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ORIGINAL RESEARCH

Longitudinal Changes in Sensory Processing and Clinical Outcomes During Spinal Cord and Dorsal Root Ganglion Stimulation to Treat Chronic Pain: A Pilot Study

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Purpose: The analgesic mechanisms and neurophysiological effects of spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS) are poorly understood. In this pilot repeated-measures study, we used quantitative sensory testing (QST) and self-reported questionnaires to investigate the effects of these therapies in chronic pain patients from pre-implantation up to one-year post-implantation. Several studies have reported stimulation-induced effects on QST, potentially clarifying how neurostimulation affects the nervous system, which is poorly understood. This pilot study aimed to probe chronic stimulation-induced changes using a wide battery of static and dynamic QST assessments as a precursor to future, larger studies.

Methods: We enrolled 33 chronic pain patients selected as candidates for SCS and DRGS at pre-implantation and at three intervals up to at least 12 months post-implantation, with 18 completing at least one post-implantation visit. At each visit, we evaluated static (pressure-pain and vibration sensitivity) and dynamic (temporal summation, conditioned pain modulation) QST measures and patients self-reported pain-related clinical outcomes.

Results: Subjects reported significant improvements in pain severity, pain interference, pain disability, sensory and affective pain indices, sleep interference, depression, and general health at all post-implantation timepoints, as well as non-significant improvements in anxiety and coping. QST results typically failed to reach statistical significance. However, non-significant trends were observed for various stimulation-induced physiological effects, notably including reduced temporal summation at the primary pain site that was not observed at a non-painful control site.

Conclusion: This exploratory study demonstrates that SCS and DRGS produce meaningful therapeutic and clinical benefits up to at least one-year post-implantation and may modulate somatosensory processing. However, caution in extrapolating results is warranted due to appreciable attrition, heterogeneous patient population, and the lack of a control group. Additional studies will be necessary to evaluate whether clinical improvements are maintained beyond one year as well as confirm potential QST trends.

Keywords: spinal cord stimulation, dorsal root ganglion stimulation, neuromodulation, neurostimulation, quantitative sensory testing, temporal summation

Introduction

Chronic pain is a major public health burden affecting 50 million Americans, 19.6 million of which have high-impact chronic pain (interfering with life/work most or every day).[1] Common treatments include both pharmacological and non-

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pharmacological approaches.[2] If these approaches are unsatisfactory, neurostimulation therapies including spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS) are potential treatment options.[3] While many patients report excellent analgesia from these treatments, these interventions are not cure-alls and there remains significant room for improvement. The SCS clinical success rate (defined as at least 50% self-reported pain reduction) is approximately 60%, and efficacy often wanes over time, motivating investigation into how these systems modulate the nervous system.[4]

Quantitative sensory testing (QST), a psychophysical method for quantifying somatosensory function in response to consistent and fixed sensory stimuli, is one approach to investigate the neurophysiological effects of these devices in humans.[5,6] Many studies have reported altered QST measures during neurostimulation suggesting the modulation of the specific underlying pathways, although evidence is mixed.[7–22]

Previous QST studies have utilized various combinations of QST testing paradigms and different timepoints to mixed results.[5] Therefore, we designed this exploratory, repeated-measures pilot study to collect a wide variety of QST and clinical outcomes in chronic pain patients with implanted neurostimulation systems from baseline (pre-implantation) up to one-year post-implantation. We collected several static and dynamic QST measures at each visit, as well as self-reported clinical outcomes via validated questionnaires. Importantly, we observed improvements in most clinical outcomes, with benefits still observed at one-year post-implantation. QST results were predominantly statistically non-significant but often displayed trends consistent with previous work, motivating future studies with larger sample sizes that build upon these data. A subset of these data was included in a previously published report evaluating the short-term effects of SCS and DRGS.[23]

Methods

Participants

The study was conducted at the University of Michigan (Ann Arbor, MI, USA) after receiving Institutional Review Board approval and complied with the Declaration of Helsinki. All subjects were candidates for SCS or DRGS therapy to treat moderate-to-severe refractory chronic pain (determined by their physicians). All subjects provided written informed consent prior to study participation, including consent for the publication of results. Exclusion criteria included: concurrent participation or recent participation (≤3 months) in other therapeutic trials, or other ongoing neurostimulation treatments; inability or unwillingness to cooperate with testing, or noncompliance with study directives; and 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.

Study Timeline and Overview

The study design included up to four research visits (Figure 1). At all visits, patients completed questionnaires detailing pain-related clinical outcomes and we performed a battery of QST procedures to probe somatosensory function. The first visit ("baseline") was conducted before participants received treatment with SCS or DRGS. Participants then entered a trial period (approximately one week), during which an external pulse generator applied stimulation (SCS or DRGS). Subjects with successful SCS or DRGS trials (eg, ≥50% pain relief achieved during the trial and reported improvement in physical function/activity) were candidates for permanent device implantation. For subjects who received permanent implants, we scheduled three post-operative visits. The first post-operative visit was ~4-6 weeks after implantation ("optimization phase"), the second visit was ~3-6 months after implantation ("sub-acute phase"), and the third visit was approximately 12 months after implantation ("chronic phase"). Participants' stimulation parameters were determined per their standard clinical care.

Self-Reported Questionnaires

At each visit, participants completed several validated questionnaires describing their clinical outcomes.

EuroQol Five-Dimension Three-Level Version (EQ-5D-3L)

Using the EQ-5D-3L,[24] participants self-rated their current health state in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each response used a three-point scale (1 = no problems, 2 = some

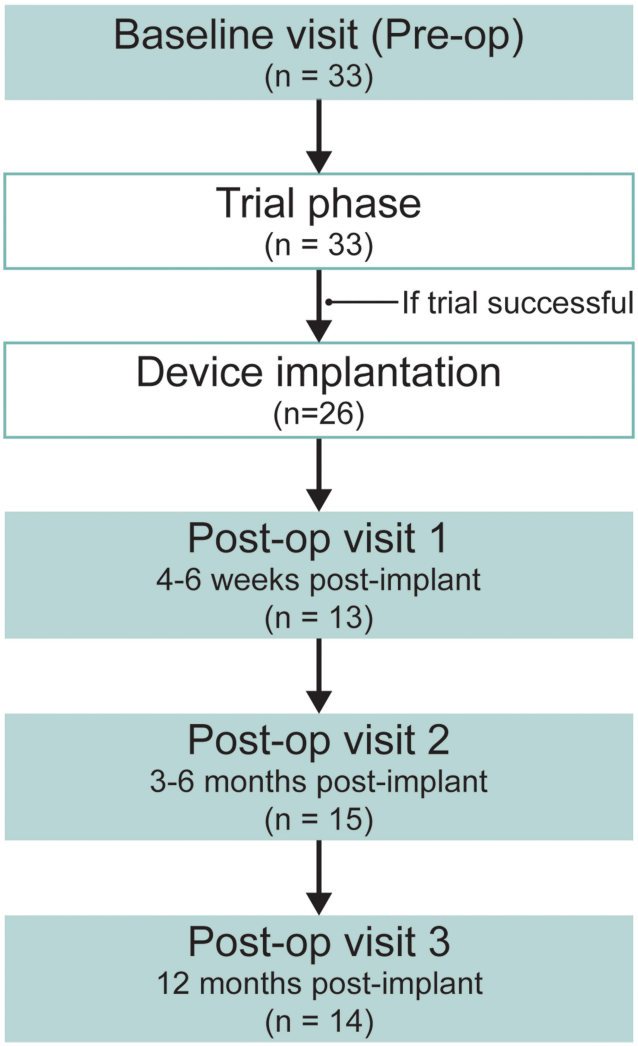

Figure 1 Study design. Research and standard-of-care procedures are denoted in green and white, respectively. We performed pre-treatment (or pre-operative) testing (baseline visit) in participants prior to the SCS or DRGS trial. We performed the post-treatment testing (post-operative visits 1, 2, and 3) in participants at approximately at 4–6 weeks, 3–6 months, and 12 months following implantation of a permanent SCS or DRGS system.

problems, 3 = extreme problems). From these, a single index score was calculated describing overall health, ranging between −1 and 1, with a higher score indicating better health.

Brief Pain Inventory (BPI)

Using the short-form BPI,[25] participants self-rated current pain, as well as their worst, best, and average pain over the previous 24 hours between 0 (no pain) and 10 (worst pain imaginable). We calculated pain severity as the average of these four values. Using a 0 to 10 scale, participants reported how their pain interfered with their general activity, mood, walking ability, work, relations with other people, sleep, and enjoyment of life over the previous 24 hours. We calculated pain interference by averaging these seven items.

General Pain Disability Index (PDI)

Using the PDI questionnaire,[26] participants self-rated on a 0 to 10 scale (0 = Completely able to function, 10 = Completely unable to function) the extent to which their chronic pain disrupted their family/home responsibilities, recreation, social activity, occupation, self-care, and life-support activity. We calculated pain disability as the sum of these responses.

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Short-Form McGill Pain Questionnaire (SF-MPQ)

Using the SF-MPQ,[27] participants self-rated to what extent 15 total potential characteristics described their pain from 0 (none) to 3 (severe). We calculated the sensory pain index as the sum of 11 sensory descriptors, and we calculated the affective pain index as the sum of four affective descriptors.

Coping Strategies Questionnaire (CSQ)

Using the CSQ,[28] participants self-rated the frequency in which they engaged in various coping mechanisms when experiencing pain on a scale of 0 to 6 (0 = never do that, 6 = always do that). We utilized the two-item CSQ, which consists of 14 total activities divided into two groups of seven ("items"). We calculated coping by summing the averages for the two items.

Patient-Reported Outcomes Measurement Information System Sleep Disturbance (PROMIS-SD)

Using the PROMIS-SD short-form questionnaire,[29] on a 1 to 5 scale (1 = best, 5 = worst), participants self-rated sleep quality during the past week in response to eight prompts. We calculated sleep interference as the sum of these responses, with higher scores indicating greater interference.

Hospital Anxiety and Depression Scale (HADS)

Using the HADS questionnaire,[30] participants self-rated on 14 total prompts, with seven related to depression and seven related to anxiety, on a scale between 0 (best) and 3 (worst). We calculated depression and anxiety scores as the sum of the responses for each category.

Quantitative Sensory Testing (QST)

We assessed somatosensory function using several QST measures (Figure 2). For each measure, we first tested a nonpainful control location (the volar forearm) and the site of worst clinical pain ("primary pain site") as identified by the subjects. If the primary pain site was too painful or hypersensitive, we performed testing in an adjacent, less sensitive pain area. Testing sites were consistent across visits. We advised participants that they could decline or immediately terminate any testing at their discretion. To reduce testing-related anxiety, we familiarized participants with all testing procedures prior to data collection during the baseline visit.

Temporal Summation (TS)

We measured TS using both 256-mN and 512-mN pinprick stimulators (MRC Systems GmbH, Heidelberg, Germany). First, we manually applied a single (~0.5-second duration) fixed-intensity (256-mN or 512-mN) stimulus perpendicular to the testing site. Shortly after, we applied ten identical stimuli at an approximate rate of 1 Hz. Immediately following the single stimulus and the train of ten stimuli, participants reported pain intensity between 0 (no pain) and 100 (worst pain imaginable). We calculated TS scores by subtracting the pain intensity of the single stimulus from that for the ten-stimulus train, with a positive TS score indicating painful TS. For each test site, we performed the TS procedures three times with a short break (~10 seconds) in between each test and averaged the results to calculate a single TS score.

Pressure Pain Threshold (PPT) and Pressure Pain Tolerance (PPTol)

In separate tests, we measured PPT and PPToL using a handheld analog pressure algometer (FPK Algometer, Wagner Instruments, Greenwich, CT, USA). We increased pressure at a rate of 0.5 kgf/cm^2 per second (up to a maximum of 10 kgf/cm^2) and participants indicated when the stimulus either first became painful (PPT) or became intolerable (PPToL). Occasionally, the maximum pressure of 10 kgf/cm^2 was reached before the participant indicated reaching threshold. In these instances, we recorded the maximum applied pressure, and noted that estimates for tests using the algometer may be slight underestimates. For each test site, we performed the PPT procedures three times with a short break (~10-15 seconds) in between each test and averaged the results to calculate a single PPT. We then performed the PPToL procedure three times, with a break (~20-60 seconds) in between each test and averaged the results to calculate a single PPToL.

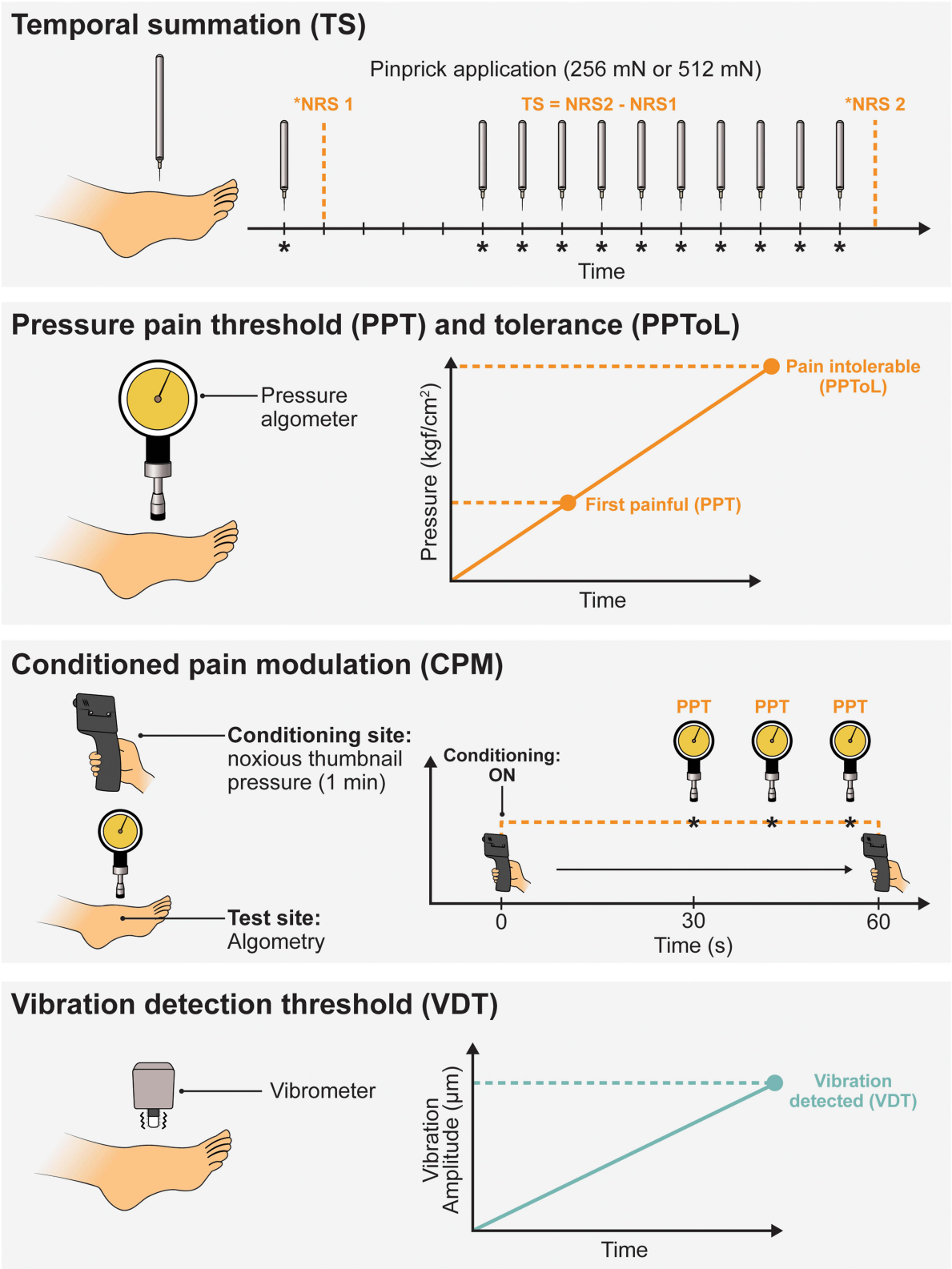

Figure 2 QST procedures. The QST protocol consisted of temporal summation (TS) of pain, pressure pain threshold (PPT) and tolerance (PPToL), conditioned pain modulation (CPM), and vibration detection threshold (VDT). All procedures, except CPM, were presented at the non-painful control site (ie, volar forearm) and primary pain site. CPM was presented at the primary pain site (test site) and non-dominant thumbnail (conditioning site) simultaneously. In the TS and CPM paradigms, the asterisks (*) indicate the timepoints for applying the respective painful stimuli.
Abbreviation: NRS, numerical rating scale.

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Conditioned Pain Modulation (CPM)

CPM measures the nervous system's endogenous ability to inhibit pain at one location due to a simultaneous painful stimulus at a remote body site (ie, "pain inhibits pain").[31] We assessed CPM by measuring PPT while the participant simultaneously experienced a noxious conditioning stimulus at a distant site. We calculated CPM as the difference between this PPT value ("conditioning PPT") and the original unconditioned PPT. The noxious conditioning stimulus was a moderately painful pressure (~30 to 50 out of 100 on the numerical rating scale) that was calibrated for each participant and applied continuously to the non-dominant thumbnail for 60 seconds using a Multimodal Automated Sensory Testing (MAST) system (Arbor Medical Innovations, Ann Arbor, MI, USA), which provided a fixed, computer-controlled pressure through a 1 cm^2 rubber-tipped probe. We began measuring PPT after the conditioning stimulus was applied for 30 seconds.

Vibration Detection Threshold (VDT)

We assessed VDT using a handheld vibrometer (VSA-3000, Medoc Ltd., Ramat Yishai, Israel). We increased amplitude at a rate of 0.3 μm/second and participants reported when they first detected vibration. For each test site, we repeated this procedure three times, with a short break (~10-20 seconds) in between each test and averaged the results to calculate a single VDT.

Statistical and Data Analysis

We analyzed all outcomes using mixed effect models with the "lme4" package in R (version 4.1.2).[32] Random intercepts accounted for baseline differences across subjects, and we assessed fixed effects at each post-implantation visit (compared to baseline). This approach accounts for the longitudinal repeated measures nature of the data with interspersed missing values. All results are presented as estimated fixed effect ± standard error. Given the exploratory nature of this pilot study, we did not conduct an a priori power analysis or adjust for multiple comparisons.

Results

Patient Demographics

We recruited 33 chronic pain patients (mean age: 48.3 years) from one research center, with data collected between August 2018 and May 2022 (Table 1). Among these study participants, 42% (14/33) were females and 45% (15/33) had

Table 1 Baseline Demographics and Clinical Characteristics of Participants

ID	Age (Years) and Sex (M/F)	Pain Site Tested	Diagnosis	Pain Duration (years)	Therapy	Implant Levels	V1 Stimulation Parameters	Visits Completed
1	73F	Left LE (leg)	Lumber stenosis with neurogenic claudication	<5	SCS	T7 - T8	N/A (Trial failure)	B
2	45F	Left LE (leg)	CRPS	>5	SCS	T8 - T10	Tonic: 150Hz, 260μs, 2.5mA	B, V2, V3
3	58M	Left LE (leg)	Lumbar radiculopathy	>5	SCS	T7 – T9	Tonic: 60Hz, 330μs, 4.7mA	B, V1, V2
4	50M	Behind left ear	Occipital neuralgia	>5	SCS	C2 - C3	*Burst: 500Hz (intraburst), 40Hz (interburst), 1000μs, 0.35mA	B, V1, V2, V3

(*Continued*)

Table 1 (Continued).

ID	Age (Years) and Sex (M/F)	Pain Site Tested	Diagnosis	Pain Duration (years)	Therapy	Implant Levels	V1 Stimulation Parameters	Visits Completed
5	21F	Below the right clavicle	Neuropathic pain in the distribution of the right cervical plexus	<5	SCS	Cervical plexus	N/A (Ineligible for follow-up)	B
6	27F	Left groin	Ilioinguinal and iliohypogastric neuralgia	>5	DRGS	L1 – L2	N/A (Trial failure)	B
7	67M	Right LB	PSPS Type 2	<5	SCS	T9 - T10	*Tonic: 40Hz, 300μs, 2.5mA *Tonic: 200Hz, 200μs, 2.2mA	B, V1, V2, V3
8	53M	Right LB	Radicular pain of lumbosacral region	<5	SCS	T7 - T9	N/A (Trial failure)	B
9	59M	Left LE (foot)	CRPS	<5	DRGS	L5 – S1	N/A (Trial failure)	B
10	55F	Bilateral UE (fingers)	Bilateral finger pain	>5	SCS	C1 - C2	N/A (Ineligible for follow-up)	B
11	31M	Right LB	Lumbar Spondylosis	>5	SCS	T8 – T9	N/A (Lost to follow-up)	B
12	55M	Right LB	PSPS Type 2	<5	SCS	T7 - T8	N/A (Trial failure)	B
13	35F	Right groin	Ilioinguinal neuralgia	<5	DRGS	T12- L1	*Tonic: 18Hz, 200μs, 0.80mA	B, V1, V2, V3
14	50M	Left groin	Ilioinguinal neuralgia	>5	DRGS	L1 – L2	Tonic: 18Hz, 300μs, 6mA	B, V1
15	51M	Left LB	PSPS Type 2	>5	SCS	T7 – T9	N/A (Trial failure)	B
16	36F	Behind right ear lobe	Right geniculate neuralgia	<5	SCS	C1 - C2	N/A (Ineligible for follow-up)	B
17	49M	Right LE (leg)	Right lumbar radiculopathy	<5	SCS	T7 - T9	Tonic: 70Hz, 290μs, 4.1mA	B, V1, V2, V3
18	57F	Left LB	Intercostal neuralgia	>5	SCS	T4 - T5	*Tonic: 90Hz, 210μs, 4.2mA	B, V2, V3
19	39F	Bilateral LE (foot)	CRPS	<5	SCS	T9 - T10	*Tonic: 200Hz, 200μs, 1.2mA	B, V2, V3
20	22F	Bilateral LE (leg)	CRPS	<5	SCS	T8 - T10	Tonic: 10,000Hz, 30μs, 7.1mA	B, V2, V3
21	52F	Right LB	PSPS Type 2	>5	SCS	T7 - T8	N/A (Lost to follow-up)	B

(*Continued*)

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Table 1 (Continued).

ID	Age (Years) and Sex (M/F)	Pain Site Tested	Diagnosis	Pain Duration (years)	Therapy	Implant Levels	V1 Stimulation Parameters	Visits Completed
22	54M	Left LB	Lumber stenosis with neurogenic claudication	>5	SCS	T8 -T9	*Tonic: 30Hz, 250μs, 1.8mA Burst: 500Hz (intraburst), 40Hz (interburst), 1000μs, 0.85mA	B, V1, V2, V3
23	66M	Right groin	Inguinal neuralgia	<5	DRGS	L1 - L2	Left array: Tonic, 18Hz, 220μs, 1.2mA Right array: Tonic, 18Hz, 300μs, 1.5mA	B, V1, V2
24	61M	Left LE (leg)	Ilioinguinal neuralgia	>5	SCS	T9 - T10	N/A (Withdrew consent)	B
25	52M	Right LB	PSPS Type 2	>5	SCS	T7 - T9	*Burst: 500Hz (intraburst), 40Hz (interburst), 1000μs, 0.30mA	B, V1, V2, V3
26	37F	Left LB	Lumbar radiculopathy	>5	SCS	T8 – T9	N/A (Lost to follow-up)	B
27	65M	Right LB	PSPS Type 2	<5	SCS	T7 - T8	Tonic: 490Hz, 510μs, 2.1mA	B, V3
28	47M	Left LE (leg)	CRPS	<5	SCS	T7 - T8	N/A (Ineligible for follow-up)	B
29	64F	Left UE (arm)	CRPS Superficial radial neuralgia	<5	SCS	C2	Burst: 500Hz (intraburst), 40Hz (interburst), 1000μs, 0.35mA	B, V1, V2, V3
30	25M	Left LE (foot)	Chemo-induced peripheral neuropathy	<5	DRGS	L5 – S1	Left array: Tonic: 18Hz, 250μs, 1.075mA Right array: Tonic: 18Hz, 300μs, 1.175mA	B, V1
31	41F	Left LB	PSPS Type 2	<5	SCS	T7 - T8	N/A (Withdrew consent)	B
32	46M	Right LE (leg)	PSPS Type 2	<5	SCS	T8 – T9	*Tonic: 1000Hz, 180μs, 5.2mA	B, V1, V2, V3
33	50M	Right LB	PSPS Type 2	>5	SCS	T8 - T10	Tonic: 10,000Hz, 30μs, 5.4mA	B, V1, V2, V3

Notes: For participants who only underwent trial stimulation, the "Implant levels" column describes the spinal levels at which the electrodes were placed for the trial stimulation. For participants that proceeded to permanent implantation, this column describes the spinal levels at which the electrodes were placed for permanent implantation. The stimulation amplitude provided in the "V1 Stimulation Parameters" column corresponds to the sensory threshold and the asterisks (*) indicate participants whose stimulation parameters changed from V1 onwards.

Abbreviations: ID; identification number; M, male; F, female; PSPS, persistent spinal pain syndrome; CRPS, complex regional pain syndrome; CLBP, chronic lower back pain; LB, low back; LE, lower extremity; UE, upper extremity; R, right; L, left; SCS, spinal cord stimulation; DRGS, dorsal root ganglion stimulation; N/A, not applicable; B, baseline; V1, post-operative visit 1; V2, post-operative visit 2; V3, post-operative visit 3.

experienced chronic pain for over 5 years. Common chronic pain etiologies included PSPS Type 2 (9/33), CRPS (6/33), and neuralgia (9/33).

Six participants did not undergo implantation of a permanent device due to unsuccessful trial stimulation and one participant did not pursue permanent implantation despite a successful trial. Eight additional participants were either lost to follow-up, became ineligible, or withdrew from the study after the baseline visit. These participants were excluded from subsequent analyses (Table 1). The remaining 18 participants completed at least one post-implantation visit, with 10 participants completing all three post-implantation visits.

Clinical Outcomes

At all post-implantation visits, statistically significant improvements compared to baseline were observed for general health, pain severity, pain interference, pain disability, sensory and affective pain indices, sleep interference, and depression compared to baseline (Table 2). We only observed a significant improvement in anxiety for post-implantation visit 1 ($p = 0.004$) and did not observe significant improvements in coping at any of the post-implantation visits. Interestingly, across most self-reported clinical outcomes, there was a noticeable pattern for the magnitude of estimated improvements to decrease at each subsequent post-implantation visit.

Table 2 Changes in Clinical Measures at Each Post-Operative Visit Relative to the Baseline Visit. Data are Given as Baseline and Fixed Effect Estimates ± Standard Errors

Clinical Outcome	Questionnaire	Score Range	Baseline	Δ V1 (p-value)	Δ V2 (p-value)	Δ V3 (p-value)
General Health	EQ-5D-3L	−1 (worst) +1 (best)	0.53 ± 0.03	0.20 ± 0.05 (<0.001)	0.20 ± 0.04 (<0.001)	0.17 ± 0.05 (<0.001)
Pain Severity	BPI	0 (best) 10 (worst)	6.32 ± 0.35	−3.75 ± 0.57 (<0.001)	−2.83 ± 0.53 (<0.001)	−2.22 ± 0.54 (<0.001)
Pain Interference	BPI	0 (best) 10 (worst)	6.80 ± 0.40	−4.17 ± 0.61 (<0.001)	−3.45 ± 0.56 (<0.001)	−2.93 ± 0.57 (<0.001)
Pain Disability	PDI	0 (best) 60 (worst)	33.97 ± 2.05	−20.22 ± 3.42 (<0.001)	−16.35 ± 3.04 (<0.001)	−17.29 ± 3.14 < (0.001)
Sensory Pain Index	SF-MPQ	0 (best) 33 (worst)	17.72 ± 1.34	−10.12 ± 2.26 (<0.001)	−7.05 ± 2.13 (0.002)	−5.71 ± 2.14 (0.010)
Affective Pain Index	SF-MPQ	0 (best) 12 (worst)	5.09 ± 0.60	−3.61 ± 0.86 (<0.001)	−3.30 ± 0.81 (<0.001)	−1.71 ± 0.82 (0.044)
Coping	CSQ	0 (best) 42 (worst)	35.72 ± 2.40	−6.45 ± 3.39 (0.063)	−3.71 ± 3.21 (0.253)	−1.60 ± 3.25 (0.625)
Sleep Interference	PROMIS-SD	8 (best) 40 (worst)	31.98 ± 1.23	−8.20 ± 1.58 (<0.001)	−6.73 ± 1.50 (<0.001)	−6.90 ± 1.52 (<0.001)
Anxiety	HADS	0 (best) 21 (worst)	7.66 ± 0.68	−2.76 ± 0.90 (0.004)	−1.68 ± 0.85 (0.056)	−1.32 ± 0.87 (0.135)
Depression	HADS	0 (best) 21 (worst)	8.03 ± 0.59	−3.93 ± 0.77 (<0.001)	−3.62 ± 0.73 (<0.001)	−2.43 ± 0.74 (0.002)

Notes: The Post-Op values are shown relative to baseline. Therefore, positive values for EQ-5D-3L represent an improvement while negative values represent an improvement for all other clinical measures.

Abbreviations: EQ-5D-3L, EuroQol five-dimension three-level; BPI, Brief Pain Inventory; PDI, Pain Disability Index; 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; Post-Op, post-operative; V, visit.

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Temporal Summation

At all post-implantation visits, TS at the primary pain site was reduced compared to baseline for both 256 and 512 mN stimuli, although these differences did not achieve statistical significance (Table 3 and Figure 3). At the primary pain site, the baseline estimate of TS was 11.43 ± 2.15 (estimated fixed effect ± standard error) for the 256 mN stimulus. Our mixed-model analysis found fixed effect estimates of −5.00 ± 3.37 (p = 0.144), −3.32 ± 3.20 (p = 0.304), and −2.76 ± 3.28 (p = 0.404) at post-implantation visits 1, 2, and 3, respectively (fixed effect estimate ± standard error). For the 512 mN device at the primary pain site, the baseline estimate of TS was 15.26 ± 2.91, and the fixed effect estimates were −5.59 ± 3.91 (p = 0.159), −5.46 ± 3.59 (p = 0.134), and −2.55 ± 3.58 (p = 0.480) at the three post-implantation visits compared to baseline (Table 3).

In contrast, changes in TS at the control site were smaller in magnitude and less consistent (Table 3 and Figure 3). The baseline estimate of TS at the control site for the 256 mN stimulus was 4.40 ± 1.35, and our analysis found fixed effect estimates of 1.90 ± 1.94 (p = 0.332), 0.34 ± 1.84 (p = 0.855), and 2.17 ± 1.89 (p = 0.256) at the three post-implantation visits compared to baseline. For the 512 mN device, the baseline estimate of TS was 7.90 ± 2.13 and fixed effect estimates at the three post-implantation visits were 3.04 ± 2.93 (p = 0.304), −1.66 ± 2.69 (p = 0.540), and 1.58 ± 2.69 (p = 0.559).

Pressure Pain Threshold and Pressure Pain Tolerance

At all visits, we found that PPT was increased compared to baseline at the primary pain site, although these differences did not achieve statistical significance (Table 3 and Figure 4). Specifically, the baseline estimate of PPT at the primary pain site was 3.49 ± 0.41 kgf/cm^2, and fixed effect estimates were 0.93 ± 0.50 (p = 0.071), 0.28 ± 0.49 (p = 0.567), and 0.99 ± 0.50 (p = 0.054) kgf/cm^2 at post-implantation visits 1, 2, and 3, respectively (fixed effect estimate ± standard error). Interestingly, we observed that PPT was similarly increased at the control site at all post-implantation visits. The baseline estimate of PPT at the control site was 4.85 ± 0.37 kgf/cm^2, and fixed effect estimates at the three post-implantation visits were 0.39 ± 0.48 (p = 0.418), 0.87 ± 0.47 (p = 0.070), and 1.15 ± 0.48 (p = 0.022) kgf/cm^2 (Table 3).

Table 3 Changes in QST Measures at Each Post-Operative Visit Relative to the Baseline Visit for Both the Primary Pain and Control Sites. Data are Given as Baseline and Fixed Effect Estimates ± Standard Errors

QST Measure	Baseline	ΔPost-Op V1 (p-value)	ΔPost-Op V2 (p-value)	ΔPost-Op V3 (p-value)
TS256 Pain Site	11.43 ± 2.15	−5.00 ± 3.37 (0.144)	−3.32 ± 3.20 (0.304)	−2.76 ± 3.28 (0.404)
TS256 Control Site	4.40 ± 1.35	1.90 ± 1.94 (0.332)	0.34 ± 1.84 (0.855)	2.17 ± 1.89 (0.256)
TS512 Pain Site	15.26 ± 2.91	−5.59 ± 3.91 (0.159)	−5.46 ± 3.59 (0.134)	−2.55 ± 3.58 (0.480)
TS512 Control Site	7.90 ± 2.13	3.04 ± 2.93 (0.304)	−1.66 ± 2.69 (0.540)	1.58 ± 2.69 (0.559)
PPT Pain Site (kgf/cm^2)	3.49 ± 0.41	0.93 ± 0.50 (0.071)	0.28 ± 0.49 (0.567)	0.99 ± 0.50 (0.054)
PPT Control (kgf/cm^2)	4.85 ± 0.37	0.39 ± 0.48 (0.418)	0.87 ± 0.47 (0.070)	1.15 ± 0.48 (0.022)
PPToL Pain Site (kgf/cm^2)	5.05 ± 0.58	1.61 ± 0.74 (0.036)	0.71 ± 0.70 (0.316)	0.79 ± 0.71 (0.275)
PPToL Control (kgf/cm^2)	7.80 ± 0.36	0.56 ± 0.41 (0.185)	0.22 ± 0.38 (0.562)	0.60 ± 0.37 (0.117)
CPM Pain Site (kgf/cm^2)	0.67 ± 0.19	0.64 ± 0.33 (0.057)	0.26 ± 0.33 (0.427)	−0.17 ± 0.34 (0.616)
CPM Control (kgf/cm^2)	1.01 ± 0.23	−0.13 ± 0.39 (0.743)	−0.65 ± 0.39 (0.105)	−0.63 ± 0.42 (0.140)
VDT Pain Site (μm/second)	16.07 ± 2.78	1.67 ± 3.19 (0.603)	0.21 ± 3.03 (0.944)	−0.95 ± 3.20 (0.768)
VDT Control (μm/second)	6.77 ± 1.12	−0.78 ± 1.56 (0.621)	0.53 ± 1.48 (0.722)	−0.73 ± 1.56 (0.644)

Abbreviations: QST, quantitative sensory testing; TS256, temporal summation at a pressure of 256 mN; TS512, temporal summation at a pressure of 512 mN; PPT, pressure-pain threshold; PPToL, pressure-pain tolerance; CPM, conditioned pain modulation; VDT, vibratory detection threshold; Post-Op, post-operative; V, visit.

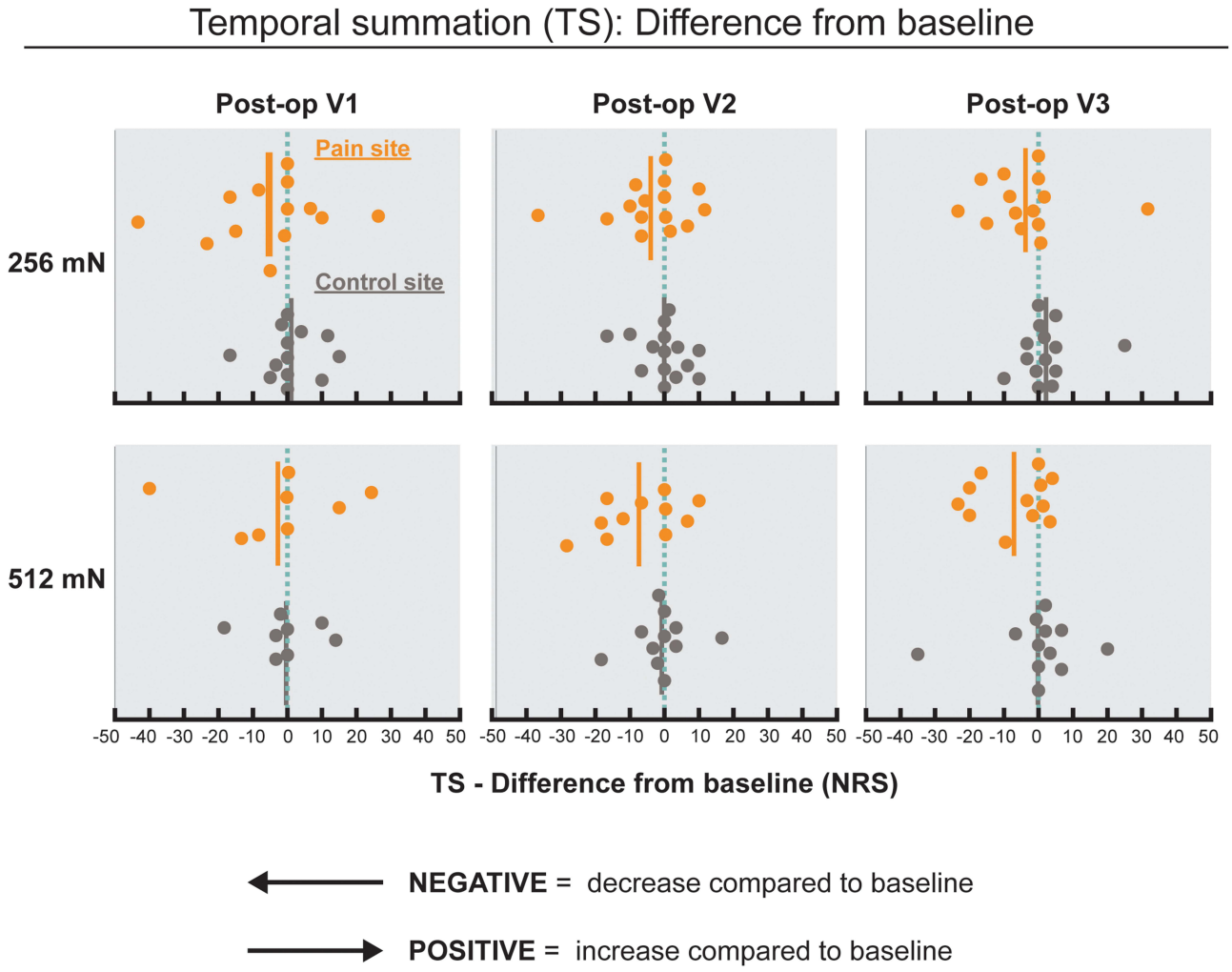

Figure 3 Stimulation-induced changes in TS. Scatter plots displaying the changes in TS relative to baseline for pinprick application with a pressure of 256 mN (top row) and 512 mN (bottom row) at the control and the primary pain sites at three post-operative visits, V1 (left column), V2 (middle column), and V3 (right column). Solid vertical lines indicate the mean of the data points.
Abbreviations: NRS, numerical rating scale; Post-op, post-operative; V, visit.

Similarly, PPToL was also increased compared to baseline at all post-implantation visits for both the primary pain and control sites. The baseline estimate of PPToL at the primary pain site was 5.05 ± 0.58 kgf/cm^2, and estimated effects were 1.61 ± 0.74 (p = 0.036), 0.71 ± 0.70 (p = 0.316), and 0.79 ± 0.71 (p = 0.275) kgf/cm^2 at post-implantation visits 1, 2, and 3, respectively. At the control site, the baseline estimate of PPToL was 7.80 ± 0.36 kgf/cm^2, and effect estimates at the three post-implantation visits were 0.56 ± 0.41 (p = 0.185), 0.22 ± 0.38 (p = 0.562), and 0.60 ± 0.37 (p = 0.117) kgf/cm^2 (Table 3 and Figure 4).

Conditioned Pain Modulation

At the primary pain site, the baseline estimate of CPM was 0.67 ± 0.19 kgf/cm^2. We did not observe statistically significant changes in CPM. However, interestingly, we observed increased CPM at post-implantation visit 1 (0.64 ± 0.33 kgf/cm^2; p = 0.057), which was reduced at post-implantation visit 2 (0.26 ± 0.33 kgf/cm^2; p = 0.427) and visit 3 (−0.17 ± 0.34 kgf/cm^2; p = 0.616). In contrast, at the control site (baseline estimate CPM of 1.01 kgf/cm^2), CPM was decreased at all post-implantation visits. The estimated effects were −0.13 ± 0.39 (p = 0.743), −0.65 ± 0.39 (p = 0.105), and −0.63 ± 0.42 (p = 0.140) kgf/cm^2 at post-implantation visits 1, 2, and 3, respectively (Table 3 and Figure 5).

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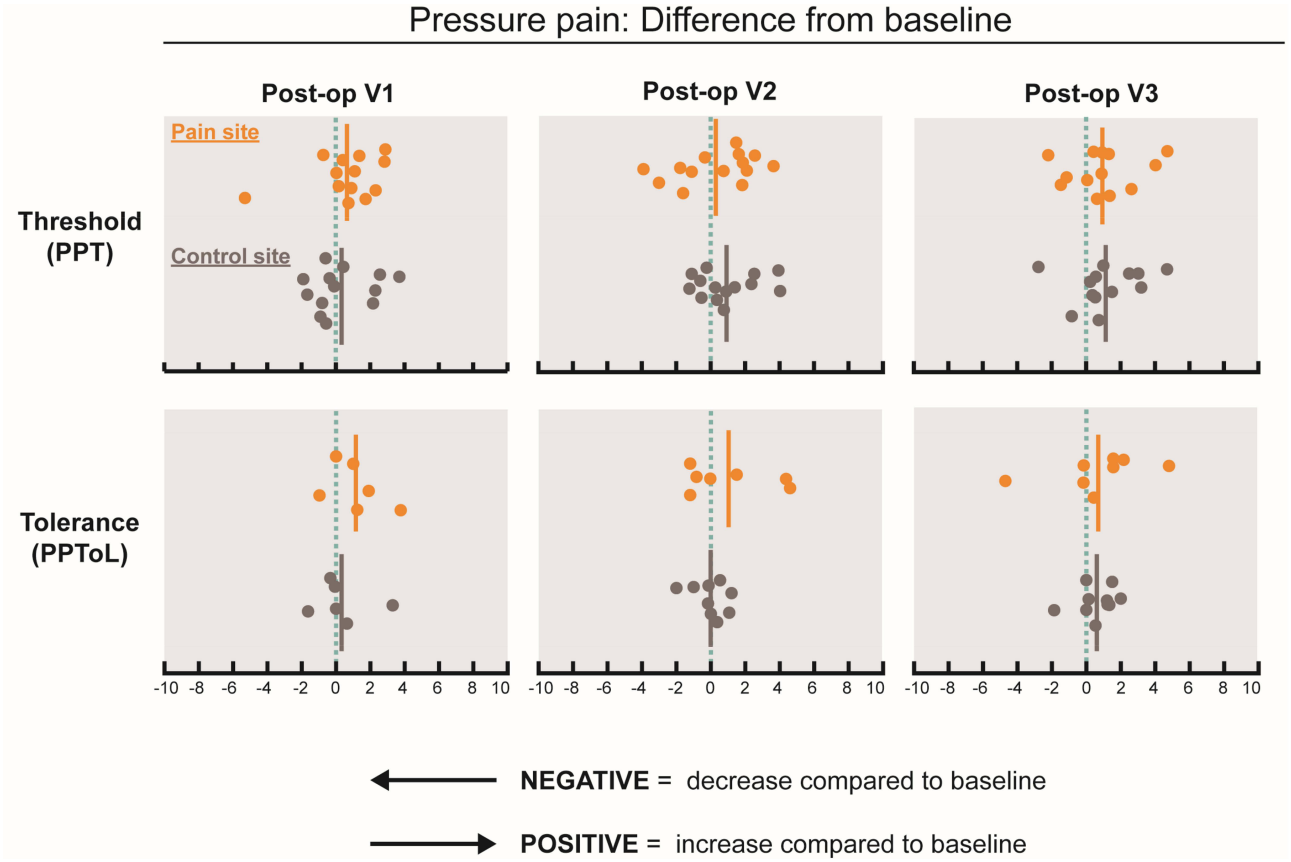

Figure 4 Stimulation-induced changes in PPT and PPToL. Scatter plots displaying the changes in PTT (tow row) and PPToL (bottom row) relative to baseline at the control and the primary pain sites at three post-operative visits, V1 (left column), V2 (middle column), and V3 (right column). Solid vertical lines indicate the mean of the data points.
Abbreviations: NRS, numerical rating scale; Post-op, post-operative; V, visit.

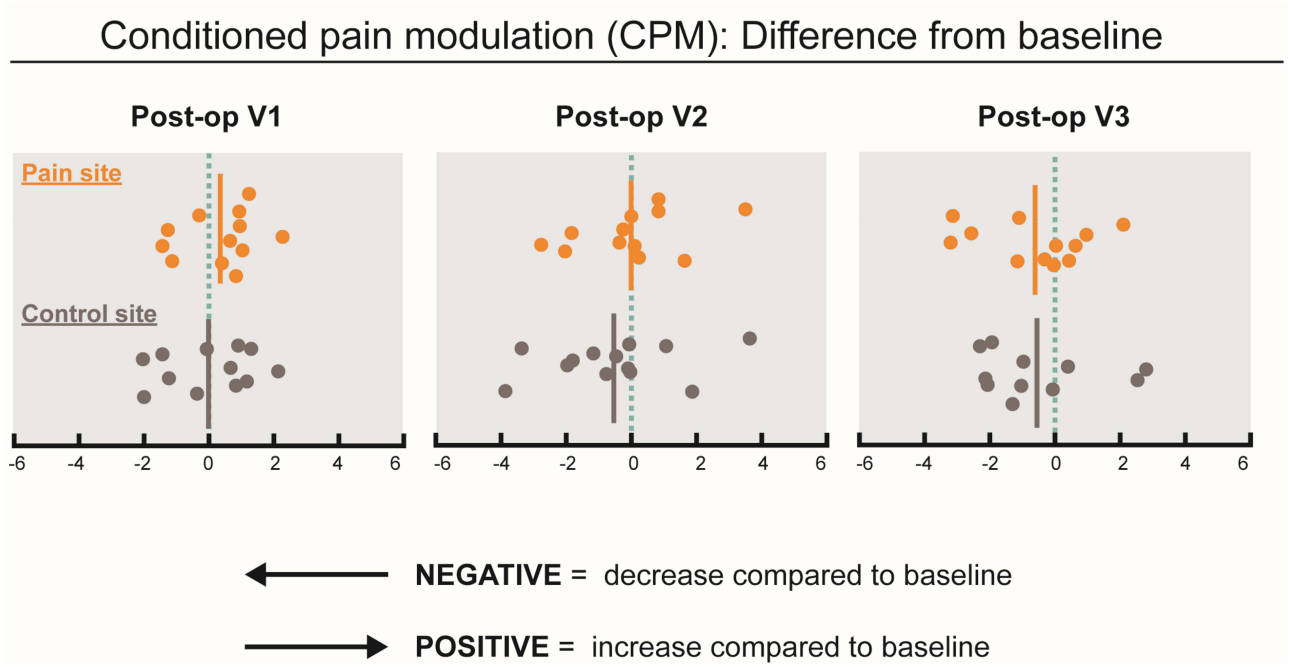

Figure 5 Stimulation-induced changes in CPM. Scatter plots displaying the changes in CPM relative to baseline at the control and the primary pain sites at three post-operative visits, V1 (left column), V2 (middle column), and V3 (right column). Solid vertical lines indicate the mean of the data points.
Abbreviations: NRS, numerical rating scale; Post-op, post-operative; V, visit.

Vibration

We observed no clear trends or significant changes in VDT at either the primary pain site or control site (Table 3). At the primary pain site, the baseline estimate of VDT was 16.07 ± 2.78 μm/second, and we found fixed effect estimates of 1.67 ± 3.19 (p = 0.603), 0.21 ± 3.03 (p = 0.944), and −0.95 ± 3.20 (p = 0.768) μm/second at post-implantation visits 1, 2, and 3, respectively (estimated fixed effect ± standard error). At the control site, the baseline estimate of VDT was 6.77 ± 1.12 μm/second and estimated effects were −0.78 ± 1.56 (p = 0.621), 0.53 ± 1.48 (p = 0.722), and −0.73 ± 1.56 (p = 0.644) μm/second at the three post-implantation visits.

Discussion

In this repeated-measures pilot study, we collected an assortment of QST and clinical outcomes from pre-implantation up to one year post-implantation in chronic pain patients receiving neurostimulation per their standard clinical care. Importantly, we observed statistically significant improvements compared to baseline in most patient-reported outcomes at all time points, although the magnitude of improvement tended to decrease over time. Results for QST measures were less clear, which likely can be partially explained by the small sample size and heterogeneity across participants. However, we found non-significant evidence that neurostimulation may reduce TS, increase PPT and PPToL, and increase CPM at the primary pain site.

Neurostimulation Improved Clinical Outcomes

Participants reported significant improvements in most clinical outcomes, including pain severity, pain interference, pain disability, sensory pain indices, affective pain indices, sleep interference, depression, and general health at all post-implantation timepoints (see Table 2 for the specific questionnaire used for each clinical outcome and the calculated effect size). These results agree with previous work and highlight the clinical value of these therapies. Interestingly, we observed that the magnitude of improvements tended to decline at the later visits, which highlights the need for long-term studies which assess clinical outcomes at one year and beyond.[33,34] While the success of these therapies in improving clinical outcomes across a heterogeneous population of stimulation modalities and painful etiologies is promising, future studies utilizing an inactive sham period will be necessary to control for patient expectations of pain relief from these sophisticated devices (ie, the placebo effect). We note that we did not correct for multiple comparisons which may amplify the observed positive trends, and that other relevant factors (eg, regression to the mean, psychophysical testing variability) should be considered.

Neurostimulation Non-Significantly Reduced TS at the Primary Pain Site

TS is considered the clinical correlate of wind-up, an observed electrophysiological phenomenon that repetitive low-frequency noxious stimulation creates a progressive increase in noxious dorsal horn signaling.[35] Preclinical work has demonstrated that SCS can inhibit windup in injured rodents, offering a promising potential mechanism for the observed analgesic effects of these neurostimulation procedures.[36] Excitingly, Eisenberg et al reported decreased noxious thermal TS at the primary pain site in SCS patients with radicular leg pain, with no observed changes on the contralateral leg, up to 3 months post-implantation.[13] Further supporting evidence has been reported by Schuh-Hofer et al who found that SCS reduced TS compared to when stimulation was off.[20] Given the permanent nature of these implants and potential for waning efficacy over time, it is important to consider whether changes in TS are sustained into the chronic implantation phase.

In this pilot study, TS at the primary pain site was decreased compared to baseline at all post-implantation visits for both 256 and 512 mN (these reductions were not statistically significant). Interestingly, this effect was not reproduced at the non-painful control site, where changes were smaller in magnitude and no clear trend was observed (Figure 3 and Table 3). Although not statistically significant, the trend displayed by these data are consistent with the hypothesis that neurostimulation-based suppression of spinal neuron hyperexcitability may contribute to the analgesic mechanisms of these therapies, which will need to be confirmed by future, larger studies.

Neurostimulation Non-Significantly Affected Pressure Pain and CPM

For both PPT and PPToL, thresholds were increased at all post-implantation visits at both the control and primary pain sites (Table 3). These increases typically failed to reach statistical significance, except for the primary pain site PPToL at post-operative visit 1 ($p = 0.036$) and the control site PPT at post-operative visit 3 ($p = 0.022$). These consistent increases in thresholds suggest that SCS and DRGS may modulate mechanical pressure pain processing, but larger studies will be necessary to conclusively demonstrate this possibility with statistical significance. Interestingly, the observation that thresholds were increased at both the primary pain site and control site suggest that this effect may be mediated, at least partially, by central mechanisms.

CPM measures the strength of the endogenous antinociceptive system in response to a simultaneous noxious stimulus. Recently, Campbell et al found that reduced baseline CPM was associated with reduced pain 3 months after SCS implantation.[11] Similarly, Schuh-Hofer et al demonstrated a positive interaction between SCS and CPM during stimulation compared to when the stimulation was turned off.[20] We investigated the plausibility of stimulation effects on CPM by measuring PPT while simultaneously applying a noxious conditioning pressure to the thumbnail.

In our study, although not statistically significant, primary pain site CPM increased at post-op visit 1 (~4-6 weeks post-implantation) compared to baseline (0.64 ± 0.33 kgf/cm^2; $p = 0.057$), which differed from the effect at the control site (-0.13 ± 0.39; $p = 0.743$). This result could be due to an effect of neurostimulation on descending pain inhibition, in concordance with previous work.

Study Limitations and Future Directions

Several study limitations deserve further consideration. First, having several missing data points reduced the power to identify statistically significant effects for the various QST procedures. Unfortunately, this problem was exacerbated by the concurrent COVID-19 pandemic which prevented data collection for many subjects at various timepoints. Additionally, the subjects represented a heterogeneous population, including participants with many pain etiologies and pain sites and receiving different forms of neurostimulation. However, given the similar clinical benefits, we felt it was reasonable as a first approach to aggregate data from this diverse population to facilitate participant recruitment and increase sample size in this preliminary study. Future studies individually considering these different populations separately either in design or data analysis will more clearly elucidate whether this is a reasonable assumption. Finally, the study lacked an inactive or sham control, and all parties were unblinded to the parameters of the neurostimulation being received. Blinded, sham-controlled studies are necessary for understanding the relative contributions of the neural stimulation and patient expectations on outcomes, especially as recent blinded studies have demonstrated the potency of placebo for SCS-induced pain relief.[37,38]

Conclusion

The results of this pilot study demonstrate clinical benefits of SCS and DRGS up to one-year post implantation. Improvements in clinical outcomes tended to decline over time, and longer studies will be necessary to assess whether these improvements stabilize to produce maintained, long-lasting improvements. We found limited, statistically non-significant evidence suggesting that SCS and DRGS may modulate sensory processing. These preliminary results inform the design of future, sham-controlled studies examining these effects, isolating specific pain etiologies and stimulation paradigms.

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Disclosure

SEH is an inventor of the Multimodal Automated Sensory Testing (MAST) device used in this study and is also a member of Arbor Medical Innovations, LLC (Ann Arbor, MI, USA), licensee of the MAST device from the University of Michigan (patent no: US9307906B2). SEH also reports grants from NIH. PGP is a consultant for NeuroOne and

Epiminder, has received research grants from the National Institutes of Health and National Science Foundation, and is a member of the North American Neuromodulation Society executive committee. SFL has equity in CereGate and Presidio Medical, Inc.; is a member of the scientific advisory boards for CereGate and Presidio Medical, Inc.; and has received research support from Abbott Neuromodulation, Medtronic, plc, Neuromodulation Specialists, LLC, and Presidio Medical, Inc. SFL also reports grants from NIH and has a patent 14/726,702 issued and a patent 18/597,657 pending. All other authors declare no conflicts of interest in this work.

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