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Quantitative Sensory Testing of Spinal Cord and Dorsal Root Ganglion Stimulation in Chronic Pain Patients

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ABSTRACT

Background/Objectives: The physiological mechanisms underlying the pain-modulatory effects of clinical neurostimulation therapies, such as spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS), are only partially understood. In this pilot prospective study, we used patient-reported outcomes (PROs) and quantitative sensory testing (QST) to investigate the physiological effects and possible mechanisms of action of SCS and DRGS therapies.

Materials and Methods: We tested 16 chronic pain patients selected for SCS and DRGS therapy, before and after treatment. PROs included pain intensity, pain-related symptoms (e.g., pain interference, pain coping, sleep interference) and disability, and general health status. QST included assessments of vibration detection theshold (VDT), pressure pain threshold (PPT) and tolerance (PPToL), temporal summation (TS), and conditioned pain modulation (CPM), at the most painful site.

Results: Following treatment, all participants reported significant improvements in PROs (e.g., reduced pain intensity [$p < 0.001$], pain-related functional impairment [or pain interference] and disability [$p = 0.001$ for both]; better pain coping [$p = 0.03$], sleep [$p = 0.002$]), and overall health [$p = 0.005$]). QST showed a significant treatment-induced increase in PPT ($p = 0.002$) and PPToL ($p = 0.011$), and a significant reduction in TS ($p = 0.033$) at the most painful site, but showed no effects on VDT and CPM. We detected possible associations between a few QST measures and a few PROs. Notably, higher TS was associated with increased pain interference scores at pre-treatment ($r = 0.772$, $p = 0.009$), and a reduction in TS was associated with the reduction in pain interference ($r = 0.669$, $p = 0.034$) and pain disability ($r = 0.690$, $p = 0.027$) scores with treatment.

Conclusions: Our preliminary findings suggest significant clinical and therapeutic benefits associated with SCS and DRGS therapies, and the possible ability of these therapies to modulate pain processing within the central nervous system. Replication of our pilot findings in future, larger studies is necessary to characterize the physiological mechanisms of SCS and DRGS therapies.

Keywords: Chronic pain, dorsal root ganglion stimulation, electric stimulation, neuropathic pain, quantitative sensory testing, spinal cord stimulation

Conflict of Interest: Dr. Brummett is a consultant for Heron Therapeutics and Aloso Health. Dr. Clauw has consulted for Pfizer, Zynerba, Aptinyx, Samumed, Cerephex, Tonix, and Daiichi Sankyo, and has received research support from Pfizer, Cerephex, and Aptinyx. Dr. Harte consults for and receives research support from Aptinyx. Drs. Harte and Clauw are inventors of the

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Multimodal Automated Sensory Testing (MAST) device used in this study. Dr. Harte is also a member of Arbor Medical Innovations, LLC (Ann Arbor, MI, USA), licensee of the MAST device from the University of Michigan. Dr. Lempka has equity in Hologram Consultants, LLC and is a member of the scientific advisory board for Abbott Neuromodulation. Dr. Lempka also holds stock options, receives research support, and serves on the scientific advisory board of Presidio Medical, Inc. All other authors declare no competing interests.

INTRODUCTION

Chronic pain that is refractory to conventional treatment modalities (e.g., pharmacological therapies, injections, nerve blocks, surgery) often necessitates treatment with neurostimulation. Spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS) are two common neurostimulation therapies for patients with refractory chronic pain conditions, such as failed back surgery syndrome (FBSS) and complex regional pain syndrome (CRPS) (1-6). While conventional (or tonic) SCS has been used for decades in the treatment of chronic pain, DRGS was developed more recently (approved by the U.S. Food and Drug Administration in 2016) to specifically target refractory focal pain (e.g., CRPS) (7). Despite the widespread clinical use of SCS and DRGS, these therapies enjoy only limited success rates (6,8,9). An incomplete understanding of the mechanisms underlying pain relief and therapeutic benefit associated with SCS and DRGS is believed to be a major contributor toward the limited success rate of these therapies (10-12). Also, recently, several new forms of SCS that incorporate novel waveform paradigms (e.g., burst SCS, kilohertz-frequency SCS) have made their way into the clinic (13-15). However, these technical innovations have not been matched by corresponding improvements in our scientific understanding of the mechanisms of action of SCS (16,17). We believe that mechanistic gaps will continue to limit the impact, optimization, and long-term reliability of SCS and DRGS therapies.

One significant knowledge gap is our understanding of how SCS and DRGS modulate pain processing within the central nervous system (16). Quantitative sensory testing (QST) can be used to infer pain processing mechanisms. There are many different types of QST procedures and modalities, some of which are "static" and measure sensory thresholds or tolerance at a point in time, whereas other measures are "dynamic" and are thought to probe specific spinal and/or supraspinal mechanisms, such as temporal summation (TS) and conditioned pain modulation (CPM). TS of pain is the perception of increased pain intensity from repetitive application of noxious stimuli. It is considered the behavioral correlate of the electrophysiological phenomenon of "wind-up" observed in the spinal dorsal horn (18-20). Individuals with many different types of chronic pain exhibit increased TS (18,21-25). Similarly, CPM refers to the phenomena of "pain inhibiting pain" and is thought to measure innate descending inhibitory activity, where the application of a noxious stimulus decreases the pain elicited by a second noxious stimulus applied elsewhere on the body (26,27). Recent evidence from human studies suggests that TS and CPM appear to change over time with SCS, possibly reflecting an effect of SCS on spinal wind-up and descending pain inhibition, respectively (28-30). These early findings are promising and emphasize the potential significance and use of dynamic pain measures, such as TS and CPM, in evaluating and/or predicting the treatment efficacy of SCS and DRGS. However, it is important that prospective investigations also include assessments that evaluate the clinical and somatosensory profiles of patients undergoing SCS and DRGS treatment. Such investigations can provide better insights into the physiological effects of SCS and DRGS and the underlying therapeutic mechanisms.

The goal of this pilot study was to investigate the physiological effects and possible mechanisms of action of SCS and DRGS therapies in chronic pain patients, using a prospective design. We tested chronic pain patients who were selected for SCS or DRGS therapy as part of standard clinical care. We performed testing prior to treatment (baseline) and following treatment with SCS or DRGS. We used validated self-report questionnaires to assess clinical outcomes (e.g., pain intensity, pain-related symptoms and disability, and general health status). We used QST to assess somatosensory outcomes (e.g., sensory-detection thresholds, pain thresholds, and tolerance) and spinal/supraspinal mechanisms (e.g., TS, CPM). We hypothesized that SCS and DRGS would produce significant improvements in clinical outcomes and decrease sensory and/or pain hypersensitivity (via measured increases in sensory-detection thresholds, pain thresholds and tolerance), reduce spinal wind-up (via attenuation of TS), and improve descending pain inhibition (via potentiation of inhibitory CPM).

MATERIALS AND METHODS

Patients

We conducted the study at the University of Michigan (Ann Arbor, MI, USA) after obtaining approval from our medical Institutional Review Board. We included chronic pain patients ≥18 years of age, who were candidates for SCS or DRGS therapy (as determined by their own physicians), and able to speak, read, and understand English. In general, patients with moderate to severe chronic, refractory pain of the trunk and/or limbs were considered suitable candidates for SCS therapy (e.g., patients diagnosed with FBSS, CRPS, neuropathic limb pain), and patients with refractory focal pain of the lower extremities were considered suitable candidates for DRGS therapy (e.g., patients with groin pain, foot pain). Patients selected for SCS and DRGS procedures cleared a standard psychological evaluation. To minimize bias, we followed consecutive enrollment to include all patients meeting the study inclusion criteria. We excluded patients: 1) who were currently participating or had recently participated (≤3 months) in any other therapeutic trials or studies, or who had other ongoing neuromodulatory treatments (e.g., peripheral nerve stimulation, transcutaneous electrical nerve stimulation) that may confound the results of the study, 2) who were unable or unwilling to cooperate with clinical testing, or who were noncompliant with study directives, or 3) who had any impairment, activity, or situation that in the judgment of the principal investigator or study staff, would prevent satisfactory completion of the study protocol or QST procedures (e.g., patients with severe cognitive, emotional, psychological, physical or sensory impairment). All patients provided written informed consent prior to study participation.

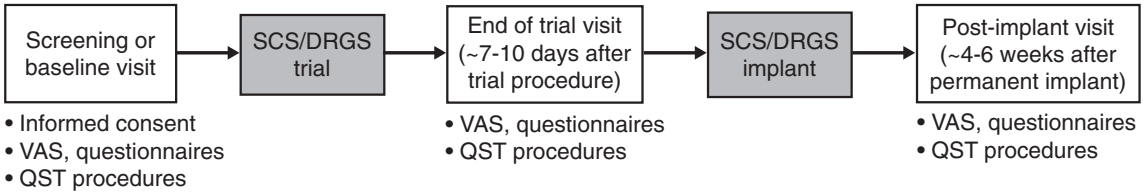

Figure 1. Study design. Research and standard-of-care procedures are denoted in white and gray, respectively.We performed pre-treatment testing in participants prior to the SCS or DRGS trial. We performed post-treatment testing in participants at approximately seven to ten days following successful trial treatment or at approximately four to six weeks following treatment with a permanent SCS or DRGS system. QST, quantitative sensory testing; VAS, visual analog scale; SCS, spinal cord stimulation; DRGS, dorsal root ganglion stimulation.

Testing Procedures and Time Points

We performed testing in the participants prior to treatment (i.e., baseline) and following treatment with SCS or DRGS. We tested participants following a successful SCS or DRGS trial (at around seven to ten days after the start of the trial procedure) or after permanent implantation of their SCS or DRGS device (at approximately four to six weeks postimplant) (Fig. 1). A successful SCS or DRGS trial was defined per the standard clinical protocol of ≥50% pain relief achieved during the trial with stable or reduced pain medications, and with at least stable levels of daily physical activity in the participant (31). For posttreatment testing, we did not adjust the settings on the participants' SCS or DRGS device or system. We only performed evaluations in the participants who were receiving clinically effective SCS or DRGS treatment (determined based on participant feedback in standard clinic visits).

Clinical Assessments

Clinical Pain

We measured clinical pain intensity using a patient-reported visual analog scale (VAS) (0–100 units) administered at the start of the study visit(s). VAS ratings are the most commonly used clinical outcome measure in SCS and DRGS (6,14,32).

Pain-Related Symptoms and Disability and General Health Status

We measured pain severity and interference, sensory and affective dimensions of pain, pain disability, pain coping, sleep interference, psychological distress, and general health status using the Brief Pain Inventory (BPI) short-form questionnaire (33), Short Form McGill Pain Questionnaire (SF-MPQ) (34), Pain Disability Index (PDI) questionnaire (35), Coping Strategies Questionnaire (CSQ) (36), Patient-Reported Outcomes Measurement Information System Sleep Disturbance (PROMIS-SD) short-form questionnaire (37), Hospital Anxiety and Depression Scale (HADS) questionnaire (38), and the EuroQol five-dimension three-level version (EQ-5D-3L) questionnaire (39), respectively, administered at the start of each study visit.

Pain Severity and Interference. Using the BPI, participants self-rated on a 11-point numerical rating scale (NRS) (0 = no pain to 10 = pain as bad as you can imagine), their current pain, as well as their worst, least, and average pain over the last 24 hours. We calculated pain severity as the mean of the four items, with higher scores indicating greater levels of pain severity. Using the same BPI and 11-point NRS, participants also self-rated how much pain had interfered (0 = does not interfere to 10 = completely interferes) with their general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life, over the last 24 hours. We calculated pain interference as the mean of the seven interference items, with higher scores indicating greater levels of pain interference.

Sensory and Affective Pain. Using the SF-MPQ, participants self-rated on a four-point intensity scale (0 = none to 3 = severe), the specific quality of pain they have (from a list of 15 pain descriptors). We calculated the sensory and affective pain indices as the sum of the intensity rank values of the words chosen for sensory and affective descriptors (11 sensory and four affective).

Pain Disability. Using the PDI, participants self-rated on a 11-point scale (0 = completely able to function to 10 = totally unable to function), their ability to function in each of the following domains: family/home responsibilities, recreation, social activities, occupation, self-care, and life-support activity. We measured pain-related disability as the sum of the responses.

Pain Coping. Using the one- and two-item versions of the CSQ, participants self-rated on a seven-point scale (0 = never do that to 6 = always do that), the extent to which they used a given coping strategy to overcome the pain. We calculated the total score as the sum of the averages of the two items on each scale.

Sleep Interference. Using the PROMIS-SD, participants self-rated each of the eight items assessing sleep disturbance on a five-point scale (1 = not at all and 5 = very much). We calculated the total score as the sum of the responses, with higher scores indicating greater levels of sleep interference.

Psychological Distress. Using the HADS, participants self-rated on a four-point scale (0 = absence to 3 = extreme presence), each of the two seven-point items (total 14 items) assessing anxiety and depression, respectively. We calculated the anxiety and depression scores by summing the responses for each of the two subscales. Higher scores indicated greater levels of anxiety and depression.

General Health Status. Using the EQ-5D-3L, participants self-rated on a three-point scale (1 = no problems to 3 = extreme problems), their health status in each of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. We calculated the total score by combining the individual scores selected for each of the five dimensions of health into a single five-digit number sequence. We subsequently converted the five-digit number sequence into a single summary score (called "index value") describing the overall health state, with lower scores indicating bad overall health and higher scores indicating good overall health.

Somatosensory Assessments

We evaluated somatosensory outcomes using static and dynamic QST. We performed testing in a quiet, temperature-controlled room (20–25°C) to avoid distraction of the participants. We performed all tests at the primary pain site for each participant (i.e., self-identified body area of worst clinical pain) and at a pain-free control site (e.g., dominant volar forearm). The order of testing was randomized. If severe hyperalgesia or allodynia

prevented us from testing at the primary pain site, we selected an adjacent, less sensitive pain area. In case of bilateral pain, we tested both sides, and considered the mean value of the measurement for data analysis. To reduce the possibility of postural compression of the nerves, we performed testing with the participant resting in a stationary position (i.e., sitting, supine, or prone). We familiarized all participants to the tasks to reduce testing-related anxiety. For all tests, we read identical and clear instructions to the participants and advised them that they could stop testing at any time without penalty if the sensations became intolerable. A single examiner (VS) performed all assessments.

Static QST Measurements

We measured sensory-detection threshold to vibratory stimuli (i.e., first noticeable sensation), and pain threshold (i.e., first noticeable pain sensation) and pain tolerance (i.e., no longer able to withstand the pain sensation) to pressure stimuli. We delivered increasing vibratory stimulation (at a rate of 0.3 μm/sec to a maximum vibration of 130 μm) and increasing pressure stimulation (at a rate of approximately 0.5 kgf/cm^2 to a maximum of 10 kgf/cm^2) using a handheld vibrometer (VSA-3000, Medoc Ltd., Ramat Yishai, Israel) and an analog pressure algometer (FPK Algometer, Wagner Instruments, Greenwich, CT, USA), respectively. We determined the vibratory detection threshold (VDT), pressure pain threshold (PPT), and pressure pain tolerance (PPToL) by averaging the values across three consecutive trials of each procedure separated by intervals of ∼10–20 sec.

Dynamic QST Measurements

Temporal Summation. We measured TS of mechanical pain using 256 millinewton (mN) and 512 mN pinprick stimulators (MRC Systems GmbH, Heidelberg, Germany) and following a standardized protocol (40,41). We performed the 256 and 512 mN tests in a randomized order with a 1-min break between testing. We applied a single fixed intensity stimulus (256 mN or 512 mN) perpendicular to the testing site for ∼0.5 sec. Following a 5-sec pause, we applied a train of ten identical stimuli with a frequency of 1 Hz (using a metronome) within an area of ∼1 cm^2. Immediately following the single stimulus and the train of ten stimuli, we asked patients to verbally rate their perceived average pain intensity using a 0–100 NRS. We averaged the values across three consecutive trials (each trial was a single stimulus followed by a train of ten stimuli) separated by intervals of ∼10 sec. We calculated TS scores by subtracting the average pain rating of the single-stimulus trials from the average pain rating of the ten-stimuli trials. If the difference was a positive number, we concluded that there was pain summation, where larger numbers indicated increased pain summation or TS. If the difference was zero or a negative number, we concluded that there was no pain summation or TS.

Conditioned Pain Modulation

We measured CPM using a noxious "conditioning" stimulus that evoked descending pain inhibition, and a "test" stimulus that determined the efficiency of the descending pain inhibition. We used pressure delivered by the algometer as the test stimulus, and contralateral thumbnail pressure pain delivered by the Multimodal Automated Sensory Testing (MAST) system (Arbor Medical Innovations, Ann Arbor, MI, USA) (42) as the conditioning stimulus. The MAST system is a QST platform designed for delivering and measuring pressure pain sensitivity (43-45). It consists of a wireless, hand-held stimulator able to provide computer-controlled pressure stimuli to the thumbnail with a mechanically driven 1 cm^2 rubber-tipped probe, and a touchscreen-based rating scale to capture participant feedback. The design and validation of the MAST system have been described previously (42). To evaluate CPM, we determined PPT before (baseline PPT from the algometry test) and during the application of a conditioning stimulus (conditioning PPT). The current protocol was modified from the method of Locke (46) and others (47,48) to use painful pressure delivered by the MAST system as conditioning stimulus instead of cold water. The MAST thumbnail pressure protocol was previously validated for CPM (27,49,50). Immediately following the algometry test, we applied a series of brief pressure pulses for 10-sec to the contralateral thumbnail (using the MAST) to determine a pressure intensity that induced a moderate level of pain for the participant (i.e., a rating of ∼30–50/100 on a NRS). After a 10-min delay, we induced CPM by applying 60 sec of this continuous pressure to the contralateral thumbnail. Parallel to the last 30 sec of conditioning, we used the algometer to reapply increasing pressures (three pressures, ∼10 sec apart) to the testing site to determine the conditioning PPT. We calculated CPM as the difference between the mean conditioning PPT and the mean baseline PPT. If the difference was positive, we concluded that there was an inhibitory (intact) CPM. If the difference was zero or negative, we concluded that there was no CPM or facilitatory (deficient) CPM, respectively.

Statistical Analysis

Patient refusal to complete portions of the QST battery resulted in missing QST data in some analyses. No power analysis was conducted for this pilot study. We used descriptive statistics to characterize our study population. We reported continuous measures as mean ± standard deviation and categorical variables as percentages. We calculated the mean values of all self-report measures and QST measures at pre-treatment and post-treatment. For the QST measures, we also calculated the mean differences in the measures between sites (primary pain site vs. control site), at pre-treatment and post-treatment. Because our sample size was small (n = 16), and our dataset was not normally distributed, we used the Wilcoxon signed-rank test, a non-parametrical test for statistical comparisons, to assess for treatment effects of SCS and DRGS. Previously published SCS studies have used the Wilcoxon signed-rank test for comparing paired samples of non-normally distributed data in relatively small and large populations of chronic pain patients (29,51). We calculated the effect size (or "r" value) for the Wilcoxon's test using previously established formula for this test (52,53). We interpreted absolute values of r between 0.10 and 0.30 as small effects, values between 0.30 and 0.50 as medium effects, and values ≥0.50 as large effects (52,53). We used Spearman' rho bivariate correlations to examine the relationships between the self-report measures and QST measures. We performed all statistical analyses using IBM SPSS version 26 (IBM Corp, Armonk, NY, USA). All analyses were two-tailed with significance set at $p < 0.05$. Due to the exploratory nature of this pilot study and because the comparisons were planned *a priori*, we did not perform procedures to correct for multiple comparisons (54,55).

RESULTS

Participant Demographics and Clinical Characteristics

We enrolled 16 chronic pain participants (ten males, six females) from August 2018 to March 2020 that were candidates for SCS or DRGS therapy. Enrolled participants were consecutive

Table 1. Baseline Demographics and Clinical Characteristics of Participants.

Patient no.	Gender/ Age (yr)/ Race	Pain diagnosis	Pain duration (yr)	Pain location	Pain side	Radiating pain	Pain description	Treatments tried prior to receiving neurostimulation	Pain medication	Smoking status	Alcohol use	Drug use	Medical history	Pain-associated symptoms
1	M/66/W	Ilioinguinal neuralgia	<5	LE (groin)	R	No	Aching, dull, burning, sharp	Injections, nerve blocks	NSAIDs, SH	Former smoker	No	No	Hypertensive	Mild fatigue, moderate sleep interference
2	M/52/W	Lumbar FBSS	>5	LB	R	Yes	Aching	PT, OT, CBT, CP, injections, nerve blocks, surgeries	Op, AD, AC, NSAIDs, MR	Nonsmoker	Past user	No	Hypertensive	Mild fatigue, moderate sleep interference
3	M/50/W	Cranial neuralgia	>5	UE (ear)	L	No	Zapping, sharp	Injections, nerve blocks, surgeries	Op, AD, NSAIDs, MR	Nonsmoker	Current user	No	Hypertensive	Mild fatigue, moderate sleep interference
4	M/50/W	Ilioinguinal neuralgia	>5	LE (groin)	L	No	Sharp, constant	Nerve blocks, surgery	Op	Current smoker	Past user	Yes	None	Allodynia, hyperalgesia, hyperesthesia, moderate fatigue, moderate sleep interference
5	M/58/W	Lumbar FBSS	>5	LE (groin)	L	Yes	Burning, stabbing, constant	PT, OT, CP, injections, nerve blocks, surgeries	Op, NSAIDs, MR, SH	Current smoker	Current user	No	None	Moderate fatigue, moderate sleep interference
6	F/35/W	Ilioinguinal neuralgia	<5	LE (groin)	R	No	Sharp, burning	CBT, nerve blocks	Op, AC, NSAIDs	Former smoker	No	No	None	Moderate fatigue, moderate sleep interference
7	M/25/W	Chemo-induced peripheral neuropathy	<5	LE (feet)	Both	Yes	Aching, shooting, sharp, dull	PT	Op, AD, AC, medical marijuana, CBD	Nonsmoker	No	No	None	Moderate fatigue, moderate sleep interference
8	M/46/W	Lumbar FBSS	<5	LB	R	Yes	Dull, burning, shooting	PT, CP, injections, surgeries	NSAIDs	Nonsmoker	Current user	No	None	Mild fatigue, moderate sleep interference
9	M/50/O	Lumbar FBSS	>5	LB	R	Yes	Sharp, stabbing, burning, dull	PT, OT, CBT, injections, surgeries	NSAIDs, MR	Nonsmoker	No	No	None	Mild fatigue, moderate sleep interference
10	F/64/W	Upper limb CRPS	<5	UE (arm)	L	No	Burning, shooting, stabbing	PT, OT, CBT, CP, AP, injections	Op, AC, NSAIDs	Nonsmoker	Current user	No	Hypertensive, obese	Allodynia, hyperalgesia, hyperesthesia, moderate fatigue, moderate sleep interference
11	M/52/W	Lumbar FBSS	>5	LB	R	Yes	Aching	PT, OT, CBT, CP, injections, nerve blocks, surgeries	Op, AD, AC, NSAIDs, MR	Nonsmoker	Past user	No	Hypertensive	Mild fatigue, moderate sleep interference
12	F/52/W	Lumbar FBSS	>5	LB	R	Yes	Burning, sharp, intense	PT, OT, CBT, CP, injections, nerve blocks, surgeries	Op, AD, AC, NSAIDs, MR, SH	Nonsmoker	Current user	No	None	Moderate fatigue, severe sleep interference
13	F/41/W	Lumbar FBSS	>5	LB	L	Yes	Burning, sharp, pins and needles, numbing	PT, OT, injections, surgeries	AD, AC, NSAIDs, MR	Current smoker	No	No	None	Allodynia, hyperalgesia, hyperesthesia, mild fatigue, severe sleep interference
14	F/36/W	Cranial neuralgia	<5	UE (ear)	R	No	Aching, shocking, electric	CBT, surgery	Op, AD, AC, NSAIDs, MR, SH	Nonsmoker	No	No	Diabetic, obese	Allodynia, hyperalgesia, hyperesthesia, moderate fatigue, severe sleep interference
15	M/47/W	Lower limb CRPS	<5	LE (leg)	L	Yes	Burning, shooting, throbbing, stabbing, aching	PT, OT, injections, nerve blocks, surgeries	AD, AC, NSAIDs, MR, SH	Former smoker	Current user	No	None	Allodynia, hyperalgesia, hyperesthesia, mild fatigue, severe sleep interference
16	F/55/W	Finger pain	<5	UE (fingers)	Both	No	Burning, throbbing, electric, tingling	Nerve blocks, surgeries	Op, AD, AC, NSAIDs, MR	Nonsmoker	Current user	No	None	Allodynia, hyperalgesia, hyperesthesia, moderate fatigue, severe sleep interference

No: number; M, male; F, female; W, white; O, other; FBSS, failed back surgery syndrome; CRPS, complex regional pain syndrome; LE, lower extremity; LB, low back; UE, upper extremity; R, right; L, left; PT, physical therapy; OT, occupational therapy, CP, chiropractic; AP, acupuncture; CBT, cognitive behavioral therapy; Op, opioids; AD, antidepressant; AC, anticonvulsant; NSAIDs, nonsteroidal anti-inflammatory drugs; MR, muscle relaxants; SH, sedative-hypnotic drugs; CBD, cannabidiol.

Table 2. Treatment Characteristics of Participants and Testing Time Points.

Patient no.	Primary pain site	Neurostimulation treatment received	Level of stimulation	Type of stimulation	Stimulator manufacturer	Clinically effective stimulation parameters	Testing time points	Tested dermatome (pain site/ control site)
1	Right groin	DRGS	Lumbar	Tonic	Abbott	18 Hz, 300 μsec, 0.875 mA	Pretrial, postimplant	L1/C5
2	Right low back	SCS	Thoracic	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.3 mA	Pretrial, postimplant	L4/C5
3	Left ear	SCS	Cervical	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.15 mA	Pretrial, postimplant	C2/C5
4	Left groin	DRGS	Lumbar	Tonic	Abbott	18 Hz, 300 μsec, 0.875 mA	Pretrial, postimplant	L1/C5
5	Left groin	SCS	Thoracic	Tonic	Boston Scientific	60 Hz, 330 μsec, 7.7 mA	Pretrial, postimplant	L1/C5
6	Right groin	DRGS	Lumbar	Tonic	Abbott	18 Hz, 200 μsec, 0.4 mA	Pretrial, postimplant	L1/C5
7	Bilateral feet	DRGS	Lumbar	Tonic	Abbott	18 Hz, 250 μsec, 1.1 mA (left) 18 Hz, 250 μsec, 0.925 mA (right)	Pretrial, postimplant	L5/C5
8	Right low back	SCS	Thoracic	Tonic	Boston Scientific	1000 Hz, 180 μsec, 4.4 mA	Pretrial, postimplant	L4/C5
9	Right low back	SCS	Thoracic	10 kHz	Nevro	10 kHz, 30 μsec, 0.9 mA	Pre-trial, post-implant	L4/C5
10	Left arm	SCS	Cervical	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.2 mA	Pretrial, postimplant	C5/C5
11	Right low back	SCS	Thoracic	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.6 mA	Pre-trial, following successful trial treatment	L4/C5
12	Right low back	SCS	Thoracic	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.6 mA	Pretrial, following successful trial treatment	L4/C5
13	Left low back	SCS	Thoracic	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.6 mA	Pretrial, following successful trial treatment	L4/C5
14	Right ear	SCS	Cervical	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.2 mA	Pretrial, following successful trial treatment	C2/C5
15	Left lower leg	SCS	Thoracic	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.5 mA	Pretrial, following successful trial treatment	L4/C5
16	Bilateral fingers	SCS	Cervical	Burst	Abbott	40 Hz, 500 Hz, 1000 μsec, 0.2 mA	Pretrial, following successful trial treatment	C5/C5

C, cervical; DRGS, dorsal root ganglion stimulation; L, lumbar; SCS, spinal cord stimulation.
Pretreatment testing occurred prior to SCS or DRGS trial. Posttreatment testing occurred at approximately seven to ten days following successful trial treatment or at approximately four to six weeks following treatment with a permanent SCS or DRGS system. The control site was the dominant volar forearm.

Table 3. Clinical Measures at Pre-treatment and Post-treatment.

Clinical measure	*n*	Instrument	Instrument score range	Pre-treatment	Post-treatment	*p* value	*r* value
Pain intensity	16	VAS	0 (no pain) to 100 (severe pain)	65.0 ± 21.0	19.4 ± 20.2	**<0.001**	**−0.63**
Pain severity	16	BPI	0 (no pain) to 10 (severe pain)	6.19 ± 1.91	2.06 ± 1.96	**0.001**	**−0.61**
Pain interference	16	BPI	0 (no interference) to 10 (maximum interference)	6.21 ± 2.15	1.73 ± 1.97	**0.001**	**−0.61**
Sensory pain index	16	SF-MPQ	0 (best) to 33 (worst)	16.4 ± 8.25	5.25 ± 5.98	**0.002**	**−0.54**
Affective pain index	16	SF-MPQ	0 (best) to 12 (worst)	4.56 ± 4.05	0.88 ± 1.58	**0.004**	**−0.51**
Pain coping	16	CSQ	0 (no coping) to 42 (always coping)	17.9 ± 6.53	14.7 ± 9.00	**0.030**	−0.38
Sleep interference	16	PROMIS-SD	8 (no interference) to 40 (maximum interference)	27.8 ± 5.28	19.6 ± 5.51	**0.002**	**−0.54**
Anxiety	16	HADS	0 (no anxiety) to 21 (maximum anxiety)	6.19 ± 3.29	3.31 ± 2.89	**0.003**	**−0.52**
Depression	16	HADS	0 (no depression) to 21 (maximum depression)	6.81 ± 3.02	2.19 ± 2.26	**0.001**	**−0.58**
Pain disability	16	PDI	0 (no disability) to 60 (maximum disability)	30.7 ± 8.94	10.4 ± 11.2	**0.001**	**−0.58**
General health index	16	EQ-5D-3L	−1 (worst) to +1 (best)	0.59 ± 0.16	0.81 ± 0.17	**0.005**	**−0.50**

Results are reported as mean ± standard deviation. Significant data ($p < 0.05$) and large effect sizes ($r \geq \pm 0.50$) are highlighted in bold.
VAS, visual analog scale; BPI, Brief Pain Inventory; SF-MPQ, Short-Form McGill Pain Questionnaire; CSQ, Coping Strategies Questionnaire; PROMIS-SD, Patient-Reported Outcomes Measurement Information System Sleep Disturbance; HADS, Hospital Anxiety and Depression Scale; PDI, Pain Disability Index; EQ-5D-3L, EuroQol five-dimension three-level version.

patients who consented to the study and who were able to complete the evaluation process. Participants were 48.7 (standard deviation = 10.6) years old on average, predominantly white (93.8%), and of different pain etiologies. Seven participants were diagnosed with lumbar FBSS (43.8%), two with CRPS (12.5%), three with ilioinguinal neuralgia (18.8%), two with cranial neuralgia (12.5%), one with chemo-induced
peripheral neuropathy (6.25%), and one with bilateral finger pain (6.25%). All participants had chronic refractory pain of the trunk and/or limbs. Six participants had low back pain (37.5%), six had lower extremity pain of the legs, groin, or feet (37.5%), and four had upper extremity pain of the arms, fingers, or ear (25.0%). Nine participants (56.3%) had radiating pain. Most participants described their pain as burning, sharp, and/or aching suggesting the likelihood of neuropathic pain. Nine of the 16 participants (56.3%) had chronic pain for <5 years, and seven (43.8%) had chronic pain for >5 years. All participants had tried multiple non-interventional (e.g., physical therapy, occupational therapy, behavioral therapy, chiropractic care, acupuncture) and/or interventional treatments (e.g., injections, nerve blocks, surgeries) before being deemed candidates for neurostimulation. All participants used pain medication. Eleven participants used opioids (68.8%), nine used antidepressants (56.3%), ten used anticonvulsants (62.5%), 14 used nonsteroidal anti-inflammatory drugs (87.5%), ten used muscle relaxants (62.5%), and five used sedative-hypnotic drugs (31.3%). Ten of the 16 participants (62.5%) were alcohol users (current or past users), six were current or former cigarette smokers (37.5%), and one reported marijuana use (6.25%). Regarding medical history, seven participants were hypertensive (43.8%), two were obese (12.5%), and one was diabetic (6.25%). Regarding pain-associated symptoms, six participants had allodynia, hyperalgesia, and/or hyperesthesia (37.5%), and all participants reported mild or moderate levels of fatigue, and moderate or severe levels of sleep interference. The demographic and clinical characteristics of the participants are summarized in Table 1.

Clinical and Somatosensory Characteristics

We used descriptive statistics to characterize the baseline clinical and somatosensory profiles for the entire study population. All participants ($n = 16$) completed the self-report questionnaires and QST assessments. Six participants chose not to complete the PPToL assessment, and six participants did not complete TS testing at the 512 mN intensity.

Treatment Characteristics

Twelve participants (75.0%) underwent successful treatment with SCS, and four underwent successful treatment with DRGS (25.0%). Eight of the 12 SCS participants (66.7%) received thoracic SCS, while four received cervical SCS (33.3%). Nine SCS participants (75%) received burst stimulation, two received tonic or conventional stimulation (16.7%), and one received 10 kHz stimulation (8.33%). Six of the 16 participants (37.5%) were assessed following successful SCS trial treatment, and ten (62.5%) were assessed following treatment with a permanent SCS or DRGS system. Thirteen participants (81.3%) were treated with an Abbott SCS or DRGS system (Abbott Laboratories, Chicago, IL, USA), two with a Boston Scientific SCS system (12.5%) (Boston Scientific Corporation, Valencia, CA, USA), and one with a Nevro SCS

system (6.25%) (Nevro, Redwood City, CA, USA). The treatment characteristics are summarized in Table 2.

Effects of SCS and DRGS on Clinical Outcomes

Following SCS or DRGS treatment, all participants reported significant improvements in clinical pain intensity, pain-related symptoms and disability, and general health status. We observed significant treatment-induced reductions in clinical pain intensity ($p < 0.001$), pain severity ($p = 0.001$), pain interference ($p = 0.001$), sensory pain index ($p = 0.002$), affective pain index ($p = 0.004$), pain disability ($p = 0.001$), pain coping index ($p = 0.030$), sleep interference ($p = 0.002$), anxiety ($p = 0.003$), and depression ($p = 0.001$), and a large treatment effect size on these measures ($r \geq -0.50$ for all measures except pain coping) (Table 3). We also observed a significant treatment-induced improvement (increase) in general health index ($p = 0.005$) and a large treatment effect size (Table 3).

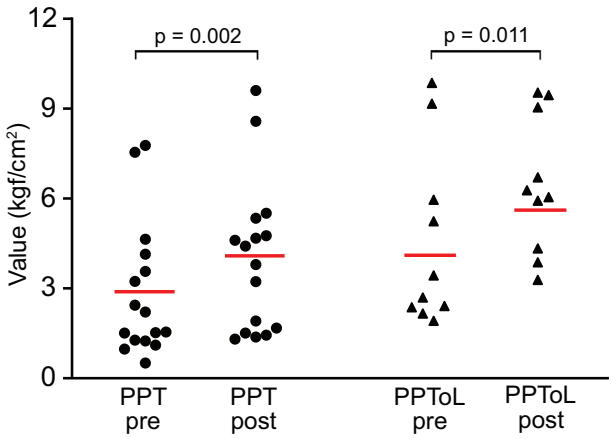

Figure 2. Column scatter plot comparing pressure pain threshold (PPT) ($n = 16$) and tolerance (PPToL) ($n = 10$) values (both in kgf/cm^2) for the primary pain (affected) site at pre-treatment and post-treatment, respectively. Mean values are indicated as solid lines. p values are indicated on top. [Color figure can be viewed at wileyonlinelibrary.com]

Effects of SCS and DRGS on QST Outcomes

Static QST Outcomes

PPT and PPToL. We observed overall increases in PPT and PPToL of participants following SCS or DRGS treatment. The observed treatment-induced increases were significant at the primary pain site ($p = 0.002$ and $p = 0.011$ for PPT and PPToL, respectively) (Fig. 2, Table 4), and not significant at the control site ($p = 0.605$ and $p = 0.391$ for PPT and PPToL, respectively) (Table 4). The observed treatment effect size was large for the primary pain site ($r = 0.56$ and $r = 0.57$ for PPT and PPToL, respectively) and small for the control site ($r = 0.09$ and $r = 0.19$ for PPT and PPToL, respectively). Notably, pre-treatment PPT and PPToL were significantly lower at the primary pain site than at the control site (mean PPT primary pain site vs. control site = 2.81 ± 2.23 kgf/cm^2 vs. 4.81 ± 1.87 kgf/cm^2, $p = 0.009$; mean PPToL primary pain site vs. control site = 3.99 ± 3.20 kgf/cm^2 vs. 7.72 ± 2.21 kgf/cm^2, $p = 0.011$) (Table 5).

Table 4. Pretreatment vs. Posttreatment Comparison of QST Measures for the Pain (Affected) Site and the Control (Unaffected) Site.

			Pain (affected) site				Control (unaffected) site			
QST measure	Unit	*n*	Pretreatment	Posttreatment	*p* value	*r* value	Pretreatment	Posttreatment	*p* value	*r* value
VDT	µm	16	12.0 ± 7.61	16.8 ± 17.6	0.501	+0.12	8.03 ± 9.18	5.92 ± 3.97	0.836	−0.04
PPT	kgf/cm^2	16	2.81 ± 2.23	3.99 ± 2.52	**0.002**	**+0.56**	4.81 ± 1.87	5.19 ± 2.67	0.605	+0.09
PPToL	kgf/cm^2	10	3.99 ± 3.20	5.68 ± 2.35	**0.011**	**+0.57**	7.72 ± 2.21	8.11 ± 1.83	0.391	+0.19
TS (256mN)	NRS	16	14.7 ± 15.6	8.02 ± 13.0	**0.033**	−0.39	7.81 ± 10.5	7.54 ± 10.9	0.889	−0.02
TS (512 mN)	NRS	10	19.8 ± 21.2	13.2 ± 13.5	0.173	−0.30	9.70 ± 12.0	6.83 ± 14.9	0.176	−0.30
CPM	kgf/cm^2	16	1.02 ± 1.24	1.35 ± 1.32	0.256	−0.20	0.86 ± 1.29	0.76 ± 0.96	0.717	+0.06

QST, quantitative sensory testing; VDT, vibratory detection threshold; PPT, pressure-pain threshold; PPToL, pressure-pain tolerance; TS, temporal summation; CPM, conditioned pain modulation; NRS, numerical rating scale; kgf, kilograms of force.
Results are reported as mean ± standard deviation. Significant data ($p < 0.05$) and large effect sizes ($r \geq \pm 0.50$) are highlighted in bold.

Table 5. Comparison of QST Measures Between the Pain (Affected) Site and the Control (Unaffected) Site at Pre-treatment.

			Pre-treatment			
QST measure	Unit	*n*	Pain (affected) site	Control (unaffected) site	*p* value	*r* value
VDT	µm	16	12.0 ± 7.61	8.03 ± 9.18	0.121	−0.27
PPT	kgf/cm^2	16	2.81 ± 2.23	4.81 ± 1.87	**0.009**	+0.46
PPToL	kgf/cm^2	10	3.99 ± 3.20	7.72 ± 2.21	**0.011**	+0.45
TS (256 mN)	NRS	16	14.7 ± 15.6	7.81 ± 10.5	**0.028**	−0.39
TS (512 mN)	NRS	10	19.8 ± 21.2	9.70 ± 12.0	0.063	−0.36
CPM	kgf/cm^2	16	1.02 ± 1.24	0.86 ± 1.29	0.877	+0.03

QST, quantitative sensory testing; VDT, vibratory detection threshold; PPT, pressure-pain threshold; PPToL, pressure-pain tolerance; TS, temporal summation; CPM, conditioned pain modulation; NRS, numerical rating scale; kgf, kilograms of force.
Results are reported as mean ± standard deviation. Significant data ($p < 0.05$) are highlighted in bold.

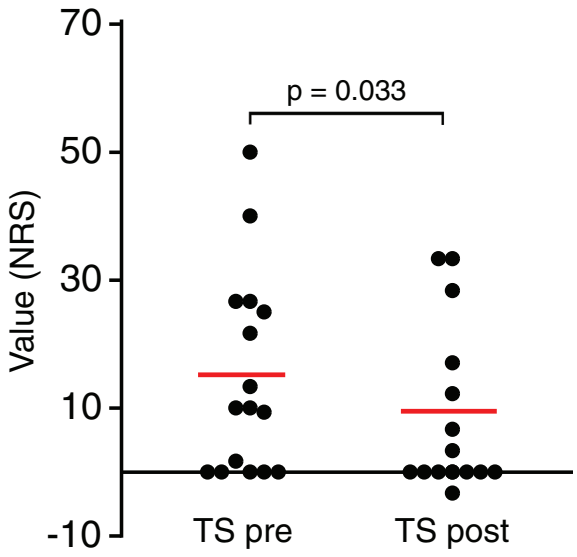

Figure 3. Column scatter plot comparing temporal summation (TS) 256 mN scores (in NRS) for the primary pain (affected) site at pre-treatment and post-treatment (n = 16). Mean values are indicated as solid lines. The p value is indicated on top. [Color figure can be viewed at wileyonlinelibrary.com]

VDT. We found no significant differences in VDT of participants at the primary pain site (p = 0.501) or at the control site (p = 0.836) following SCS or DRGS treatment (Table 4), and also no significant differences between the pretreatment VDT at these sites (p = 0.121) (Table 5).

Dynamic QST Outcomes

TS. We observed an overall reduction in TS (256 mN) scores of participants following SCS or DRGS treatment. The observed treatment-induced reduction in TS scores were significant at the primary pain site (p = 0.033) (Fig. 3, Table 4), and not significant at the control site (p = 0.889) (Table 4). The observed treatment effect size was medium for the primary pain site (r = −0.39) and small for the control site (r = −0.02). Notably, pre-treatment TS (256 mN) scores were significantly higher at the primary pain site than at the control site (mean TS score primary pain site vs. control site = 14.7 ± 15.6 NRS units vs. 7.81 ± 10.5 NRS units, p = 0.028), respectively (Table 5). We found no significant differences in TS (512 mN) scores of participants at the primary pain site (p = 0.173) or at the control site (p = 0.176) following SCS or DRGS treatment (Table 4), and also no significant differences between the pre-treatment TS (512 mN) scores at these sites (p = 0.063) (Table 5).

CPM. We found no significant differences in CPM of participants at the primary pain site (p = 0.256) or at the control site (p = 0.717) following SCS or DRGS treatment (Table 4), and also no significant differences between the pre-treatment CPM at these sites (p = 0.877) (Table 5).

Relationships Between Clinical Outcomes and QST Outcomes

Pre-treatment and Post-treatment Correlations

At pre-treatment, TS (256 mN) scores showed a strong positive correlation with self-reported pain interference scores (r = 0.772, p = 0.009). PPT showed a moderate negative correlation with self-reported pain coping scores (r = −0.570, p = 0.021) and a moderate positive correlation with general health status scores (r = 0.634, p = 0.008). VDT, PPToL, TS (512 mN), and CPM showed no significant correlations with any of the clinical outcome measures at pre-treatment.

At post-treatment, PPT and PPToL both showed moderate negative correlations with self-reported pain coping scores (r = −0.634, p = 0.008; r = −0.616, p = 0.019). VDT, TS (256 mN), TS (512 mN), and CPM showed no significant correlations with any of the clinical outcome measures at post-treatment.

Difference Correlations

Change (reduction) in TS (256 mN) scores from pre-treatment to post-treatment showed a moderate positive correlation with change (reduction) in self-reported pain interference scores (r = 0.669, p = 0.034) and pain disability scores (r = 0.690, p = 0.027). We also found moderate negative correlations between the change (increase) in VDT and the change (reduction) in self-reported sleep interference scores (r = −0.629, p = 0.009). Change (increase) in PPToL showed strong positive correlation with change (reduction) in affective pain index scores (r = 0.798, p = 0.010). Change in CPM from pre-treatment to post-treatment showed no significant correlations with change in any of the clinical outcome measures.

DISCUSSION

In this pilot prospective study, we used QST and self-reported variables to investigate the physiological effects and possible mechanisms of action of SCS and DRGS therapies in chronic pain participants. We found that SCS and DRGS treatment provided significant improvements in clinical pain intensity, pain-related symptoms and disability, and overall health. From the QST measures, we found significant treatment-induced increases in PPT and PPToL at the most painful site, and a significant reduction in TS, but found no effects on VDT and CPM. We found potentially meaningful correlations between a few QST measures and self-report measures. Notably, we found significant correlations between PPT and pain coping, PPToL and affective pain, TS and pain interference, and TS and pain disability, indicating possible associations between these variables.

Effect of SCS and DRGS on Clinical Outcomes

We found that SCS and DRGS treatment significantly improved pain intensity in the participants (mean improvement ∼70%). Specifically, 93.8% (15/16) of the participants reported greater than 30% improvements in pain relief and 62.5% (10/16) of participants reported greater than 70% improvements in pain relief with treatment. Given that a 30% or greater improvement in pain relief is clinically significant (56), our findings highlight the substantial clinical benefit participants attained with SCS and DRGS therapies. Noticeably, the magnitude of attained pain relief is similar to previously reported pain scores in prospective SCS and DRGS studies (2-4, 6, 57). In addition to pain relief, participants also reported clinically significant (30% or greater) improvements in activities of daily living (mean improvement ∼66%), sensory and affective dimensions of pain (mean improvement ∼68% and ∼ 81%, respectively), psychological distress (mean improvement ∼55%), sleep (mean improvement ∼30%), and overall health (mean improvement ∼37%), with treatment. The improvements in pain-related symptoms, especially with mood and sleep, speak to a centrally mediated mechanism of action of SCS and

DRGS (58, 59). Overall, our current findings on the treatment effects of SCS and DRGS are consistent with previous findings and demonstrate the significant clinical benefits of these therapies. Future studies should continue to examine these clinically important variables and how they are affected over time by these treatments.

Effects of SCS and DRGS on Somatosensory Outcomes

We found that SCS and DRGS treatment significantly reduced pressure pain hypersensitivity in the participants. A similar effect of SCS was reported by Marchand et al. (60) and Ahmed et al. (61) for heat pain hypersensitivity in chronic pain patients; whereas Kemler et al. reported a non-significant effect of SCS on static (e.g., pressure-evoked) and dynamic (e.g., brush-evoked) mechanical hypersensitivity in CRPS patients (62). We found that participants showed increased sensitivity at baseline (i.e., low PPTs, low PPToLs), indicating hyperalgesia, and the possible presence of pain sensitization within the central nervous system (central sensitization) or peripheral nervous system (peripheral sensitization) (63). Because sensitivity was higher at the most painful site and lower at a remote pain-free site, it is likely that pain sensitization was mostly local. However, following treatment, notable improvements in pressure pain hypersensitivity (or hyperalgesia) were achieved (i.e., higher PPTs, higher PPToLs). The treatment-induced improvements in symptoms were significant at the most painful site and nonsignificant at the remote pain-free site, suggesting that the effects of stimulation were also mostly local. An early SCS study by Shealy et al. first demonstrated a stimulation-induced increase on deep muscle pain thresholds in chronic pain patients (64). Additionally, studies have also suggested that local mechanical (e.g., pressure-pain) hyperalgesia is mostly mediated by activity of myelinated Aδ fibers and unmyelinated C fibers (65-67). Therefore, our observed findings on the reduction of local hyperalgesia following SCS or DRGS treatment could be attributed to the stimulation-induced suppression of Aδ/C fiber activity, which in turn could partly be contributing to the ongoing pain relief (or analgesia) in the participants (60, 62, 68). A potential change in Aδ/C fiber activity could be due to a centrally mediated mechanism of action or a peripherally mediated mechanism of action of SCS/DRGS, or both. However, it was impossible for us to determine these mechanisms using our current methods. Future studies are needed to investigate and identify specific mechanisms that are likely involved in the modulation of hyperalgesia and underlying Aδ/C nerve fiber activity in chronic pain patients treated with SCS or DRGS.

We found that SCS and DRGS treatment showed no effects on VDT in the participants. Early SCS studies by Lindblom and Meyerson, and Eisenberg et al. have reported significant effects of stimulation on VDT in chronic pain patients (69, 70). However, more recent studies have reported minor effects or no effects on VDT with SCS (28, 51, 71). We anticipated that SCS and DRGS treatment would significantly modulate (increase) VDT via stimulation-induced excitation of low-threshold, large-diameter Aβ fibers in the dorsal columns of the spinal cord, and in the dorsal root ganglia, at spinal levels innervating the pain region(s) or corresponding dermatome of the body, respectively. Failure to observe treatment effects on VDT may have been due to the variability in stimulation effects of SCS and DRGS across participants due to relative changes in body position at testing. Since we tested participants across different body positions (e.g., upright, supine, prone), variable stimulation (i.e., overstimulation or understimulation) of the target Aβ fibers may have resulted from position-related differences in the thickness of the cerebrospinal fluid layer interposing the epidurally placed electrode (of the SCS or DRGS lead) and the target (72, 73). The variability in stimulation effects would particularly be greater for SCS than DRGS due to the larger interposed cerebrospinal fluid layer thickness. Future studies should further investigate the potential effects of relative changes in body positions on VDT testing in SCS and DRGS patients.

Effects of SCS and DRGS on Spinal/Supraspinal Mechanisms

We found that SCS and DRGS treatment significantly attenuated TS of mechanical pain in the participants. In general, participants exhibited pain summation at baseline (high TS scores) and increased pain summation at the primary pain site (∼47% higher TS scores compared to the control site). However, following treatment, a significant reduction in pain summation was achieved. Participants reported ∼45% lower TS scores when tested at the primary pain site. Previous studies have explored the effects of SCS on TS. Campbell et al. reported SCS-induced decreases in TS of thermal pain in chronic pain patients (28), while Eisenberg et al. reported similar effects in patients with clinical radicular pain (29). In a more recent study, Schuh-Hofer et al. demonstrated SCS-induced decreases in mechanical pain TS in chronic pain patients (30). Our current findings on the treatment-induced effects of SCS and DRGS on TS verify previous findings on the effects of SCS on TS, and together demonstrate the ability of SCS and DRGS therapies to modulate (reduce) TS of pain in chronic pain patients. At the preclinical level, animal experiments have demonstrated the ability of SCS to modulate spinal wind-up of C-fiber inputs in wide dynamic range (WDR) neurons (74, 75). At the clinical level, TS of pain is thought to reflect pain facilitation, whereby repeated painful stimuli result in increased pain (18, 76, 77). TS of pain is closely associated with central sensitization, and represents enhanced excitability of the WDR neurons in the dorsal horn of the spinal cord (i.e., wind-up) in response to the repetitive painful stimuli (78-80). This association is relevant, as WDR neurons are candidates for the transmission cells in the gate-control pain circuit, and they are critical for spinal pain processing and the development of neuropathic pain (81, 82). Therefore, the attenuation of TS following SCS or DRGS treatment, may well be attributed to the stimulation-induced depression of hyperexcitability of WDR neurons, which in turn may partly be contributing to the ongoing pain relief or analgesia in the participants.

We found that SCS and DRGS treatment showed no effects on descending pain inhibition in the participants measured by CPM. Only two studies have previously investigated the effects of SCS on CPM. Campbell et al. showed that in 24 chronic pain patients treated with SCS, reduced inhibitory CPM at baseline was correlated with decreased self-reported clinical pain at three months postimplantation, suggesting that chronic pain patients with evidence of reduced endogenous (descending) pain inhibition may obtain the greatest benefit from SCS (28). In a recent study, Schuh-Hofer et al. showed that in eight chronic pain patients with existing SCS implants, stimulation was able to strengthen descending pain inhibition (30). However, in our study, we observed no treatment effects of SCS or DRGS on descending pain inhibition. It is possible that the heterogeneity in pain etiology of our study population may have attributed to the lack of treatment effects. It is also possible that the lack of effects may have been due to our modified protocol used for CPM testing. However, this is unlikely because we observed a net CPM (inhibitory) effect in the participants at both pre-treatment (mean CPM value = 1.02 ± 1.24 kgf/cm^2) and post-treatment (mean CPM value = 1.35 ± 1.32 kgf/cm^2) suggesting that our CPM method likely worked in modulating descending pain. Future studies

should investigate the possible treatment effects of SCS and/or DRGS on CPM in more homogeneous patient populations, using similar (27, 49, 50) or related CPM methodology. Furthermore, a control group may also be needed in these investigations to verify the possibility of treatment effects of stimulation on CPM.

Relationships Between Clinical Outcomes and Somatosensory Outcomes

We found potentially meaningful correlations between a few QST measures and self-reported measures. We observed a moderate negative correlation between PPT and self-reported pain coping at pre-treatment and post-treatment. Similarly, we observed a strong positive correlation between the treatment-induced increase in PPToL and the treatment-induced reduction in affective pain. These results suggest that psychological variables, such as pain coping and pain affect (i.e., feelings of unpleasantness and emotions associated with pain) may influence the development and/or perception of pain sensitivity in the participants, or vice-versa. Perhaps a more important finding of our study is the observed relationship between TS and self-reported pain interference. These variables showed a strong positive correlation with each other at pre-treatment and a moderate positive correlation with each other to changes with treatment. This finding is particularly important because it involves the measurement of evoked pain (i.e., degree of TS) by dynamic QST that is thought to better represent a sensitized nociceptive system as compared to pain measured by static QST (e.g., pain thresholds, pain tolerance) (83). Future studies are necessary to verify these possible relationships between QST and self-report measures. Future studies should also continue to use dynamic QST measures (e.g., TS, CPM) and explore possible relationships between these measures and clinical pain intensity.

Study Strengths and Limitations

The strength and novelty of this study is its prospective design and the use of a large number of validated QST measures (e.g., VDT, PPT, PPToL, TS, CPM) to investigate the physiological effects and possible mechanisms of action of SCS and DRGS therapies in chronic pain patients. However, there are several limitations of our study. First and foremost is the small sample size (n = 16) and the mixed population sample of the study (e.g., SCS vs. DRGS, trial vs. implant, male vs. female). We acknowledge that our pilot study was primarily designed to be hypothesis generating and to generate exploratory results intended to lay the groundwork for more complete research studies in the future. Therefore, this study is just the first step in our larger research program. We also recognize the challenges and importance of obtaining a large and homogenous population sample for research in this field. To specifically address concerns regarding the study's heterogenous design, we conducted some sensitivity analyses to determine if the treatment-reported effects of SCS and DRGS on clinical outcomes and QST outcomes are roughly the same when compared to SCS vs. DRGS, trial vs. implant, male vs. female. These initial sensitivity analyses suggest similar trends across conditions (data not shown) and these findings will help generate specific hypotheses for future, large, mechanistic studies in SCS and DRGS. But overall, the takeaway message from our combined analyses is that SCS and DRGS therapies appear to modulate experimental pain in chronic pain participants, and that more work needs to be done to verify findings and subgroup analyses. Second, while our study included a large number of validated QST measures to investigate the possible physiological mechanisms of action of SCS and DRGS in chronic pain patients, several additional QST measures could also be considered that might show additional results (e.g., cold detection thresholds, heat detection thresholds, cold pain threshold, heat pain threshold, mechanical detection threshold, mechanical pain threshold, and dynamic mechanical allodynia) (40). Third, we included participants with diverse pain etiologies that may have obscured our ability to accurately interpret study results related to the therapeutic efficacy or underlying mechanisms of SCS and DRGS. Furthermore, we included all forms of SCS, including several newer forms of SCS (e.g., burst SCS, kilohertz-frequency SCS). Recent evidence suggests that these newer forms of SCS may provide pain relief via different therapeutic mechanisms of action relative to conventional SCS (13-15, 84-86). To provide better insights into the anticipated efficacy and underlying therapeutic mechanisms of SCS and DRGS, future studies should include more homogeneous populations consisting of patients with specific pain etiologies (e.g., FBSS, CRPS, groin pain) who are receiving specific types of stimulation (e.g., tonic SCS, burst SCS, kilohertz-frequency SCS). These studies should aim to establish relationships between the mechanisms of action of specific types of SCS or DRGS and the pathological mechanisms of specific pain conditions. These relationships are essential to predict the therapeutic efficacy of SCS and DRGS and to ultimately improve patient selection.

CONCLUSIONS

The results of this pilot study suggest significant clinical and therapeutic benefits associated with SCS and DRGS therapies, and the possible ability of these therapies to modulate pain processing within the central nervous system. Replication of our results in future, larger studies is necessary to characterize the physiological mechanisms of SCS and DRGS therapies.

Authorship Statements

All authors were responsible for the study concept and design. Dr. Sankarasubramanian and Dr. Chiravuri recruited the patients. Dr. Chiravuri performed the neurostimulation trials and Dr. Patil performed the stimulator implants. Dr. Sankarasubramanian conducted the study and performed the quantitative sensory testing assessments. Dr. Mirzakhalili and Carlos J. Anaya assisted Dr. Sankarasubramanian with data collection. Ryan Scott performed the statistical analyses. Dr. Sankarasubramanian analyzed and interpreted the data, and prepared the manuscript draft, tables, and figures with guidance from Dr. Harte and Dr. Lempka. All authors provided intellectual input and assisted with manuscript revisions. All authors approved the final version of the manuscript.

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COMMENT

The exact mechanism of action for pain relief with spinal cord stimulation and dorsal root ganglion stimulation is still unclear. This pilot study from the University of Michigan suggests that reversal of central sensitization is the main effect. Future studies of this type will drive neuromodulation for years to come.

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