Defining the Boundaries of Patient Perception in Spinal Cord Stimulation Programming

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ABSTRACT

Objectives: Recent developments in spinal cord stimulation (SCS) programming have initiated new modalities of imperceptible stimulation. However, the boundaries of sensory perception are not well defined. The BEnchtop NEuromodulation Following endIng of Trial study aimed to create a map of perceptual threshold responses across a broad range of SCS parameters and programming to inform subperception therapy design.

Materials and Methods: This multicenter study was conducted at seven US sites. A total of 43 patients with low back and/or leg pain who completed a percutaneous commercial SCS trial were enrolled. Test stimulation was delivered through trial leads for approximately 90 minutes before removal. SCS parameters, including amplitude, frequency, pulse width (PW), electrode configuration, cycling, and multifrequency stimulation were varied during testing. Paresthesia threshold (PT), comfort level (CL), perceptual coverage area, and paresthesia quality (through patient selection of keywords) were collected. Differences were evaluated with analysis of variance followed by post hoc multiple comparisons using t-tests with Bonferroni correction.

Results: PT was primarily determined by PW and was insensitive to frequency for constant frequency stimulation (range: 20 Hz – 10 kHz; F(1284) = 69.58, p < 0.0001). For all tests, CL was approximately 25% higher than PT. The dominant variable that influenced paresthesia quality was frequency. Sensations described as comfortable and tingling were most common for frequencies between 60 Hz and 2.4 kHz; unpleasant sensations were generally more common outside this range. Increasing distance between active electrodes from 7 mm to 14 mm, or cycling the SCS waveform at 1 Hz, decreased PT (p < 0.0001). Finally, PT for a low-frequency stimulus (ie, 60 Hz) was unaffected by mixing with a sub-PT high-frequency stimulus.

Conclusions: In contrast to previous work investigating narrower ranges, PW primarily influenced PT, independently of frequency. Paresthesia quality was primarily influenced by pulse frequency. These findings advance our understanding of SCS therapy and may be used to improve future novel neuromodulation paradigms.

Keywords: Cycling, electrode configuration, paresthesia threshold, perception, SCS

INTRODUCTION

Spinal cord stimulation (SCS), a neuromodulation therapy used in the management of chronic neuropathic pain, emerged in 1967, shortly after the seminal paper on the gate control theory of pain perception.1 Traditionally, SCS is applied using biphasic, rectangular pulse trains with frequencies ranging from 20 Hz to 300 Hz.2–4 Although stimulation frequencies up to 10 kHz are possible with some commercial systems. This mode of stimulation is delivered at amplitudes believed to activate large, sensory Aβ fibers in the dorsal column (DC), which in turn antidromically activate inhibitory networks in the dorsal horn and suppress pain transmission.5–7 Activation of DC fibers also produces a tingling sensation, commonly referred to as paresthesia. Since the recent advent of

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Site: This work was a multi-center study conducted at seven US sites.
paresthesia-free SCS modalities, paresthesia has generally fallen out of favor, with most patients preferring paresthesia-free, or subperception, SCS therapy.\textsuperscript{3,8}

In the last decade, numerous new stimulation paradigms have been introduced, most of which use stimulation that does not induce paresthesia.\textsuperscript{9} Several studies have indicated pain relief in the absence of paresthesia.\textsuperscript{10–17} In many cases, subperception stimulation has achieved superior pain relief to that of traditional SCS therapies\textsuperscript{15,18–19} and reduced traditional requirements for overlap of SCS-based paresthesias and the region of chronic pain.\textsuperscript{20} These findings generated renewed interest in SCS parameter programming and novel potential mechanisms of pain relief.\textsuperscript{21–24} However, precise psychophysical responses to stimulation within an extended frequency parameter space have not yet been reported.

The basic psychophysical properties of traditional, low-frequency (LF) SCS therapy have been well studied.\textsuperscript{22,25} Previous research suggests that increasing pulse width (PW) and frequency decreases paresthesia threshold (PT).\textsuperscript{26,27} The finding that increasing PW decreases PT closely follows the strength-duration relationship found in other neural systems\textsuperscript{28} and is predicted by both classical\textsuperscript{29} and modern\textsuperscript{30} neural models. Increasing PW also may induce larger paresthesia areas, which tend to expand in the caudal direction.\textsuperscript{27,31} Various electrode configurations have been assessed by measuring changes in PT at different contact spacings. He et al found that PT increases with separation between bipolar contacts ranging from 10 mm to 30 mm.\textsuperscript{32} Similarly, Holshheimer and Wesselink reported a minimum threshold <10 mm, with lower thresholds for the tripolar guarded cathode configuration than with bipolar stimulation in a modeling study.\textsuperscript{13}

Although previous research provides a foundation for understanding SCS perception properties, most studies tested a small number of parameters and were generally limited to traditional, LF SCS modalities. Modern SCS therapies include frequencies ranging from 20 Hz to 10 kHz with variable PWs, cycling (ie, repeatedly turning stimulation on and off), and a variety of contact configurations. The objective of the BENchtop NEuromodulation Following ending of Trial (BENEFIT-01) study was to provide detailed assessments of ways these parameters influence stimulation perception to promote development of future SCS therapy.

**MATERIALS AND METHODS**

**Study Design**

This multicenter study was conducted at seven US clinical sites by physicians with experience using SCS therapy. The study protocol and informed consent forms were approved by the institutional review board of each study site. All patients provided written informed consent before participation.

**Study Participants**

Consenting patients under the care of study investigators were assessed for study eligibility. Key inclusion criteria were 1) age ≥18 years and 2) patient initiated or planned to undergo an SCS trial with a Food and Drug Administration-approved system for an approved indication. Key exclusion criteria were 1) trial with SCS system requiring lead extensions; 2) clinically significant signs of infection at the implant site; 3) history of opioid addiction; 4) implanted pacemaker, implanted cardioverter defibrillator, or other medical contraindications; 5) lead migration during SCS trial causing inability to deliver therapy; or 6) ongoing paresis, clumsiness, numbness, or pain below the level of the lead contacts associated with the trial period.

**Paresthesia Threshold and Comfort Level**

PT, comfort level (CL), paresthesia coverage (PC), and paresthesia quality (PQ) were evaluated for each stimulation test. Participants were tested in four sets of stimulation tests, sets typically performed in the same order with randomized test order (see Hardware and Stimuli, later subsections: Tonic Frequency, Cycling, Multifrequency Stimuli, and Configuration). However, test order within each set was randomized for each participant. Amplitude transitions included a 2-second linear onset ramp to avoid stimulation transients. A standard iterative procedure was used to determine PT and CL (Supplementary Data Fig. S1).

**PQ and Coverage**

PQ was evaluated at CL by directing participants to select the most representative one of six keywords covering a broad range of common sensations (ie, massaging, vibrating, tingling, pressure, tightness, or jabbing) and one of two descriptive adjectives (ie, comfortable or unpleasant). During stimulation at CL, participants also asked to shade a dermatome map to indicate location of sensation (Fig. 1). For each participant, the average PC (number of activated dermatome sections) was computed for 60 μs, 120 μs, and 200 μs. Maps were not obtained for tests in which CL could not be measured or the PC was unchanged from the previous test.

**Hardware and Stimuli**

On the last day of the commercial trial, programming and imaging data were obtained, and the study stimulation system was connected in place of the commercial trial stimulator for testing during a single visit over one to two hours. Trial leads were subsequently explanted on the same day as the clinic visit. Stimuli were delivered to each participant using custom hardware designed and manufactured by BIOTRONIK, SE & Co KG, Berlin, Germany to deliver precise stimuli that were organized into four sets (Supplementary Data Section S1).

**Tonic Frequency**

Tonic frequency tests comprised constant-frequency stimulation between 20 Hz and 10 kHz, with a cathodic PW between 30 μs and 200 μs (Supplementary Data Tables S1 and S2, Tonic Frequency 1 and 2; Figs. 2–4).

**Cycling**

The cycle tests were designed to investigate how modulating the amplitude (rapidly turning stimulation on and off) of the SCS waveform influences perception (Supplementary Data Table S3, Fig. 5 inset).

**Multifrequency Stimuli**

The multifrequency experiment investigated perceptual interactions between LF paresthesia-based therapy and high-frequency (HF) sub-PT therapy. Multifrequency stimuli tests comprised an HF and LF stimulus delivered in an alternating pattern using the same set of electrodes (Supplementary Data Table S4, Fig. 6 inset).

**Electrode Configuration**

Electrode configuration tests assessed ways electrode configuration affected PT, CL, PC, and PQ. Specific electrode configurations...
(Supplementary Data Table S5, Fig. 7a) were chosen based on those typically observed in clinic and on predictions from a computational model. Waveform parameters were fixed across all configurations to a tonic frequency of 60 Hz with a 200 μs PW.

For participants with two SCS leads, a labeling convention was used to denote right and left leads. The left lead was placed on the participant’s left side in the epidural space and contacts numbered 1 to 8 (superior–inferior). The right lead was placed on the participant’s right side and contacts numbered from 9 to 16 (superior–inferior). The study sample contained both aligned and staggered electrode configurations.

Analysis

Large variation in PT and CL among participants was noted, presumably due to physiology- and lead placement-induced variation. For plotting, data were first normalized within each participant’s data set before combining across participants. In most cases, PT and CL values were normalized to the respective mean PT of each participant across all tests. However, for the first set of tonic-frequency tests, values were normalized to the mean PT computed across the first seven tests (20 Hz–2.4 kHz) because thresholds at higher frequencies were above the safety limit of the system (15 mA) for many subjects.

Statistical analyses were performed in MATLAB and Jupyter Notebook. The raw data were first tested for normality (Lillifors test) and homoscedasticity (Bartlett’s test if normal and Levene’s test if not normal). Nonnormal data were analyzed using either nonparametric tests or linear mixed-effects (LME) models that do not assume normality. PT and CL were treated as outcome measures of stimulation amplitude, which was considered to be a continuous variable consistent with previous studies. Specifically, the PT and CL data were fit to LME models treating subjects as a random effect. Marginal analysis of variance was performed on the mean effect estimates from LME models for multivariate analysis, followed by post hoc multiple comparison tests after Bonferroni correction. For discrete variables (eg, PC), Freidman tests followed by Wilcoxon signed-rank tests were used. For cycling tests at 10 kHz, detection of paresthesia was analyzed using a Kruskal-Wallis test followed by sign tests. The relative difference between CL and PT (CL−PT difference) was computed for each test within each participant (CL−PT difference = (CL−PT)/PT). For the multivariate analysis, raw differences between CL and PT (CL−PT) were fit with an LME model with subject as a random effect. Test results with \( p < 0.05 \) were considered significant.

PQ was normalized by relative frequency of occurrence within each test. Trends noted in the PQ data were tested for significance by first dividing all tests into two groups for each participant. Keywords were similarly assigned to two groups, thus transforming them into a binary response (eg, jabbing reported or jabbing not reported). From this grouping, two × two contingency tables were formed for each participant. Finally, we used the Cochran–Mantel–Haenszel test for significance (a generalization of chi-squared test, used for correlated data).
Statistical outliers, exceeding three standard deviations from the mean, were removed for plotting purposes. Outliers were removed before statistical testing (never >5% of the total).

RESULTS

The objective of the BENEFIT-01 study was to determine ways clinically relevant SCS parameters influence stimulation perception. To this end, stimulation sets with varying SCS parameters were tested in the short term in patients at the conclusion of their commercial trial period. For each test, PT, CL, PC, and PQ were measured on the basis of patient feedback (Materials and Methods section).

Study Participants
A total of 43 participants were enrolled at seven clinical sites in the USA between July 2017 and November 2017. Of these participants, one did not undergo testing, and two withdrew consent before testing. Data were analyzed for 40 participants who initiated testing and completed all or a subset of stimulation tests.

Demographic and clinical characteristics and commercial trial information for the tested study population are listed in Table 1. The accountability of all 40 participants engaged in SCS testing is shown in Supplementary Data Table S6.

Tonic Frequency
Tonic-frequency tests assessed ways PT, CL, PC, and PQ depended on both frequency and PW. Data from the first parameter set were collected from 27 participants. Consistent with previous studies, the raw threshold amplitudes were highly variable between subjects. For example, the PT for the 60-Hz, 200-μs test had a range of 0.3 mA to 12.1 mA (mean = 5.6 mA, SD = 3.3 mA). For plotting purposes, PTs and CLs measured within each subject were therefore normalized before averaging across subjects (Fig. 2a; Materials and Methods; nonnormalized mean [SD] provided in Supplementary Data).

In general, PT increased as frequency increased, and PW decreased. For the region between 20 Hz and 250 Hz with a constant PW of 200 μs, PT was approximately constant, with a subtle decrease >20 Hz. Similarly, PT was roughly constant for frequencies between 0.6 Hz and 2.4 kHz, at which PW was held...
constant at 120 μs, and approximately 20% higher than that measured at lower frequencies with a 200 μs PW. As frequency increased from 2.4 kHz to 10 kHz (PW decreased from 120 μs to 30 μs), PT steadily increased with an approximately constant slope. At 10 kHz, PT was approximately 3.5 times that of PT for the lowest frequencies (longest PWs) tested. However, PT could only be measured at 10 kHz for a small subset of participants (n = 5) because stimulation was subthreshold for the remaining participants at the maximum study system amplitude (15 mA).

The PQ data revealed several trends that were not directly subjected to statistical testing. Across all tonic-frequency tests, tingling was the keyword selected most often (51.9%); this sensation was usually described as comfortable (85.7%). After tingling, the keywords vibrating (26.2%), tightness and jabbing (7.1%), pressure (4.3%), and massaging (3.4%) were most common (Fig. 2b). Jabbing was most frequently reported for the 20-Hz stimulus versus other frequencies and was most often described as unpleasant (66.7%). Several participants indicated that jabbing...
The keywords tightness and pressure were more common for the highest-frequency/shortest-PW tests (5 kHz–10 kHz) and were most often described as unpleasant (55.6% and 60.0%, respectively). This effect was tested and shown to be statistically significant (p < 0.001, Cochran-Mantel-Haenszel test). Notably, several participants indicated that a release or relaxation was felt when stimulation was stopped. As stimulation frequency increased and PW decreased, participants typically continued to describe PQ as uncomfortable tingling. Exceptions included unpleasant jabbing or pulsing sometimes felt at 20 Hz and pressure and tightness often felt at >1.2 kHz.

In a subset of participants (n = 13), PT and CL were measured using PWs of 60, 120, and 200 µs (or 180 µs) delivered at frequencies of 0.6, 1.2, and 2.4 kHz. The mean PT and CL responses to the reduced tonic-frequency parameter set are presented in Figure 3. For each of the three frequencies, the relative decrease in the reduced tonic-frequency parameter set are presented in Figure 3. For each of the three frequencies, the relative decrease in PW and frequency on PC by combining data from the tonic-frequency tests, there was not a significant interaction between PW and frequency.

Because PT for 10-kHz continuous could be measured in only three participants, we compared the number of patients who experienced PT at 1 Hz (15.2%, t = 12.448, p = 0.0001) to that of the 600-Hz stimuli (51.3% and 30.6%, respectively; Wilcoxon signed-rank, z = 3.191, p = 0.00014), whereas no significant differences were observed between other PWs (|z| < 0.877, p ≥ 0.144).

Cycling

Mean PT and CL for the cycle tests are shown in Figure 5. Cycling had a significant effect on PT for the 1.2 kHz waveform (F(2106) = 12.448, p < 0.0001). There was a small but significant reduction in PT at 1 Hz (15.2%, t = −4.894, p < 0.0001) but not 50 Hz cycling (6.0%, p > 0.05), relative to the continuous condition. Similarly to the tonic-frequency tests, there was not a significant effect of cycle rate on percent CL PT difference (F(2135) = 1.699, p = 0.187). Cycling also had a significant effect on PT for the 10-kHz waveform. Because PT for 10-kHz continuous could be measured in only five subjects, we compared the number of patients who experienced PT for continuous versus 1- and 50-Hz cycle rates. Cycling significantly influenced the number of patients who experienced paresthesia during the 10-kHz tests (Kruskal-Wallis test, F(2107) = 21.21, p < 0.0001). A significantly greater fraction of participants experienced paresthesia when the 10-kHz waveform was cycled at 1 Hz than with the unmodulated 10-kHz stimulus (64.9% and 20%, respectively, sign test, z = -4.13, p < 0.0001). This relationship also was seen for 50-Hz cycling, albeit with a lower effect size (44.4%, sign test, z = -3.18, p < 0.01).

When the effects of cycling the 1.2-kHz stimulus on PC and PQ were examined, cycling parameters did not significantly influence PC. In contrast, cycle rate strongly affected PQ. Participants frequently reported a jabbing sensation for the 1-Hz cycle rate but not for the continuous and 50-Hz cycle rates (48.7% and 0%,
respectively, $p < 1\times10^{-9}$). Furthermore, the 1-Hz rate was more than twice as likely as other rates to cause an unpleasant sensation (51.4% and 23.6%, respectively, $p < 0.001$).

### Multifrequency Stimuli

Responses to the multifrequency tests are summarized in Figure 6. Participants who completed all three multifrequency tests were included in the analysis ($n = 21$). Neither mean PT nor CL in response to 60-Hz stimulation was significantly influenced by either HF stimulus included in the multifrequency test ($F(258) = 0.904, p = 0.411$). Although addition of sub-PT HF stimulus did not significantly influence PC for the LF stimulus (data not shown), it did influence PQ, specifically the descriptive adjectives. The fraction of unpleasant responses to the 60-Hz control stimulus (42.9%) decreased with the addition of a 1.2-kHz (28.6%) or 10-kHz sub-PT component (19.1%). However, only the decrease in the 10-kHz multifrequency condition was statistically significant ($p = 0.025$).

### Electrode Configuration

Different electrode configurations of anodes (A), cathodes (C), and open (O) contacts were tested in 22 participants (Fig. 7a). Of these, five had differences in thresholds between the adjacent bipolar configurations (AC/CA) >25%. Given this large positional variation, data from these five participants were excluded from further analysis, and statistical tests were performed in remaining participants ($n = 17$). PT differed significantly with electrode configuration ($F(6111) = 8.130, p < 0.0001$) (Fig. 7b). Trends suggested that the COA and AOCOA configurations had the lowest relative mean thresholds (0.88 and 0.87, respectively), followed by ACA, AC, CA, and CCOA. The guarded-double cathode configuration (ACCA) had the highest threshold. A subset of the paired comparisons was shown to be statistically significant (Fig. 7b).

The efficiency of each configuration was estimated measuring its electrical impedance ($Z$) and combining it with PT to compute the power threshold ($\text{Power} = [\text{PT}]^2Z$; Fig. 7c). Electrode configuration had a significant impact on power threshold ($F(698) = 2.715, p = 0.018$). AOCOA had the lowest relative power threshold (75% of the mean value) followed by ACA (0.85). The next lowest thresholds were from COA, ACCA, and CCOA (1.02, 1.02, and 1.06, respectively). The AC (1.09) and CA (1.2) configurations had the highest power thresholds. Although not all pair-wise comparisons were statistically significant, the trends suggested that the spaced

### Table 1. Demographics and Clinical Characteristics.

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<th>Characteristic</th>
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<td>Age at enrollment, Mean ± SD (range), y</td>
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<td>Sex, n (%)</td>
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<td>Pain diagnosis, n (%)</td>
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<td>Persistent spinal pain syndrome type 2 (postsurgical)</td>
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<td>Previous back surgery, n (%)</td>
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<td>Taking opioid analgesics, n (%)</td>
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</tr>
<tr>
<td>No</td>
<td>18 (45.0)</td>
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</table>

*Participants may have >one pain diagnosis.
configurations were more efficient than their adjacent counterparts.

The most notable trend in PC was greater coverage for the AOCOA relative to the adjacent configuration (ACA); however, this trend was not statistically significant (median = 2 dermatome sections greater; \( p = 0.069 \), Wilcoxon signed-rank test). When PQ of the different electrode configurations was measured, tingling was the most common keyword selected (69.3%), which was consistent with tonic-frequency results. Distributions of keywords or adjectives did not significantly vary across configuration tests, which was expected given that SCS frequency was fixed across configurations.

Adverse Events

No adverse events or unanticipated adverse device effects were reported during the study.

DISCUSSION

The primary objective of the BENEFIT-01 study was to lay the groundwork for further evolution of subperception therapy paradigms by clearly establishing ways SCS parameters influence the boundary of paresthesia perception, and thus how they influence DC activation. Multiple key findings arose: 1) Stimulation frequency does not significantly influence PT or CL; rather, PW primarily drives the boundary of perception; 2) stimulation frequency primarily influenced PQ once PT was reached; 3) narrow PW, kHz frequency stimulation is associated with an onset response, which can be detected when stimulation is switched on; and 4) bipolar adjacent or guarded cathode electrode selection exhibits lower DC neuromodulation efficiency than does a spaced bipole or spaced guarded cathode electrode configuration, respectively. In addition, CL, corresponding to upper bound of therapeutic range in typical paresthesia-based therapy, was consistently approximately 25% above PT. This CL/PT difference was not significantly influenced by either frequency or PW.

Our results differ from a previous study that reported a strong influence of frequency on PT. The authors found an approximately 500% decrease in PT, in addition to a decrease in therapeutic range because stimulation frequency increased from 40 Hz to 1200 Hz. Given the low statistical significance of the frequency effects on PT we measured (\( F(1284) = 0.47, p = 0.49 \)), deficiency in statistical power is highly unlikely to explain the differences. There are several other possibilities for these differences. Abejón et al used a commercial, implanted stimulation system and each participant’s preferred therapy electrode arrangement. This study used a custom, validated system with active charge balancing at all frequencies to minimize the influence of imbalanced residual charge at HFs. We also used a consistent electrode arrangement for all participants and randomized test order to reduce the impact of sensitization.

These results agree with strength-duration curves of DC fiber responses to stimuli of various PWs and frequencies (Weiss Law), showing, for what we believe is the first time, a clear link between these mathematical models and perception threshold within this wide parameter range.

Frequency was the dominant variable that influenced PQ. Many participants described stimulation at 20 Hz as unpleasant owing to jabbing sensations that likely resulted from the detection of individual stimulation pulses. This response pattern is consistent with 20 Hz being below the flutter fusion rate for the somatosensory system (~40 Hz), above which individual stimulus events become perceptually fused. At frequencies >2.4 kHz, a subset of participants described unpleasant tightness or pressure, likely due to motor recruitment through dorsal horn reflex loops. Although a minority of participants described nearly all paresthesias as unpleasant, most described paresthesia as a comfortable tingling for frequencies between 60 Hz and 2.4 kHz. This range can be described most accurately as a paresthesia comfort window. Previous studies have reported that a “therapeutic window” of stimulation exists; however, as studies in the last decade have shown, the therapeutic window for analgesia extends below PT, with many parameter sets running in a subperception therapeutic mode.

The increased rate of sensations associated with muscle recruitment at narrower PWs and higher pulse frequencies beyond the rate of DC entrainment suggest that sensory dorsal horn synaptic networks may respond to nontonic DC activation differently from tonic focal DC activation. Additional study is required to optimize parametric selection for subperception therapies and avoid motor reflex overstimulation, which may be difficult for patients to discern near threshold.

In the 1.2-kHz cycle tests, 1-Hz cycling created an unpleasant jabbing sensation for some participants and reduced PT by approximately 15% on average. Similarly, the 10-kHz stimulus became perceptible at 1 Hz for many participants who experienced no paresthesia for the unmodulated stimulus. In contrast, cycling a 1.2-kHz waveform at 50 Hz did not affect PT, PC, or PQ. It is likely that 1-Hz cycling decreases PT by producing a repetitive reflex onset response arising from an initial volley of neural depolarization induced at the beginning of stimulation. The commonly reported jabbing sensation may have resulted from a burst of paresthesia or muscle contraction. However, other mechanisms are possible (eg, adaptation at high cycle rates), which could be investigated directly in future studies using animal models. Clinically, our results suggest that a cycling strategy (for power saving) could be used for sufficiently low amplitudes relative to PT or with sufficiently high cycling frequency without the need for patient reprogramming. The influence of cycling on therapeutic effectiveness requires further investigation.

Adding a sub-PT HF stimulus with an LF stimulus did not affect PT, PC, or PQ (keyword selection) for LF therapy. However, it was observed that a large fraction of subjects (42.9%) described the 60-Hz control stimulus as unpleasant. This result was unexpected given that a frequency of approximately 60 Hz is common in conventional SCS programming and typically well tolerated by patients. Although the cause is not clear, it may result from evaluation of paresthesia quality at comfort level, which was targeted to the high end of the therapeutic range and probably at a higher amplitude than average therapeutic levels. Nevertheless, a small but significant decrease in the fraction of unpleasant responses was reported by participants in the multifrequency condition. This may indicate that an HF, sub-PT stimulus can ameliorate a degree of unpleasant sensations arising from traditional paresthesia-based therapy. Potential additive pain relief from a dual-therapy strategy warrants further study.

Z, PT, and PC were used to evaluate the efficiency of different electrode configurations. These parameters generally interact in complicated ways. For example, some configurations had lower Z (thus reducing power at constant amplitude) but typically at the expense of higher thresholds and reduced PC areas (thus requiring high amplitudes and increasing power). The spaced configurations were the most power-efficient configurations (COA and AOCA).
Although their Zs were higher than others, this was offset by having the lowest PT.

These conclusions differ from a previous computational modeling study that found adjacent electrodes in bipolar and tri-polar configurations with standard contact separation of 4.0 mm to 4.5 mm were optimal.6,33 However, optimal parameters were defined in that study as those causing the greatest relative difference between activation thresholds of DC and dorsal root (DR) axons, a different criterion than that applied for subperception neuromodulation efficiency. Although we focused on PTs rather than DC/DR thresholds to determine optimal parameters, specific results from Holsheimer’s modeling and clinical studies6,31,33 do not contradict the current findings.

This study did not focus on standard clinical outcomes such as clinically significant changes in therapy efficacy. Instead, it focused on determining which therapy parameters have a statistically significant influence on patient perception. Nonetheless, the findings advance our understanding of SCS therapy and may be used to optimize future novel neuromodulation paradigms. First, using narrow PWs may ensure a large range of amplitudes are available in the subperception range. Second, maintaining stimulation between 60 Hz and 2.4 kHz may reduce risk of overstimulation through difficult-to-detect deep muscle reflex activation. Finally, targeting selection of spaced stimulating electrodes to optimize neuromodulation efficiency in a subperception mode should prolong charging periods and device lifetimes.

CONCLUSIONS

In conclusion, a consistent decrease in PT with increases in PW was observed independent of frequency. Pulse frequency was the primary determinant of paresthesia quality, with the highest level of comfort felt between 60 Hz and 2.4 kHz. Spacing between active electrodes reduced threshold for paresthesia perception compared with adjacent electrodes. By applying these electrode and stimulation parameter selection concepts, the efficiency of novel neuromodulation paradigms may be improved.

Authorship Statements

Sean Sleet and Andrew Kibler were involved in the study design, data collection, and data analysis. All authors had access to relevant data, were involved in interpreting the findings, and participated in drafting, reviewing, and approving this manuscript.

Conflict of Interest

John Hatheway has received funding from Medtronic, Nalu, Biotronik, and Boston Scientific. Michael Yang has consulted for and participated in research sponsored by Boston Scientific and Nevro, as well as participated in research sponsored by Saluda. Michael Fishman was a former Director for North American Neuromodulation Society and has consulted for Abbott, Neuromodulation, Aurora Pain Care, Biotronik, Bridge Therapeutics, Brixton Biosciences, Institute for Musculoskeletal Education, Medtronic, and Saluda Medical; is the cofounder of Celéri Health and Occam’s Razor and holds stock for Celéri Health, Occam’s Razor, Aurora Spine, and Thermacardi; has conducted research with Abbott, Biotronik, Boston Scientific, Foundation Fusion Solutions (Cornerloc), InterAxon, Medtronic, Nalu Medical, PainQX, Seikagaku, SGX Medical, and Thermacard; is an employee of the Center for International Pain & Spine, and his spouse is an employee of Global Medical. Michael Verdolin has consulted for Medtronic, Vertiflex, and Boston Scientific. Tony MclJunkin has consulted for Nevro and has conducted research with Nevro and Saluda. Steven Rosen has conducted research with Saluda and Boston Scientific and has consulted for Flowonix. Sean Sleet and Andrew Kibler are paid employees of BIOTRONIK NRO, Inc, a subsidiary of BIOTRONIK SE & Co. KG. Kasra Amidelfan has consulted for Medtronic, Boston Scientific, Nevro, Biotronik, and Nalu, and holds minor options for Nalu.

SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of Neuromodulation: Technology at the Neural Interface at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neum.2023.08.011.

REFERENCES


**COMMENTS**

This is a very interesting study that evaluates the influence of common programming settings on the perception of stimulation in patients who undergo commercial tests, performed immediately before their removal. Understanding the clinical findings of perception threshold, comfort level, and how to optimize the spent energy without impairing the clinical response can help guide the next updates for neuromodulation systems.

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Optimization of neurostimulation parameters is a fundamental point in this field. The study of single aspects, in addition to the electrode configuration and their spacing in the outcome of patients treated with SCS, allows us to improve our knowledge and be more effective in treatments.

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