

## Retrospective Review

# e Effects of Kilohertz Frequency on Paresthesia Perception Thresholds in Spinal Cord Stimulation

Kas Amirdelfan, MD<sup>1</sup>, David Provenzano, MD<sup>2</sup>, Cong Yu MD<sup>3</sup>, Paul Verrills, MD<sup>4</sup>,  
Ricardo Vallejo, MD PhD<sup>5</sup>, Maged Guirguis, MD<sup>6</sup>, Jordan Tate, MD<sup>7</sup>, and Kerry Bradley, MS<sup>8</sup>

From: <sup>1</sup>IPM Medical Group, Walnut Creek, CA; <sup>2</sup>Pain Diagnostics & Interventional Care, Sewickley, PA; <sup>3</sup>Swedish Hospital, Seattle, WA; <sup>4</sup>Metro Pain Group, Melbourne, AUS; <sup>5</sup>Millennium Pain Center, Bloomington, IL; <sup>6</sup>Ochsner Health System, New Orleans, LA; <sup>7</sup>Southern Pain & Spine, Jasper, GA; <sup>8</sup>Nevro Corporation, Redwood City, CA

Address Correspondence:  
Kerry Bradley, MS  
Nevro Corporation  
1800 Bridge Pkwy  
Redwood City, CA 94065  
E-mail: bradley@nevro.com

Disclaimer: This study was funded by Nevro Corp..

Conflict of interest: See pg. E89 for full COI information.

Article received: 04-09-2024  
Revised article received: 08-08-2024  
Accepted for publication: 10-24-2024

Free full article:  
www.painphysicianjournal.com

**Background:** Paresthesia-based spinal cord stimulation (SCS) depends upon dorsal column (DC) fiber activation to engage pain-relieving neural mechanisms. However, the mechanisms for 10-kHz paresthesia-free SCS have not been fully elucidated. Preclinical work has shown selective drive of inhibitory dorsal horn neurons, while other hypotheses suggest that DC fibers may be activated. To provide clinical data for guiding mechanism work, we analyzed paresthesia perception thresholds (PPT) over a range of low to high kHz frequency and compared those values to the stimulation parameters from the therapeutic 10-kHz SCS programs used by patients.

**Objective:** The goal of this study was to provide clinically relevant stimulation parameters for translational mechanism work.

**Study Design:** Retrospective chart review of technical data collected during baseline evaluation from two prospective clinical studies.

**Setting:** Acute outpatient follow-up.

**Methods:** Data were extracted from study files of enrolled patients who had used fully implanted SCS for at least 3 months with leads positioned in the epidural space at the T8-T11 vertebral levels to treat their chronic intractable back and/or leg pain. PPTs had been measured using a bipole program at 10 kHz at pulse width (PW) = 30  $\mu$ s, and at 50 Hz, 500 Hz, 1 kHz, and 5 kHz at PW = 80  $\mu$ s. Therapeutic stimulation amplitudes for 10 kHz at 30  $\mu$ s were obtained from patients' IPG log files at the time of study enrollment.

**Results:** PPTs were obtained from 23 patients with failed back surgery syndrome (11 M/ 12 F; 60  $\pm$  15 years old). PPTs at PW = 80  $\mu$ s were PPT (50 Hz) = 7.9 (5.7 - 9.7) mA, PPT (500 Hz) = 7.0 (5.2 - 9.1) mA, PPT(1 kHz) = 7.0 (5.5 - 8.5) mA, and PPT (5 kHz) = 6.1 (4.1- 7.9) mA; all higher frequencies had statistically significantly lower PPTs than PPT(50 Hz at 80  $\mu$ s). For 10 kHz at 30  $\mu$ s, the PPT was higher than 15 mA for 13 (56%) of the subjects; for the remaining 44%, the PPT = 8.3  $\pm$  4.0 mA was statistically significantly larger than the therapeutic stimulation pulse amplitudes = 2.4  $\pm$  0.4 mA.

**Limitations:** Retrospective chart review, small number of patients.

**Conclusions:** Therapeutic 10-kHz SCS uses stimulation amplitudes far lower than the PPT, providing evidence that therapeutic 10-kHz SCS does not activate dorsal column axons. Additionally, the PPT decreases with increasing kHz frequency, suggesting that a presumed asynchronous pattern of activation from kHz stimulation does not raise the threshold at which sensation occurs.

**Key words:** Kilohertz, frequency, paresthesia, perception threshold, spinal cord stimulation

**Pain Physician 2025: 28:E81-E91**

**S**pinal cord stimulation (SCS) has been used to treat chronic intractable pain for over half a century. The technique's first clinical applications

were derived from Melzack and Wall's gate control theory, which hypothesized that the activation of large diameter afferent fibers that mediated innocuous

sensation would in turn drive inhibitory interneurons in the spinal dorsal horn, which ideally would lead to reductions in the firing of pain-projecting central neurons (1,2). Activation of those large A beta fiber collaterals in the dorsal columns (DC) and dorsal roots of the spinal cord generates a paresthesia, experienced as an abnormal sensation, often described as a “tingling” or “buzzing” (3).

The amplitude and pulse width of the SCS stimulation pulses are the predominant factors in determining the activation of the dorsal column and dorsal root fibers. The paresthesia perception threshold is typically defined as the minimum stimulation pulse amplitude (at a given pulse width) at which paresthesia is first reported by the patient (4,5). As the stimulation pulse amplitude increases above this threshold, more dorsal column and/or dorsal root fibers are recruited, and the perceived paresthesia spreads over wider regions of the body and grows stronger in perceived intensity. In traditional SCS, the primary technical outcome of an SCS procedure is to generate a paresthesia that maximally overlaps the patient’s painful areas, a process that has been demonstrated to maximize the patient’s pain relief. Critically, paresthesia-pain overlap needs to be achieved with paresthesia that is relatively comfortable: if the perceived strength of the sensation becomes too intense before adequate overlap is achieved, then the therapy may be a technical failure, since the patient will not allow the stimulation amplitude to be increased to a level that achieves pain coverage (6-8).

Even if good paresthesia-pain overlap is achieved at a stimulation amplitude that yields comfortable paresthesia intensity, postural challenges from the activities of daily living can alter the intensity and distribution of paresthesia (9-11). As the patient changes body positions during the day and evening, the spinal cord moves within the thecal sac to positions closer and farther from the stimulating contacts, and the fixed-amplitude SCS correspondingly recruits either a greater or lesser number of dorsal fibers (12). This phenomenon can distinctly alter the intensity of paresthesia sensation, from overly strong or “shocking” to very weak. Technologies have been developed to better control the intensity of paresthesia: in a situation analogous to “cruise control” in an automobile, the stimulation pulse amplitude is adjusted automatically by the device based on a measured signal that varies with the posture (e.g., the evoked compound action potential of spinal dorsal fiber activation or a device-mounted posture-sensitive accelerometer). These “closed-loop”

solutions are intended to stabilize the intensity of the paresthesia to retain comfort for the patient while using traditional SCS (13-15).

Because of these challenges involved in paresthesia generation and management, various SCS stimulation strategies have been attempted in recent years to achieve pain relief while minimizing the perception of stimulation-induced paresthesia. The most well-studied strategy is 10-kilohertz (kHz) SCS, which is “paresthesia-independent”: stimulation-induced paresthesia has no role in therapeutic programming, leads are positioned in the epidural space via anatomic landmarks, stimulation programs are administered via standardized algorithms instead of paresthesia-pain overlap, and the patient never experiences paresthesia at any time during daily or nightly use (16-23). These frank clinical differences from low-frequency, paresthesia-based SCS suggest that paresthesia-free high-kHz SCS works via different mechanisms.

The mechanistic bases of high-kHz SCS have not been fully clarified; preclinical work has suggested that 10-kHz SCS can drive inhibitory interneurons selectively while avoiding excitatory interneurons in the spinal dorsal horn at stimulation amplitudes that do not activate dorsal columns (24,25). Other studies focusing on the molecular effects of low-intensity 10-kHz SCS have observed lower levels of MAPK proteins and reduced spinal glutamate release in the dorsal horn (26,27).

Preclinical and computational modeling studies using 10-kHz SCS at higher stimulation amplitudes have shown activation of both inhibitory and excitatory dorsal horn neurons, possibly due to some dorsal column recruitment, with a net effect of suppression (28-30). Other preclinical and modeling work has yielded hypotheses suggesting that dorsal column axons might be activated at high-kHz settings without causing a patient to experience paresthesia due to the relative inefficiency of synaptic transmission from the stimulation-induced stochastic firing pattern (31).

Given the variability of proposed mechanisms using different stimulation parameter ranges, it is therefore critical to understand and utilize clinically relevant parameters when performing translational mechanism work. In this study, we analyzed clinical paresthesia perception thresholds over a range of low-to-high-kHz frequency, and we compared these values to the stimulation parameters from the therapeutic high-kHz programs used by patients. From these results, we hope to provide better guidance for mechanism work for high-kHz SCS.

## METHODS

This study is a retrospective chart review of unpublished technical data collected during baseline evaluation from 2 prospective clinical studies conducted at 7 sites in the United States and one site in Australia. For the clinical studies, all sites obtained investigational review board or ethics committee approvals (as appropriate to the country of the site), and all patients provided informed consent (DC Study: ISRCTN54708653, WIRB Study # 1171857; DOSE Study: WIRB Study #1162195). The studies were conducted in accordance with local clinical research and data protection regulations, good clinical practice guidelines ISO14155, and the Declaration of Helsinki.

### Device Description

The rechargeable Senza SCS system (Nevro Corp.) received the CE Mark in 2010, approval from the Australian Therapeutic Goods Administration in 2011, and U.S. Food and Drug Administration approval in 2015 for use in the management of chronic intractable pain of the trunk and/or limbs. This system delivers electrical stimulation to the spinal cord through the use of a fully implantable pulse generator (IPG) and epidural leads, which carry 8–16 platinum iridium electrodes. Although this system can deliver stimulation frequencies from 2 Hz to 10 kHz, only paresthesia-free 10-kHz SCS using a pulse width (PW) of 30  $\mu$ s (hereafter referred to as “therapeutic 10-kHz SCS”) was provided in the present studies for therapeutic purposes. All other tested frequencies were administered only acutely in the clinic under experimental conditions as part of the study protocols.

### Procedures

For the studies, candidates were identified from existing patients who were using fully implanted therapeutic 10-kHz SCS at each clinical site. These patients were screened consecutively. Those who signed the informed consent form underwent evaluations to determine their eligibility based on the inclusion and exclusion criteria of the particular study for which they were considered. Patients meeting all the inclusion criteria and none of the exclusion criteria for the relevant study were enrolled. The common inclusion/exclusion criteria for all studies are listed in Table 1, including criteria for this retrospective analysis. Inclusion/exclusion criteria that were unique to different studies did not confound the goals, analyses, or conclusions of this post facto analysis.

### Data Collection

#### *Clinical Data*

Baseline data included patient demographics, duration of pain, duration of implant prior to study entry, distribution of pain, pain diagnoses, and numeric rating scale (NRS) pain intensity scores using therapeutic 10-kHz SCS at study entry. An NRS score of 0 indicated “no pain,” and 10 indicated “worst possible pain.”

#### *Paresthesia Thresholds and Therapeutic Stimulation Pulse Amplitudes*

During baseline evaluation, paresthesia perception thresholds (PPT) were measured with each patient in a seated position, using a modified method of limits (32). The stimulation contact combination consisted of an 8-mm bipole from the patient’s “favorite program,” generally located near the T9-T10 disc space. The algorithm for PPT measurements was as follows: first, an attempt was made to measure the PPT at 10 kHz at a PW of 30  $\mu$ s. Next, the stimulation PW was changed to 80  $\mu$ s, and PPTs were measured at each of the following frequencies: 50 Hz, 500 Hz, 1 kHz, and 5 kHz. The incremental amplitude step size for all threshold measurements was 0.1 mA. To avoid carry-over effects of paresthesia, after each measurement, stimulation was turned off immediately and at least one minute elapsed between the next measurement.

The pulse amplitudes for the patient’s therapeutic 10-kHz SCS program were collected from program usage logs that were uploaded from their IPG at the time of enrollment.

### Analyses

Descriptive statistics were calculated for each analyzed variable, including the number of observations, proportions, mean, median, and standard deviation. Data are generally reported as mean  $\pm$  SD or median (25%ile – 75%ile) as appropriate to the data distribution. The normality and symmetry of the data were evaluated by the Shapiro-Wilk test, and where appropriate, parametric (e.g., analysis of variance [ANOVA]) and nonparametric (e.g., Kruskal-Wallis and Mann-Whitney) methods were used. Pearson’s correlation was used to assess the strength of relationship between variables. A *P*-value less than or equal to 5% (*P* < 0.05) was considered statistically significant.

Table 1. *Inclusion and exclusion criteria.*

Inclusion Criteria	Exclusion Criteria
1. Have been diagnosed with chronic, intractable back pain with or without leg pain secondary to failed back surgery syndrome (FBSS).	1. Have a medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures or accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator.
2. Have been implanted with the Nevro® Senza® SCS system with dual leads, approximately over vertebrae T8-T11, for at least 3 months, and are using the system with single-area, continuous 10-kHz stimulation programs at least 18 hours daily, as determined by subject reporting and confirmation via device diagnostics, for at least 21 days prior to enrolling in this study.	2. In the opinion of the investigator, have an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance with intervention, and/or ability to evaluate treatment outcome.
3. If taking them, be on stable chronic pain medications, as determined by the Investigator, for at least 28 days prior to enrolling in the study and be willing to stay on those medications with no dose adjustments until study completion or study withdrawal, whichever comes first.	3. Have a current diagnosis of a progressive neurological disease such as multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, rapidly progressive diabetic peripheral neuropathy, brain or spinal cord tumor, central deafferentation syndrome, complex regional pain syndrome, or acute herniating disc, as determined by the investigator.
4. Be 18 years of age or older at the time of enrollment.	4. Have any clinical evidence of mechanical instability or progressive neurologic pathology that warrants surgical intervention.
5. Be willing and able to comply with study-related requirements, procedures, and visits.	5. Have undergone an interventional procedure and/or surgery to treat back or leg pain other than Senza® HF10 therapy in the last 30 days.
6. Be capable of subjective evaluation, able to read and understand EC- or IRB-approved written questionnaires, and able to read, understand, and sign the EC- or IRB-approved written informed consent, all of which will be in Australian English (for AU) or American English (for US).	6. Have a condition currently requiring or likely to require diathermy.
7. Be compliant in using the patient programmer and recharger as determined by the Investigator.	7. Have metastatic malignant disease or active local malignant disease.
8. As determined by the investigator, be compliant in adjusting programs using the device remote control.	8. Have a life expectancy of less than one year.
9. Considering daily activity and rest, report a recall average back pain relief of > 50% compared with pre-implant and a recall average NRS score of < 5 for back pain during the previous 14 days prior to study enrollment.	9. Have an active systemic or local infection.
10. Have complete algorithmic testing of PPTs for 50 Hz, 500 Hz, 1 kHz, and 5 kHz using 80 µs and 10 kHz using 30 µs.	10. Be pregnant (if female and sexually active, patient must be using a reliable form of birth control, surgically sterile, or at least 2 years postmenopausal).
11. Have an accessible IPG log file documenting the stimulation program usage amplitude during the time of study enrollment.	11. Have, within 6 months of enrollment, a significant untreated addiction to dependency-producing medications or have a history of substance abuse (including alcohol and illicit drugs).
	12. Be concomitantly participating or plan to participate in another clinical study overlapping in time with the present clinical study.
	13. Have an existing drug pump and/or another active implantable device (switched on or off) such as a pacemaker or other non-Senza® SCS device.

## RESULTS

### Patients

PPTs were measured in 27 patients. Four patients did not have complete data sets and were removed from the analysis. For the 23 patients analyzed, demographics and clinical characteristics were as shown in Table 2.

### Thresholds

#### 10-kHz Stimulation

For therapeutic 10-kHz SCS, we found a mean stimulation pulse amplitude of  $2.4 \pm 0.4$  mA. During acute testing to find the PPT (10 kHz at 30 µs), only 44% (10/23) of patients reported paresthesia at or below 15 mA, the maximum output of the stimulator. For these patients, the

PPT (10 kHz at 30 μs) was 8.3 ± 4.0 mA; this measurement was statistically significantly higher than their therapeutic 10-kHz SCS pulse amplitude ( $P = 0.001$ ) (Fig. 1).

As a metric for assessing the likelihood of dorsal column (DC) activation during therapeutic 10-kHz SCS, we calculated the ratio of the amplitude of therapeutic 10-kHz SCS to the acutely measured PPT (10 kHz at 30 μs). For the patients who reported paresthesia using 10 kHz at 30 μs, this ratio was 37 ± 21 %. However, over half of the patients had a PPT (10 kHz at 30 μs) that was greater than 15 mA. If we conservatively assume that the PPT (10 kHz at 30 μs) was 15.1 mA for these 56% of patients, we can pool the data for all patients to estimate the maximum possible ratio of therapeutic 10-kHz SCS amplitude to the PPT (10 kHz at 30 μs) to be 25 ± 17%.

To assess if the stimulation amplitude for therapeutic 10-kHz SCS was related to the distance between the electrodes and the spinal cord, we took advantage of the fact that the paresthesia threshold might be considered as a rough surrogate of this distance (33). We calculated but found no significant correlation between the PPT (50 Hz at 80 μs) and the amplitude for therapeutic 10-kHz SCS across patients ( $r[23] = 0.16, P = 0.45$ ) (Fig. 2). We also found no significant correlation between the NRS scores for the patients' back and leg pain and the PPT (50 Hz at 80 μs) ( $r_{Back}[23] = -0.17, P = 0.44; r_{Leg}[19] = -0.04, P = 0.87$ ).

Table 2. Demographics and clinical conditions of analyzed patients.

Demographics of Analyzed Patients	
Gender, M/F, n	11/12
Age, y	60 ± 15
Pain duration, y	9 ± 7
Implant duration before study entry, y	1.9 ± 1.7
Pain scores at study entry	
Back pain	2.2 ± 1.5
Leg pain	1.6 ± 1.2
Distribution of leg pain, n	
Unilateral	11
Bilateral	8
None	4
Other Diagnoses*, n	
Radiculopathy	17
Mild/moderate spinal stenosis	12
Degenerative disc disease	12
Spondylosis	6
Neuropathic pain	5
Spondylolisthesis	4
Lumbar facet-mediated pain	2
Sacroiliac dysfunction	1
Internal disc disruption/annular tear	1
Other chronic pain	6

\*Patient could have more than one additional diagnosis.

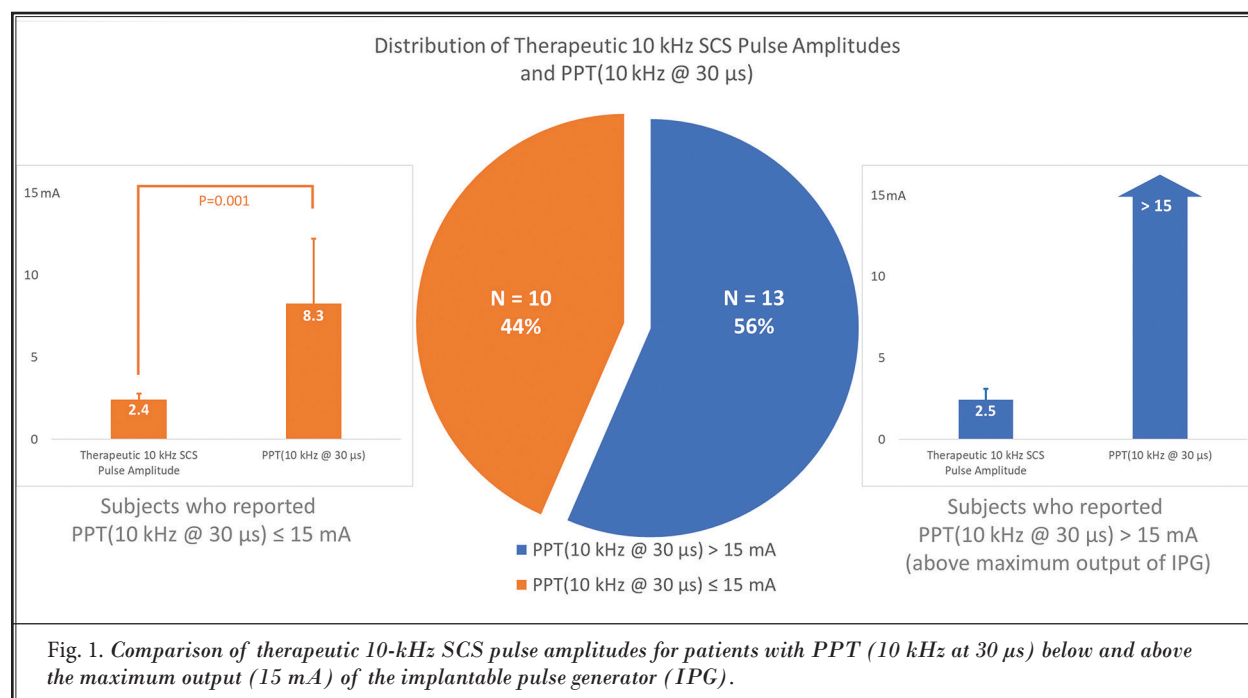


Fig. 1. Comparison of therapeutic 10-kHz SCS pulse amplitudes for patients with PPT (10 kHz at 30 μs) below and above the maximum output (15 mA) of the implantable pulse generator (IPG).



### Variation in PPT with Frequency

Using a PW = 80  $\mu$ s, all 23 patients reported paresthesia below 15 mA for all tested frequencies up to 5 kHz. We found the following: PPT (50 Hz at 80  $\mu$ s) = 7.9 (5.7 – 9.7) mA, PPT (500 Hz at 80  $\mu$ s) = 7.0 (5.2 – 9.1) mA, PPT (1 kHz at 80  $\mu$ s) = 7.0 (5.5 – 8.5) mA, and PPT (5 kHz at 80  $\mu$ s) = 6.1 (4.1- 7.9) mA. After the PPTs for 500 Hz, 1 kHz, and 5 kHz to the PPT (50 Hz at 80 $\mu$ s) were normalized for each patient, the relative PPTs across frequencies were compared using the Kruskal-Wallis test, with post-hoc Nemenyi and Q-tests to compare inter-frequency PPT differences. This analysis revealed that the PPT was statistically significantly different with varied frequency (H [3] = 36.8,  $P < 0.001$ ), and the relative PPT for higher frequencies were statistically significantly lower than the PPT (50 Hz at 80  $\mu$ s) (Fig. 3).

## DISCUSSION

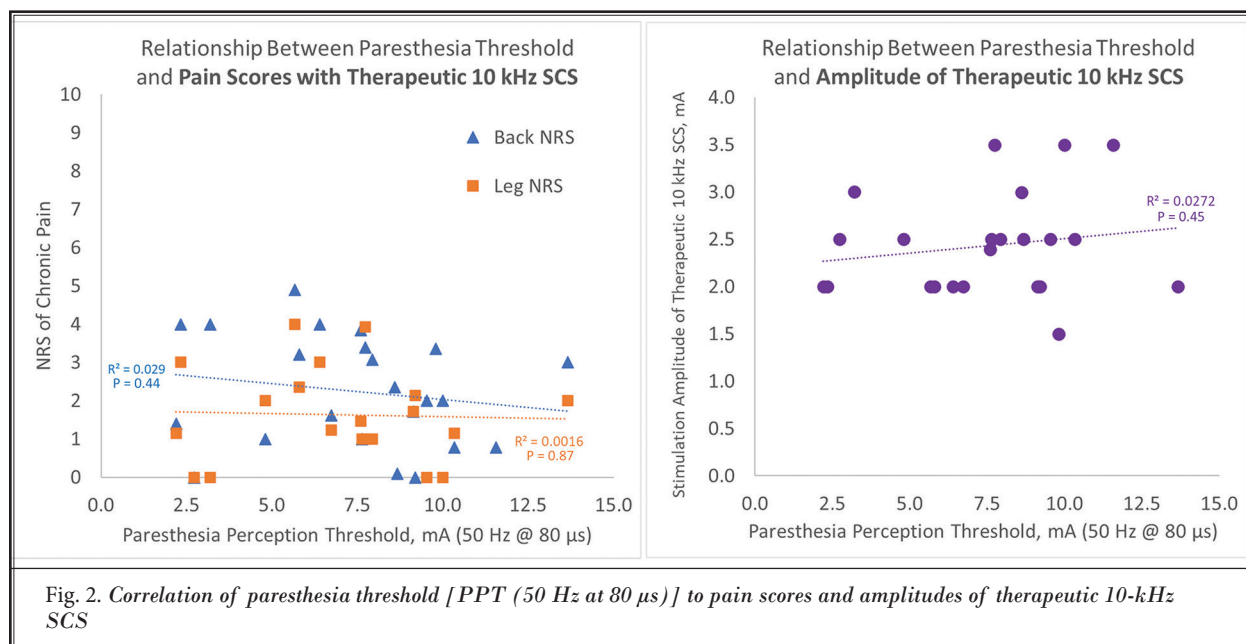
### Relationship of Paresthesia Perception Threshold to Stimulation Amplitude

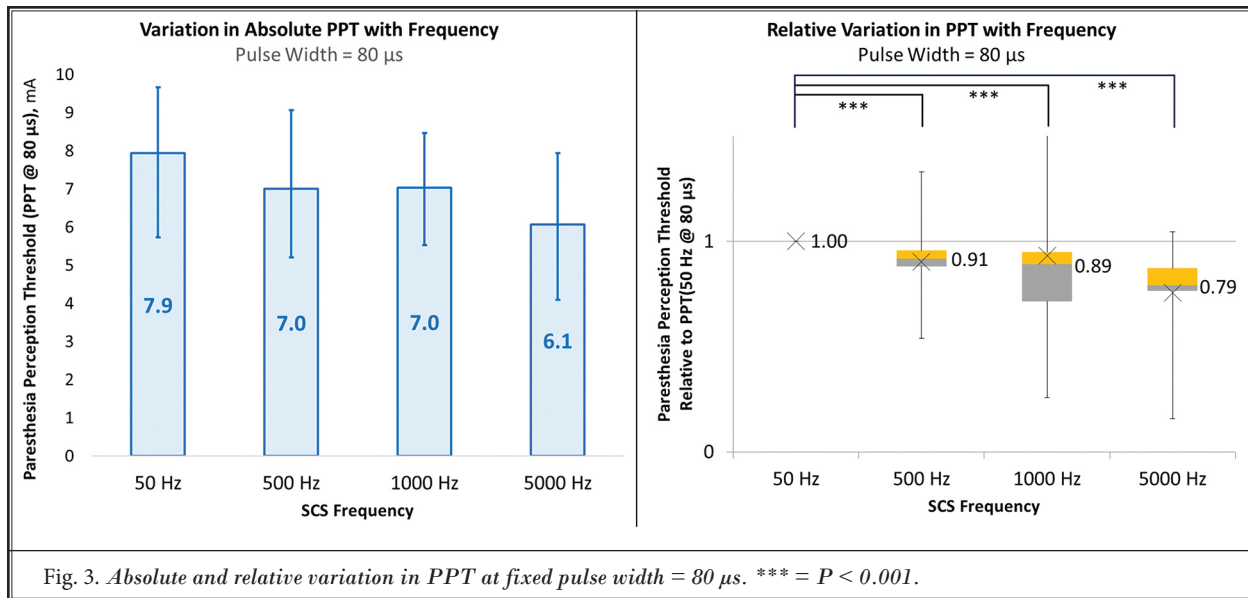
Recent SCS strategies seeking to reduce or eliminate paresthesia have used lower frequencies or alternative waveforms, with varying degrees of clinical success (34-39). The mechanistic bases for these strategies are still under exploration. Because these strategies intend to avoid generating paresthesia, they most likely deliver stimulation at some level below the DC activation threshold, since the DC fibers are predominantly responsible for paresthesia sensation,

and their activation threshold is essentially the same as the clinical paresthesia threshold (3,14,40). For the purposes of translation and hypothesis generation, it is thus important to understand the PPT for any strategy and the relative percentage of PPT at which a therapeutic current is clinically programmed to be able to infer whether the DC fibers are being stimulated and therefore play a role in pain relief.

For 10-kHz SCS, a recent publication reported that only 20% of tested patients reported a PPT (10-kHz at 30  $\mu$ s) and that the mean threshold for these patients was  $7.1 \pm 4.8$  mA (4). In this study, we found that 44% of patients reported a PPT below 15 mA where the mean PPT (10 kHz at 30  $\mu$ s) was  $8.3 \pm 4.0$  mA. Differences between these data are perhaps due to the different test conditions and implanted state of the patients: the former study was performed during the temporary SCS trial, while our results were tested on patients who had been implanted with permanent IPGs for many months. Nonetheless, the results both studies are in gross agreement and suggest that most chronic low back pain patients with leads in the middle or low thoracic epidural space will not experience paresthesia, even at the maximum pulse amplitude (15 mA) of the stimulator.

The mechanistic implications of these results are important. For all patients, we found the average therapeutic 10-kHz SCS stimulation amplitude to be  $2.4 \pm 0.4$  mA, in keeping with previous reports from large-





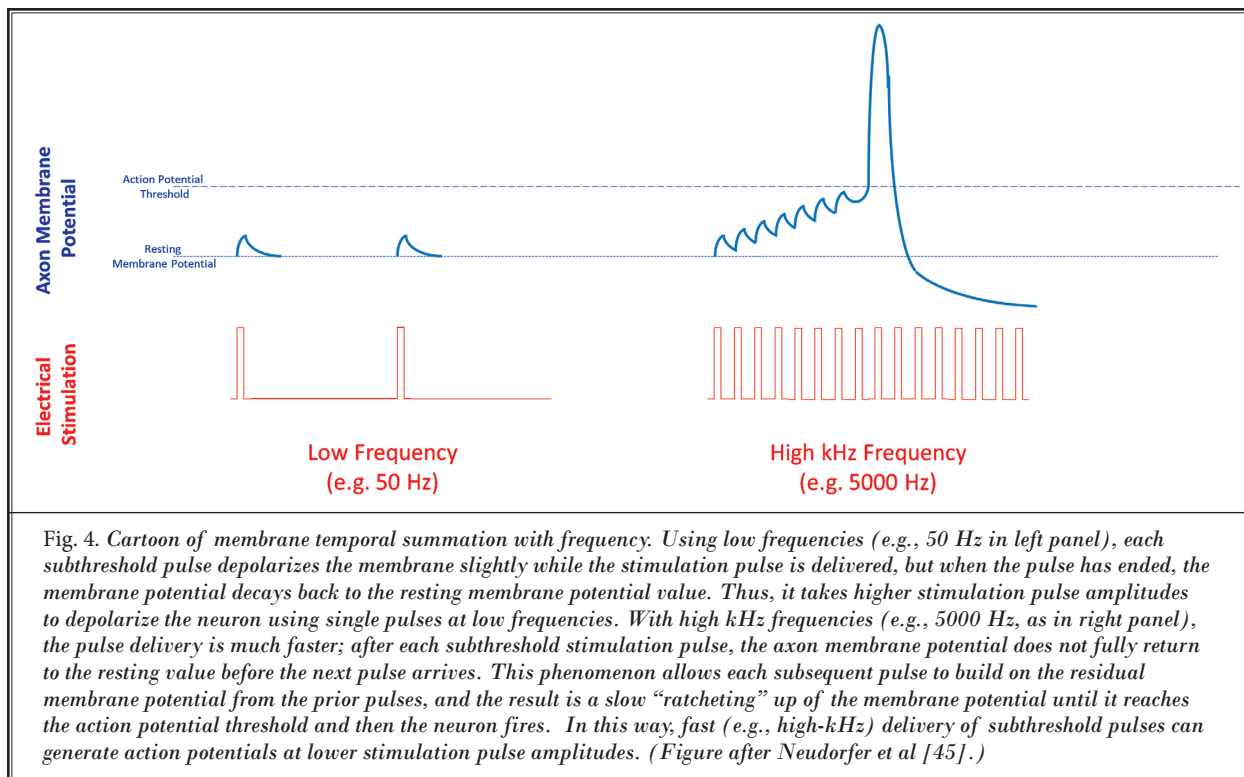
scale, long-term randomized controlled trials (16,18). Based on this finding, the maximum possible ratio of therapeutic 10-kHz SCS amplitude to the PPT (10 kHz at 30 μs) is approximately 25%. This very low therapeutic intensity provides a rational explanation for the lack of paresthesia experienced during the use of therapeutic 10-kHz SCS and why patients typically use this procedure 24 hours each day and do not need their remote controls to adapt the stimulation amplitude to their activities of daily living (41). Additionally, 10-kHz SCS is “paresthesia-independent,” since contact combinations from which therapeutic 10-kHz SCS is successfully delivered generate little or no paresthesia-pain overlap (when programmed to generate paresthesia) (22). In summary, these clinical results suggest strongly that the mechanism of 10-kHz is not mediated by DC axon activation.

#### Relationship of Paresthesia Perception Threshold to Frequency

Computational models have been employed to evaluate the axon activation threshold and have suggested that the threshold is reduced as the frequency increases into the kHz range (42,43) (Fig. 4). This effect has also been seen in preclinical and clinical settings (44-46). The decrease in the activation threshold is attributed to a form of “membrane temporal summation,” which occurs when a train of stimulation pulses (each “subthreshold” to the single-pulse or low-frequency-pulse threshold) is delivered to the axon. In its simplest form, with each delivered subthreshold pulse, the neu-

ral membrane voltage is slightly depolarized, though not enough to generate an action potential. If the time between the stimulation pulses is long relative to the membrane relaxation time constant, the effect of prior subthreshold stimulation pulses is nil or negligible, so each pulse is effectively acting on a membrane near or at resting potential. As the frequency is increased, the time between stimulation pulses is decreased, allowing for the effect of each new subthreshold pulse to build on the summed residual effect of prior subthreshold pulses. The net effect is a “ratcheting” up of the membrane potential toward the threshold; once the threshold is reached, the neuron will fire an action potential.

Computational models have also suggested that the pattern of activation in the kHz range becomes highly variable due to differences in refractory period response and pulse timing and that these effects occur at and above the activation threshold (42,47,48). It has recently been hypothesized that the PPT from DC activation may be dependent upon this pattern of neural activation (31). In particular, since DC fibers cannot reliably follow stimulation rates above a few hundred hertz, the resulting pattern of activation may be less synchronized at higher frequencies, which may result in less efficient transmission through the DC nuclei, the thalamus, and ultimately the sensory cortex, where paresthesia perception is consciously appreciated. The clinical manifestation of this compromised supratentorial transmission might then be an elevated PPT at these higher frequencies. Meanwhile, the antidromic neural traffic that would influence the spinal segmental circuitry involved in pain relief may still



be retained, thus resulting in DC-mediated pain relief without paresthesia.

However, we observed that stimulation frequencies above 50 Hz were associated with significant reduction in PPT to a much greater degree than were lower frequencies. For the pattern hypothesis, Sagalajev et al reported electrophysiologic data from animals and computational modeling data, but the study's human data were based on only a single patient. Here, we provide systematic clinical data from 23 patients that do not support the concept that higher kHz frequencies would increase the PPT; in contrast, higher kHz frequencies make paresthesia perception more likely (at the same stimulation amplitude and PW). This finding suggests that membrane temporal summation is more important for the PPT than the pattern of activation. Clinical microneurography and microstimulation studies suggest why this may be so: in focal peripheral nerve stimulation with intraneural microelectrodes, it was shown that a single action potential in one or very few fibers was responsible for human percept, indicating a robust receptor-to-cortex pathway for touch (49-51). Thus, it seems more likely that the pattern of dorsal column activation plays a role in other aspects of paresthesia, such as the quality and/or perceived body distribution of the sensation itself (52).

In this study, we observed a statistically significant, ever-decreasing change in PPT as the stimulation frequency was increased above 50 Hz to 500 Hz, 1 kHz, and 5kHz. In another recent clinical study, decreases in paresthesia thresholds were not observed in the testing of PPTs using a fixed PW of 60  $\mu$ s and increasing frequencies of 600 Hz, 1.2 kHz, and 2.4 kHz (4). Once again, differences in the patients' experiences with SCS and study methodology may have resulted in the different outcomes. We also note that the reduction in the threshold up to ~1 kHz was only 10% but was twice that at 5 kHz (~21%). Data from human peripheral nerve studies also suggest that higher kHz frequencies will yield a much larger reduction in threshold, where a decrease in activation threshold was more profound for frequencies above 2.5 kHz (53).

Other investigators have studied the SCS PPT with respect to stimulation pulse frequency. Abejon et al (54) focused on a lower frequency range (40 - 1200 Hz), utilized a much higher PW setting (300  $\mu$ s) than we did (80  $\mu$ s) as well as different manufacturers' IPGs, and employed each patient's therapeutic contact combination, whereas we used a fixed bipole. Abejon et al (54) observed a distinct and large (~70%) reduction of stimulation thresholds in the 40 - 1200 Hz range. In contrast, we observed a much smaller (~9%), non-



significant difference between 50 Hz and 500 Hz or 1000 Hz. Our stimulation threshold for 50 Hz at 80  $\mu$ s was approximately 7.9 mA, in good agreement with Yearwood et al (55), while the PPT seen by Abejon et al (54) for 40 – 60 Hz at 300  $\mu$ s was nearly 7 mA, approximately 56% higher than the corresponding value from Yearwood et al. Notably, in a separate study of the effects of PW in the same clinic, the PPT at 50 Hz at 80  $\mu$ s was ~ 14mA, and 50 Hz at 300  $\mu$ s was ~ 6.5mA, again much higher than found by Yearwood et al. The reasons for these discrepancies are not clear but may be attributable to methodological differences between the studies.

Finally, we observed that there was no correlation between the therapeutic 10-kHz SCS value used by patients and their PPT (50 Hz at 80  $\mu$ s). In traditional paresthesia-based SCS, in which the PPT is strongly dependent on the distance between the spinal cord and the electrodes, the therapeutic amplitude is thus correlated to this distance. With 10-kHz SCS, however, we found that the therapeutic amplitude was in a relatively narrow range (1.5 - 3.5 mA) while the PPT (50 Hz at 80  $\mu$ s) varied widely. Additionally, there was no correlation of the therapeutic 10-kHz SCS pain relief scores for each patient's back or leg to the PPT (50 Hz at 80  $\mu$ s). This, coupled with the mean back and leg pain relief scores of 2.2 and 1.6, respectively, indicates that patients got good relief with these stimulation amplitudes despite likely having a distinctly variable distance between the electrodes and the cord.

### Limitations

This study was a retrospective chart review of paresthesia thresholds collected as observational data within the context of 2 clinical studies. Since these studies had different goals that were not necessarily related to the paresthesia threshold, these data were not captured with the intent of assessing therapeutic effects of paresthesia and frequency. Nonetheless, these data were collected systematically by trained personnel using predefined procedures. We therefore have confidence in the accuracy of the measured thresholds. This analysis was also conducted on a limited number of patients; thus, the small sizes of the studies ( $n = 31$  and  $n = 13$ ) from which the data were drawn and the fact that thresholds were not obtained in all enrolled patients may introduce bias to the results.

We did not capture qualitative aspects of the

experienced paresthesia, which might have provided some insight into the different perceived patterns of the activation from different frequencies. Because the hypothesis regarding the pattern of dorsal column activation is related to the paresthesia threshold, however, this omission does not necessarily limit the conclusions of our analysis.

### CONCLUSIONS

We found that the stimulation amplitude for therapeutic 10-kHz SCS was far lower than the paresthesia perception threshold using the same stimulation settings, providing evidence that therapeutic 10 kHz SCS did not activate dorsal column axons. Additionally, we measured that the paresthesia threshold decreased with increasing kHz frequency, suggesting that a presumed asynchronous pattern of activation did not raise the threshold at which sensation occurs. Finally, we observed no correlation among paresthesia threshold (a surrogate measure of electrode-to-spinal-cord distance), pain relief, and therapeutic 10-kHz SCS thresholds. These clinical findings further underscore that therapeutic 10-kHz SCS appears to be "paresthesia-independent" and that hypotheses for high-kHz mechanisms should be predominantly guided by clinical responses.

### Conflicts of Interest

Investigators and Nevro author contributed to manuscript writing and critical revision. Dr. Amirdelfan: research contracts, hourly consulting fees, speaking fees for Nevro; scientific advisory board for Biotronik, Nevro, Presidio and Saluda; minor stock options with Nalu and Saluda. Dr. Provenzano: consultant for Avanos, Boston Scientific, Medtronic, Nevro, and SI Bone; Pain Diagnostics and Interventional Care has received research support from Abbott, Avanos, Boston Scientific, Nevro, and Stimgenics. Dr. Yu: research support from Nevro. Dr. Verrills: consulting fees from Presidio and Saluda; speaking fees from Saluda. Dr. Vallejo: stock in Capri Medical and C-Flow. consultant for clinical and research support for the study described from Nevro. Dr. Guirguis: consultant for Nevro, Boston Scientific, and Saluda. Dr. Tate: consulting fees from Abbott, Curonix, Medtronic, Nevro, and Saluda; speaking fees from Abbott, Curonix, Medtronic, Nevro, and Saluda. Mr. Bradley: employee of Nevro Corp; stock in Abbott, Boston Scientific, and Nevro.

## REFERENCES

- Melzack R, Wall PD. Pain mechanisms: A new theory. *Science* 1965; 150:971-979.
- Shealy CN, Mortimer JT, Hagfors NR. Dorsal column electroanalgesia. *J Neurosurg* 1970; 32:560-564.
- Hunter JP, Ashby P. Segmental effects of epidural spinal cord stimulation in humans. *J Physiol* 1994; 474:407-419.
- Hatheway J, Yang M, Fishman M, et al. Defining the boundaries of patient perception in spinal cord stimulation programming. *Neuromodulation* 2024; 27:108-117.
- North RB, Lempka SF, Guan Y, et al. Glossary of neurostimulation terminology: A collaborative neuromodulation foundation, institute of neuromodulation, and international neuromodulation society project. *Neuromodulation* 2022; 25:1050-1058.
- North RB, Ewend MG, Lawton MT, Piantadosi S. Spinal cord stimulation for chronic, intractable pain: Superiority of "multi-channel" devices. *Pain* 1991; 44:119-130.
- Oakley JC, Prager JP. Spinal cord stimulation: Mechanisms of action. *Spine (Phila Pa 1976)* 2002; 27:2574-2583.
- Barolat G, Massaro F, He J, Zeme S, Ketcik B. Mapping of sensory responses to epidural stimulation of the intraspinal neural structures in man. *J Neurosurg* 1993; 78:233-239.
- Abejon D, Rueda P, Parodi E, Del Saz J. Effects of movement and postural positions in spinal cord stimulation in the new rechargeable systems. *Pain Physician* 2014; 17:345-352.
- Cameron T, Alo KM. Effects of posture on stimulation parameters in spinal cord stimulation. *Neuromodulation* 1998; 1:177-183.
- Olin JC, Kidd DH, North RB. Postural changes in spinal cord stimulation perceptual thresholds. *Neuromodulation* 1998; 1:171-175.
- Holsheimer J, den Boer JA, Struijk JJ, Rozeboom AR. Mr assessment of the normal position of the spinal cord in the spinal canal. *AJNR Am J Neuroradiol* 1994; 15:951-959.
- Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain* 2012; 153:593-601.
- Pilitsis JG, Chakravarthy KV, Will AJ, et al. The evoked compound action potential as a predictor for perception in chronic pain patients: Tools for automatic spinal cord stimulator programming and control. *Front Neurosci* 2021; 15:673998.
- Schultz DM, Webster L, et al. Sensor-driven position-adaptive spinal cord stimulation for chronic pain. *Pain Physician* 2012; 15:1-12.
- Petersen EA, Stauss TG, Scowcroft JA, et al. Effect of high-frequency (10-kHz) spinal cord stimulation in patients with painful diabetic neuropathy: A randomized clinical trial. *JAMA Neurol* 2021; 78:687-698.
- Petersen EA, Stauss TG, Scowcroft JA, et al. Durability of high-frequency 10-kHz spinal cord stimulation for patients with painful diabetic neuropathy refractory to conventional treatments: 12-month results from a randomized controlled trial. *Diabetes Care* 2022; 45:e3-e6.
- Kapural L, Yu C, Doust MW, et al. Novel 10-kHz high-frequency therapy (hf10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: The senza-rct randomized controlled trial. *Anesthesiology* 2015; 123:851-860.
- Kapural L, Yu C, Doust MW, et al. Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. *Neurosurgery* 2016; 79:667-677.
- Kapural L, Jameson J, Johnson C, et al. Treatment of nonsurgical refractory back pain with high-frequency spinal cord stimulation at 10 kHz: 12-month results of a pragmatic, multicenter, randomized controlled trial. *J Neurosurg Spine* 2022:1-12.
- Stauss T, El Majdoub F, et al. A multicenter real-world review of 10 kHz scs outcomes for treatment of chronic trunk and/or limb pain. *Ann Clin Transl Neurol* 2019; 6:496-507.
- De Carolis G, Paroli M, Tollapi L, et al. Paresthesia-independence: An assessment of technical factors related to 10 kHz paresthesia-free spinal cord stimulation. *Pain Physician* 2017; 20:331-341.
- Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. *Pain Med* 2014; 15:347-354.
- Lee KY, Bae C, Lee D, et al. Low-intensity, kilohertz frequency spinal cord stimulation differently affects excitatory and inhibitory neurons in the rodent superficial dorsal horn. *Neuroscience* 2020; 428:132-139.
- Lee KY, Lee D, Kagan ZB, Wang D, Bradley K. Differential modulation of dorsal horn neurons by various spinal cord stimulation strategies. *Biomedicines* 2021; 9.
- Liao WT, Tseng CC, Chia WT, Lin CR. High-frequency spinal cord stimulation treatment attenuates the increase in spinal glutamate release and spinal miniature excitatory postsynaptic currents in rats with spared nerve injury-induced neuropathic pain. *Brain Res Bull* 2020; 164:307-313.
- Liao WT, Tseng CC, Wu CH, Lin CR. Early high-frequency spinal cord stimulation treatment inhibited the activation of spinal mitogen-activated protein kinases and ameliorated spared nerve injury-induced neuropathic pain in rats. *Neurosci Lett* 2020; 721:134763.
- Lee KY, Lee D, Wang D, Kagan ZB, Bradley K. Simultaneous 10 kHz and 40 hz spinal cord stimulation increases dorsal horn inhibitory interneuron activity. *Neurosci Lett* 2022; 782:136705.
- Kuo SW, Zhang T, Esteller R, Grill WM. In vivo measurements reveal that both low- and high-frequency spinal cord stimulation heterogeneously modulate superficial dorsal horn neurons. *Neuroscience* 2023; 520:119-131.
- Fan W, Sdrulla AD. Differential modulation of excitatory and inhibitory populations of superficial dorsal horn neurons in lumbar spinal cord by abeta-fiber electrical stimulation. *Pain* 2020; 161:1650-1660.
- Sagalajev B, Zhang T, Abdollahi N, et al. Absence of paresthesia during high-rate spinal cord stimulation reveals importance of synchrony for sensations evoked by electrical stimulation. *Neuron* 2024; 112:404-420 e406.
- Yearwood TL, Hershey B, Bradley K, Lee D. Pulse width programming in spinal cord stimulation: A clinical study. *Pain Physician* 2010; 13:321-335.
- He J, Barolat G, Holsheimer J, Struijk JJ. Perception threshold and electrode position for spinal cord stimulation. *Pain* 1994; 59:55-63.
- De Ridder D, Vanneste S, Plazier M, van

- der Loo E, Menovsky T. Burst spinal cord stimulation: Toward paresthesia-free pain suppression. *Neurosurgery* 2010; 66:986-990.
35. Deer T, Slavin KV, Amirdelfan K, et al. Success using neuromodulation with burst (sunburst) study: Results from a prospective, randomized controlled trial using a novel burst waveform. *Neuromodulation* 2018; 21:56-66.
  36. Sweet J, Badjatiya A, Tan D, Miller J. Paresthesia-free high-density spinal cord stimulation for postlaminectomy syndrome in a prescreened population: A prospective case series. *Neuromodulation* 2016; 19:260-267.
  37. Provenzano DA, Rebman J, Kuhel C, Trezn H, Kilgore J. The efficacy of high-density spinal cord stimulation among trial, implant, and conversion patients: A retrospective case series. *Neuromodulation* 2017; 20:654-660.
  38. Paz-Solis J, Thomson S, Jain R, Chen L, Huertas I, Doan Q. Exploration of high- and low-frequency options for subperception spinal cord stimulation using neural dosing parameter relationships: The halo study. *Neuromodulation* 2022; 25:94-102.
  39. Metzger CS, Hammond MB, Paz-Solis JF, et al. A novel fast-acting subperception spinal cord stimulation therapy enables rapid onset of analgesia in patients with chronic pain. *Expert Rev Med Devices* 2021; 18:299-306.
  40. Gmel GE, Santos Escapa R, Parker JL, Mugan D, Al-Kaisy A, Palmisani S. The effect of spinal cord stimulation frequency on the neural response and perceived sensation in patients with chronic pain. *Front Neurosci* 2021; 15:625835.
  41. Amirdelfan K, Yu C, Doust MW, et al. Long-term quality of life improvement for chronic intractable back and leg pain patients using spinal cord stimulation: 12-month results from the SENZA-RCT. *Qual Life Res* 2018; 27:2035-2044.
  42. Parker JL, Gorman RB, Karantonis DM, et al. Frequency response of dorsal column fibers. Paper presented at: 13th World Congress of the International Neuromodulation Society; May 31, 2017; Edinburgh, Scotland.
  43. Reilly JP, Freeman VT, Larkin WD. Sensory effects of transient electrical stimulation--evaluation with a neuroelectric model. *IEEE Trans Biomed Eng* 1985; 32:1001-1011.
  44. Bromm B, Girndt E. [Demonstration, extinction and summation of subliminal stimuli in the isolated node of Ranvier by stimulation with short reverse double pulse]. *Pflugers Arch Gesamte Physiol Menschen Tiere* 1967; 296:1-13.
  45. Neudorfer C, Chow CT, Boutet A, et al. Kilohertz-frequency stimulation of the nervous system: A review of underlying mechanisms. *Brain Stimul* 2021; 14:513-530.
  46. Vargas L, Musselman ED, Grill WM, Hu X. Asynchronous axonal firing patterns evoked via continuous subthreshold kilohertz stimulation. *J Neural Eng* 2023; 20.
  47. Matsuoka AJ, Rubinstein JT, Abbas PJ, Miller CA. The effects of interpulse interval on stochastic properties of electrical stimulation: Models and measurements. *IEEE Trans Biomed Eng* 2001; 48:416-424.
  48. Crosby ND, Janik JJ, Grill WM. Modulation of activity and conduction in single dorsal column axons by kilohertz-frequency spinal cord stimulation. *J Neurophysiol* 2017; 117:136-147.
  49. Johansson RS, Vallbo AB. Detection of tactile stimuli. Thresholds of afferent units related to psychophysical thresholds in the human hand. *J Physiol* 1979; 297:405-422.
  50. Ochoa J, Torebjork E. Sensations evoked by intraneural microstimulation of single mechanoreceptor units innervating the human hand. *J Physiol* 1983; 342:633-654.
  51. Rowe MJ. Synaptic transmission between single tactile and kinaesthetic sensory nerve fibers and their central target neurones. *Behav Brain Res* 2002; 135:197-212.
  52. Zhu C, Esteller R, Block J, Lechleiter K, Frey R, Moffitt MA. Exploratory evaluation of spinal cord stimulation with dynamic pulse patterns: A promising approach to improve stimulation sensation, coverage of pain areas, and expected pain relief. *Front Pain Res (Lausanne)* 2023; 4:1339892.
  53. Deletis V, Shils J, Anso J, et al. Effects of 10-khz subthreshold stimulation on human peripheral nerve activation. *Neuromodulation* 2023; 26:614-619.
  54. Abejon D, Rueda P, Vallejo R. Threshold evolution as an analysis of the different pulse frequencies in rechargeable systems for spinal cord stimulation. *Neuromodulation* 2016; 19:276-282.
  55. Abejon D, Cameron T, Feler C, Perez-Cajaraville J. Electric parameters optimization in spinal cord stimulation. Study in conventional nonrechargeable systems. *Neuromodulation* 2010; 13:281-286.

