Exploration of High- and Low-Frequency Options for Subperception Spinal Cord Stimulation Using Neural Dosing Parameter Relationships: The HALO Study

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ABSTRACT

Objectives: Subperception spinal cord stimulation (SCS) is described mostly utilizing waveforms that require high energy. However, the necessity of these waveforms for effective subperception has not been established. We aimed to explore whether effective subperception pain relief can be achieved using frequencies below 1 kHz.

Materials and Methods: Thirty chronic pain patients implanted with SCS were enrolled as part of a multicenter, real-world, consecutive, observational case series. An effective stimulation location was determined using a novel electric field shape designed to preferentially modulate dorsal horn elements. Subsequently, programs at lower frequencies (600, 400, 200, 100, 50, and 10 Hz) were provided with pulse-width and amplitude adjusted to optimize response.

Results: All tested frequencies (1 kHz down to 10 Hz) provided effective subperception relief, yielding a mean of 66–72% reduction in back, leg, and overall pain. It was found that to maintain analgesia, as frequency was decreased, the electrical or "neural" dose had to be adjusted according to parameter relationships described herein. With the reduction of frequency, we observed a net reduction of charge-per-second, which enabled energy savings of 74% (200 Hz) and 97% (10 Hz) relative to 1 kHz. Furthermore, pain reduction was sustained out to one year, with 85% of patients reporting a preference for frequencies of 400 Hz or below.

Conclusions: We have derived an electric field configuration and, along with previous learnings in the kHz range, a set of neural dosing parameter relationships (10–10,000 Hz), which enable the expansion of effective subperception SCS to low frequency and achieve major energy savings.

Keywords: Chronic pain, electric field shape, personalized neuromodulation, spinal cord stimulation, stimulation dosage, stimulation waveform, subperception SCS

Conflict of Interest: Dr. Paz-Solís and Dr. Thomson are consultants for Boston Scientific. Mrs. Jain, Mrs. Chen, Dr. Huertas, and Mr. Doan are salaried employees of Boston Scientific.

INTRODUCTION

For several decades following the advent of spinal cord stimulation (SCS), conventional paresthesia SCS was the primary therapy approach. Paresthesia SCS is delivered at low frequency (40–100 Hz) and amplitude levels that result in a tingling sensation. Targeting for paresthesia SCS is guided by the overlap of paresthesia with the painful area, resulting in rapid onset of analgesia. The quick onset of analgesia allows rapid programming that can be effectively evaluated before the patient leaves the clinic. Paresthesia SCS is shown to provide effective pain relief,1,2 and technological advancements in SCS systems to more precisely target the dorsal columns have enabled improved outcomes.4

In 2006 and 2007, it was reported that effective analgesia could also be achieved in the absence of paresthesia (subperception).5,6 Since then, subperception modalities have expanded7,8 offering alternative therapeutic options to patients. Modalities include the use of higher frequencies (e.g., 1–10 kHz)9,10 and/or trains of intermittent pulses also at higher frequencies (e.g., 500 Hz bursts),11,12 and amplitude levels that are set below (e.g., 20–80%).
the paresthesia or perception threshold (Pth). However, although these modalities have enabled an absence of paresthesia, the reliance on notably higher frequencies sacrificed some of the classic benefits of paresthesia SCS. In particular, the device charging burden is much higher, and programming cannot be rapidly optimized and evaluated in a single session due to a slow onset of analgesia in kHz stimulation (up to 1–2 days’ wash-in) and a consequent blind anatomical search. Furthermore, the reliance on high-energy waveforms for subperception has not been fully justified, and important questions remain to be answered, such as what the actual role of frequency is or to what extent it is related to clinical outcomes.

Recent reports (PROCO) demonstrated that equivalent analgesia can be achieved in subperception SCS at different kHz frequencies (1–10 kHz). A key learning from the PROCO randomized controlled trial (RCT) was that to achieve effective analgesia at a given frequency, proper adjustment of amplitude and pulse-width was required. This concept, introduced as “neural dosing”, indicated that analgesia in subperception most likely relies on using a correct combination of stimulation parameters, according to a set of “neural dosing parameter relationships,” delivered at the right neural target, rather than on a single parameter in isolation, such as frequency.

In this study, we aimed to explore High- and Low-Frequency Options (HALO) for subperception SCS (1 kHz to 10 Hz). We hypothesized that effective subperception is achievable at sub-kHz frequencies if neural dosing relationships are correctly applied. The objectives were to explore: (1) whether the neural dosing relationships hold true below 1 kHz, and if so, what are those relationships; (2) how low can we go in frequency while maintaining effective analgesia, and if energy savings are achieved; and (3) if a novel electric field designed to preferentially engage the dorsal horn along a broader span is a valid approach to effective neural targeting in subperception.

MATERIALS AND METHODS

Study Design

This is a multicenter, consecutive, observational case series that assesses pain relief outcomes in patients implanted with an SCS system (Precision Spectra/Spectra WaveWriter, Boston Scientific, Valencia, CA) for use in the treatment of approved chronic pain indications (i.e., “on-label”) conducted at two centers (Hospital La Paz [HLP], Madrid, Spain; and Basildon and Thurrock University Hospitals [BTUH], Basildon, UK). This real-world observational case series is a subgroup of PRO (Patient Retrospective Outcomes: NCT01550575), an ongoing assessment of real-world outcomes of SCS for chronic pain based on retrospective chart review, which is structured to allow assessment of subcohorts. This subgroup consisted of consecutive patients at participating sites who returned for follow-up programming as part of standard-of-care.

Participants

A total of 30 patients (mean age = 54.0 years [range 35–74], females: 22 of 30) were included in this case series (22 at HLP and 8 at BTUH). Patients were diagnosed with failed back surgery syndrome (N = 29) or chronic radiculopathy (N = 1) causing chronic neuropathic pain of low back and lower limbs. Patients were implanted with dual 16-contact percutaneous leads (1 mm contact spacing between 3 mm contacts, Infinion CX, Boston Scientific) and a 32-electrode implantable pulse generator system (IPG) (Precision Spectra/Spectra WaveWriter, Boston Scientific). Typical lead placement for these patients spanned the T8–T10 vertebrae with approximately 2–3 mm mediolateral separation (Fig. 1a). The implantation procedure and criteria for permanent implant consisted of intraoperative paresthesia testing and/or >50% pain relief during a trial phase and were based on established standards and performed per each center’s standard practice. As part of standard-of-care, patients underwent a set of consecutive reprogramming visits to optimize both their outcomes and levels of charging in subperception. Ethics Committee approval was obtained from each site, and the study was conducted in accordance with GCP (ISO14155) guidelines and the Declaration of Helsinki.

Sweet Spot Search Using a Novel Electric Field Shape Configuration

The search of effective stimulation location(s) (i.e., sweet spot) in kHz stimulation is performed classically using conventional 8- or 9-mm physical bipoles and guided by anatomical references. However, this approach is likely to be suboptimal due to two main factors: (1) the anatomical region of search and the spatial variability of the sweet spot are large relative to the size of the bipolar, as was observed in PROCO RCT (Fig. 1b); and (2) conventional bipole do not generate large dorsal horn effects at subperception amplitudes as shown by computational analyses (Fig. 2b).

In this study, we made use of a novel electric field configuration (Contourc) to perform the sweet spot search. Contour has been specifically designed for subperception SCS to preferentially modulate synaptic terminals in the superficial dorsal horn while minimizing dorsal column activation. To that end, the field is shaped to create a constant electric field (dV/dy) along the rostrocaudal axis that is hypothesized to selectively engage the synaptic terminals of similarly aligned inhibitory interneurons in the dorsal horn (Fig. 2b). This is supported by computational and experimental studies demonstrating that terminals may be preferentially polarized over axons of passage or cell bodies using geometries designed to maximize the local electric field. Furthermore, this electric field has a broader span (~16 mm of anode–cathode distance) than a conventional bipolar (8–9 mm), aiming at targeting multiple sweet spots with a single field. Contour is built using precise amounts of current at each electrode in the tightly spaced leads (1 mm contact spacing), and it is tailored to each individual based on patient-specific measurements and lead placement (Fig. 2a). Therefore, this field configuration is intended to bring new benefits to subperception SCS with respect to classic anatomical search using conventional bipoles by: (1) accelerating the search process by targeting multiple sweet spots with a single field thanks to the expanded size and (2) engaging dorsal horn elements more strongly and uniformly.

The search was conducted with 2–3 initial Contour fields at 1 kHz and located across the lead span (T8–T10), starting from the T9/T10 area based on PROCO sweet spot anatomical distribution (Fig. 1b,c). Patients evaluated each program for a minimum of three days, and the most effective stimulation location, based on pain relief (>50%), was determined and subsequently utilized for frequency titration (sub-kHz).

Frequency Titration: Neural Dose Optimization

After the search process, to improve power usage and explore the role of frequency in subperception over three to four consecutive visits, patients were provided with a set of programs with
select sub-kHz frequencies: 600, 400, 200, 100, 50, and 10 Hz. All programs used the same field identified in the sweet spot search at 1 kHz. For each frequency, few stimulation programs with titration of pulse-width and amplitude were provided in order to enable optimization of the neural dose. An initial estimate of effective pulse-width per frequency was determined by extrapolating the frequency-pulse-width curve (i.e., nonlinear relationship) identified in the PROCO RCT (Fig. 1d). This estimation was progressively updated by recalculation of the curve based on cumulated experience. For each program, the amplitude perception threshold (Pth) was measured (and verified at standard sitting/standing/lying positions) and therapeutic amplitude was set below and scaled with respect to that level. Patients were instructed to evaluate and accommodate different levels of subthreshold amplitude (20–80% of Pth) to obtain the best pain relief and test each of the program settings for a minimum of three days. At each visit, patients underwent a clinical interview with site research personnel and reported, based on a paper diary, average pain scores (back, leg, overall) in a 0–10 Numeric Rating Scale (NRS) for each of the program settings tested. Patients continued to use their preferred program(s) until follow-up as per standard-of-care.

Data Collection and Statistical Analysis
Demographic information, medical history, stimulation parameters, pain locations, and pain intensity data were collected for all patients as documented as part of their routine clinic follow-up. All

Figure 1. a. Typical lead placement: dual parallel 16-contact percutaneous lead placement spanning T8–T10 vertebrae with approximately 2–3 mm mediolateral separation. b. Spatial distribution of sweet spots over T8–T11 found in PROCO RCT using conventional high frequency (unpublished data from the PROCO RCT). c. Representation of exemplary anatomical search with three Contour expanded electric field (dV/dy) configurations, which is engineered to preferentially engage dorsal horn elements. d. Depiction of frequency-pulse-width relationship extrapolation from PROCO RCT for optimal neural dose at the set of selected sub-kHz frequencies (adapted from Thomson, 2018).

Figure 2. a. Example of Contour electric field configuration at T9 with exemplary anode and cathode distribution (current fractions are customized to each patient based on individual measurements and lead placement). b. Neurophysiological effects predicted by computational modeling. Voltages were derived from a finite element model of the spinal cord. A constant electric field (dV/dy) along the rostrocaudal plane (RC) of the spinal cord is hypothesized to more selectively engage, as compared with a conventional 8 mm bipole, the synaptic terminals of similarly oriented inhibitory interneurons in the superficial dorsal horn. ML, mediolateral plane.
data collection was completed by site research personnel with no involvement by sponsor. Statistical analyses included categorizing by frequency, descriptive statistics (mean, standard deviation, or standard error) and comparison of NRS pain score (back, leg, overall), pulse-width, duty cycle (frequency \times pulse-width), and charge-per-second (frequency \times pulse-width \times amplitude). For each patient and frequency, only the program(s) that were shown to be effective (≥50% pain relief) were used to generate the pain plots and the neural dose relationships. A repeated measures ANOVA (analysis of variance) was used to evaluate the pain score at the baseline and at various program frequencies; more specifically, the PRO Mixed model in SAS was used (SAS version 9.4, Cary, NC).

RESULTS

Pain Relief

A total of 30 patients underwent frequency titration for a mean period of 6 months, and the outcomes were collected. Figure 3 shows the mean NRS pain scores (back, leg, and overall) for baseline (before SCS) and the patients’ preferred programs after neural dose optimization, categorized by frequency. The mean back NRS pain scores decreased from 8.2 ± 0.2 (baseline, mean ± standard error of the mean) to 3.1 ± 0.2 (1 kHz), to 2.5 ± 0.3 (200 Hz), and to 3.1 ± 0.2 (10 Hz) (Fig. 3a). This yielded a mean of 67% back pain relief across all frequencies (p < 0.0001), with 200 Hz providing the largest back pain reduction (71%). Importantly, the null hypothesis that pain scores were different at the different frequencies was rejected (p > 0.05), indicating that all frequencies provided equivalent back pain relief. Similar results were obtained for leg(s) and overall pain relief (Fig. 3b,c, respectively). Across all frequencies, there was a mean 72% leg pain reduction (p < 0.0001) and 65% overall pain reduction (p < 0.0001). Again, although not statistically significant, 200 Hz provided the largest reduction for leg(s) (76%) and overall (68%) pain with respect to baseline. Each preferred program was evaluated a mean of 14 days across frequency and patients.

The Sweet Spot Distribution

In most of patients (25/30), an effective sweet spot location was determined with a single search visit following the described strategy, yielding an average of 1.2 visits to sweet spot allocation. The contact-wise spatial distribution of the most effective electric field location from each patient, as determined from the search process, is represented in Figure 4a. This distribution was generated by adding counts for each of the contacts over the rostrocaudal extent of the most effective electric field of each patient (generally five contacts for 1 mm contact-spaced leads; see representation in Fig. 3a). It was observed that a large percent of the counts (55%), based on the anatomical sweet spot search strategy that was used, were concentrated in the rostrocaudal span of five contacts located at caudal T9, T9-10 intervertebral disk, and rostral T10. Specifically, one contact at rostral T10 cumulated 18 counts, and the other four contacts cumulated 16 counts each, which indicates that those contact levels were used to generate the most effective electric field in 18 and 16 patients (N = 30), respectively. This incident area can be then targeted with a single Contour field configuration. The other 45% percent of the counts spread across T8–T10 following a normal distribution-like shape.

The Neural Dosing Curves

Optimization of the neural dose (adjustment of amplitude and pulse-width) was required to be able to achieve effective and equivalent pain relief across frequency. Figure 4b,c depicts the identified empirical relationships using the novel field shape between frequency and pulse-width, and frequency and charge-per-second, for frequencies below 1 kHz. It was observed that as frequency was increased, the pulse-width in a nonlinear fashion enabled the pain relief to be maintained (Fig. 4b). More specifically, the mean (± standard deviation) pulse-width increased with decreasing frequency from 122 ± 14 μs (1 kHz) to 209 ± 28 (200 Hz) and to 350 ± 24 μs (10 Hz). For each step, the magnitude of the decrease in frequency was larger than the increase in the pulse-width, and as a result the net duty cycle (frequency \times pulse-width) decreased with frequency, specifically from 12.2% (1 kHz) to 4.2% (200 Hz) and to 0.35% (10 Hz). Therapeutic amplitude was observed to be relatively constant (mean 2.6 ± 0.9 mA) across frequencies following the described pulse-width adjustments; thus no significant association was found between subperception therapeutic amplitude and frequency. Charge-per-second (amplitude \times pulse-width \times frequency) was also found to significantly decrease as frequency is decreased (Fig. 4c). Specifically, charge-per-second decreased from 326 ± 145 μC/s (1 kHz) to 108 ± 42 μC/s (200 Hz) and to 9 ± 3 μC/s (10 Hz), thus providing the potential for large energy saving by decreasing frequency. Compared to 1000 Hz, efficiency increased by 74% at 200 Hz and by 97% at 10 Hz.

Frequency Preference and Long-Term Follow-Up

Patients selected their preferred program(s) for long-term evaluation. Patients reported a preference for different frequency options, indicating that no particular frequency was best for all patients. Specifically, 46% selected intermediate frequencies (400 or 200 Hz), 39% of patients preferred the lower frequencies (100, 50, or 10 Hz), and the remaining 15% preferred the higher frequencies (1 kHz or 600 Hz) (Fig. 5). When subdivided by frequency, 200 Hz was the most preferred option (25%), consistent with the lowest mean pain score in the NRS data. Effective pain relief was sustained at long-term follow-up (mean of one year since beginning of frequency titration and mean of two years since implant), with a mean pain reduction of 62% in overall (NRS \text{p} = \text{0.0001}), 60% in back (NRS \text{p} < \text{0.0001}), and 39% of patients preferred the lower frequencies (100, 50, or 10 Hz), and the remaining 15% preferred the higher frequencies (1 kHz or 600 Hz) (Fig. 5). When subdivided by frequency, 200 Hz was the most preferred option (25%), consistent with the lowest mean pain score in the NRS data. Effective pain relief was maintained at long-term follow-up (mean of one year since beginning of frequency titration and mean of two years since implant), with a mean pain reduction of 62% in overall (NRS = 3.10; \text{p} < \text{0.0001}), 59% in back (NRS = 3.18; \text{p} < \text{0.0001}), and 73% in leg (NRS = 2.82; \text{p} < \text{0.0001}) pain with respect to baseline. Furthermore, the use of medication, measured as daily equivalent intake of opioids, was also significantly reduced in the long term with respect to baseline (from 29.48 to 12.26 mg; \text{p} = \text{0.007}).

DISCUSSION

In this study, effective and equivalent analgesia was achieved in subperception SCS at frequencies from 1 kHz down to 10 Hz using a novel electric field shape configuration. Consistent with prior learnings in the kHz range, \text{13,14} to maintain pain relief as frequency was decreased, pulse-width and amplitude had to be adjusted following an empirically determined relationship, which resulted in notable reduction in charge-per-second. These data support the idea that effective subperception therapy is not achieved by the optimization of any single parameter (e.g., a single outperforming frequency or waveform), but rather that there is a family of effective parameter combinations, and any given frequency can be effective if targeting is appropriate and the other stimulation parameters are adequately adjusted. Furthermore, the present observations at low frequency challenge our current mechanistic
thinking and the notion that high-frequency and/or high-energy stimulation is required for effective subperception SCS.

Our results are consistent, despite some differences in methodology, with other studies that have also shown effective outcomes using sub-kHz frequencies. In a CRPS cohort, Kriek et al. found that paresthesia and three subperception modalities including 500 Hz, 1200 Hz, and BurstDR were effective and superior to placebo.\(^ {19} \) Also, recent studies using sub-kHz waveforms at subthreshold levels (e.g., high-density settings or BurstDR) have shown effective outcomes\(^ {19-23} \) and brain effects in areas related to pain relief.\(^ {24} \) However, it must be noted that these studies have mostly stimulated in the range of 400–500 Hz, and the lower frequencies (200 Hz and below) have not been extensively described. In this lower range, one study from 2007 reported effective analgesia in angina pectoris utilizing subthreshold standard rate (75–85 Hz),\(^ {5} \) although these results were not fully replicated in a following study.\(^ {25} \) Another study showed that subthreshold standard rate stimulation had a modest but clinically insufficient effect.\(^ {26} \) This

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**Figure 3.** Numerical Rating Scale of Pain Intensity (NRSPI) for back (a), leg (b), and overall (c) pain grouped by frequency and with respect to baseline. Error bars denote standard error of the mean.

**Figure 4.** a. Contact-wise sweet spot rostrocaudal distribution using Contour field shape targeting strategy (one field shape exemplarily represented); the neural dosing curves (10 Hz – 1 kHz); b. relationship between frequency and pulse-width; c. relationship between frequency and charge-per-second. Lines denote mean ± standard deviation. Note that charge-per-second is more sensitive to a single amplitude step (0.1 mA) as frequency increases, and this may account for the larger standard deviation at higher frequencies.
contrasts with our results, where 85% of patients preferred 400 Hz and below, and 200 Hz elicited the lowest pain scores and was the most preferred option. These differences may be explained by the variability in indication, the SCS system, targeting strategy (i.e., the electric field), and possible failure to titrate parameter settings in prior studies.

With respect to the search process, in line with PROCO RCT we observed a certain degree of interindividual spatial variability of the sweet spot across T8–T10. This indicates that lead placement and programming require search and individualization as the sweet spot, despite the existence of some spatial trend, is not limited to any fixed anatomical location. Our expanded electric field can then be useful to accelerate the search process as it was observed in our sample by requiring a single search visit in most patients and by covering up to 55% and 82% of the anatomical sweet spot area with one and two electric field configurations, respectively. Our field is also intended to produce a broader effect over dorsal horn rostrocaudal terminals, and in line, a recent hypothesis has proposed the dendrites of islet interneurons, oriented in the rostrocaudal direction, as the primary site of action of SCS. An enhanced activity of these islet cells may restore inhibition to dorsal horn excitatory interneurons, which would in turn reduce the activity of nociceptive-specific projection neurons.

The identified parameter relationships, including constant amplitude and a small adjustment of pulse-width relative to the magnitude of the decrease in frequency, enabled notable energy
savings (an approximately 3x charge-per-second reduction for a 10x frequency reduction). For example, it is estimated that at mean settings at 10 Hz Boston Scientific rechargeable IPG can deliver therapy for over 100 days before requiring a recharge, and the nonrechargeable IPG can last up to 12 years. These relationships also have implications in the way frequencies are compared in SCS studies. In a clinical example, Al-Kaisy et al. reported that 5882 Hz was superior to 3030 and 1200 Hz, but the criteria to set amplitude were based on perception and charging burden instead of optimal outcome, and charge-per-second delivered at 1200 Hz was significantly higher than our observed settings.20,23 Similarly in preclinical studies, Lee et al. compared the effects of 1, 5, and 10 kHz on superficial dorsal horn neurons using a fixed pulse-width of 30 μs.29 Shechter et al. (1 and 10 kHz) and Song et al. (500 Hz, 1 kHz, and 10 kHz) also compared high frequencies at a fixed pulse-width of 24 μs.29,30 However, according to our observations, a head-to-head frequency comparison is not likely to be valid if the other parameters have not been properly adjusted.

The present results, combined with those of PROCO RCT, have enabled us to derive a set of parameter combinations that result in effective subperception therapy across a broad range of frequency in SCS (10–10,000 Hz). These parameter combinations or relationships are represented in Figure 6 and contextualized with alternative waveform settings described in the literature. In the relationship between frequency and pulse-width, it was observed that our pulse-width values were substantially lower than those proposed in some studies using high-density settings (e.g., 500 μs at 500 Hz),20,23,28,32 which enabled our duty cycle to decrease with frequency (e.g., from 12.2% [1 kHz] to 4.2% [200 Hz]) (Fig. 6a). This is in contrast with the higher charge or density hypothesis that pulse-width must be titrated with frequency so that duty cycle (or pulse density) remains constant around 20–25%.34 Similarly, our 168 μs mean interpolated pulse-width at 500 Hz contrasts with the five pulses of 1000 μs that are packaged at this same frequency in the BurstDR waveform (also duty cycle 20%).11,34 Finally, SENZA and PROCO studies were concordant on pulse-width at 10 kHz, essentially due to bandwidth constraints.9,35

In the relationship between frequency and charge-per-second, it was observed that the computed charge-per-second of some studies using alternative waveforms were contained within the envelope of the curves (SENZA,36 Tavel et al.,26 Vesper et al.27), whereas others were not (SUNBURST,10 Al-Kaisy et al.16) (Fig. 6b). Of note, Tavel et al. identified that a subpopulation of patients from the SUNBURST study with lower amplitudes (mean A = 1.4, inside the curves) had better outcomes than those with higher amplitudes (mean A = 1.73, outside the curves). This suggests that our neural dosing charge-per-second curves may be indicative of adequate electrical dose at a given frequency for effective outcome. Another interesting observation is the fact that, depending on amplitude, BurstDR lay inside our charge-per-second curves despite the use of a substantially larger pulse-width at 500 Hz (5 × 1000 vs. 168 μs; Fig. 6a). A possible explanation could be that the larger pulse-width compensates for the cycle-off time inherent in burst. We also noted that the envelope of Figures 4c and 6b increased with frequency, which indicates that the use of high-dose settings (e.g., high frequency or large pulse-width) reduces the ability to control resolution of stimulation dose. As an example, it can be calculated that a 0.1 mA increment induces a larger charge-per-second increment when utilizing 10 kHz (+30 μC/s), 1 kHz (+10–15 μC/s), or BurstDR (+20 μC/s) than when using a lower effective dose (e.g., neural dosing settings at 200 Hz [+4.2 μC/s]).

These derived rules of neural dosing can be considered a first step in a unified framework for dosing stimulation in SCS. In support of this notion is the fact that parameter settings that others have shown to be effective could be represented as single points on the neural dosing curves of the present model. Having the understanding and ability to use multiple effective stimulation doses, instead of working with a single modality, may help practitioners manage the large variability that exists in SCS: (1) between subjects due to differences in physiology, disease etiology, lead type and placement, etc., and (2) within subjects due to disease progression and accommodation to chronic stimuli. In contrast, committing to a single waveform, despite being simpler, does not allow patients to reduce charging, explore their response with other doses, or change dose over time,20 and may increase the likelihood of explantation.39

The primary limitation of the present study is that it lacks randomization and wash-out periods between frequencies. Another limitation is that patients were not systematically provided with parameter combinations that were not expected to be effective. Furthermore, the identified dosing relationships and the levels of pain relief achieved may be dependent on the targeting method or the SCS system that was used since it is expected that factors such as field shape, lead type, electrode spacing, number of electrodes, single or multiple electrical sources could influence pain relief, and optimal parameter settings.4,40 Future work may include expanding the present neural dosing model to include other dimensions that potentially impact electrical dosing in SCS, such as (1) cycling and other temporal parameters, (2) stimulation location and field shape, and (3) wash-in/wash-out time, etc. Also of interest is the replication of these observations in other samples, the longer follow-up of these patients to evaluate whether there is potential to prevent from habituation effects using these lower doses, and to explore the use of modulation of frequency/neural dose over time.

CONCLUSION

Effective subperception pain relief was achieved in SCS at sub-kHz frequencies (down to 10 Hz) using a novel electric field shaped to preferentially modulate the dorsal horn. Following the neural dosing curves reported in our study, our field configuration enabled effective targeting and a significant increase in efficiency. These findings will enable effective and energy-efficient therapy as well as personalized stimulation dosing across patients and over time. Finally, these results provide insights useful in the search for mechanisms of action and guidance on requirements for useful comparison of subperception settings in clinical and preclinical experiments.

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Wendy Gu from Boston Scientific for the analysis of the PROCO study data (Fig. 1b,d).

Authorship Statements
Dr. Paz-Solis and Dr. Thomson were the principal investigators and performed the implantation and clinical evaluation of patients. Mr. Doan, Mrs. Jain, and Dr. Huertas designed the study. Dr. Huertas performed the research and prepared the draft manuscript. Mrs. Chen and Dr. Huertas analyzed the data. All authors have reviewed and approved the final version of the manuscript.

How to Cite This Article:

REFERENCES

This article explores the analgesic response of patients to optimized subperception SCS. The authors have shown a robust result
at decreasing frequencies (down to 10 Hz) as long as pulse width was increased and both amplitude and sweet spot optimized. This is reasonable evidence that there is not just a single set of sub-perception parameters that work but that there is a whole series of subperception settings that exist on a plane with now somewhat partially defined edges to that plane. Which point on the plane is best is unknown and for how many that point might be best is also unknown.

This is the first part in a seminal examination of the sub-perception landscape that is akin to the pioneering work of Barolat in 1991 (Barolat G, Zeme S, Ketcik B. Multifactorial analysis of epidural spinal cord stimulation. Stereotact Funct Neurosurg. 1991;56:77–103.) that mapped the plane of suprathreshold stimulation. More work needs to follow here, and that work will come from this group and from others. Next steps will include how our stimulation paradigms can not only be subperception and energy efficient but also how they can communicate more physiologically with the nervous system, can have a low burden of tolerance, and indeed the ultimate goal can overwrite the pain engram so neuromodulation does not have to be for life but can ultimately be curative of chronic pain itself. These goals are not abstract but I believe achievable and will be the next great push forward in our field. As of today, we can use this work of Paz et al. to guide our frequency, pulse-width, and amplitude selection and determine where on the plane of response we can find the peak for an individual patient. This is a most exciting time to be in the field of neuromodulation!

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This is an excellent study about one of the most interesting topics in neuromodulation: stimulation parameters. This work opens a door to perform low-frequency subperception SCS. It must be borne in mind that SCS-induced paresthesia may be unpleasant for patients. The reduction in energy consumption reported in this article is significant in terms of costs.

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