. 4e). It should be noted, however, that the patients treated with 10-kHz stimulation constitute only a small fraction of the patients.

The spinal level of stimulation did not seem to be a predictor for carryover time (Fig. 4f).

Patients from the Belgian and (in particular) Canadian centers experienced longer carryover time than did patients from the other centers (Fig. 4g).

The results from the analyses of the continuous variables are summarized in Table 5 and in Figure 5a to c. Neither the age of the patients nor the duration of the painful condition or SCS treatment was associated with carryover time.

Because a few patients had remarkably long carryover times, we decided to set a cap at 120 hours given 95% of the study population had carryover time shorter than that. Selecting 72 hours or 96 hours would have led to capping of carryover time in approximately 10% and 8% of the study population (data not shown).

The carryover time in the first (n = 158) and second (n = 130) round of deactivation showed consistency (Supplementary Data Fig. S1). This does serve to strengthen the results, although the patients themselves could be inclined to expect the same carryover time in round 2 as they noted in their first round.

Safety

No adverse events were registered.

DISCUSSION

This study is, to our knowledge, the first to investigate the carryover effect in SCS in an experimental setting. The data presented here 1) confirm the existence of a carryover effect, 2) quantify the duration of the carryover effect, and 3) investigate possible correlations with clinical parameters.

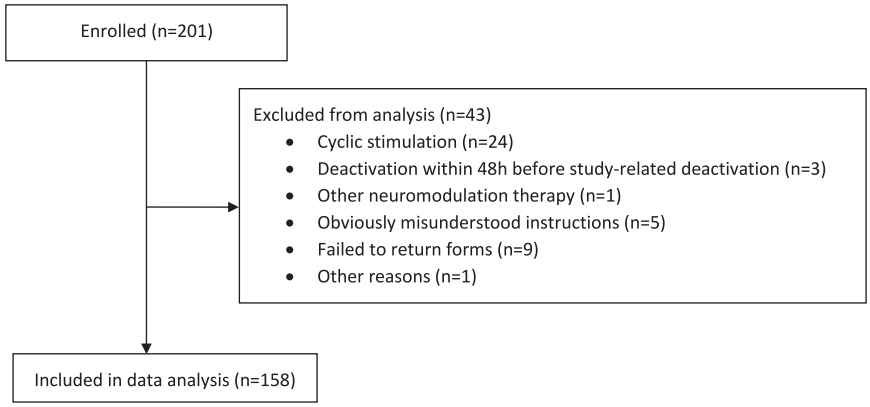

Figure 2. Flowchart illustrating the reasons for exclusions from data analysis of patients enrolled in the EChO study.

In our study population, there was a remarkably large interindividual variation among patients with SCS, with a significant fraction of patients having carryover duration of >24 hours, a finding with both clinical and profound scientific implications.

Study Participants

This reservation among many potential candidates entails potential selection bias: 1) Patients with experience of very rapid pain increase after switching off the IPG may be less likely to participate, leading to an overestimation of carryover time in our data; 2) patients with a complex course of their SCS treatment (eg, multiple surgical revisions and/or reprogramming of their device) may be more reluctant to participate; 3) patients with a very large, sometimes life-changing, pain-relieving effect of SCS may feel less inclined to participate; and 4) patients with a more anxious disposition may be less willing to participate. These biases may limit the external validity of our results given the patients included may not fully represent the population of patients treated with SCS.

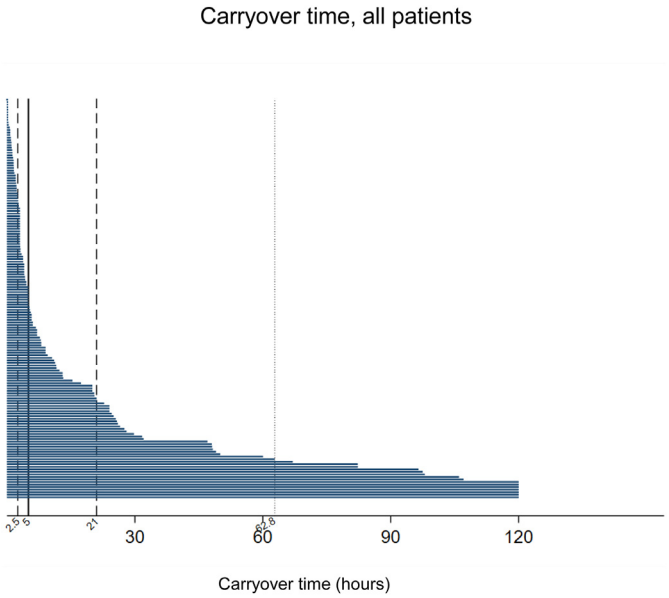

Figure 3. Diagram illustrating the carryover time in hours of the entire study population (n = 158). Median is shown with a full line, 25% and 75% IQR with a dashed line, and the 90% percentile with a dotted line. [Color figure can be viewed at www.neuromodulationjournal.org]

Outcome Parameter

This study was not aimed at exploring the effectiveness of SCS therapy but only at investigating the carryover effect; only patients who reported beneficial effect of SCS treatment were asked to participate. It should be noted that the participants were, in most cases, not pain free even with active stimulation.

To quantify the carryover time, a marker for "remission of treatment effect," preferably as a dichotomous yes/no parameter, was optimal. For many patients, however, the return of pain is a gradual effect rather than a sudden onset. Moreover, for a subjective experience such as pain, there is no objective marker.

We decided that a clinically significant increase in pain as measured on conventional 0-to-10 NRS was the best available marker for loss of treatment effect, and an increase of 3 was deemed a distinct, clinically significant increase. Thus, a maximum score of 7 on pain NRS was chosen as an inclusion criterion to allow an increase of 3 NRS points.

The patients in this trial handled their own device settings and were thus not blinded as would have been preferable. However, a blind design in which patients do not have access to their own control device would require full-time attendance by a healthcare professional who could reactivate the SCS system. Owing to the often long carryover times, the resources required for a study of this magnitude would be extremely substantial.

Carryover Time

The study documents a large interindividual variation in the carryover time, ranging from mere minutes to several hours and even days. It is a common clinical experience that whereas some patients react almost instantaneously with resurgence of their pain to deactivation of their SCS device, most patients tolerate well a temporary deactivation, eg, related to reprogramming or surgical IPG replacement. Nevertheless, we were surprised to see the very long carryover times listed by many of the study participants, reflected in a median across all groups of five hours.

Excluding the patients with >120-hour (5%) or 72-hour (10%) carryover time leads to a lower upper limit of the IQR but otherwise rather robust results with median [IQR] of 5 [2.5;20] and 4.5 [2.25;12.6].

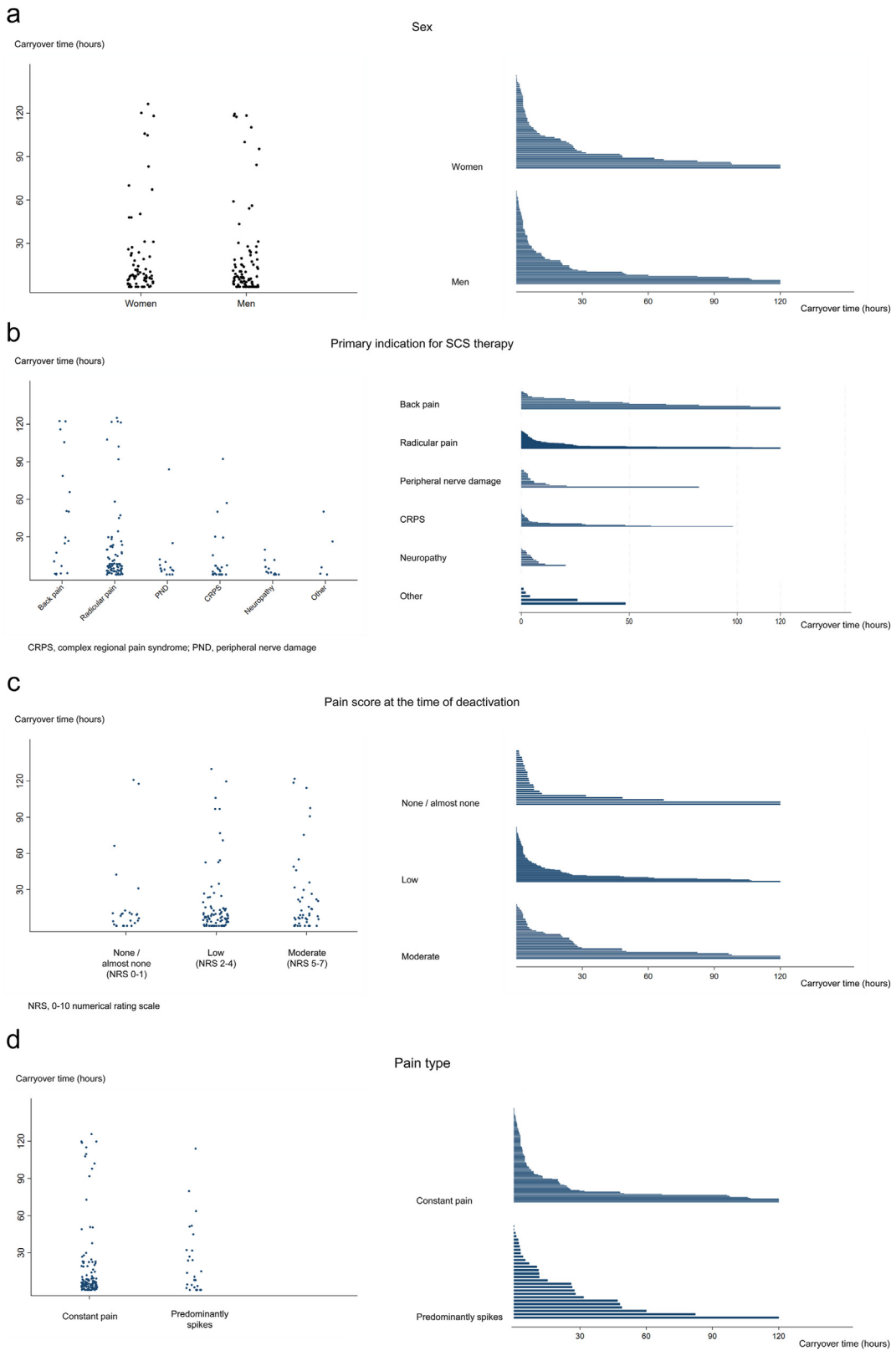

Figure 4. Diagrams illustrating the carryover time in hours, stratified by the categorical variables listed in Table 4. a. Sex. b. Primary indication for SCS therapy. c. Pain score at the time of deactivation. d. Pain type. e. Stimulation paradigm. f. Lead location. g. Recruiting center. [Color figure can be viewed at www.neuromodulationjournal.org]

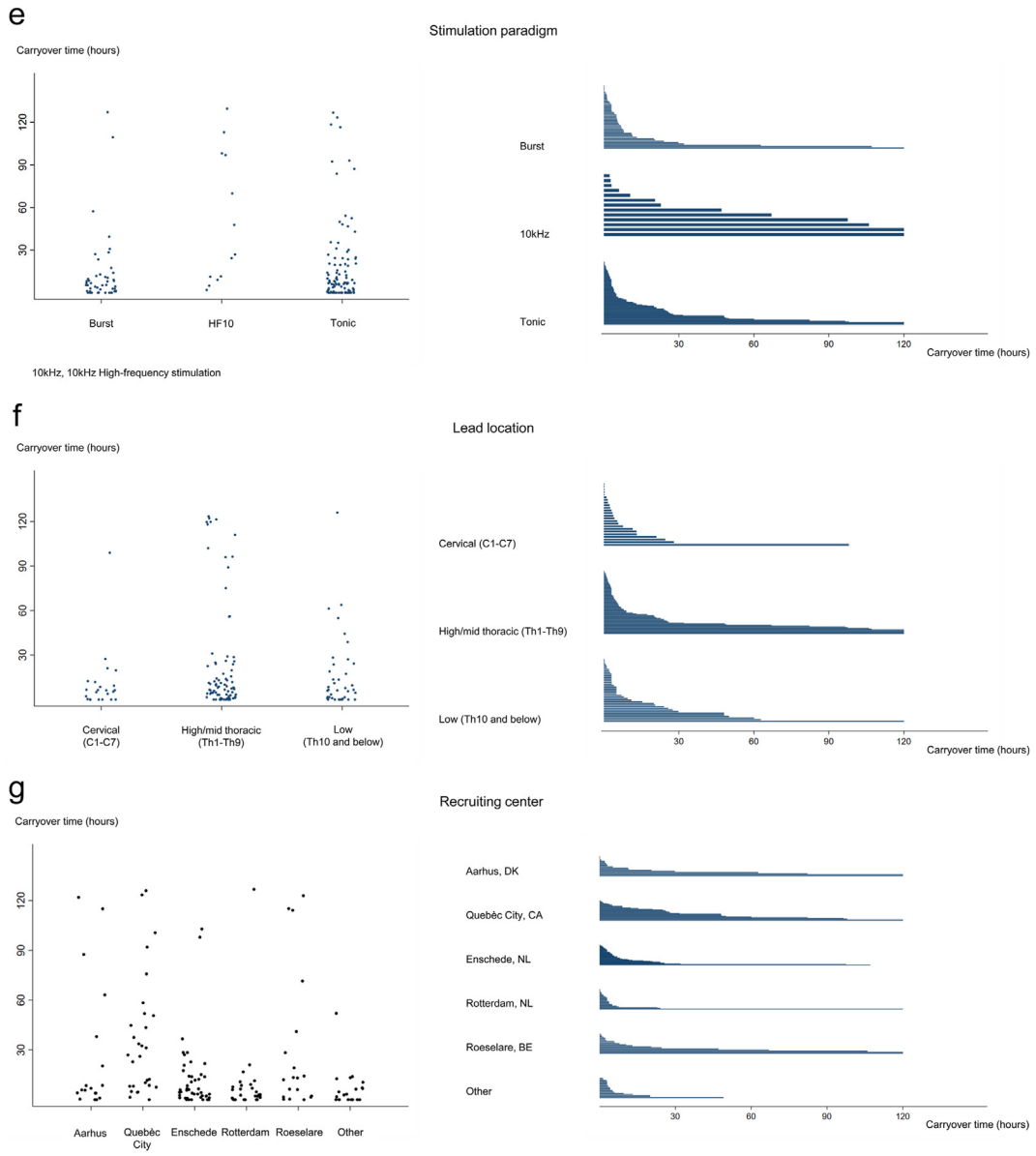

Figure 4. Continued. [Color figure can be viewed at www.neuromodulationjournal.org]

In a 2011 survey,[15] 61 patients with SCS completed a telephone interview during which they were asked to recall how long they normally felt the effect of SCS treatment after deactivation of the device. Full effect of SCS treatment was felt for >120 minutes by ten patients, and partial effect for >120 minutes by 21 patients (notably, the options were limited to 120 minutes). Comparison with our intervention-based study with set criteria for reactivation is, however, difficult. A 1987 conference abstract also briefly describes carryover effect of "up to several hours" in five of six patients with spinal cord injury treated with SCS.[16]

Although not dealing with SCS, a recent review provided an overview of the proposed neuroplastic changes occurring in related therapy PNS.[17] According to the theory of "peripherally induced reconditioning of the central nervous system" described by the authors, a sustained pain relief could happen even after stimulation deactivation when many Aα/β fibers have been activated. Selective activation of those fibers could temporarily reverse neuronal hyperexcitability and changes in descending supraspinal circuits induced by chronic pain.

In addition, SCS has been shown to induce neurochemical changes in the spinal cord.[3,18] It could be hypothesized that these changes respond with a certain latency to deactivation of the stimulation and may be a candidate for further research into the underlying mechanisms behind the carryover effect.

Reverse Carryover Time

When reactivating SCS therapy after deactivation, there is a certain time interval before the effect of the treatment establishes. The time it takes for the effect of the SCS therapy to return to predeactivation state is often termed reverse carryover. This parameter also was registered in the study, but the author group decided to treat reverse carryover separately so as

Table 5. Clinical Characteristics, Continuous Parameters.

Continuous parameter	*n*	Median	IQR 25;75%	Range	Coefficient α	*p* Value*
Age (y)	158	62.5	47.0;69.3	27.9–84.6	0.0044 [−0.5; 0.5]	0.985
Duration (mo)						
Pain condition	157	139.7	87.7;245.2	29.8–593.7	−0.001 [−0.04; 0.04]	0.965
SCS treatment	158	53.2	30.4;101.6	6.9–275.2	0.0028 [−0.09; 0.10]	0.952
Pain score (NRS) at deactivation	158	3	2;5	0–7	1.6629 [−0.94; 4.27]	0.209

*From the linear regression analysis.

not to render the present analysis unnecessarily lengthy and unwieldy.

Carryover Time and Clinical Condition

The carryover effect of SCS in back pain has been suggested to be related to muscle relaxation,[15] which may serve to partially explain the longer carryover effect in this group than the other indications.

Intriguingly, it also is the clinical experience of the authors that many patients with CRPS tend to react quickly with increasing pain after SCS device deactivation. Whether this is in fact related to the nature of the disease is speculative.

Patients with a low pain score (NRS 0–4) at deactivation tended to have shorter carryover time, whereas those with higher pain score had longer. A possible explanation is that some patients with high pain scores may not respond very well to the treatment at all, making it difficult for them to ascertain a definite change in their

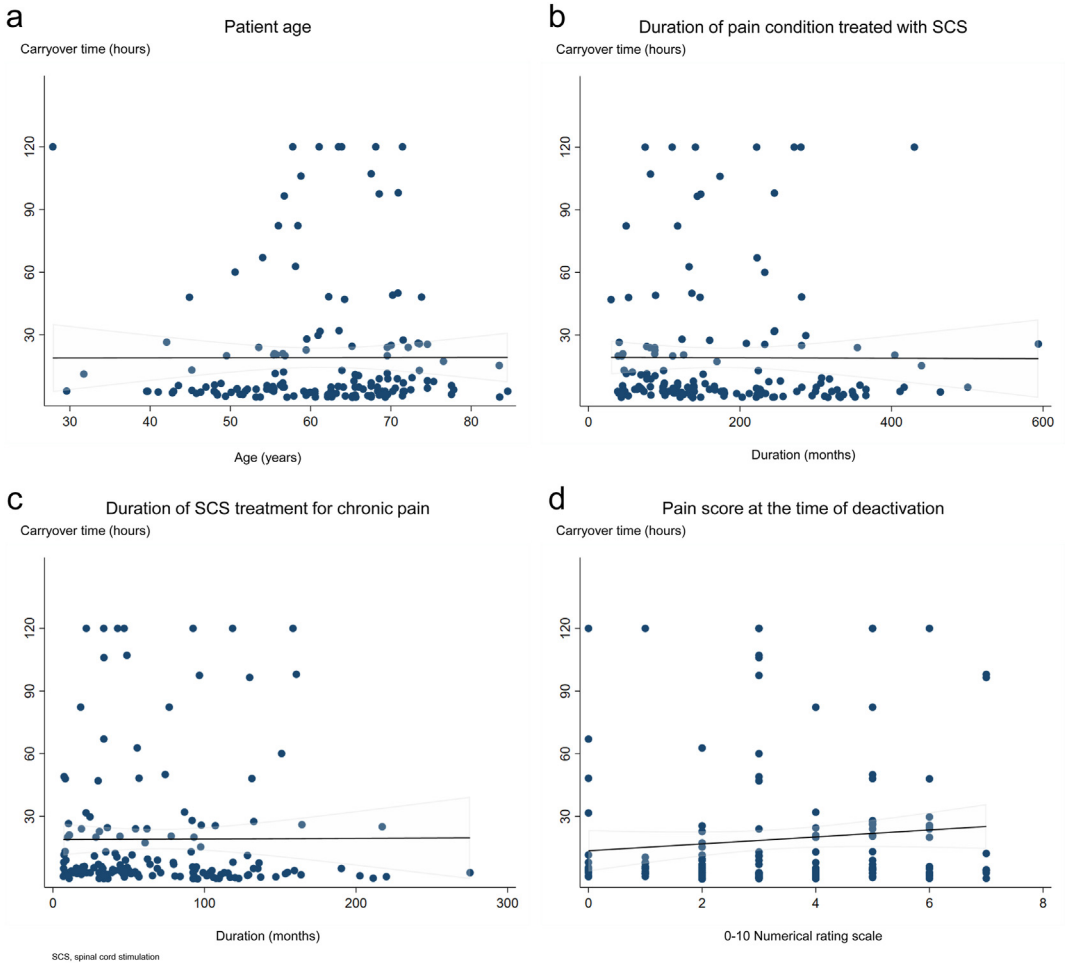

Figure 5. Diagrams illustrating the carryover time in hours, plotted against the continuous variables listed in Table 5. The line represents linear regression (with 95% confidence intervals). a. Patient age. b. Duration of pain condition treated with SCS. c. Duration of SCS treatment for chronic pain. [Color figure can be viewed at www.neuromodulationjournal.org]

condition. When analyzing the effect of NRS at the time of deactivation as a continuous variable rather than grouping into categories, the relation showed the same trend but was nonsignificant ($p = 0.2$, linear regression analysis; Table 5 and Fig. 5d).

Several of the clinical indications analyzed are not uniformly distributed regarding age and sex (eg, CRPS is more common in younger female patients, whereas the prevalence of degenerative back disease increases with age), but if this finding was important, it did not manifest in the analysis for those two variables.

Duration of the painful condition leading to SCS treatment ranged from a few years to almost 50 years. Although some advocate that long symptom duration before the initiation of SCS treatment is associated with less likelihood of a successful outcome, it has never been firmly documented.[19] Symptom duration does not seem correlated with carryover time either in this study.

In some patients, the pain-relieving effect of SCS appears to wane or disappear entirely over time, whereas in other patients, it seems to be stable.[20,21] In this study, we included patients with only months of treatment duration up to >20 years. We saw no correlation between treatment duration and carryover time; it should be stressed that patients with a long SCS treatment history participating in this study are obviously those who have continued effect of SCS over the years; thus, they may not represent the entire patient population with SCS.

Carryover Time and SCS Treatment Parameters

The carryover times of the three subgroups of lead location do not display a significant difference. The indication for SCS treatment generally determines the lead placement, with cervical leads and low thoracic/lumbar leads usually implanted for upper and lower extremity pain and midthoracic for back pain. Thus, there is a certain confounding between indication and lead placement.

The same applies, to some degree, to the stimulation paradigm. The traditional and most thoroughly examined waveform for SCS is tonic stimulation that evokes paresthesia in the treated body area, often described as buzzing or tingling.

Ten kHz was introduced as a treatment modality especially aimed at treating back pain,[22] a pain condition often difficult to treat with tonic SCS. Although 10 kHz has found use in treating other pain conditions, it is often used to treat back pain, as also is the case in our study, in which nine of 13 patients with 10 kHz have primary back pain (Supplementary Data Table S1).

Remarkably, even though both 10 kHz and burst are characterized by being paresthesia-free (as opposed to tonic), patients treated with burst and tonic show similar carryover times, whereas the (relatively few) patients with 10 kHz have significantly longer effects.

Several possible associations with clinical/treatment parameters were tested, some of them likely interlinked (eg, a high number of patients with 10 kHz with predominant back pain). In this exploratory study, we have not attempted to correct for these correlations.

Further Limitations

We did not ask patients to provide details about their regular medication, but we asked them to remain on their usual drug regimen to avoid any impact of a medication change on pain levels. We cannot exclude the possibility that certain substances may affect the carryover time.

The difference in carryover time in the Canadian and (to some degree) Belgian centers is remarkable. Subgroup analyses showed a higher pain score at the time of deactivation in the Canadian patients (Supplementary Data Table S2), possibly indicating less treatment effect on average, and more patients treated with tonic stimulation (Supplementary Data Table S3) than in the other centers. A subgroup analysis showed more Belgian patients treated for back pain and more patients using high-frequency stimulation (Supplementary Data Tables S3–S4). Moreover, most of the Canadian patients already routinely deactivated their SCS device at home intermittently; this constitutes a possible selection bias toward patients with longer carryover times.

Clinical and Scientific Implications

A quantification and understanding of the carryover effect potentially hold several implications for the application of SCS therapy.

Cyclic Stimulation

Although not systematically investigated, the carryover effect is used in clinical practice by providing intermittent stimulation to patients. Advantages obviously include saving precious battery capacity, but intermittent breaks also have been claimed to have a beneficial clinical effect by resensitizing the central nervous system or to avoid habituation to the effect of stimulation.[23,24]

Intermittent treatment regimens involve both recommending patients to turn off their device manually during part of the day[15] and, as increasingly used, setting the IPG in automated ON/OFF cycles.[8] For paresthesia-free stimulation paradigms, the ON/OFF shift is not felt by the patient, but clinical outcome of the strategy varies. An author of a clinical trial notes that with cyclic 10 kHz, "it appears that there is a generally dichotomous response."[25] One might speculate that individual differences in carryover time could explain the differences in clinical response.

Crossover Studies

In clinical investigations using crossover designs, carryover effects have been theorized to affect the outcome,[7,9,26] whereas others did not estimate carryover effects to have affected the results.[27] The same applies to investigative studies relying on deactivation of the device, eg, using quantitative sensory testing[28,29] or neuroimaging,[30] in which results of examinations in the OFF phase may still be affected by carryover.

The results of this study point to the importance of including investigation of the individual study participant's carryover time when designing a study paradigm.

Clinical Treatment Optimization

Optimizing treatment in a clinical context routinely involves trialing different stimulation settings with respect to both the electrode configurations and, particularly with the emergence of new stimulation paradigms, the stimulation settings. When evaluating the pain-relieving effect of a revised device programming, it should be considered that the patient may have a significant carryover effect.

CONCLUSION

It is a common clinical observation that in patients with chronic pain treated with SCS, there is a variable time interval when the

treatment still has effect after a deactivation of the device. This study confirms this phenomenon, often termed carryover or echo effect, and documents that the duration of the effect varies greatly among individuals. The results also suggest that the effect may be determined by the nature of the pain condition and the treatment provided, and furthermore point to the importance of factoring in the carryover effect in clinical trial designs.

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Authorship Statements

Kaare Meier contrived the project, created the data collection data base, and wrote the original protocol with significant contribution from Martine Bordeleau, Sylvine Carrondo Cottin, and Cecile C. de Vos. The previously mentioned authors wrote the manuscript and acquired funding, with significant input from Cecile C. de Vos, Sylvine Carrondo Cottin, Martine Bordeleau, and Ioanna Milidou. Cecile C. de Vos contributed significantly to data acquisition, to the study design, and to the manuscript, acquired funding, and approved the final manuscript. Martine Bordeleau contributed significantly to the study design and to the manuscript and approved the final manuscript. Sharon van der Tuin contributed significantly to data acquisition and critically revised, contributed to, and approved the final manuscript. Bart Billet contributed significantly to data acquisition and critically revised, contributed to, and approved the final manuscript. Thomas Ruland contributed to data acquisition and critically revised, contributed to, and approved the final manuscript. Morten Rune Blichfeldt-Eckhardt contributed to data acquisition and critically revised, contributed to, and approved the final manuscript. Matthias Winkelmüller contributed to data acquisition and critically revised, contributed to, and approved the final manuscript. Helga Angela Gulisano contributed to data acquisition and critically revised, contributed to, and approved the final manuscript. Kliment Gatzinsky contributed to data acquisition and critically revised, contributed to, and approved the final manuscript. Anne Lene Knudsen contributed to data acquisition and critically revised, contributed to, and approved the final manuscript. Jens Christian Hedemann Sørensen contributed to data acquisition and critically revised, contributed to, and approved the final manuscript. Ioanna Milidou performed the data analyses with Kaare Meier and wrote the statistics section, had direct access to the full data set, and critically revised and approved the final manuscript. Sylvine Carrondo Cottin contributed significantly to data acquisition, contributed significantly to the study design and to the manuscript, acquired funding, and approved the final manuscript. All authors agree to be accountable for all aspects of the submitted work.

Conflict of Interest

Bart Billet serves as a consultant for Abbott, Saluda, Bioelectronics, and Medtronic. Helga Angela Gulisano has received lecture fees from Medtronic. Jens Christian Hedemann Sørensen has received consulting fees from Novo Nordic and has a patent application for wireless brain-computer interface and stock options with Cenexum ApS and Neurizon ApS. Kaare Meier has received speaker's fees from Abbott and has coownership of data base company Neurizon. Kliment Gatzinsky has received honoraria from Boston Scientific for lectures and serves on the advisory boards for Medtronic and Boston Scientific. Thomas Ruland reports consulting fees from Abbott. The remaining authors report no conflict of interest.

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SUPPLEMENTARY DATA

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COMMENTS

The authors conducted an innovative study to explore wash-out periods of SCS, a topic that has received little attention until now. As revealed by this study, considerably large wash-out periods were found. Presumably, these could be related to the definition of wash-out period being a pain increase of 3 on the NRS. I am curious to see the results with more objective markers of the wash-out period, or functionality definitions.

Lisa Goudman, PhD
Brussels, Belgium

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This study delves into a crucial, yet understudied, aspect of spinal cord stimulation (SCS) therapy— the duration of the carryover effect after deactivation. Although it has been commonly assumed that there is a variable period before the patient perceives the return of pain after deactivation, this research offers a systematic characterization and quantification of this carryover effect. The implications of these findings are substantial, particularly in the realm of neuromodulation. The study's insights can prove valuable in designing crossover clinical trials necessitating appropriate washout periods and in scenarios such as trialing patients with different waveform paradigms or implementing SCS holidays. By shedding light on the temporal dynamics of the therapeutic effects after deactivation, this research contributes significantly to optimizing the application and understanding of SCS therapy in various clinical settings.

Ryan D'Souza, MD
Rochester, MN, USA