CRCNS: Model-based Characterization of Spinal Cord Stimulation for Pain

NCT04732325

CRCNS: Model-based characterization of spinal cord stimulation for pain

A randomized, double-blind, placebo-controlled, crossover, mechanistic study investigating the pain-relieving effects of multiple forms of spinal cord stimulation (SCS) (i.e., tonic 50 Hz, burst, tonic 1 kHz, sham) in 25 patients undergoing SCS as part of their standard of care for chronic pain management.

Study Chairman or Principal Investigator:

Scott F. Lempka, PhD
Assistant Professor, Biomedical Engineering
Assistant Professor, Anesthesiology
University of Michigan

Supported by:

The National Center for Complementary and Integrative Health

Grant number: 1R01AT010817-01

Study Intervention Provided by:

N/A

Sponsor of IND (IDE):

N/A. This study is post-approval mechanistic study using FDA-approved devices that will be used in accordance with approved labeling.

Tool Revision History

Version Number: 0.1
Version Date: July 13, 2020
Summary of Revisions Made: Initial draft.

Version Number: 0.2
Version Date: November 16, 2020
Summary of Revisions Made: Updated consent language to include an optional electronic consent.

Version Number: 1.0
Version Date: December 22, 2020
Summary of Revisions Made: First approved version.

Version Number: 1.1
Version Date: August 17, 2021
Summary of Revisions Made: Updated study personnel.

Version Number: 1.2
Version Date: February 23, 2022
Summary of Revisions Made: Minor grammatical and formatting corrections. Removal of the Treatment Assignment Tool – University of Michigan (TATUM) from the text because the Michigan Institute for Clinical & Health Research (MICHR) has discontinued use of this tool (see Sections 4.3, 6.2.2, and 9.2). Update to the intra-burst frequency range used in Burst-SCS (see Section 5.1). Update to allow participants to retain the patient programmer for participant safety (see Sections 6.2.3 and 9.2). Update to the sham stimulation condition to help maintain the study blind (see Sections 5.1, 6.2.2, 6.2.3, and 9.2).

Version Number: 1.3
Version Date: May 24, 2024
Summary of Revisions Made: Updated study personnel (see STUDY TEAM ROSTER). Added clarifying details regarding the target population size of 25 randomized participants (see PRÉCIS and Section 4).

TABLE OF CONTENTS

Page

STUDY TEAM ROSTER

Scott F. Lempka, PhD — **Principal Investigator**
Biomedical Engineering
University of Michigan
2800 Plymouth Rd, NCRC 014-184
Ann Arbor, MI 48109
Phone: (734) 764-2401
Email: lempka@umich.edu

Steven Harte, PhD — **Co-Investigator**
Domino's Farms/Lobby M
Ann Arbor MI 48106
Phone: (734) 998-6939
Email: seharte@med.umich.edu

Parag Patil, MD, PhD — **Co-Investigator**
UH South F2306
Michigan Medicine
1500 East Medical Center Drive, SPC 5338
Ann Arbor, MI 48109-5338
Phone: (734) 615-1520
Email: pgpatil@med.umich.edu

Chad Brummett, MD — **Co-Investigator**
Burlington Building Floor 1
325 E Eisenhower Pkwy
Ann Arbor, MI 48108-3364
Phone: (734) 615-7246
Email: cbrummet@med.umich.edu

Srinivas Chiravuri, MD — **Co-Investigator**
Burlington Building Floor 1
325 E Eisenhower Pkwy
Ann Arbor, MI 48108-3364
Phone: (734) 615-7246
Email: chiravun@umich.edu

Daniel J. Clauw, MD — **Co-Investigator**
Domino's Farm, 24 Frank Lloyd Wright Dr.
Lobby M, Ste 3100
Ann Arbor MI 48105-5737
Phone: (734) 615-7246
Email: dclauw@med.umich.edu

Katherine A. Scott, BSN, RN — **Administrative Staff**
Domino's Farm, 24 Frank Lloyd Wright Dr.
Lobby M, Ste 3100
Ann Arbor MI 48105-5737
Phone: 734-998-7022
Email: jrsj@umich.edu

Michael Gantos, BS **Study Coordinator**
325 E Eisenhower PKWY Ste #100
Burlington Building
Ann Arbor, MI 48108
Phone: (734) 763-5226
Email: gantosmi@med.umich.edu

PARTICIPATING STUDY SITES

University of Michigan
Scott Lempka, PhD **Principal Investigator**
NCRC 014-184
2800 Plymouth Rd
Ann Arbor, MI 48109
Phone: (734) 764-2401
Email: lempka@umich.edu

PRÉCIS

Study Title

CRCNS: Model-based characterization of spinal cord stimulation for pain

Objectives

Primary Objective: The primary objective of this study is to compare the ability of multiple forms of SCS to modulate pain processing. We will assess pain and sensory processing using quantitative sensory testing (QST). Our primary outcome is the effect of multiple forms of SCS on dynamic central pain-processing mechanisms measured by the perception of pain in response to sequential stimuli (temporal summation).

Exploratory Objectives: We will assess SCS-induced endogenous pain inhibition by measuring dynamic pain sensitivity concurrent with the application of a conditioning stimulus (conditioned pain modulation). We will also evaluate the effects of SCS using static QST measures of sensory detection threshold, pain threshold, and/or tolerance to various somatosensory stimuli (e.g., vibration, pressure-pain). We will also assess the efficacy of multiple forms of SCS on relevant clinical measures including pain intensity, pain quality, pain spread, and quality of life. Finally, we will combine these clinical measurements with patient-specific computational models that will include: 1) electric-field models to estimate the direct neural response to SCS, and 2) circuit models to estimate the effects of SCS on pain processing in the spinal cord.

Design and Outcomes

In a single-center, randomized, double-blind, placebo-controlled, crossover pilot study, we will investigate the physiological effects and mechanisms of action of multiple forms of SCS (i.e., tonic 50 Hz, burst, tonic 1 kHz, sham) in 25 patients undergoing SCS. In this exploratory mechanistic study, we will evaluate the effects of somatosensory stimuli (e.g., vibration and pressure-pain stimuli) using static QST measures of sensory detection threshold, pain threshold, and/or tolerance to stimuli. We will assess dynamic central pain-processing mechanisms by measuring the perception of pain in response to sequential stimuli (temporal summation), and endogeneous pain inhibition by measuring

pain sensitivity concurrent with the application of a conditioning stimulus (conditioned pain modulation). We will also obtain outcome measures to assess changes in pain intensity, pain quality, pain spread, and quality of life. We hypothesize that clinically effective forms of SCS will decrease temporal summation, reduce pain sensitivity, and improve conditioned pain modulation.

Interventions and Duration

Spinal cord stimulation (SCS) is a neuromodulation therapy used to treat medically refractory chronic pain. SCS systems are typically completely internalized systems that consist of two main components. The first component is an implanted pulse generator (IPG) that typically has a titanium casing and is most commonly implanted in the posterior hip area. The second component is electrode arrays consisting of 8-32 metal electrodes that are typically made out of platinum-iridium and implanted in the epidural space near the dorsal aspect of the spinal cord. There are two main types of SCS electrode arrays. The first type is cylindrical electrode arrays that can be implanted on an outpatient basis under local anesthesia using a Touhy needle. The second type of arrays is a paddle- or plate-style electrode array in which a surgeon performs a laminotomy for implantation. In SCS, the IPG generates short duration electrical pulses that are then applied to the tissues through the implanted electrode arrays. Subjects will be receiving SCS as part of their clinical care and study participation will be approximately 1-3 months in duration for each participant.

Sample Size and Population

For this study, we will randomize 25 subjects receiving SCS as part of their clinical care for chronic pain management. Subjects will have chronic pain of the trunk and/or limbs that is refractory to other conventional forms of treatment.[8,9] Patients will be recruited without regard to racial or ethnic background. Patients will be enrolled without regard to gender. Male and female patients of any ethnic background will be eligible for enrollment. The research will not involve children (patients < 18 years of age), pregnant women, fetuses, or prisoners. Because these patients will be recruited at the University of Michigan, we expect them to primarily reside in Michigan and surrounding states.

1. STUDY OBJECTIVES

1.1 Primary Objective

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
The primary objective of this study is to assess how multiple forms of SCS alter sensory processing.	The primary endpoint will be SCS-induced changes in temporal summation (TS).	TS refers to an increased perception of pain in response to sequential stimuli of equal physical strength and it is a QST model of neural

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		plasticity and central hyper-excitability.

1.2 Secondary Objectives

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Tertiary/Exploratory		
The exploratory objectives of this study are to assess SCS-induced changes in static and dynamic sensory processing and the efficacy of SCS on pain quality, pain spread, and quality of life. The exploratory objectives of this study are also to use computational models to investigate the physiological effects and corresponding analgesic mechanisms of SCS.	We will assess the effects of SCS on endogenous pain inhibition by measuring pain sensitivity concurrent with the application of a conditioning stimulus (i.e., conditioned pain modulation (CPM)). We will evaluate the effects of SCS using static QST measures of sensory detection threshold, pain threshold, and/or tolerance to various somatosensory stimuli (e.g., vibration, pressure-pain). We will assess the effects of SCS on pain intensity using patient-reported VAS pain ratings for back pain, leg pain, and general pain.[1,2] Additional outcomes will include several self-reported patient questionnaires, such as the McGill Pain Questionnaire to assess quality of pain,[3] Michigan Body Map to quantify the degree of widespread body pain,[4] EuroQol questionnaire to characterize quality of life,[5] and questionnaires from the Patient Reported Outcomes Measurements Information (PROMIS).[6] Finally, we will combine these clinical measurements with patient-specific computational models that will include: 1) electric-field models to estimate the direct neural response to SCS, and 2) circuit models to estimate the	These outcome measures will describe the physiological effects of SCS on the processing of different types of sensory stimuli. These measures will also provide insight regarding the efficacy of multiple forms of SCS on spinal and supraspinal pain processing. VAS ratings are the most common outcome measure in SCS and thus we will be able to compare our outcomes to other clinical studies.[1,2,7–10] The patient-reported questionnaires are validated measures that are widely used in the field of pain research and clinical care. With regards to the computer modeling, our previous results with computer models,[11–13] support the concept that patient-specific computer models can advance

	effects of SCS on pain processing in the spinal cord.	our scientific understanding and directly improve clinical outcomes with SCS and other neurostimulation therapies. Therefore, the outcome measures and computer modeling will help improve our scientific understanding of the pain-relieving effects of SCS and guide the development of new hypotheses and the design of future clinical studies.

1.3 Specific Aims

Aim 1: To characterize the anti-nociceptive effects of SCS.

In a randomized, double-blind, placebo-controlled, crossover study, we will investigate the physiological effects and corresponding mechanisms of action of multiple forms of SCS (i.e., tonic 50 Hz, burst, tonic 1 kHz, sham) in 25 patients undergoing SCS. We will assess dynamic central pain-processing mechanisms by measuring the perception of pain in response to sequential stimuli (temporal summation),[14] and endogenous pain inhibition by measuring pain sensitivity concurrent with the application of a conditioning stimulus (conditioned pain modulation).[15] We will also evaluate the effects of somatosensory stimuli (e.g., vibration and pressure-pain stimuli) using static QST measures of sensory detection threshold, pain threshold, and/or tolerance to stimuli. Furthermore, we will obtain outcome measures to assess changes in pain intensity, pain quality, pain spread, and quality of life. We hypothesize that clinically effective SCS will decrease temporal summation, improve conditioned pain modulation, and reduce pain sensitivity.

Aim 2: To define the direct neural response to SCS.

We hypothesize that patient-specific models capture the details necessary to quantitatively describe the neural response to SCS and to correlate model-based predictions with experimental measurements of pain modulation. Therefore, we will develop patient-specific electric-field models that account for sources of interpatient variability (e.g. anatomy, electrode locations, stimulation parameters) for the 25 patients from Aim 1. We will define finite element models from the patient-specific preoperative and postoperative medical imaging. To estimate the direct neural response to SCS, we will then place multi-compartment neuron models within the patient-specific spinal cord anatomy.

Aim 3: To identify the effects of SCS on pain processing in the spinal cord.

The basic hypothesis of this study is that the physiological effects of SCS can be correlated with modulation of specific fiber pathways that help regulate pain processing within the spinal cord. However, the specific analgesic mechanisms of clinically effective SCS remain

unknown. Therefore, we will develop a population firing-rate circuit model of pain processing in the spinal cord. We will use the direct neural response to SCS from Aim 2 as the inputs to our circuit model. We will determine what types of spinal cord modulation best correlate with experimental measurements of pain modulation during SCS.

Exploratory Aim: Model-based optimization of SCS

Due to our poor scientific understanding of how SCS works and the limited individualization of this therapy, we hypothesize that current clinical implementation of SCS is suboptimal. Therefore, in this exploratory analysis, we will use our computational models to identify stimulation protocols (e.g., alternative waveform parameters) that may improve the desired physiological effects and corresponding pain relief.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

SCS was first tested in patients in 1967, two years after Melzack and Wall published the gate control theory of pain.[16,17] Conventional SCS involves tonic electrical stimulation at a moderate frequency (e.g., 40-60 Hz) with the goal of exciting large-diameter (Aβ) sensory afferents in the dorsal columns to create paresthesias (e.g., tingling, buzzing, pin and needles, pressure) over the painful areas (Fig. 2.1A).[18] According to the gate-control theory, some of the Aβ fibers have collaterals that project to the affected spinal levels. SCS results in antidromic activation of the Aβ fibers that in turn (via their collaterals) lead to inhibition of nociceptive-specific or wide dynamic range projection neurons in the dorsal horn (Fig. 2.1). In neuropathic pain conditions, excessive nociceptive inputs are believed to produce hyperexcitability in these projection neurons (i.e., central sensitization). Antidromic activation of Aβ fibers from SCS is hypothesized to inhibit output from these projection neurons largely through the activation of inhibitory interneurons that help close the "gate" and prevent the transmission of pain signals to the brain.[19] There is additional experimental evidence that orthodromic Aβ axonal activation may also help reduce pain via supraspinal mechanisms, such as descending inhibition.[20]

Stimulator programming involves assessing a variety of parameter combinations (e.g., amplitude, pulse width, frequency, stimulation configuration) with the goal of maximizing the overlap of SCS-induced paresthesias with a patient's painful areas. Clinical experience suggests that sufficient pain-paresthesia overlap increases the likelihood for pain relief.[21] It is important to note, that SCS-induced pain relief occurs over a time course of seconds to several hours. However, SCS-induced paresthesias occur rapidly (~1 s) and serve as a surrogate for pain relief that make it practical to test several sets of stimulation parameters within a standard clinical visit. Although widely used for decades, the success rate of SCS, defined as the proportion of patients receiving ≥ 50% pain relief, is approximately 58%.[22]

In an attempt to improve the clinical efficacy of SCS, several novel waveform paradigms have emerged on the clinical market within the last several years. Burst-SCS is one of these new approaches that delivers intermittent bursts of electrical pulses (five pulses at 500 Hz, delivered 40 times per second) to mimic thalamic bursting within the nervous system (Fig. 2.1B).[2] Burst-SCS demonstrates two potential advantages over conventional low-frequency SCS: 1) improved pain relief, and 2) pain relief without concomitant paresthesias. Paresthesia-free pain relief can be extremely beneficial because SCS-induced paresthesias may disturb sleep, be experienced as excessive or uncomfortable, and vary with body position.[23]

Burst-SCS was approved by the FDA in 2016 based on the results of a large multi-center clinical trial that reported Burst-SCS to be significantly more effective than conventional SCS (60% vs. 51% success rate).[24] Preliminary evidence suggests that Burst-SCS modulates both ascending pain-evoking and descending pain-inhibitory pathways involved in pain

processing and may function through different mechanisms than conventional SCS.[20,25] However, these potential mechanisms of action require validation with additional studies.

KHFSCS is another novel form of SCS that applies tonic stimulation pulses at a rate ≥ 1 kHz. In 2015, the FDA approved a KHFSCS system that applies stimulation at a rate of 10 kHz and provided dramatic pain relief (~80%) without generating paresthesias (Fig. 2.1B).[26] The pain-relief mechanisms of KHFSCS are currently unknown. Kilohertz stimulation frequencies have shown the ability to generate rapid and reversible conduction block in peripheral nerve models.[27] This idea of conduction block was a driving force behind the development of KHFSCS with the idea that it could block the propagation of painful signals to the brain. However, theoretical and experimental data suggest that conduction block is unlikely at the low stimulation amplitudes used clinically (i.e. 0.5-5.0 mA).[12,28–30] These studies also suggest that the direct activation of dorsal column axons is also unlikely with clinical KHFSCS. A recent study examined the paresthesias generated by low-frequency stimulation in a group of patients that had been receiving KHFSCS as part of their standard clinical care.[31] In these KHFSCS patients, the paresthesias generated by low-frequency stimulation (utilizing the same electrodes as with KHFSCS) did not overlap with the patients' painful areas. This data suggested that pain-paresthesia overlap is not necessary and that KHFSCS may be functioning through different mechanisms of action relative to low-frequency SCS. Several additional mechanisms of action of KHFSCS have also been presented, such as asynchronous activation, desynchronization of clusters of neurons firing in synchrony, reduced "wind-up" and suppression of spontaneous activity in dorsal horn cells, and excitability changes from possible tissue heating due to the increased power deposited in tissue during KHFSCS.[20,32,33]

While KHFSCS is an exciting new approach, there are several unanswered questions and limitations with current clinical implementation of this technology. For example, it is not clear what stimulation rate in the kilohertz frequency range provides the optimal pain relief. A recent clinical study demonstrated equal pain relief at several frequencies in the kilohertz range (i.e. 1, 4, 7, and 10 kHz) and stimulation at a lower frequency (e.g. 1 kHz) may provide equivalent pain relief at lower energy demands.[34] Additionally, although it can be advantageous to provide pain relief without concomitant paresthesias, these rapid-onset paresthesias serve as a surrogate to select clinically effective stimulation parameters with paresthesia-based low-frequency SCS. With paresthesia-free KHFSCS, parameter efficacy can only be determined by patient-reported pain relief after several hours of stimulation.

It is an exciting time in the field of SCS and neurostimulation for pain. Over the last several years, there have been dramatic technological advancements to develop novel approaches that may improve the clinical efficacy of these neurostimulation therapies. These advancements include novel waveform paradigms, such as Burst-SCS and KHFSCS, innovations in lead design to increase the number of electrode contacts and improve the lead mechanical properties, improvements in IPG capabilities to increase battery lifetime, reduce invasiveness, and provide closed-loop stimulation. These innovations along with decades of clinical experience, have produced potentially powerful therapies to improve the lives of patients suffering from chronic pain. However, these advancements have outpaced our scientific understanding of these technologies. Remaining unanswered questions may limit the impact, optimization, and long-term reliability of these SCS therapies.

From the clinical side, we do not understand why SCS works well in some patients, but fails in others. We do not have clear indicators to reveal which patient may initially respond to SCS but will fail in the long term. The subjective nature of pain and corresponding pain ratings make it difficult to assess the true efficacy of these approaches. Along similar lines, we do not have objective biomarkers or surrogates of pain and pain relief to help optimize the clinical programming procedures, especially with regards to novel SCS waveform paradigms. Finally, how early should we intervene with SCS? SCS is typically only considered after several other

treatment options have failed. However, evidence suggests that outcomes may be improved with earlier intervention with SCS.[35,36]

From a scientific perspective, what are the mechanisms of action behind SCS-induced analgesia? What are the specific mechanisms of action for tonic SCS, Burst-SCS, and KHFSCS? To answer these questions, we need to improve our knowledge of spinal cord anatomy and physiology, anatomical factors that affect the electric fields generated in the tissue, and how these electric fields translate into physiological and perceptual effects.[37] We also don't have a clear understanding of how SCS modulates central pain processing or the degree to which placebo effects confound the results of scientific studies.[38–40]

To better understand the mechanisms of action of SCS, it is critical to perform systematic, well-powered, randomized, double-blind, placebo-controlled, preclinical and clinical studies. While it is difficult (but possible) to perform placebo-controlled studies with paresthesia-based approaches, new paresthesia-free paradigms are well suited for placebo-controlled trials.[34,38,39,41] To further clarify the mechanisms of action of SCS and which patients might respond in the long term, objective measures characterizing the physiological effects of SCS (e.g., quantitative sensory testing, functional neuroimaging) could be combined with conventional patient-reported subjective outcome measures.[40] It is also important to establish a relationship between the mechanisms of action of SCS and the pathological mechanisms of a specific pain condition. This relationship is essential to predict the therapeutic efficacy of SCS and to improve patient selection.

Future research should also move towards developing patient-specific approaches to understand mechanisms of SCS. Due to limitations in animal models of chronic pain (e.g., inability of animals to report their pain, and unclear translation of animal results to humans),[42,43] it is important that we develop methods to systematically study SCS in human subjects. For example, patient-specific computational models that account for interpatient variability in anatomy and electrode locations are commonly used in other neurostimulation therapies, such as deep brain and transcranial electric stimulation, to investigate mechanisms of action and provide clinical decision support.[44,45] However, this type of patient-specific modeling approach is uncommon in SCS.[46] We believe that patient-specific approaches in SCS may be critical to understand the mixed clinical outcomes of SCS and will help optimize the clinical effectiveness of current and novel SCS technologies.

2.2 Study Rationale

More than 1.5 billion people worldwide and ~100 million American adults suffer from chronic pain.[47,48] Chronic pain is debilitating as it impacts most aspects of a person's life, including physical inability, emotional distress, and/or psychological impairment.[49] Unfortunately, conventional medical management is often insufficient in relieving chronic pain.[50] Opioid analgesics are frequently prescribed despite the lack of clinical evidence supporting their long-term use to treat chronic pain and the associated epidemic of opioid abuse, addiction, and death from overdose in the United States.[51,52] Less conventional forms of therapy, such as SCS and other forms of neurostimulation, may offer a better alternative. However, despite advances in technology, the success rates of these neurostimulation approaches have plateaued and significant opportunities remain to improve clinical efficacy. Limited outcomes of both conventional medical management and neurostimulation procedures can largely be attributed to our poor scientific understanding of how these therapies relieve chronic pain.

Spinal cord stimulation (SCS) is a neurostimulation therapy that can be considered for patients who are refractory to other treatment options (e.g., pharmaceuticals).[53,54] In SCS, electrical pulses modulate neural activity in the spinal cord in an attempt to prevent pain signals from reaching the brain. SCS is widely used all over the world and exceeds USD 1.8 billion in annual sales, with as many as 50,000 spinal cord stimulators implanted annually.[55,56] While SCS

can provide dramatic pain relief in some patients, a large number of patients fail to respond to this therapy. Success rates also vary widely across studies and efficacy declines over treatment time.[22] This limited success can largely be attributed to the fact that we don't know how it works. Therefore, the goal of this project is to investigate the pain-relief mechanisms of SCS by combining clinical measurements of pain modulation with detailed computational models of SCS.

In this study, we will adopt a systematic, well-controlled, patient-specific approach to characterize SCS. We believe this type of approach is necessary to improve our scientific understanding of chronic pain and how to treat it. This study will also help develop the experience and technology necessary to characterize neurostimulation approaches for other neurological disorders. To investigate the anti-nociceptive effects of SCS, we will conduct a placebo-controlled study in 25 patients undergoing SCS for chronic pain. We will obtain outcome measures and use quantitative sensory testing (QST) to assess spinal and supraspinal pain processing. Because these mechanistic questions are difficult to answer experimentally, we will combine these clinical measurements with patient-specific computational models that will include: 1) electric-field models to estimate the direct neural response to SCS and 2) circuit models to estimate the effects of SCS on pain processing in the spinal cord.

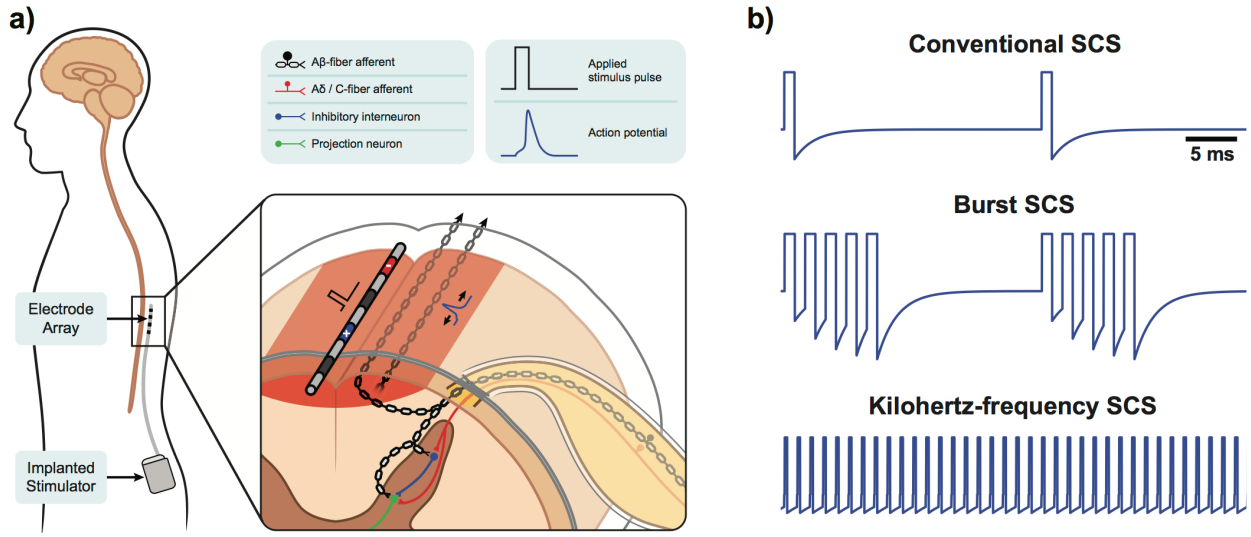

Figure 2.1. *Spinal cord stimulation (SCS). (A) An electrode array is implanted in the epidural space dorsal to the spinal cord to stimulate Aβ axons and create analgesia. (B) Conventional SCS applies short-duration pulses at 40-60 Hz. Burst SCS is a new type of paresthesia-free stimulation that applies bursts of stimulation at 40 Hz. Kilohertz-frequency SCS is another novel form of paresthesia-free stimulation that applies pulses at ≥ 1 kHz.*

Patients to be enrolled in this study will be undergoing SCS to manage their chronic pain as part of their clinical care and will be subject to the standard risks associated with this therapy. These risks are not part of this research. However, the participants will also be subject to potential risks associated with the experimental procedures described in this study. The risks associated with this research study can be best understood if separated in the following categories: risk related to electrical stimulation by the implanted spinal cord stimulator, risk of the medical imaging procedures, risk of outcome measures, risk related to quantitative sensory testing, and risk of loss of confidentiality.

<u>Risk related to electrical stimulation</u>

During the stimulator programming session, electrical stimulation delivered to the spinal cord is titrated over a range of amplitudes. Side effects related to higher stimulation, such as muscle contractions, may occur, but are known to be reversible by either reducing the amplitude of stimulation or by stopping the stimulation entirely. Whenever using electricity to stimulate tissue, there is also the possibility of a shock hazard, including an electrical burn. However, only electrical stimulators approved by the US Food and Drug Administration for SCS will be used in this study. Therefore, the risk of tissue damage or electrical shock during the electrical stimulation is minimal.

When determining the amplitude at which the stimulation first becomes uncomfortable (i.e., discomfort threshold), the participant will experience some discomfort due to uncomfortable paresthesias or muscle contractions. It is also possible that the participant will experience similar discomfort during the remainder of the parameter selection or programming process. In either case, the stimulation amplitude will be decreased immediately or the stimulation turned off completely. To avoid or minimize participant discomfort, the stimulation amplitude will first be set to a low amplitude and increased in small increments.

Risk of medical imaging procedures

Each participant will receive a thoracic or cervical X-ray computed tomography (CT) scan to determine the locations of the implanted electrodes. This CT is not part of the participant's standard clinical care and requires the participant to undergo additional exposure to radiation. One of the major risks associated with radiation exposure is an increased risk of cancer. The patient consent form will identify the cumulative risks of radiation exposure from both potential standard of care imaging procedures and the additional research-related tests.

Risk related to quantitative sensory testing (QST)

Overall, the QST procedures may cause minor but temporary physical discomfort. However, the QST experiments will follow strict safety standards and will be as brief as possible. The intensity of each stimulus will be limited to levels that are deemed safe and acceptable. Additionally, study personnel are trained by the investigators to be sensitive to participant discomfort and concerns. The participant can inform the person to stop the QST at any time that the pain or unpleasantness of the task becomes intolerable.

The Multimodal Automated Sensory Testing (MAST) may cause some temporary physical discomfort on the thumbnail. The MAST system includes multiple software, electrical, and mechanical safeguards to ensure that the amount of pressure applied does not exceed safe limits, including a safety release pin that the subject can turn to immediately release the pressure actuator from his or her thumb. The test is terminated at or before 10 kg/cm^2 of pressure, which is a commonly used maximum pressure level in human sensory testing and does not result in physical injury. Subjects will always have personal control over the stimulus and can stop it at any time or express instructions to stop the stimuli. The subjects can also withdraw their thumb from the device.

The vibrometer, pressure algometer, and the pointed skin probe are commonly used in QST studies and should not cause any tissue injury at the maximum forces applied in this study. However, these instruments may cause minor physical discomfort in the areas of testing that is expected to resolve within minutes of test completion. These instruments may also cause small skin indentations and/or skin reddening that is expected to resolve within a few hours. These tests will be halted if the participant reports a pain rating of 100 out of 100.

Risk of outcome measures

The outcome measures will include standardized self-reported pain ratings and symptom questionnaires. Other measures will include electronic drawings of the anatomical location(s) of

each participant's pain over his/her body. We consider the outcomes measures to be used in this study to be of minimal risk. There is still a possibility of discomfort associated with being asked personal questions about medical history, symptoms, or feelings. The subject may refuse to answer any question on the questionnaires or surveys that may be uncomfortable.

Risk of loss of confidentiality

This research involves initially obtaining identifiable patient-subject private information (e.g., name, contact information) or biospecimens (e.g., urine samples) due to collecting standard of care data in addition to the research data for the project. Therefore, loss of participant confidentiality is a potential risk in this research. However, we will follow necessary steps to minimize this risk.

3. STUDY DESIGN

In a single-center, randomized, double-blind, placebo-controlled, crossover pilot study, we will investigate the physiological effects and mechanisms of action of multiple forms of SCS (i.e., tonic 50 Hz, burst, tonic 1 kHz, sham) in 25 patients undergoing SCS. In this exploratory mechanistic study, we will assess dynamic central pain-processing mechanisms by measuring the perception of pain in response to sequential stimuli (temporal summation), and endogenous pain inhibition by measuring pain sensitivity concurrent with the application of a conditioning stimulus (conditioned pain modulation). We will evaluate the effects of somatosensory stimuli (e.g., vibration and pressure-pain stimuli) using static QST measures of sensory detection threshold, pain threshold, and/or tolerance to stimuli. We will also obtain outcome measures to assess changes in pain intensity, pain quality, pain spread, and quality of life. We hypothesize that clinically effective forms of SCS will decrease temporal summation, reduce pain sensitivity, and improve conditioned pain modulation.

In this study, we will perform a post-approval mechanistic study. We will perform a mechanistic study using FDA-approved devices that will be used in accordance with approved labeling. We will implement a randomized, double-blind, placebo-controlled, crossover study. This study design will allow us to test the physiological effects of multiple forms of SCS within individual participants. It will also allow us to quantify the effects of sham stimulation. We believe variability in SCS are largely due to "placebo" effects and/or lack of understanding of their mechanisms of action. A majority of previous clinical studies were performed in an unblinded manner whose results may have been confounded by a "placebo" effect.[1,7–9,57] One major criticism of previous SCS studies is the absence of blinding due to the presence of stimulation-induced paresthesia(s). With the advent of paresthesia-free SCS waveforms, such as Burst-SCS and KHFSCS, the paradigm is shifting. Clinical studies using Burst-SCS and KHFSCS have reported success in stimulating without producing paresthesias. However, a majority of these studies were performed in an unblinded manner. Therefore, the effect of "placebo" remains to be quantified. Comparing the physiological effects of Burst-SCS and KHFSCS to sham (no) stimulation will help systematically control for placebo effects and will help identify the true pain-relieving effects of SCS. For the fourth and final treatment allocation, all participants will receive seven days of tonic 50 Hz SCS that will generate paresthesias over their painful areas. This treatment is performed last because participants will likely know that they are receiving active stimulation due to the paresthesias and this design will minimize the chance of breaking the blind during the previous treatments. During the study, subjects will be instructed to maintain a stable level of medications for control of chronic pain symptoms.

As described in Section 9.5, the primary outcome will be SCS-induced changes in temporal summation (TS). TS refers to an increased perception of pain in response to sequential stimuli of equal physical strength (Fig. 9.1A). It is a quantitative sensory testing (QST) model of neural plasticity and central hyper-excitability that is thought to reflect the

progressive increase in neuronal firing of dorsal horn neurons in response to repetitive nociceptive C-fiber stimulation (i.e., windup).[58] We will also evaluate several exploratory outcome measures. We will assess SCS-induced endogenous pain inhibition by measuring dynamic pain sensitivity concurrent with the application of a conditioning stimulus (conditioned pain modulation). We will also evaluate the effects of SCS using static QST measures of sensory detection threshold, pain threshold, and/or tolerance to various somatosensory stimuli (e.g., vibration, pressure-pain). We will also assess the efficacy of multiple forms of SCS on relevant clinical measures including pain intensity, pain quality, pain spread, and quality of life. Finally, we will combine these clinical measurements with patient-specific computational models that will include: 1) electric-field models to estimate the direct neural response to SCS, and 2) circuit models to estimate the effects of SCS on pain processing in the spinal cord.

As described in Section 4.3, this study will occur at a single site, the University of Michigan. Subjects will be receiving SCS as part of their clinical care and study participation will be approximately 1-3 months in duration for each participant. We expect the total study duration to be approximately 3 years.

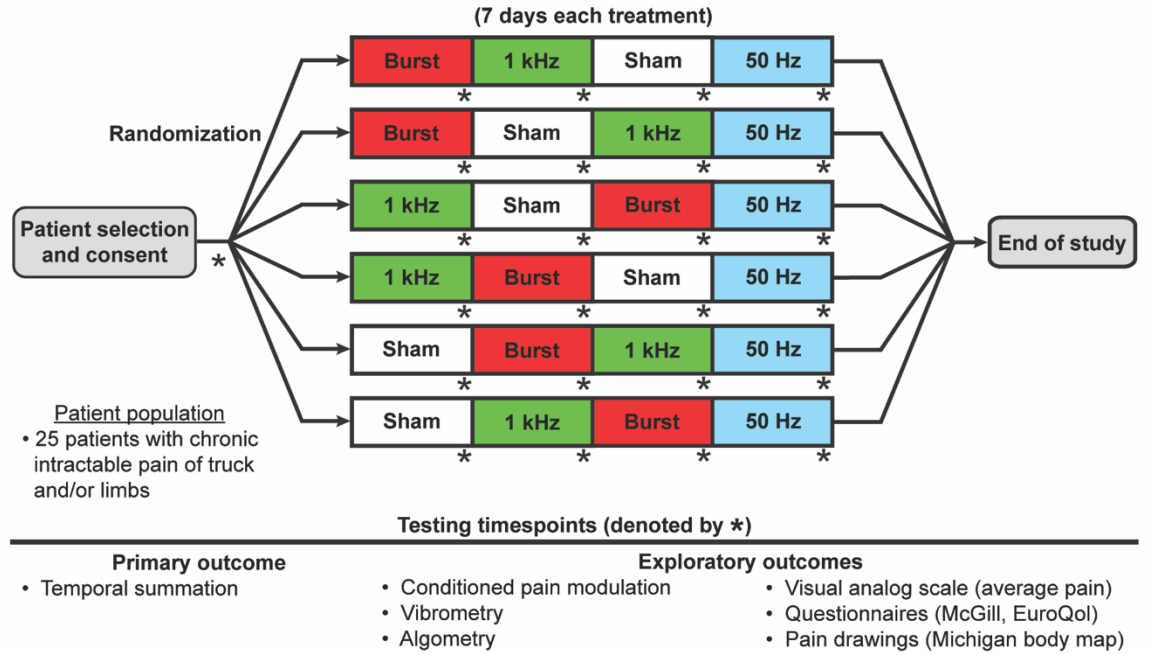

Figure 3.1. *Clinical study design.*

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

For this study, we will recruit subjects receiving SCS as part of their clinical care for chronic pain management. We will recruit subjects until we are able to randomize 25 participants. Patients will be elected without regard to racial or ethnic background. Patients will be enrolled without regard to gender. Male and female patients of any ethnic background will be eligible for enrollment. The research will not involve children (patients < 18 years of age), pregnant women, fetuses, or prisoners. We expect participants to primarily reside in Michigan and surrounding states. According to the results of a recent multicenter clinical trial of SCS,[26] with regard to gender, we expect the enrolled population to consist of 10/25 males and 15/25 females. With regard to ethnicity, we expect the patient enrollment to consist of 24/25 Non-Hispanic/Latino and 1/25 Hispanic/Latino. With regard to race, we expect the patient enrollment to consist of 23/25 White, 1/25 Black or African American, 0-1/25 American Indian/Alaska Native, 0-1/Asian, 0-1/25 Native Hawaiian or Other Pacific Islander, and 0-1/25 More than One

Race. This is only a targeted distribution and the final enrollment will ultimately depend on candidates presenting to the study who fulfill the inclusion and exclusion criteria and choose to consent to the study.

4.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Chronic intractable pain of the trunk and/or limbs.
- Undergoing SCS as part of standard clinical care for chronic pain management.
- Candidate will have been implanted with a commercial SCS device that can apply the necessary treatments (i.e., tonic 50 Hz, burst, tonic 1 kHz, sham).
- Candidates who are 18 years or older and can speak, read, and understand English.
- Ability to understand study procedures and to comply with them for the entire length of the study.
- Must be willing to participate in COVID-19 symptom screening and answer questions about COVID-19 diagnosis 1-3 days before a scheduled visit.
- Must be willing to wear a face covering during study visits.

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Subjects who are pregnant or nursing.
    - For both chronic pain subjects and healthy subjects of childbearing potential, and having no intrauterine device (IUD) or hysterectomy, and who are able to become pregnant, we will perform a urine pregnancy test to confirm pregnancy.
- Subjects with current, habitual, or previous use within the last 12 months of artificial nails, nail enhancements, or nail extensions that cover any portion of either thumbnail. Exceptions, including brief and/or occasional use, may be permissible at the discretion of the study personnel.
- Subjects who are unable or unwilling to cooperate with clinical testing.
- Subjects having any impairment, activity or situation that in the judgment of study personnel would prevent satisfactory completion of the study protocol
- Inability or unwillingness of individual or legal guardian/representative to give written informed consent.
- Subjects who currently have or tested positive in the last 14 days for COVID-19, or are symptomatic for COVID-19.

Note: The research will not involve children (patients < 18 years of age), pregnant women, fetuses, or prisoners.

4.3 Study Enrollment Procedures

This study will occur at a single site, the University of Michigan. We will actively and passively recruit participants. We will actively recruit patients from clinics at the University of Michigan (UM), such as clinics in the Department of Anesthesiology and the Department of Neurosurgery. These departments will have access to the purpose of the study, intended patient population, and inclusion/exclusion criteria. For this study, we will consider chronic pain patients who are being treated with SCS from their own doctors as part of their standard clinical care. For active recruitment, our team of pain specialists (e.g., anesthesiologists and/or

neurosurgeons) and other study personnel at UM will identify potential candidates and inform them about the study. The study coordinator or a person from the study team will contact the candidates (e.g., via telephone) to discuss details about the study (e.g., eligibility determination) and/or to verify interest. The necessary contact information (e.g., telephone number) of the candidates will be obtained by searching appointment logs and/or medical records.

For passive recruitment, we will post publicly accessible flyers and brochures throughout UM Clinics, and also in various locations around Michigan Medicine (e.g., University Hospital). We will also post flyers and brochures across various other Pain Clinics and Hospitals in Livingston, Washtenaw, and/or Wayne County. IRB-approved flyers and brochures will be hung in several locations (e.g., waiting areas) in these clinics and hospitals. These flyers will have contact information of the study team (e.g., email, phone) and will also have a description of the study (resource included in section 8-1.8 of the IRB application). Interested candidates may initiate contact with the study team.

As detailed in Section 6.2, potential subjects who are interested in participating in the study will be contacted by a member of the study team responsible for enrollment to assess interest and eligibility. Interested candidates will have the study and the eligibility criteria explained to them. If at this point they wish to continue with enrollment, the candidate will be invited to participate in a study screening visit. Screening will be done over phone to verify eligibility. The research team will adopt an optional electronic informed consent procedure using SignNow. This option will be our preferred method for obtaining consent. For eligible and interested candidates, a study team member will discuss the study with the patient and obtain consent over the phone. The consent form will be read to the participant and time will be allowed for questions or if the patient would like to read/review the consent form on their own before electronically signing.

For eligible candidates, we will schedule an enrollment visit and/or other subsequent visits. We may also email candidates the consent forms to study and think about participation. For interested and eligible candidates, we will schedule the enrollment visit and/or other subsequent visits. All potential subjects will be assigned a unique screening ID. Those volunteers who do not meet the eligibility criteria or who choose not to participate in the study at either the telephone Pre-Screen or the Screening Visit will be logged. Personal identifiers will be kept until the study has been closed to recruitment, at which time they will be destroyed. This will prevent repeat screenings of potential participants.

Screen failures will be defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of issues, such as pregnancy, or recent use of artificial nails may be rescreened. Rescreening will be limited to one occurrence per individual. Rescreened participants should be assigned the same participant number as for the initial screening.

Candidates who do not have access to the internet will sign the consent form during the screening visit. The screening visit will begin with the informed consent interview. During the consent interview we will explain the study verbally and in writing. If interested, candidates will sign an informed consent, and will be given a copy. We will conduct the consent interview in a private setting (e.g., examination room, office), allowing sufficient time for prospective subjects to make an informed decision. Furthermore, we will also offer candidates the option of taking the informed consent form home to study and think about participation, with a follow up with one of the investigators or study personnel. Once the subject has formally consented to participate they will undergo a screening examination by a member of the study team. After the screening

visit, study personnel will follow up with the patient after consent and screening to schedule all research visits.

Each visit will take approximately 1-4 hours to perform all of the desired assessments. The screening visit will take approximately 2 hours, the behavioral sessions will take approximately 2 hours, the imaging session will last approximately 1 hour, and each programming session will last approximately 1 hour.

As described in Section 6.2.2, we will randomize each participant to one of the six treatment arms.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Spinal cord stimulation (SCS) is an FDA-approved neurostimulation therapy for patients suffering from refractory chronic pain. SCS systems are typically completely internalized systems and consist of two main components. The first component is an implanted pulse generator (IPG) that typically has a titanium casing and is most commonly implanted in this posterior hip area. The second component is electrode arrays consisting of 8-32 metal electrodes that are typically made out of platinum-iridium and implanted in the epidural space near the dorsal aspect of the spinal cord. There are two main types of SCS electrode arrays.[59] The first type is cylindrical electrode arrays that can be implanted on an outpatient basis under local anesthesia using a Touhy needle. The second type of arrays is a paddle- or plate-style electrode arrays in which a surgeon performs a laminotomy for implantation. The IPG generates electrical pulses that are applied to the tissues through the implanted electrode arrays.

Dosing and Administration: Subjects will receive burst, tonic 1 kHz, tonic 50 Hz. and sham SCS. Each treatment will be applied for a duration of seven days. Participants will be blinded during programming. Burst-SCS will be applied at a burst-rate of ~40-60 Hz, intra-burst frequency of ~200-500 Hz, and ~2-5 pulses per burst. KHFSCS will be applied at a rate of ~1 kHz. To ensure proper blinding, we will set the amplitude of stimulation so that participants do not feel any stimulation-induced paresthesias.[2] We will perform sham SCS by setting the amplitude to 0 mA.[2] For some systems, if the stimulation amplitude is decreased to 0 mA, the system will report that the stimulation is OFF and the participants will know that they are not receiving stimulation. Therefore, for these systems, we will perform sham SCS by setting the stimulation parameters to their minimal values: pulse width (~20 μs), frequency (~2 Hz), and amplitude (~0.1 mA). These settings will correspond to a small fraction (<0.05%) of the amount of current normally applied during active SCS and will provide a sham condition that helps maintain the study blinding. After the third treatment allocation, each participant will receive seven days of tonic 50 Hz SCS that will generate paresthesias over their painful areas. After testing is completed, we will interrogate the stimulator to ensure that the stimulation settings were not altered during any treatment allocation.

5.2 Handling of Study Interventions

The spinal cord stimulation (SCS) systems to be used in this study are commercially available and will be used in accordance with approved labelling. No modifications will be made for this study. For this study we will consider commercial SCS devices from companies, such as Boston Scientific Corporation (Valencia, CA), Abbott Laboratories (Chicago, IL), or Nuvectra (Plano, TX). These commercial systems have the capabilities to apply the types of SCS that will be considered in this study: tonic 50 Hz, burst, and tonic 1 kHz.

Commercial SCS systems will have been prescribed by the participant's physician as part of their standard clinical care for chronic pain management. In this study, we will only consider

subjects who are implanted with commercial systems that can apply all of the desired treatments (i.e., tonic 50 Hz, burst, tonic 1 kHz, sham). However, there are differences in how each commercial system applies the different treatments. Therefore, we will track the device type for each participant and examine potential device-related differences in our outcome analyses.

5.3 Concomitant Interventions

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. The patient population that will be considered in this study will typically be on concomitant medications to manage their chronic pain. Fluctuations in these pain medications could affect the study endpoints. Therefore, during this study, we will instruct subjects to maintain a stable level of medications for control of chronic pain symptoms. We will also track medication use by having each participant report their prescription and over-the-counter medication and supplement use at each visit. At screening and at all study visits, we will have patients complete a concomitant medications survey that has the participants report the following information for each medication and supplement: drug name, total daily dosage (quantity), total daily usage (units), frequency taken, indication, start date, and end date (will leave blank if still taking).

5.3.1 Allowed Interventions

Participants may remain on current medications used to manage and treat chronic pain symptoms. All treatments, whether prescription or over-the-counter, will be tracked and recorded on the concomitant medication form. Participants will be asked to refrain from changing their existing ongoing treatments during the course of the study.

5.3.2 Required Interventions

There are no required interventions, however, participants will be asked and assessed for willingness to limit the introduction for any new medications or treatment modalities for control of chronic pain symptoms during the study.

5.3.3 Prohibited Interventions

Participants will be excluded from the study if they are participating in other therapeutic trials, or have completed a trial within the last 30 days from their enrollment date.

5.4 Adherence Assessment

All necessary outcome measures and documents will be completed during the study visits. However, we will check for adherence to the specific type of stimulation (i.e., tonic 50 Hz, burst, tonic 1 kHz, sham). At the end of each treatment allocation and after the testing is completed, we will interrogate the participant's implanted stimulator to ensure that the stimulation settings were not altered during the specific treatment phase. For this study, we will only consider randomized participants who successfully completed the Sham SCS treatment along with at least one other active (i.e., burst, tonic 1 kHz, tonic 50 Hz) SCS treatment along with the associated outcome measures for each treatment.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

	Screening/ enrollment visit	**Randomization[a]**	**Treatment**	**Treatment**	**Treatment (50 Hz SCS)**	**Final visit**
	Visit 1 Day -62 to Day 0	*Visit 2* Day 0 ± 2 days	*Visit 3* Day 7 ± 2 days	*Visit 4* Day 14 ± 2 days	*Visit 5* Day 21 ± 2 days	*Visit 6* Day 28 ± 2 days
Informed Consent	X					
Hospital Anxiety and Depression Scale (HADS)	X	X	X	X	X	X
EQ-5D Health Questionnaire	X	X	X	X	X	X
Demographics	X					
Concomitant Medications	X	X	X	X	X	X
Socio-demographics	X					
Urine Pregnancy Test	X					
Brief Pain Inventory (BPI)	X	X	X	X	X	X
Coping Strategies Questionnaire (CSQ)	X	X	X	X	X	X
Michigan Body Map (MBM)	X	X	X	X	X	X
PainDETECT	X	X	X	X	X	X
Pain Disability Index (PDI)	X	X	X	X	X	X
Fibromyalgia Survey Questionnaire (FSQ)	X	X	X	X	X	X
Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form Questionnaire (PROMIS-SD)	X	X	X	X	X	X
Short Form McGill Pain Questionnaire (SFMPQ)	X	X	X	X	X	X
Visual Analog Scale (VAS) – included in SFMPQ	X	X	X	X	X	X
Vitals (heart rate, blood pressure, respiration rate, blood temperature), height and weight	X	X	X	X	X	X
Multimodal Automated Sensory Test (MAST)	*b*	X	X	X	X	X
Vibrometer Test	*b*	X	X	X	X	X
Algometer Test	*b*	X	X	X	X	X
Temporal summation (TS) – PinPrick Test	*b*	X	X	X	X	X
Conditioned Pain Modulation (CPM) Test	*b*	X	X	X	X	X
Computed tomography (CT)		X				
Randomization		*c*				
Treatment (Burst, 1kHz, 50Hz, Sham SCS)		*d*	X	X	X	X

Stimulator programming		X	X	X	X	X
Adverse Events	X	X	X	X	X	X
Study debriefing						X

[a] *The randomization visit (Visit 2) may also occur on the same day as the screening/enrollment visit (Visit 1)*
[b] *Familiarization only*
[c] *Randomization will occur at the end of Visit 2*
[d] *Treatment will begin at the end of Visit 2*

6.2 Description of Evaluations

The schedule of study procedures and assessments is 6.1 Schedule of Evaluations. The descriptions of the procedures to be performed at each visit are provided below.

Screening/enrollment (Visit 1)

- Review study procedures and requirements with participant
- Review informed consent, only for candidates that do not consent electronically via SignNow.
- Collect demographic and sociodemographic information
- Conduct psychological screening assessment (HADS)
- Collect vital signs (heart rate, blood pressure, respiration rate, body temperature, height and weight)
- Obtain medical history (EQ-5D Health Questionnaire) and FM Survey Questionnaire [FSQ]
- Collect symptoms of chronic pain
    - Pain disability Index (PDI)
    - Short Form McGill Pain Questionnaire (SFMPQ)
    - Michigan Body Map (MBM)
    - PainDETECT
    - Brief Pain Inventory (BPI)
    - Visual Analog Scale (VAS) and SFMPQ
- Determine impact of chronic pain on daily life (CSQ)
- Administering a urine pregnancy test to women of childbearing potential
- Document current concomitant medications
- Familiarize participant to the sensory testing procedure
    - Multimodal Automated Sensory Test (MAST)
    - Vibrometer Test
    - Algometer Test
    - PinPrick Test
    - Conditioned Pain Modulation (CPM) Test
- Documentation of any adverse events

Randomization (Visit 2)

After a participant has been deemed a candidate for the study, this visit can occur on the same day as Visit 1 (screening/enrollment).

- Collect vital signs (heart rate, blood pressure, respiration rate, body temperature, height and weight)
- Review and record any changes in concomitant medications
- Rate participants current pain on a scale Visual Analog Scale (VAS) and SFMPQ
- Collect
    - Pain disability Index (PDI)
    - Short Form McGill Pain Questionnaire (SFMPQ)
    - Michigan Body Map (MBM)
    - PainDETECT
    - Brief Pain Inventory [BPI]
    - Visual Analog Scale (VAS) and SFMPQ
    - Coping Strategies Questionnaire (CSQ)
    - Hospital Anxiety and Depression Scale (HADS)

    - EQ-5D Health Questionnaire
    - Fibromyalgia Survey Questionnaire (FSQ)
- Conditioned Pain Modulation (CPM) Test – Assessment to examine how the body naturally controls pain
- Measure participant's sensitivity to different stimuli
    - Vibrometer Test
    - Algometer Test
    - PinPrick Test (Temporal summation)
    - Multimodal Automated Sensory Test (MAST)
- Randomization*
- Deliver treatment (Burst, 1kHz, or Sham SCS)
- Stimulator programming
    - Perception threshold
    - Discomfort threshold
    - Paresthesia mapping
- Documentation of any adverse events
- Computed tomography (CT) scan

*At the end of the Visit 2, randomization will occur. We will randomize participants to one of six randomly allocated sequences that each contain four treatments: burst, 1 kHz, sham, and 50 Hz SCS. Participants will receive each treatment for seven days.

Treatment (Visit 3)
After participants have received approximately seven days of the first treatment, we will perform the study procedures listed below. After performing these study procedures, the stimulation parameters will be adjusted to apply the second treatment allocation in the respective treatment arm. Participants will be blinded during programming.

- Collect vital signs (heart rate, blood pressure, respiration rate, body temperature, height and weight)
- Review and record any changes in concomitant medications
- Rate participants current pain on a scale Visual Analog Scale (VAS) and SFMPQ
- Collect
    - Pain disability Index (PDI)
    - Short Form McGill Pain Questionnaire (SFMPQ)
    - Michigan Body Map (MBM)
    - PainDETECT
    - Brief Pain Inventory [BPI]
    - Visual Analog Scale (VAS) and SFMPQ
    - Coping Strategies Questionnaire (CSQ)
    - Hospital Anxiety and Depression Scale (HADS)
    - EQ-5D Health Questionnaire
    - Fibromyalgia Survey Questionnaire (FSQ)
- Conditioned Pain Modulation (CPM) Test – Assessment to examine how the body naturally controls pain
- Measure participant's sensitivity to different stimuli
    - Vibrometer Test
    - Algometer Test
    - PinPrick Test (Temporal summation)
    - Multimodal Automated Sensory Test (MAST)
- Deliver treatment (Burst, 1kHz, or Sham SCS)

- Stimulator programming
    - Perception threshold
    - Discomfort threshold
    - Paresthesia mapping
- Documentation of any adverse events

Treatment (Visit 4)
After participants have received approximately seven days of the second treatment, we will perform the study procedures listed below. After performing these study procedures, the stimulation parameters will be adjusted to apply the third treatment allocation in the respective treatment arm. Participants will be blinded during programming.

- Collect vital signs (heart rate, blood pressure, respiration rate, body temperature, height and weight)
- Review and record any changes in concomitant medications
- Rate participants current pain on a scale Visual Analog Scale (VAS) and SFMPQ
- Collect
    - Pain disability Index (PDI)
    - Short Form McGill Pain Questionnaire (SFMPQ)
    - Michigan Body Map (MBM)
    - PainDETECT
    - Brief Pain Inventory (BPI)
    - Visual Analog Scale (VAS) and SFMPQ
    - Coping Strategies Questionnaire (CSQ)
    - Fibromyalgia Survey Questionnaire (FSQ)
- Conditioned Pain Modulation (CPM) Test – Assessment to examine how the body naturally controls pain
- Measure participant's sensitivity to different stimuli
    - Vibrometer Test
    - Algometer Test
    - PinPrick Test (Temporal summation)
    - Multimodal Automated Sensory Test (MAST)
- Deliver treatment (Burst, 1kHz, or Sham SCS)
- Stimulator programming
    - Perception threshold
    - Discomfort threshold
    - Paresthesia mapping
- Documentation of any adverse events

Treatment (50 Hz SCS) (Visit 5)
After participants have received approximately 7 days of the third treatment, we will perform the study procedures listed below. After performing these study procedures, the stimulation parameters will be adjusted to apply the final treatment allocation (tonic 50 Hz SCS). Although participants will be blinded during programming, 50 Hz SCS generates paresthesias and so participants will likely be aware that they are receiving active stimulation.

- Collect vital signs (heart rate, blood pressure, respiration rate, body temperature, height and weight)
- Review and record any changes in concomitant medications
- Rate participants current pain on a scale Visual Analog Scale (VAS) and SFMPQ
- Collect
    - Pain disability Index (PDI)

    - Short Form McGill Pain Questionnaire (SFMPQ)
    - Michigan Body Map (MBM)
    - PainDETECT
    - Brief Pain Inventory (BPI)
    - Visual Analog Scale (VAS) and SFMPQ
    - Coping Strategies Questionnaire (CSQ)
    - Fibromyalgia Survey Questionnaire (FSQ)
- Conditioned Pain Modulation (CPM) Test – Assessment to examine how the body naturally controls pain
- Measure participant's sensitivity to different stimuli
    - Vibrometer Test
    - Algometer Test
    - PinPrick Test (Temporal summation)
    - Multimodal Automated Sensory Test (MAST)
- Deliver treatment (50 Hz SCS)
- Stimulator programming
    - Perception threshold
    - Discomfort threshold
    - Paresthesia mapping
- Documentation of any adverse events

Final study visit (Visit 6)

After participants have received approximately 7 days of 50 Hz SCS, we will perform the study procedures listed below. After performing these study procedures, the participant's SCS system will be returned to the clinically-effective stimulation settings that were previously determined through standard-of-care procedures.

- Collect vital signs (heart rate, blood pressure, respiration rate, body temperature, height and weight)
- Review and record any changes in concomitant medications
- Rate participants current pain on a scale Visual Analog Scale (VAS) and SFMPQ
- Collect
    - Pain disability Index (PDI)
    - Short Form McGill Pain Questionnaire (SFMPQ)
    - Michigan Body Map (MBM)
    - PainDETECT
    - Brief Pain Inventory (BPI)
    - Visual Analog Scale (VAS) and SFMPQ
    - Coping Strategies Questionnaire (CSQ)
    - Fibromyalgia Survey Questionnaire (FSQ)
- Conditioned Pain Modulation (CPM) Test – Assessment to examine how the body naturally controls pain
- Measure participant's sensitivity to different stimuli
    - Vibrometer Test
    - Algometer Test
    - PinPrick Test (Temporal summation)
    - Multimodal Automated Sensory Test (MAST)
- Stimulator programming
    - Perception threshold
    - Discomfort threshold
    - Paresthesia mapping

- Documentation of any adverse events
- Study debriefing

6.2.1 Screening Evaluation

This study will occur at a single site, the University of Michigan. We will actively and passively recruit participants. We will actively recruit patients from clinics at the University of Michigan (UM), such as clinics in the Department of Anesthesiology and the Department of Neurosurgery. These departments will have access to the purpose of the study, intended patient population, and inclusion/exclusion criteria. For this study, we will consider chronic pain patients who are being treated with SCS from their own doctors as part of their standard clinical care. For active recruitment, our team of pain specialists (e.g., anesthesiologists and/or neurosurgeons) and other study personnel at UM will identify potential candidates and inform them about the study. The study coordinator or a person from the study team will contact the candidates (e.g., via telephone) to discuss details about the study (e.g., eligibility determination) and/or to verify interest. The necessary contact information (e.g., telephone number) of the candidates will be obtained by searching appointment logs and/or medical records.

For passive recruitment, we will post publicly accessible flyers and brochures throughout UM Clinics, and also in various locations around Michigan Medicine (e.g., University Hospital). We will also post flyers and brochures across various other Pain Clinics and Hospitals in Livingston, Washtenaw, and/or Wayne County. IRB-approved flyers and brochures will be hung in several locations (e.g., waiting areas) in these clinics and hospitals. These flyers will have contact information of the study team (e.g., email, phone) and will also have a description of the study (resource included in Section 8-1.8 of the IRB application). Interested candidates may initiate contact with the study team.

Potential subjects who are interested in participating in the study will be contacted by a member of the study team responsible for enrollment to assess interest and eligibility. Interested candidates will have the study and the eligibility criteria explained to them. If, at this point, they wish to continue with enrollment the candidate will be invited to participate in a study screening visit. Screening will be done over phone to verify eligibility. For eligible candidates, we will schedule an enrollment visit and/or other subsequent visits. We may also email candidates the consent forms to study and think about participation. For interested and eligible candidates, we will schedule the enrollment visit and/or other subsequent visits. All potential subjects will be assigned a unique screening ID. Those volunteers who do not meet the eligibility criteria or who choose not to participate in the study at either the telephone Pre-Screen or the Screening Visit will be logged. Personal identifiers will be kept until the study has been closed to recruitment, at which time they will be destroyed. This will prevent repeat screenings of potential participants.

Consenting Procedure

The research team will adopt an optional electronic informed consent procedure using SignNow. This option will be the preferred method for obtaining consent. A study team member will reach out to a candidate over the telephone to discuss the study and obtain consent with the patient over the phone using SignNow. The consent form will be read to the participant and time will be allowed for questions or if the patient would like to read/review the consent form on their own. All candidates will receive an electronic copy of the consent form after signing. If a candidate does not have access to the internet the following steps will be taken.

The screening visit will begin with the informed consent interview. During the consent interview we will explain the study verbally and in writing. If interested, candidates will sign an informed consent, and will be given a copy. The other signed consent form will be placed within the study binder. We will conduct the consent interview in a private setting (e.g., examination

room, office), allowing sufficient time for prospective subjects to make an informed decision. Furthermore, we will also offer candidates the option of taking the informed consent form home to study and think about participation, with a follow up with one of the investigators or study personnel. Once the subject has formally consented to participate they will undergo a screening examination by a member of the study team. After the screening visit, study personnel will follow up with the patient after consent and screening to schedule all research visits.

It is important to note that we will withhold information regarding the type of treatment (i.e., different forms of active stimulation vs. sham), and the order of treatment the subjects will receive during the study (concealment). Instead, we will inform subjects that we are adjusting the settings on their SCS device. We will inform candidates that the purpose of this study is to investigate the physiological effects and potential mechanisms of action of different types of SCS. We will also explain to each candidate that there will be no expected benefit to him/her by participating in this research study. However, it is possible (although not anticipated) that during this research new stimulator settings may be found that could be beneficial. We will also explain that the knowledge gained from this research may be beneficial for others, society, and/or science.

Note: We will debrief subjects at the conclusion of their last research visit (i.e., Visit 6). Concealment is necessary to conduct this research study to avoid potential for altering subject behavior such that study results are biased.

We will request for waiver of consent as part of the project to obtain the necessary contact information (e.g., telephone number) of candidates for recruitment prior to them signing a consent. We believe that this research could not practicably be carried out without the waiver or alteration. This is because we will need to obtain the contact information (e.g., telephone number) of candidates for recruitment prior to them signing a consent. This is essential to discuss details about the study (e.g., eligibility determination) and/or to verify interest.

We will request alterations to the informed consent process to include incorporating specific elements of concealment as part of this research. We will withhold information regarding the type of treatment (Burst-SCS, KHFSCS, Sham SCS, 50 Hz SCS) and the order of treatment that the subjects will receive during the study (concealment). To reliably compare the effects of active vs. sham SCS in subjects receiving SCS therapy as part of their standard of care, it is essential that we withhold information regarding the type of treatment and the order of treatment the subjects receive during the study. This blinding could potentially avoid altering subject behavior during the blinded phase of the study thereby justifying its use in achieving the goals of this research.

We do not believe that the waiver or alteration would cause harm, insults, injury to relationships, loss of job or insurance, injury to their health or well-being, etc. Potential risks might be related to loss of patient confidentiality. However, we will minimize this risk through several procedures. For example, we will make sure that the patient-subject information (e.g., contact information) obtained from appointment logs or medical records is stored only on secure (UM) computers, and that this information is maintained in a password-protected computer program at all times. Furthermore, we will make sure that only study team members listed on the IRB application will have access to this information. Therefore, this criterion affirms the request for a waiver or alteration of the informed consent.

Screening

Potential subjects who are interested in participating in the study will be contacted by a member of the study team responsible for enrollment. Interested candidates will have the study and the eligibility criteria explained to them. If, at this point, they wish to continue with enrollment the candidate will be invited to participate in a study screening visit.

The screening visit begins with the informed consent interview. Once the subject has formally consented to participate (by either signing the consent electronically or in person) they will undergo a screening examination by a member of the study team. This includes:

- Completing demographic, sociodemographic, and medical history questionnaires
- Collecting and reviewing patient's pain rating and self-reported questionnaires and surveys
- Assessing fibromyalgia status by completing Fibromyalgia Symptom Questionnaire (FSQ)
- Conducting a physical assessment (height and weight) and collecting vital signs
- Completing and reviewing Psychological Screening questionnaires (HADS)
- Administering a urine pregnancy test to women of childbearing potential
- Documenting and reviewing current concomitant medications

Completion of these screening procedures will allow the study personnel to verify that the subject meets the full inclusion/exclusion criteria. For this study utilizing a single consent form, randomization should occur within two months of completing the screening procedures.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

This study will occur at a single site, the University of Michigan. If a subject expresses interest in the study and completes the informed consent process, their eligibility based on the full inclusion/exclusion criteria will be verified during the screening visit. Study personnel will follow up with the subject after consent to schedule all research visits. The subject will be deemed enrolled upon meeting the study eligibility criteria.

Baseline Assessments

If patients meet eligibility criteria, we will ask them (during the screening visit) if they would like to enroll in the study. If they enroll, we will ask them to sign an informed consent form/document, and invite them to be part of various study visits. During the baseline at Visit 1, the following assessments will be performed:

- Assess patients' psychological status (e.g., anxiety, depression) using self-reported patient questionnaires/surveys (e.g., EuroQol questionnaire, EQ-5D[5] and Hospital Anxiety and Depression Scale, HADS).[60]
    - If patients meet criteria for extreme anxiousness or depression (as indicated in the EQ-5D questionnaire or an equivalent score of 11-21 on HADS) we will offer/provide them with a "Depression Resource Handout". However, patients can still continue their participation in the study.
- Collect patients' vital signs (heart rate, blood pressure, respiration rate, and body temperature), height, and weight.
- Collect demographics, sociodemographics, and concomitant medications from the patients.

Randomization

Within two months of enrollment, we will randomize subjects to one of six randomly allocated sequences consisting of the following treatments: burst, 1 kHz, sham, and 50Hz SCS. Subjects will receive each treatment for seven days following one of the six randomly allocated

sequences (crossover design) (Fig. 3.1). We will perform testing before the start of the randomization and at the end of each seven-day treatment period. Subjects will be blinded during programming. To ensure proper blinding, we will set the amplitude of stimulation so that patients do not feel any stimulation-induced paresthesias (except for 50 Hz SCS which requires paresthesias).[2] Sham SCS will be performed by setting the amplitude to 0 mA.[2] For some systems, if the stimulation amplitude is decreased to 0 mA, the system will report that the stimulation is OFF and the participants will know that they are not receiving stimulation. Therefore, for these systems, we will perform sham SCS by setting the stimulation parameters to their minimal values: pulse width (~20 μs), frequency (~2 Hz), and amplitude (~0.1 mA).

6.2.3 Blinding

We will have two research teams. One team will be unblinded and will perform stimulator programming/adjustment, and the other team will be blinded and will perform clinical testing and collect study outcome measures.

Participants will be blinded during programming. During the stimulator programming session, we will adjust the settings on the subjects' SCS device. We will adjust the settings such that subjects will receive seven days of a specific treatment allocation. To ensure proper blinding during the first three treatment allocations, we will set the stimulation amplitude so that the participants do not feel any stimulation-induced paresthesias. Sham SCS will be performed by setting the amplitude to 0 mA. For some systems, if the stimulation amplitude is decreased to 0 mA, the system will report that the stimulation is OFF and the participants will know that they are not receiving stimulation. For these systems, we will perform sham SCS by setting the stimulation parameters to their minimal values: pulse width (~20 μs), frequency (~2 Hz), and amplitude (~0.1 mA). Therefore, participants will not experience stimulation-induced paresthesias during Sham SCS. However, during an active treatment allocation, stimulation-induced paresthesias may sometimes occur (usually as a tingling sensation) due to positional changes (e.g., bending, lifting) and/or extreme movement. To minimize the occurrence of these stimulation-induced paresthesias, we will have the participants assume multiple positions (e.g., sitting, standing, supine, prone) during the programming session and ensure that the stimulation amplitude is low enough to avoid stimulation-induced paresthesias in any of these bodily positions. Therefore, the participant experience should be similar for the first three treatments. After completion of the first three treatment allocations, each participant will receive seven days of tonic 50 Hz SCS that will generate paresthesias over their painful areas. While having 50 Hz SCS as the last treatment in all participants may introduce a potential order effect, this treatment is performed last because patients will likely know that they are receiving active stimulation due to the paresthesias and this design will minimize the chance of breaking the blind during the first three treatment allocations.

During this study, it is possible that participants may experience insufficient pain relief and/or discomfort during some of the treatments. Therefore, to reduce patient risk we will allow patients to keep the patient programmer. The participants will be instructed not to adjust the stimulation settings during each treatment. At the end of each treatment allocation, we will interrogate the participant’s implanted stimulator to ensure that the stimulation settings were not altered during the specific treatment phase. For some systems, patients are given a magnet that can be used to turn the stimulation off in the case of an emergency. For participants with these systems, we will instruct the participants to use the magnet, if needed, in the case of emergency. The magnet can be used to turn the stimulation on or off, in the absence of the programmer.

It is possible that during some treatment allocations, such as during Sham SCS, participants may experience insufficient pain relief. If participants complain of significant discomfort and they are considering exiting the study, we will have the unblinded study

personnel examine the current treatment allocation to determine if the participant is receiving stimulation settings that vary substantially from their clinical parameters. If necessary, the participant can decide to have the stimulation settings returned to those determined to be effective through standard-of-care programming procedures.

6.2.4 Followup Visits

- Visit 3 (*Day 7 ± 2 days)*:
  - Vital signs
  - Concomitant medications
  - Surveys and questionnaires
  - Quantitative sensory testing
  - Administer treatment
  - Stimulator programming
  - Adverse events
- Visit 4 (*Day 14 ± 2 days)*:
  - Vital Signs
  - Concomitant medications
  - Surveys and questionnaires
  - Quantitative sensory testing
  - Administer treatment
  - Stimulator programming
  - Adverse Events
- Visit 5 (*Day 21 ± 2 days)*:
  - Vital Signs
  - Concomitant medications
  - Surveys and questionnaires
  - Quantitative sensory testing
  - Administer treatment
  - Stimulator programming
  - Adverse Events

6.2.5 Completion/Final Evaluation

The following procedures will be performed during the final visit (*Visit 6* – Day 28 ± 2 days):

- Vital Signs
- Concomitant medications

- Surveys and questionnaires
- Quantitative sensory testing
- Stimulator programming
- Adverse Events
- Study debriefing

After the completion of all study procedures, the participants stimulation parameters will be returned to the settings selected through standard-of-care programming procedures.

As detailed in Section 8, there are many reasons for participants to discontinue the study early. Subject participation is strictly voluntary and the research strictly knowledge driven; therefore, a subject may withdraw from further participation in the study without penalty or harm. Any reason(s) the subject may give for terminating his or her participation will be kept confidential. We will store the study documents according to the procedures outlined in the Section 11.3 of this protocol. Study personnel will be authorized to release a subject from further study participation according to the following guidelines:

- The researcher believes that it is not in the subject's best interest to stay in the study.
- Subject becomes ineligible to participate.
- Subject's condition changes such that they need treatment that is not allowed while taking part in the study.
- Subject does not follow instructions from the researchers.
- The study is suspended or canceled.

Upon termination of a subject, the investigators will ensure the subject is dismissed with any study documents to which they are entitled. Subjects will be compensated for their completed study visits prior to termination. Investigators will require no further obligation or participation from a terminated subject. The reason for participant discontinuation or withdrawal from the study will be recorded on the appropriate Case Report Form (CRF).

Discontinuation from SCS will require discontinuation from the study, and remaining study procedures will not be completed. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Participant safety will be monitored while individuals are enrolled in the study. The table below lists expected risks by study intervention/procedure, as well as criteria for management and modification of the study intervention regimen or participant assessments if an adverse event occurs.

Known Potential Risks	***Criteria for Management***	***Intervention Modification (if any)***
Electrical stimulation	• Muscle contractions • Shock hazard (i.e., electrical burn) • Participant complains of	• Stimulation amplitude will first be set to a low amplitude. • We will only use stimulators approved by the U.S. Food

	discomfort	and Drug Administration.
Medical Imaging procedures (CT)	• Exposure to radiation and increased risk of cancer • Participant may experience discomfort or anxiety from being in the confined space • Claustrophobia	• Participant consent form will identify the cumulative risks of radiation and exposure. • Pads and blankets will be provided to reduce discomfort.
Quantitative Sensory Testing (QST)	• May cause minor but temporary physical discomfort	• Study personnel are trained by the investigator to be sensitive to participant discomfort and concerns. • Participants are able to stop the QST at any time.
Multimodal Automated Sensory Testing (MAST)	• Participant complains of physical discomfort on the thumbnail	• Participants will always have personal control over the stimulus and can top it at any time or express instructions to stop. • Participants can withdraw their thumb from the device or turn a safety release pin to immediately release the pressure actuator.
The Vibrometer, Pressure Algometer, Pointed Skin Probe, and Conditioned Pain Modulation (CPM) Test	• Participant complains of discomfort in the areas of testing • Skin irritation/redness	• The test can be halted if the participant reports a pain rating of 100. • The participant can inform study personnel to stop the test at any time that the pain or unpleasantness of the task becomes intolerable.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and adverse events (AEs) will be provided to the Independent Monitoring Committee (IMC) semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reasons for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the IMC and will be forwarded to the Institutional Review Board

(IRB) and National Center for Complementary and Integrative Health (NCCIH). The IRB and other applicable recipients will review progress of this study on an annual basis.

7.3 Adverse Events and Serious Adverse Events

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An AE or suspected adverse reaction will be considered "serious" if, in the view of either the investigator or sponsor, it is any AE that:

- Is fatal;
- Is life threatening, meaning the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form or progressed, might have caused death;
- Causes a persistent or significant disability or incapacity;
- Requires or prolongs inpatient hospitalization. Inpatient hospitalization will be considered a hospitalization if it is longer than 24 hours or requires an intervention to treat emergent symptomatology (non-diagnostic);

Other important medical events may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes as listed in this definition. We will report SAEs to the IRBMED per the IRBMED Standard AE Reporting Plan at https://az.research.umich.edu/file/864. If the SAEs are not related to the study, we will report them at Continuing Review. If the SAEs are related to the study, we will report them within seven days or sooner to the IRB. We will also report AEs and SAE's to the Principal Investigator (PI). If there is any evidence of a pattern of unanticipated AEs (regardless of causality), or SAEs, we will immediately have an independent third party review these data. Based on the conclusions of this third party, the PI will either terminate the study or convene the Data Safety and Monitoring Board (DSMB) to make recommendations.

7.4 Reporting Procedures

Severity of event: We will grade the signs and symptoms as mild, moderate, severe, or life threatening according to the following definitions:

Grade	Definition
Mild	Causing no limitation of usual activity
Moderate	Causing some limitations of usual activities
Severe	Causing inability to carry out usual activities
Life Threatening	Patient was at immediate risk of death from the event

Relationship to study intervention: All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship

between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.

- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Expectedness: The study Principal Investigator (PI) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Time period and frequency for event assessment and follow-up: The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Reporting adverse events: We will report SAEs to the IRBMED per the IRBMED Standard AE Reporting Plan at https://az.research.umich.edu/file/864. If the SAEs are not related to the study, we will report them at the study continuing review. If the SAEs are related to the study, we will report them within seven days or sooner to the IRB. We will also report AEs and SAEs to the Principal Investigator (PI). If there is any evidence of a pattern of unanticipated AEs (regardless of causality), or SAE, we will immediately have an independent third party review these data. Based on the conclusions of this third party, the PI will either terminate the study or convene a Data Safety and Monitoring Board (DSMB) to make recommendations.

Reporting events to participants: We will inform both the subject and the subject's physician in the event that a potentially significant, unexpected disease or condition is identified incidental to a study treatment or procedure.

Reporting of pregnancy: As part of this research, participants may undergo specific medical imaging procedures, such as X-ray computed tomography (CT). For this research, we will consider pregnancy a contraindication for these medical imaging procedures. Therefore, before performing any medical imaging procedure as part of this research, we will perform a urine pregnancy tests for participants of child bearing potential, and having no intrauterine device (IUD) or hysterectomy, and who are able to become pregnant. If a participant becomes pregnant or nursing after enrollment and/or does not wish to take the pregnancy test at the screening visit, the participant will be excluded from the imaging procedures but will be allowed to remain in the study and participate in the remaining study procedures. This information will be

reported to the IRB as an Other Reportable Information or Occurrences (ORIO) within seven calendar days of becoming aware of the event or information.

7.5 Followup for Adverse Events

Study personnel will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.6 Safety Monitoring

All research personnel involved in any way in this project will have completed training in the protection of human research participants per guidelines issued by the United States Department of Health and Human Services, Office for Human Research Protection. The protocol will undergo review and approval by the University of Michigan IRBMED and other necessary regulatory and oversight entities prior to implementation.

We do not expect serious side effects or AEs from this research. AEs that do occur will be reported according to FDA guidelines, and reports will be sent to the University of Michigan IRBMED as required. The Principal Investigator (PI) will be notified when an AE occurs and will determine the attribution and relatedness of each adverse event.

We will also create and work with an independent Data Safety Monitoring Board (DSMB) to monitor safety issues. The DSMB will meet periodically throughout the duration of the study. The DSMB will also report its findings of any adverse events or decisions regarding modification of the protocol to the University of Michigan IRBMED committee.

The study coordinator and project leads will meet monthly with the PI to assess overall study progress, including regulatory matters, recruitment, adverse events, data quality, and to review any interim analyses. Outcomes of these meetings will be reported to the University of Michigan IRBMED on a quarterly basis. All protocols and consent forms are approved by the University of Michigan IRB and reviewed yearly.

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). The sponsor clinical monitoring service may conduct periodic on-site reviews of the study, including study initiation visit, periodic site visit and a study closeout visit.

8. INTERVENTION DISCONTINUATION

Discontinuation from SCS will require discontinuation from the study, and remaining study procedures will not be completed. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Subject participation is strictly voluntary and the research strictly knowledge driven; therefore, a subject may withdraw from further participation in the study without penalty or harm. Any reason(s) the subject may give for terminating his or her participation will be kept confidential. We will store the study documents according to the procedures outlined in Section 11.3 of this protocol. We will require no further information of the subject and the subject will be compensated for his/her completed study visits prior to termination.

Study personnel will be authorized to release a subject from further study participation according to the following guidelines:

- The researcher believes that it is not in the subject's best interest to stay in the study.
- Subject becomes ineligible to participate.
- Subject's condition changes such that he/she needs treatment that is not allowed while taking part in the study.
- Subject does not follow instructions from the researchers.
- The study is suspended or canceled.

Upon termination of a subject, the investigators will ensure the subject is dismissed with any study documents to which he/she is entitled. Subjects will be compensated for their completed study visits prior to termination. Investigators will require no further obligation or participation from a terminated subject.

The reason for participant discontinuation or withdrawal from the study will be recorded on the appropriate Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

We will use descriptive statistics to present participants' demographics and various outcome measures. Categorical data will be presented as frequencies and percentages. Normally distributed continuous data will be presented with means and standard deviations. Non-normal continuous data will be presented with medians and interquartile ranges.

Because this study will employ the crossover design, for inferential tests, we will use linear mixed-effects models to analyze continuous outcomes (e.g., temporal summation, pain intensity on the visual analog scale (VAS)). These models will include a participant-level random intercept to account for correlations of measurements from the same participant. For binary outcomes (e.g., ≥50% improvement in VAS scores), we will use mixed effects logistic models. We will obtain the least-squares estimates (e.g., mean temporal summation, mean VAS score, or probability of have a ≥50% improvement in VAS) for the treatments and perform group comparisons with the appropriate contrasts. We will establish statistical significance with two-sided $p<0.05$.

9.2 Sample Size and Randomization

The primary endpoint will be spinal cord stimulation (SCS)-induced changes in temporal summation (TS). We will calculate TS scores by subtracting the average pain rating of the single-stimulus trials from the average pain rating of the ten-stimuli trials (see Section 9.5.1). If the difference is a positive number, we will conclude that there was pain summation, where larger numbers will indicate increased pain summation or TS. If the difference is zero or a negative number, we will conclude that there was no pain summation or TS. As described in Section 3, we will consider four types or factor levels of SCS: Burst-SCS, KHFSCS, 50 Hz SCS, and Sham SCS. We will consider a repeated-measures design in which all four levels are tested in each participant. We will employ linear mixed-effects models in our analysis. Therefore, our null hypothesis will be that the group means with regards to TS are all equal. Our alternate hypothesis will be that the not all of the group means of TS are equal. If we can reject the null

hypothesis, we will perform the appropriate post-hoc analyses to determine specific differences. To determine specific treatment effects, we will perform the following pairwise tests: Burst vs. Sham, 1 kHz vs. Sham, and 50 Hz vs. Sham. These tests do not require an adjustment for multiplicity because they are hierarchical.

We will perform statistical analysis on SCS-induced changes in TS measured by differences in the corresponding TS. For our study, we assumed a sample size of 20 (25 recruited with an attrition rate of 20% that was estimated from prior SCS studies that employed a similar crossover study design[39,41]), 80% power, and 5% level of significance with two-tailed tests. Using a paired t test, this will allow us to detect a within-subject effect size (i.e., standardized difference score, d_z) of 0.68, reflecting the difference between active and sham SCS. While this study is exploratory, in the most comparable study conducted to date, eight subjects with neuropathic pain underwent SCS.[61] Assuming a correlation value of 0.5 between TS measured in the same subject, the d_z for the effects of "ON" versus "OFF" stimulation was 0.89. A similar effect size in our study will achieve a statistical power greater than 95% with a sample size of 20.

Treatment Assignment Procedures

We will have two research teams. One team will be unblinded and will perform stimulator programming/adjustment, and the other team will be blinded and will perform clinical testing and collect study outcome measures.

Within two months of enrollment, we will randomize subjects to one of six randomly-allocated sequences consisting of the following treatments: burst, 1 kHz, sham, and 50Hz SCS. Subjects will receive each treatment for seven days following one of the six randomly allocated sequences (crossover design) (Fig. 3.1). We will perform testing before randomization and at the end of each seven-day treatment period.

Participants will be blinded during programming. During the stimulator programming session, we will adjust the settings on the subjects' SCS device. We will adjust the settings such that subjects will receive seven days of a specific treatment allocation. To ensure proper blinding during the first three treatment allocations, we will set the stimulation amplitude so that the participants do not feel any stimulation-induced paresthesias. Sham SCS will be performed by setting the amplitude to 0 mA. For some systems, if the stimulation amplitude is decreased to 0 mA, the system will report that the stimulation is OFF and the participants will know that they are not receiving stimulation. For these systems, we will perform sham SCS by setting the stimulation parameters to their minimal values: pulse width (~20 μs), frequency (~2 Hz), and amplitude (~0.1 mA). Therefore, participants will not experience stimulation-induced paresthesias during Sham SCS. However, during an active treatment allocation, stimulation-induced paresthesias may sometimes occur (usually as a tingling sensation) due to positional changes (e.g., bending, lifting) and/or extreme movement. To minimize the occurrence of these stimulation-induced paresthesias, we will have the participants assume multiple positions (e.g., sitting, standing, supine, prone) during the programming session and ensure that the stimulation amplitude is low enough to avoid stimulation-induced paresthesias in any of these bodily positions. Therefore, the participant experience should be similar for the first three treatments. After completion of the first three treatment allocations, each participant will receive seven days of tonic 50 Hz SCS that will generate paresthesias over their painful areas. While having 50 Hz SCS as the last treatment in all participants may introduce a potential order effect, this treatment will be performed last because patients will likely know that they are receiving active stimulation due to the paresthesias and this design will minimize the chance of breaking the blind during the first three treatment allocations.

Participants will be instructed not to adjust the stimulation settings during each treatment. At the end of each treatment allocation, we will interrogate the participant's implanted stimulator to ensure that the stimulation settings were not altered during the specific treatment

phase. For some systems, patients are given a magnet that can be used to turn the stimulation off in the case of an emergency. For participants with these systems, we will instruct patients to use the magnet, if needed, in the case of emergency. The magnet can be used to turn the stimulation on or off, in the absence of the programmer.

It is possible that during some treatment allocations, such as during Sham SCS, participants may experience insufficient pain relief. If participants complain of significant discomfort and they are considering exiting the study, we will have the unblinded study personnel examine the current treatment allocation to determine if the participant is receiving stimulation settings that vary substantially from their clinical parameters. If necessary, the participant can decide to have to the stimulation settings returned to those determined to be effective through standard-of-care programming procedures.

9.3 Definition of Populations

For this study, we will utilize a per-protocol analysis dataset. We will only consider randomized participants who completed the Sham SCS treatment along with at least one other active (i.e., burst, tonic 1 kHz, tonic 50 Hz) SCS treatment along with the associated outcome measures for each treatment.

9.4 Interim Analyses and Stopping Rules

Planned interim analyses: There are no planned interim analyses.

Safety analyses: In this post-approval mechanistic study, we will not evaluate a formal safety endpoint. We will code adverse events (AEs) according to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. We will calculate AEs once for a given participant. We will present AEs with regards to severity, frequency, relationship, and expectedness. We will present serious AEs leading to premature discontinuation from the study in a table. We will collect and summarize adverse events, including the proportion of participants who experience at least one AE and the number of AEs per participant. We will also determine if the AE rates for this study were consistent with pre-study assumptions derived from AE rates in previously published studies. Potential differences in the AE rates between this study and prior studies could have significant implications for interpreting the results of this study.

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

9.5 Outcomes

9.5.1 Primary Outcome

Temporal Summation (TS). The primary endpoint will be SCS-induced changes in temporal summation (TS). TS refers to an increased perception of pain in response to sequential stimuli of equal physical strength (Fig. 9.1A). It is a quantitative sensory testing (QST) model of neural plasticity and central hyper-excitability that is thought to reflect the progressive increase in neuronal firing of dorsal horn neurons in response to repetitive nociceptive C-fiber stimulation (i.e., windup).[58] In this assessment, we will use a handheld pointed skin probe to apply fixed-intensity stimuli of 256 mN or 512 mN. The weight of the pointed skin probe (i.e., 256 mN or 512 mN) will be selected based on the sensitivity of the patient's painful and control testing sites. In this paradigm, we will apply a single fixed intensity stimulus (256 mN or 512 mN) using a handheld pointed skin probe perpendicular to the subject's skin for approximately 0.5 seconds. Following a 5-second pause, we will apply a train of 10 identical stimuli (256 mN or 512 mN) with a frequency of 1 Hz within an area of 1 cm^2.

Immediately following the single stimulus and the train of 10 stimuli, we will ask the subjects to report the pain intensity of the stimulus using a 0-100 NRS. We will conduct this testing paradigm (a single stimulus followed by a train of 10 stimuli) three times with the same 256 mN or 512 mN stimulator, and each cycle will be separated by at least 10 seconds. We will calculate 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 is a positive number, we will conclude that there was pain summation, where larger numbers will indicate increased pain summation or TS. If the difference is zero or a negative number, we will conclude that there was no pain summation or TS. The primary endpoint will be the continuous TS values calculated at the end of each seven-day treatment period. Furthermore, at 15- and 30-seconds following the last train of 10 stimuli, we will ask subjects to rate any residual pain sensation in the testing area using the 0-100 NRS.

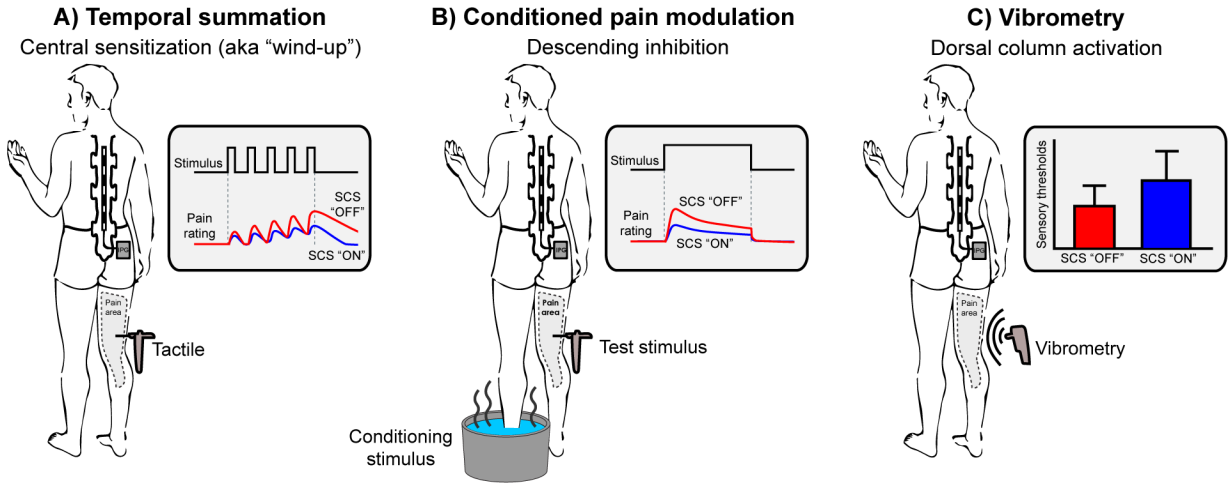

Figure 9.1. *Quantitative sensory testing (QST). (A) Temporal summation (TS), (B) Conditioned pain modulation (CPM), and (C) Vibrometry.*

9.5.2 Exploratory Outcomes

We will consider all other outcome measures in our study as exploratory outcomes. We will perform a battery of psychophysical pain tests in the participants. The overall objective of these tests is to evaluate pain processing at different levels of the neuraxis. We will assess generalized mechanical sensitivity using a Multimodal Automated Sensory Testing (MAST) device (Fig. 9.2). We will assess spinal segmental sensitivity using a vibrometer and a pressure algometer. We will assess descending pain inhibition using the test of conditioned pain modulation (CPM). We will conduct all tests, including patient familiarization and training. For each test, we will read scripted instructions to the patients, and we will advise them that they can stop testing at any time without penalty if the sensations become intolerable.

Generalized Mechanical Sensitivity. We will assess generalized mechanical sensitivity using the MAST device.[62] The device consists of: 1) a wireless, hand-held thumbnail pressure stimulator with a circular 10 mm^2 rubber tip, 2) client interface displaying a pain-rating scale, and 3) a clinician interface used to design and control testing paradigms and generate data reports (Fig. 9.2). In this study, we will use the MAST device to deliver mechanical stimuli in the form of a series of automated (ascending) pressures onto the thumbnail bed (Fig. 9.2B).

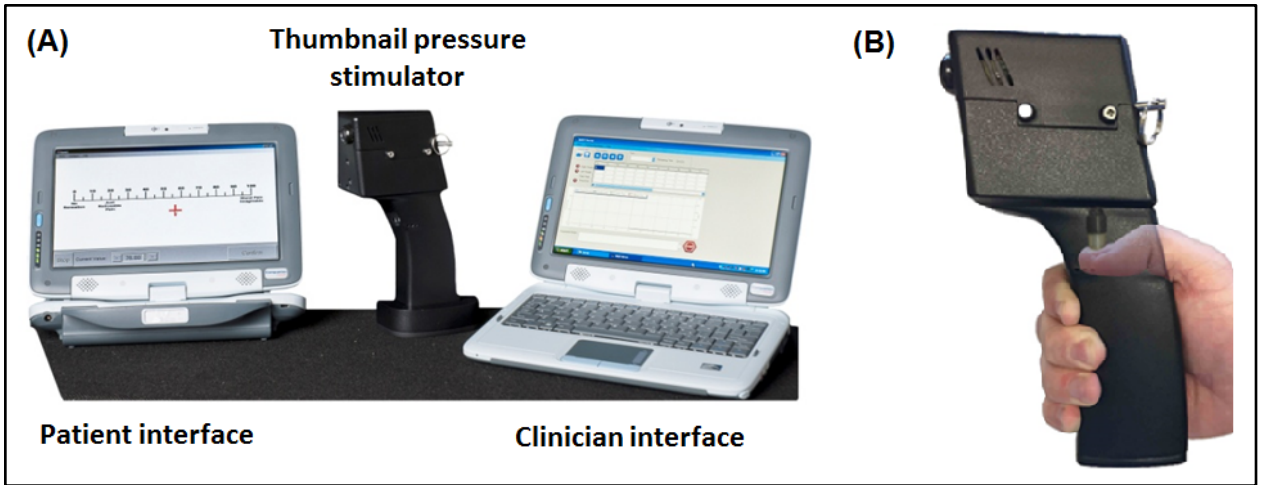

Figure 9.2. *Generalized mechanical sensitivity assessed using the MAST system. (A) MAST system components: thumbnail pressure stimulator, patient interface displaying a pain-rating scale, and clinician interface used to design and control testing paradigms and generate data reports. (B) Close-up view of the thumbnail pressure stimulator.*

First, we will apply 1-2 light "sample" pressures to the participant's thumbnail to ensure proper thumb positioning. Once the subject's thumbnail is in the proper position, we will conduct the familiarization procedure. We will apply a series of discrete pressure-pain stimuli to the subject's left or right thumbnail. After each pressure is released, we will ask the subjects to rate their pain on a VAS or a 0-100 numerical rating scale (NRS), with 0 representing "no pain" and 100 representing "worst possible pain". If any pressure is intolerable, subjects are allowed to let us know and the pressure will be released immediately. Subjects can also release the pressure themselves by pressing the 'STOP' button on their screen. Following familiarization, we will conduct the MAST ascending test, where we will apply an ascending series of discrete pressure stimuli with a duration of 2.5-5 s beginning at 0.25 kg/cm^2 and increasing in 0.25-0.50 kg/cm^2 steps to the subject's opposite thumbnail. We will ask the subjects to rate their pain using a VAS or a 0-100 NRS. Testing is completed when a pain rating >80 using a VAS or a 0-100 NRS is received or after 10 kg/cm^2 of pressure has been applied. The MAST system will calculate, in kilograms of force, the patient's pain detection threshold, tolerance, and moderate and high supra-threshold pain values. Following this test, a second series of tolerable pressures (as determined from the MAST ascending test) may be delivered in a random order. Note: This paradigm may require minor modifications during the execution of this protocol. These modifications will not exceed the parameters described above, i.e., maximum pressure intensity will never exceed 10 kg/cm^2.

Spinal Segmental Sensitivity. We will assess spinal segmental sensitivity using a manual vibrometer[63] and a pressure algometer[64,65] at the primary pain site (Fig. 9.3). The primary pain site is defined as the area of maximum pain intensity (i.e., the area of worst possible pain) as reported by the patient. If severe hyperalgesia or allodynia prevents testing of the primary pain site, we will select an adjacent, less sensitive pain area. We will also perform testing at mirror sites (site directly opposite to the tested pain site) and/or bilaterally at several control sites (e.g., trapezius, lateral epicondyle, forearm). We will perform testing with the subject resting in a stationary position (e.g., sitting, supine, prone) to reduce the possibility of postural compression of the nerves being tested.

We will use a handheld vibrometer (VSA-3000, Medoc Inc., Ramat Yishai, Israel) with a 1 cm^2 circular probe (Fig. 9.3A) to deliver vibratory, non-painful stimuli to determine sensitivity to vibration. We will apply an ascending series of vibratory stimuli. Subjects will report the first

sensation of vibration (denoted as vibratory threshold). We will average the vibratory thresholds across two or three consecutive trials at each site separated by intervals of approximately 20 to 60 seconds. We may also apply a random sequence of fixed intensity vibratory stimuli, 1-3 times each, to the individual sites.

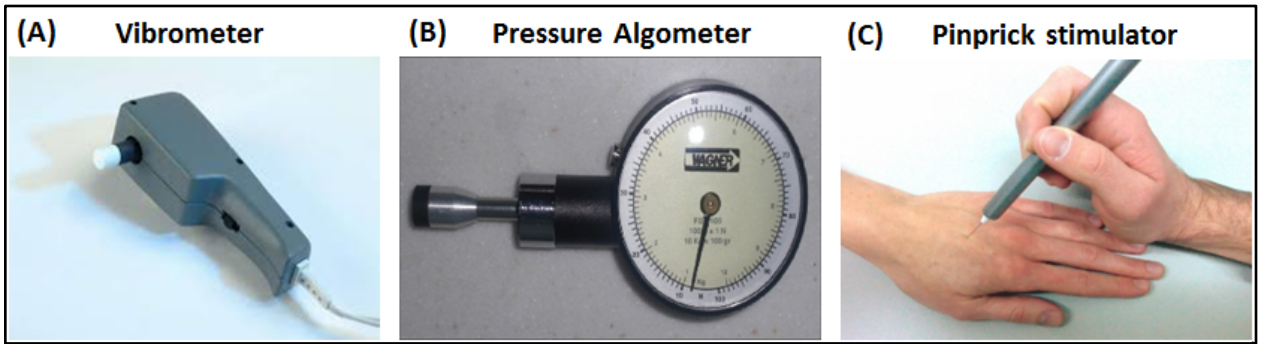

Figure 9.3. *Spinal segmental sensitivity assessed using a (A) Vibrometer and a (B) Algometer. TS is assessed using a (C) PinPrick stimulator.*

We will use a handheld, analog pressure algometer (FPK Algometer, Wagner Instruments, Greenwich, CT) with a 1 cm^2 flat rubber probe (Fig. 9.3B) to deliver pressure-pain stimuli. We will increase the pressure at a rate of approximately 0.30 kg/cm^2 or 30-50 kPa/s (100 kPa/s maximum rate), to a maximum of 10 kg/cm^2. Subjects will report their first sensation of pain (pressure-pain detection threshold) and pressure-pain tolerance. We will average the pressure-pain thresholds and pressure-pain tolerance across two or three consecutive trials at each site separated by intervals of approximately 20 to 60 seconds. We may also apply a random sequence of fixed intensity pressures, 1-3 times each, to the individual sites. We will ask the subjects to report the pain intensity of the pressure stimuli using a VAS or a 0-100 NRS.

Conditioned Pain Modulation (CPM). We will use CPM to test the effect of a noxious "conditioning" stimulus on a "test" stimulus to determine the efficiency of (supraspinal) descending pain inhibition (Fig. 9.1B). We will use pressure delivered by the algometer as the test stimulus, and a contralateral thumbnail pressure (using MAST) as the conditioning stimulus. We will determine pressure-pain thresholds before and after application of a conditioning stimulus. The conditioning stimulus is a 60-second continuous pressure to the contralateral thumbnail at the exact or similar pain intensity as the test stimulus. During the first 30-s, subjects will rate the intensity of the thumbnail pressure alone on a VAS or a 0-100 NRS. Parallel to the last 30-seconds of CPM conditioning while the subjects' thumb is still in the MAST device, we will reapply the test stimulus and determine pressure-pain thresholds. We will conduct the CPM test separately on the pain site and the control site. We will evaluate CPM as the mean difference in pressure-pain thresholds before and after application of a conditioning stimulus. If the difference in pressure-pain threshold is found to be negative, the subject is considered to have achieved an inhibitory CPM response; if the difference in pressure-pain threshold is found to be zero or positive, it is concluded that the subject did not exhibit a CPM response.

Other important considerations. If the participant has been diagnosed with peripheral neuropathy in the upper extremity that could potentially interfere with the MAST results, we will skip the MAST and thumb-based CPM procedures. However, the participant will complete the other tests. If the participant has a missing, severely malformed, or injured thumb on which testing is to be performed, we will conduct MAST testing on the opposite thumb, provided it is not missing nor injured. For example, we would conduct both familiarization and testing on the dominant thumb if the non-dominant thumb was abnormal, or vice-versa. To permit sufficient tissue recovery, we will provide a rest interval of 5-10 minutes between the MAST familiarization

protocol and the MAST test, if we conduct testing on the same thumb. We will record the thumb on which familiarization and testing occurred. If both thumbs are missing and/or injured, we will skip the MAST and the thumb-based CPM tests. However, the participant will complete the other tests.

Visual analog scale (VAS). We will measure intensity of back pain, leg pain, and general pain using patient-reported ratings on the VAS. VAS ratings are the most commonly-used clinical outcome measure in SCS. Operationally, a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end, such as “no pain” and “worst possible pain”. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks. The main advantage of using VAS ratings is that it will allow us to compare our outcomes to other clinical results available in the literature.[1,2,7–9,41,66]

Self-reported patient questionnaires. We will measure additional exploratory outcomes using several self-reported patient questionnaires. We will measure secondary outcomes using several self-reported patient questionnaires. We will use the Short-Form McGill Pain Questionnaire (SFMPQ)[67] and the Pain Disability Index (PDI)[68] to assess the patient’s description of the quality of pain. The main component of the SFMPQ consists of 15 descriptors (11 sensory and 4 affective) rated on a 4-point intensity scale (0=none to 3=severe). Three pain scores are derived from the intensity rank values of the words chosen for sensory, affective and total descriptors. The SFMPQ also includes the present pain intensity index (i.e., the VAS), and an evaluative overall intensity of total pain experience. The PDI is a six-question survey regarding daily living activity. Range is 0 (completely able to function) to 10 (totally unable to function), with higher number indicating greater disability. We will use the Brief Pain Inventory (BPI) to assess the severity of pain and its impact on daily functioning.[69] The BPI is a nine-question survey with scores ranging from 0 to 10, with higher scores indicating more severe pain and greater interference with functioning. We will use the Michigan Body Map (MBM) to assess body areas where chronic pain is experienced, and specifically quantify the degree of widespread body pain in the patient (i.e., pain centralization).[4] We will also use the Fibromyalgia Survey Questionnaire (FSQ) in combination with the MBM to assess pain centralization.[70] We will use the PainDETECT to detect neuropathic pain components in patients.[71] We will use the Hospital Anxiety and Depression Scale (HADS) to assess anxiety and depression,[60] Patient Reported Outcomes Information System Sleep Disturbance Short Form questionnaire (PROMIS SD) to assess sleep interference, and Coping Strategies Questionnaire (CSQ) to assess catastrophizing in patients.[72] We will use the EQ-5D Health Questionnaire to characterize the patient’s quality of life.[5] We will administer these questionnaires on paper and/or using the Qualtrics survey platform.

Patient-specific computer modeling. The goal of this computational modeling is to develop patient-specific computer models that correctly simulate the neural response to SCS. Existing computer models of SCS largely ignore inter-patient variability. We hypothesize that patient-specific models capture the details necessary to quantitatively describe the axonal response to SCS and to correlate model-based predictions with clinical outcomes. Therefore, we will develop patient-specific computer models of SCS for the 25 participants. These computer models will consist of two components: 1) a patient-specific electrical volume conductor model, and 2) a spinal cord model. We will develop these patient-specific models in three steps:

1) Calculate the patient-specific extracellular voltages generated by SCS.
2) Define axon models in the spinal cord.
3) Assess the axonal response to SCS by coupling the electric fields to the axon models.

Prior to electrode implantation, participants will have received an MRI or CT myelogram of the spine as part of their standard of care. We will use this imaging to provide detailed localization of the spinal cord and relevant anatomy. If we do not have access to the appropriate

preoperative imaging, the participant will be excluded from the CT imaging procedures in this study and we will not perform modeling analyses for this participant. However, the participant will be allowed to remain in the study and participate in the remaining study procedures. This information will be reported to the IRB as an Other Reportable Information or Occurrences (ORIO) within seven calendar days of becoming aware of the event or information.

Postoperatively, we will determine the electrode locations with a 3D CT scan. We will use the commercial software package, Mimics Innovation Suite (Materialise, Belgium), to co-register the MRI and CT. Once the imaging data has been co-registered, we will segment the implanted electrodes, spinal cord, CSF, dura, epidural space, and bone to generate a patient-specific finite element model (FEM) (Fig. 9.4). We will discretize the FEM with tetrahedral elements and employ higher node densities near the electrodes to ensure model accuracy. To achieve a model solution, we will specify the current at the electrode(s) (Dirichlet boundary conditions) and specify insulating and ground surfaces (Neumann boundary conditions) and solve the Poisson equation. We will parameterize each patient-specific FEM with established conductivity values.[73–77]

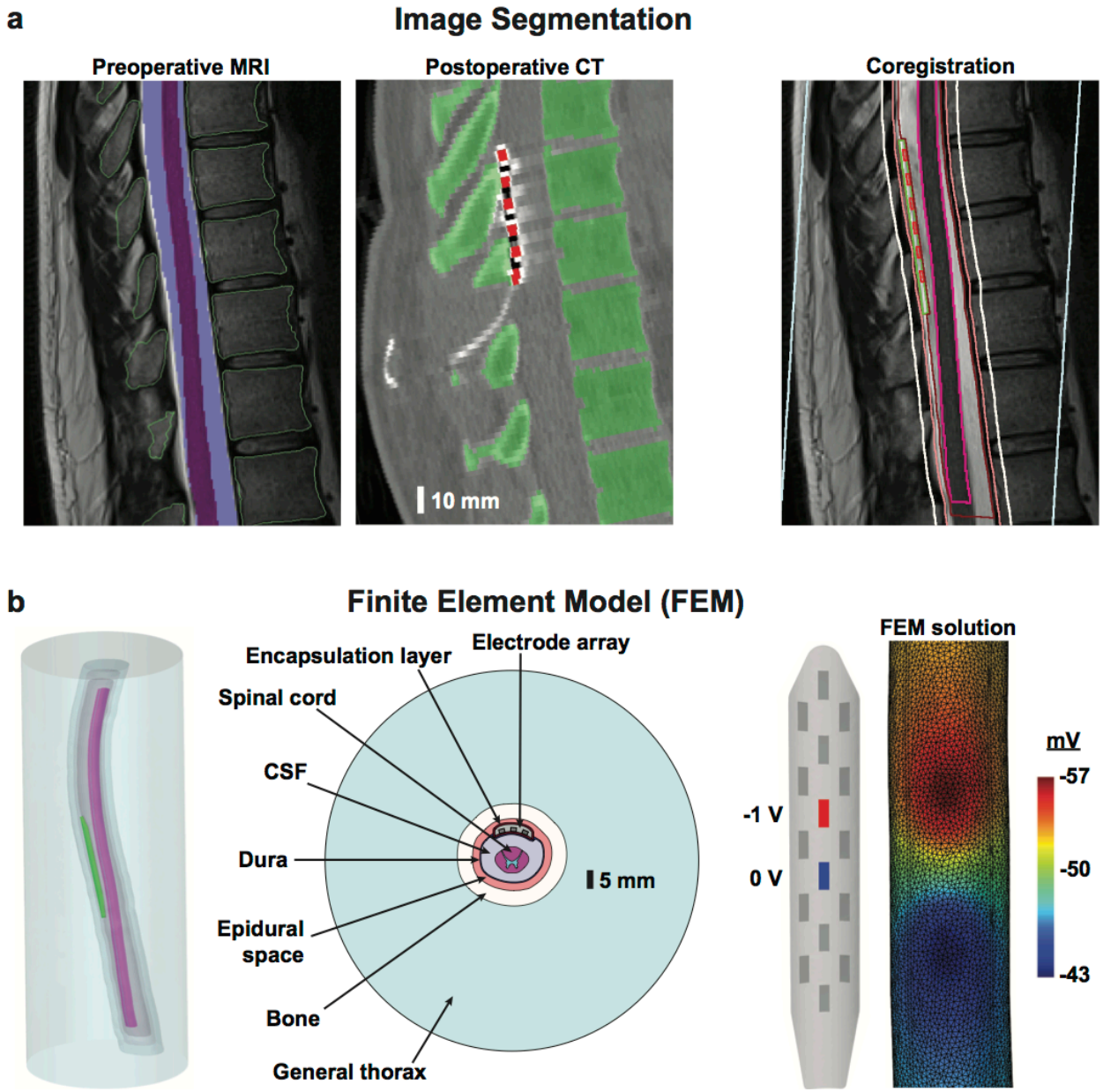

Figure 9.4. *Patient-specific finite element model (FEM). (A) In this example, we used preoperative MRI scans to define the participant's anatomy (e.g., spinal cord, cerebrospinal fluid (CSF), spine) and a postoperative X-ray computed tomography (CT) scan to define the 3D electrode locations. (B) We coregistered the 3D objects segmented from the preoperative and postoperative images to define a patient-specific FEM. The figure on the top right shows outlines of the 3D FEM objects in the preoperative MRI. The figure on the bottom right shows the voltages generated on the surface of the spinal cord for a -1 V bipolar stimulus (Note: In this figure, the electrode array and spinal cord are not drawn on the same scale).*

After we have calculated the electric fields during SCS, we will populate the model with multi-compartmental models of myelinated Aβ somatosensory axons in the dorsal column (DC) and their collaterals within the dorsal horn.[78] We will incorporate physiological fiber size distributions, axon collaterals, and the 3D orientations of dorsal root (DR) fibers as they enter the spinal cord.[79–81] Each of these factors has been shown to affect activation thresholds.[76,82,83]

For each patient, we will determine 3D axon trajectories based on the patient's spinal cord anatomy segmented from his/her MRI scan. We will construct electrically-equivalent models by importing an axon's 3D geometrical data into the software package, NEURON.[84] We will generate multi-compartment cable models by segmenting each neural process into compartments and joining neighboring compartments via axial resistances determined by the compartment length and diameter.[85] Each compartment will also contain a representative set of linear and non-linear transmembrane conductances. We will base these nonlinear membrane currents on the traditional Hodgkin-Huxley formalism.[86] We will use a repertoire of three active sodium channel conductances ($Na_v1.7$, $Na_v1.8$, $Na_v1.9$) along with two potassium channel conductances (K_{DR} (delayed rectifier) and K_A (A-type)) to represent the membrane biophysics of the sensory axons. The mathematical details of these conductances have been previously described in the literature.[87,88] This numerical multi-compartment approach represents a method to incorporate the necessary 3D neuron geometries and the ion channel kinetics at the nodes of Ranvier.

The third step in our model analysis will be to assess the direct axonal response to each type of SCS. For each patient, we will perform this step by applying the patient-specific extracellular voltages (step 1) to the 3D patient-specific axon models (step 2) (Fig. 9.5). We will then calculate the axonal responses and activation thresholds for individual axons.

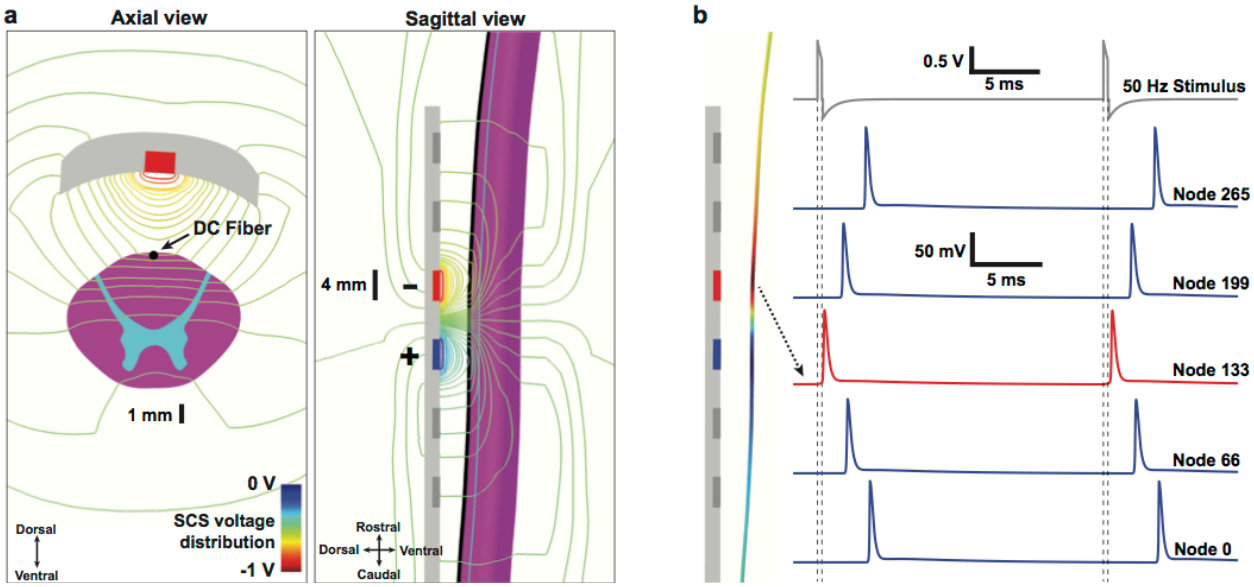

Figure 9.5. *Axonal response to SCS. (A) Axial and sagittal views of isopotential lines of the extracellular voltages generated by SCS. The voltage distributions were calculated from the patient-specific finite element model. (B) To estimate the direct axonal response to SCS, we interpolated the SCS-induced extracellular voltages onto the axon models. With sufficient depolarization, action potentials were initiated in an axon and propagated in both orthodromic and antidromic directions. The figure shows the time-dependent transmembrane voltages at several nodes in a dorsal column (DC) axon and illustrates action potential generation with a 50 Hz SCS waveform.*

We will validate the design and parameters of our patient-specific computer models with detailed clinical measurements in each patient. We will determine two stimulation thresholds that are standard measurements with clinical SCS programming[89]:

Perception threshold (PT) = amplitude at which the participant first detects the stimulation, usually felt as a tingling sensation (i.e., paresthesia), related to

Discomfort threshold (DT) = DC fiber activation amplitude at which the stimulation becomes uncomfortable due to motor effects or other discomfort, related to DR fiber activation

While we do not know the neuromodulatory effects of various forms of clinically effective SCS, such as burst and kilohertz-frequency SCS, it is well accepted that stimulation at PT and DT correspond to dorsal column and dorsal root fiber activation, respectively.[76] Therefore, in each participant, we will measure the PT and DT for tonic 50 Hz, burst, and 1 kHz SCS. At PT, we will also have each patient indicate the areas of stimulation-induced paresthesias by drawing on a human figure on a tablet.[90] These drawings will help ensure that the models predict the correct activation in the spinal cord somatotopy corresponding to the paresthetic regions. If necessary, we will adjust the model parameters (e.g., tissue conductivities) until the models predict the appropriate activations at PT and DT for 50 Hz, burst, and 1 kHz SCS.

Spinal circuit model. We will implement a circuit model of pain processing in the dorsal horn based on the gate-control theory of pain.[17] This circuit model will include populations of inhibitory interneurons (*I*), excitatory interneurons (*E*), wide-dynamic range (i.e., neurons that respond to both nociceptive and non-nociceptive inputs) projection neurons (*W*), and a mid-brain neuronal population (*T*) (Fig. 9.6). It will also include inputs from three types of afferent fibers: large-diameter myelinated somatosensory Aβ, thinly myelinated nociceptive Aδ, and unmyelinated nociceptive C fibers.

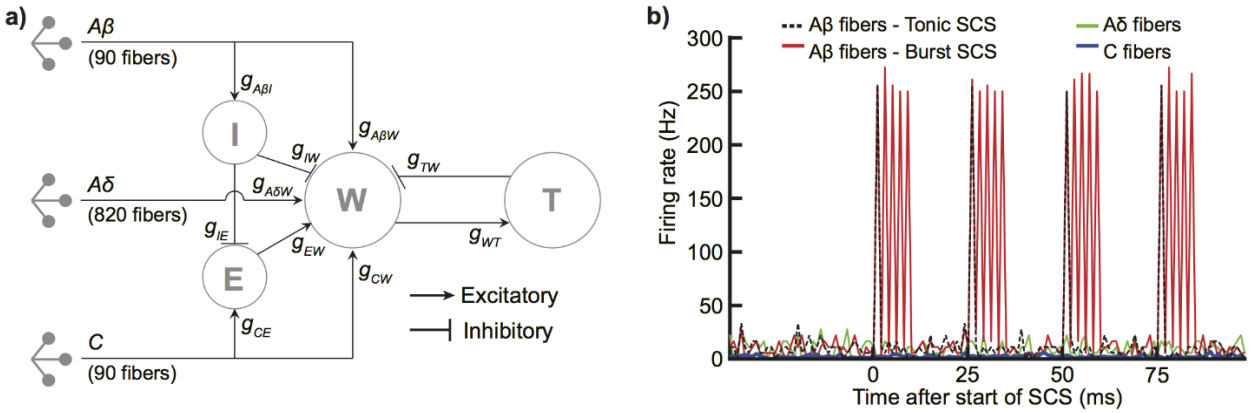

Figure 9.6. *Circuit model of pain processing in the spinal cord. a) The model includes connections to/from the mid-brain and the following populations: inhibitory interneurons (I), excitatory interneurons (E), WDR projection neurons (W), and a mid-brain neuronal population (T). The model also includes three afferent fiber populations: Aβ, Aδ, and C fibers. b) Average firing rates for the three afferent fiber populations. SCS is applied at time = 0 ms. Tonic and burst SCS each increase the firing rates of the* Aβ *fibers.*

We will use a population-level firing-rate formalism to describe the average firing rates of the *I*, *E*, *W*, and *T* populations in the dorsal horn circuit. We will assume that the rate of change of the average firing rate in Hz (i.e., the average number of spikes per unit time) of the *W*, I, *E*, and *T* neuron populations, f_W, f_I, f_E, and f_T, respectively, will be determined by nonlinear response functions.[91] We will represent the monotonically-increasing firing-rate response functions using hyperbolic tangent functions and assuming a sigmoidal shape. The shape of the hyperbolic tangent functions will be defined by the average and maximum firing rates of the respective populations so that the input-output curve of each population qualitatively agrees with experimental observations.[92] The firing rate of the *W* population will be the primary output of the model. The firing rate of wide-dynamic range projection neurons is correlated with the

magnitude of pain[93] and has been used in animal studies as a proxy for SCS efficacy.[19,94–96]

The input to our circuit model will be the activity of the Aβ, Aδ, and C afferent fibers with relative densities based on the literature (9% Aβ; 9% Aδ; 82% C).[97,98] The three fibers types have different diameters and myelination properties that result in different conduction velocities. Because the temporal aspects of the inputs are critical to pain processing and the response to SCS, we will use published conduction velocities for each fiber type (Aβ: 14-30 m/s; Aδ: 2.2-8 m/s; C: 0.6-1.5 m/s).[99] For peripherally generated afferent stimulation (e.g., painful stimulus), we will generate recurring events at the Aβ, Aδ, and C fiber inputs with arrival latencies assuming ~1 m between the site of stimulation and the dorsal horn network. To represent baseline afferent input activity during chronic pain conditions, we will apply Poisson spike trains with means and variances consistent with those of spike trains recorded in animal models of neuropathic pain (Aβ mean = 2.2 spikes/s, Aδ mean = 2.2 spikes/s, C mean = 1.5 spikes/s)[100,101] and we will set 30% of the Aβ and Aδ fiber inputs to exhibit bursting behavior.[96,100,102] To represent afferent input activity in response to a painful stimulus, we will apply primary afferent spike trains with individual interspike intervals with mean frequencies representative of peripheral afferent activity during steady-state natural "pinch" stimulation (Aβ mean – 9 spikes/s, Aδ mean – 9 spikes/s, C mean = 2.5 spikes/s).[103] To input this spiking activity into our population-level model, we will compute the average firing rate in each group of fibers by a moving average over a time window of 10 ms. These baseline population firing rates for the three types of afferents will be the inputs into the model, in addition to the Aβ activity induced by electrical stimulation as described below.

To determine the effects of tonic 50 Hz, burst, and 1 kHz SCS on pain processing in the spinal cord, we will couple the axonal responses predicted by the patient-specific electric-field models (Fig. 9.5) to this population firing-rate model of pain processing in the dorsal horn (Fig. 9.6). It is well accepted that SCS leads to modulation of the large-diameter Aβ fibers.[76] Therefore, we will use the patient-specific electric-field models to estimate how the activity of individual fibers in the Aβ population are modulated by SCS. To do this, as part of our quantitative sensory testing procedures, we will first identify a primary pain site corresponding to the dermatome at which pain is the most intense for each patient. We will define a circuit model of pain processing for the spinal level corresponding to this primary pain site. It is well known that Aβ afferents give off collaterals from their ascending and descending branches at levels other than those at which they entered the spinal cord and that Aβ collaterals plays a key role in the gate theory of pain.[17] Thus, we will incorporate data from the literature describing the rostral/caudal extent of Aβ fibers entering at all levels of the spinal cord and the distribution of their collaterals to determine which spinal segments have collaterals that project and have inputs into the primary pain level.[81] These specific axons will serve as inputs that connect to the *I* and *W* populations in the circuit model of pain processing at the primary pain site. We will use the patient-specific electric field models to determine how these axons are modulated by the different types of SCS.

We will validate the output of our population firing-rate model in multiple steps. We will ensure that our model reproduces well-known phenomenon, such as central sensitization or "wind-up". Wind-up is an increased excitability of the neurons in the spinal cord, particularly the wide-dynamic range projection neurons, due to repetitive stimulation of C fibers. Therefore, we will generate repetitive low-frequency (1 Hz) C-fiber inputs and compare the output of our *W* population to previous experimental data demonstrating wind-up.[94,96,104–107] As described in Section 9.5.1, temporal summation (TS) of pain is the human analogue of wind-up, and so we will also match the output or degree of central sensitization to the experimental measurements of TS. In our primary outcome considering SCS-induced changes in TS, we will apply a repetitive 1 Hz stimulus and have the patient rate their pain as a function of time. In human subjects, each subsequent stimulus becomes more painful and is believed to represent wind-up

within the spinal cord. Therefore, we will be able to compare increases in the pain ratings from our participants (reflecting wind-up) to increases in the output of the *W* population in our model.

We will also validate that our circuit model reproduces descending inhibition. We will compare our model results to the experimental measurements performed in the CPM paradigm. During this CPM paradigm, a patient receives a conditioning stimulus and a painful test stimulus and rates the pain of this test stimulus (Fig. 9.1B). In human patients, the conditioning stimulus has the effect of reducing the pain levels of the test stimulus and is believed to represent descending pain inhibition.[108] Therefore, we will compare the reduced pain levels observed during CPM in each patient to the changes in *W* output in our model produced by increased inputs from the *T* population. We will represent the test stimulus as increased inputs from the all three afferent populations (Aβ = 9 spikes/s, Aδ = 9 spikes/s, C = 2.5 spikes/s).[96,103] We will represent the conditioning stimulus by increasing the weighting parameter between the *T* and *W* populations that would produce increased inhibition of *W*.[92]

We will use the validated model to investigate the underlying mechanisms of pain relief induced by SCS. We will compare the model output (i.e., *W* population firing rate) on a patient-by-patient basis. We will also compare the model outputs predicted between the groups of responders versus non-responders. For patients who obtained successful pain relief with SCS, we will compare the model output for clinically effective stimulation parameters versus clinically ineffective stimulation parameters.

9.6 Data Analyses

Analysis of the primary efficacy endpoint(s): The primary endpoint will be SCS-induced changes in temporal summation (TS) (see Section 9.5.1). We will use a repeated-measures approach in which the continuous TS values will be calculated at the end of each seven-day treatment period, i.e., type of SCS. To analyze SCS-induced changes in TS measured at the end of each treatment period, we will use linear mixed-effects models that will include a participant-level random intercept to account for correlations of measurements from the same participant. We will obtain the least-squares estimates of the mean TS for the treatments and perform group comparisons with the appropriate contrasts. We will establish statistical significance with two-sided $p<0.05$. We will utilize a per-protocol analysis dataset. We will only consider randomized participants who completed the Sham SCS treatment along with at least one other active (i.e., burst, tonic 1 kHz, tonic 50 Hz) SCS treatment along with the associated outcome measures for each treatment.

Analysis of the secondary endpoint(s): N/A.

Baseline descriptive statistics: We will use descriptive statistics to assess data quality and characterize relationships between variables. We will list the aggregate data using means and standard deviations for normally distributed data and medians and interquartile ranges for non-normal data. We will consider several baseline demographics and clinical characteristics, such as gender, pain duration, pain diagnosis, previous back surgery, and co-treatments (e.g., opioids, antidepressants, anticonvulsants, NSAIDs/simple analgesics, other). We will consider the QST outcome measures characterizing baseline static and dynamic pain processing. Finally, we will also consider the exploratory outcome measures related to baseline pain intensity, pain quality, pain spread, and quality of life.

Sub-group analyses: This study is an exploratory mechanistic study examining the physiological effects of multiple forms of SCS on sensory processing. Due to the small number of participants that will be considered in this study (i.e., n=20), we will not analyze primary or exploratory endpoints based on age, race/ethnicity, or other demographic characteristic(s). However, sex has been shown to be an important variable to consider in chronic pain and sensory processing. Therefore, although we may not detect significant differences due to the

small sample size in this exploratory study, we will consider sex as a biological variable when analyzing the primary and exploratory endpoints.

Tabulation of individual participant data: We will list individual participant data with regards to the primary outcome. For each type of SCS (Burst-SCS, 1kHz SCS, 50Hz SCS, Sham SCS), we will list the TS value calculated for each individual participant. We will use the mean TS value to quantify SCS-induced changes in TS. For the exploratory endpoints, we will list the aggregate data using means and standard deviations for normally distributed data and medians and interquartile ranges for non-normal data.

Exploratory analyses: To investigate the anti-nociceptive effects of SCS, we are proposing to conduct an exploratory, mechanistic, placebo-controlled study in 25 patients undergoing SCS for chronic pain. We will use quantitative sensory testing (QST) to assess spinal and supraspinal pain processing. In addition to the primary outcome described in Section 9.4.2, we will perform several exploratory analyses. We will evaluate the effects of somatosensory stimuli using static QST measures of sensory detection threshold, pain threshold, and/or tolerance to stimuli (i.e., vibratory threshold, pressure-pain threshold). We will also assess dynamic central pain-processing mechanisms, such as endogenous pain inhibition, by measuring pain sensitivity concurrent with the application of a conditioning stimulus (i.e., conditioned pain modulation (CPM)).[15] Furthermore, we will obtain outcome measures to assess changes in pain intensity, pain quality, pain spread, and quality of life. Additional exploratory outcomes will include patient-reported VAS ratings for back, leg, and general pain,[1,2] and several self-reported patient questionnaires, such as the Short-Form McGill Pain Questionnaire to assess quality of pain,[3] Michigan Body Map to quantify the degree of widespread body pain,[4] EQ-5D to characterize quality of life,[5] Pain Disability Index (PDI) to measure pain-related disability,[68] and questionnaires from the Patient Reported Outcomes Measurements Information (PROMIS)[6]. We will identify responders as patients who demonstrate a ≥ 50% reduction in average pain intensity (as measured by the VAS) with active SCS as compared to sham stimulation, a standard criterion for success with SCS.[22] We hypothesize that patients who respond to specific types of SCS will show decreased spinal segmental sensitivity, particularly decreased vibration sensitivity and pressure-pain sensitivity. We believe that effective SCS will also modulate dynamic central pain-processing mechanisms. We hypothesize that effective types of SCS (i.e., patients who show ≥50% reduction in average pain intensity) will reduce TS (primary outcome) and improve inhibitor CPM.

Because these mechanistic questions are difficult to answer experimentally, we will also perform exploratory analyses with patient-specific computational models that will include: 1) electric-field models to estimate the direct neural response to SCS, and 2) circuit models to estimate the effects of SCS on pain processing in the spinal cord. We hypothesize that patient-specific models capture the details necessary to quantitatively describe the neural response to SCS and to correlate model-based predictions with experimental measurements of pain modulation. Therefore, we will develop patient-specific electric-field models that account for sources of interpatient variability (e.g., anatomy, electrode locations, stimulation parameters) for the 25 participants. We will define finite element models from the patient-specific preoperative and postoperative medical imaging. To estimate the direct neural response to SCS, we will then place multi-compartment neuron models within the patient-specific spinal cord anatomy.

The basic hypothesis of this study is that the physiological effects of SCS can be correlated with modulation of specific fiber pathways that help regulate pain processing within the spinal cord. However, the specific analgesic mechanisms of clinically effective SCS remain unknown. Therefore, as a second component of our computational modeling approach, we will develop a population firing-rate circuit model of pain processing in the spinal cord. We will use the direct neural response to SCS estimated from the electric-field models as the inputs to our circuit model. We will determine what types of spinal cord modulation best correlate with experimental measurements of pain modulation during SCS.

Finally, due to our poor scientific understanding of how SCS works and the limited individualization of this therapy, we consider current clinical implementation of SCS to be suboptimal. Therefore, in this exploratory analysis, we will use our computational models to identify stimulation protocols (e.g., alternative waveform parameters) that may improve the desired physiological effects and corresponding pain relief.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

All study related information will be collected via self-reported questionnaire as per the table below.

Form Name	Data Collection Method
Screening & Demographics	
Informed Consent	Study Coordinator / Team Member
Demographics	Participant
Socio-demographics	Participant
Concomitant Medications	Participant
Vitals (heartrate, blood pressure, respiration rate, blood temperature), height and weight	Clinical staff
Self-Report Patient Questionnaires	
Short Form McGill Pain Questionnaire (SFMPQ)	Participant
Pain Disability Index (PDI)	Participant
Brief Pain Inventory (BPI)	Participant
Michigan Body Map (MBM)	Participant
Fibromyalgia Survey Questionnaire (FSQ)	Participant
PainDETECT	Participant
Hospital Anxiety and Depression Scale (HADS)	Participant
Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form Questionnaire (PROMIS-SD)	Participant
Coping Strategies Questionnaire (CSQ)	Participant
EQ-5D Health Questionnaire	Participant
Visual Analog Scale (VAS) – included in SFMPQ	Participant
Generalized Mechanical Sensitivity	
Multimodal Automated Sensory Test (MAST)	Participant / Study Coordinator / Team Member
Spinal Segmental Sensitivity	
Vibrometer Test	Participant / Study Coordinator / Team Member
Algometer Test	Participant / Study Coordinator /

	Team Member
PinPrick Test	Participant / Study Coordinator / Team Member
Quantitative Sensory Testing (QST)	
Conditioned Pain Modulation (CPM) Test	Participant / Study Coordinator / Team Member
Stimulator programming	
Burst, 1kHz, 50Hz, Sham SCS	Participant / Study Coordinator / Team Member
Safety	
Adverse Events	Study Coordinator / Team Member

10.2 Data Management

The University of Michigan Division of Pain Research, Chronic Pain and Fatigue Research Center, and other study personnel will be responsible for the collection of all source information. All Case Report Forms will be approved by the University of Michigan IRB.

Participants will complete electronic surveys or paper-based questionnaires. Electronic questionnaires will be completed via the Qualtrics Research Core at the University of Michigan. Data will be verified and checked for completeness and initialed by the study coordinator or other team member prior to the completion of the visit. All data will be entered into a research database (REDCap) by the study team.

Study data will be collected and managed using REDCap electronic data capture tools hosted at University of Michigan. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

10.3 Quality Assurance

10.3.1 Training

All study team members are required to be certified by the University of Michigan Program for Education and Evaluation in Responsible Research and Scholarship (PEERRS). In addition, research staff are required to follow study specific operating procedures as documented in the Manual of Operations and approved by the study PI.

10.3.2 Quality Control Committee

There is no quality control committee for this study, however, the study team will perform internal quality management of study conduct, data collection, documentation and completion. An individualized quality management plan will be developed to describe quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database that will be generated. Any missing data or data anomalies will be communicated to the study team for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and collected, documented (recorded), and physiological effects of spinal cord stimulation for pain reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.3.3 Metrics

All outcome measures will be assessed for quality. If an outcome's value is above or below the possible range for that outcome, the data will be flagged for review.

10.3.4 Protocol Deviations

Protocol deviations will be documented on the visit checklist at each visit by the study team member responsible for that visit. The study coordinator will review the deviation and report to the study team via the Deviations Tracking Log. Corrective Actions, if required, will be noted in the subject file and study documentation. Major protocol deviations that may adversely impact safety of participants, or impact integrity/validity of the data and minor protocol deviations as part of a pattern and/or suggesting a systemic problem in study conduct that potentially places subjects or others at a greater risk of harm than was previously known or recognized will be reported as an Other Reportable Information or Occurrences (ORIO) within seven days of becoming aware of the event or information. Minor protocol deviations that do not impact safety of participants or impact integrity/validity of the data – for example, schedule deviations, minor informed consent deviations (wrong version date, wrong expiration date, as long as the content is same) will be reported as part of scheduled continuing review.

10.3.5 Monitoring

The Independent Monitoring Committee (IMC) for this study is comprised of Drs. Emily Levin, Daniel Leventhal, and Catherine Spino. Drs. Levin, Leventhal, and Spino are not associated with this research project and work independently of the PI, Dr. Scott Lempka. They are not part of the key personnel involved in this grant. No member of the Committee has collaborated or co-published with the PI within the past three years. They are qualified to review the participant safety data generated by this study because of their unique expertise.

Emily Levin, MD is a board-certified neurosurgeon with specialization in neurostimulation approaches to treat movement disorders, pain, and other neurological disorders. Dr. Levin is a Clinical Assistant Professor in Neurosurgery at the University of Michigan. She is also the Chief of Neurosurgery and the Associate Chief of Surgery at the Veterans Administration Health Center in Ann Arbor, MI and co-directs the deep brain stimulation program for movement disorders.

Daniel Leventhal, MD, PhD is a neurologist and Assistant Professor of Neurology in the Movement Disorders division at the University of Michigan. His primary clinical duties are at the VA Ann Arbor Healthcare System, where he co-directs the Deep Brain Stimulation program for Movement Disorders. Dr. Leventhal also directs a basic science laboratory at the University of Michigan that performs experimental studies to investigate the brain circuit abnormalities that contribute to the clinical manifestations of Parkinson Disease and related disorders.

Catherine Spino, PhD is a Research Professor of Biostatistics at the University of Michigan. Dr. Spino is the Director of the Statistical Analysis of Biomedical and Educational Research (SABER) unit, which provides statistical and operational excellence to single- and multi-center clinical studies. She has been the director of multiple data coordinating centers for single- and multi-center clinical studies. Dr. Spino has more than 25 years of experience in the

design, conduct and analysis of data from clinical studies in a variety of therapeutic areas, as well as extensive experience and expertise in managing data and coordinating centers.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

11.2 Informed Consent Forms

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the study record. To complete the informed consent process at the end of study participation, study staff will inform the subject when his/her participation has come to an end and will document the discussion in the study record.

11.3 Participant Confidentiality

The study requires obtaining direct patient identifiers due to collecting standard of care data in addition to the research data for the project. We will assign subject numbers to patients and those numbers will be used in the research. We will maintain a password-protected file linking subject numbers to identifying information on a UM computer. Research personnel will store identified study data in accordance with standard regulations and will not be disclosed or shared with any outside third parties. Identifying information will be severed from study data that is reported. Only relevant research personnel listed in the institutional review board (IRB) study application will have access to study files and folders. We will protect the data on a laptop computer or on a removable device by encryption.

11.4 Study Discontinuation

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) and/or other study personnel will promptly inform

study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study the visit schedule. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and the IRB.

12. COMMITTEES

There are no additional committees associated with this study.

13. PUBLICATION OF RESEARCH FINDINGS

The clinical trial will be registered and the results information submitted to ClincalTrials.gov as outlined in the policy and according to the specific timelines stated in the policy. All informed consent documents will include statements that specifically indicate the posting of all clinical trial information to ClincalTrials.gov. The University of Michigan has an internal policy in place to ensure the clinical trials results reporting occur in compliance with policy requirements. This policy is enacted through the University of Michigan Medical School Clinical Trials Support Office.

We will also ensure that results are available to the public at large through timely publication of data and we will leverage the University of Michigan's communication liaisons to issue press releases on findings to disseminate findings to a lay audience. Additionally, the study governance does not include a Steering Committee.

14. REFERENCES

1. De Ridder D, Vanneste S, Plazier M, van der Loo E, Menovsky T. Burst spinal cord stimulation: Toward paresthesia-free pain suppression. Neurosurgery 2010;66(5):986–90.
2. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World Neurosurg [Internet] 2013;80(5):642-649.e1. Available from: http://dx.doi.org/10.1016/j.wneu.2013.01.040
3. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1975;1(3):277–99.
4. Brummett CM., Bakshi RR., Goesling J., et al. Preliminary validation of the Michigan Body Map. Pain 2016;157(6):1205–12.
5. Rabin R, Charro F De. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33(5):337–43.
6. Cook KF, Dunn W, Griffith JW, et al. Pain assessment using the NIH Toolbox. Neurology 2013;80(Issue 11, Supplement 3):S49–53.
7. Courtney P, Espinet A, Mitchell B, et al. Improved Pain Relief With Burst Spinal Cord Stimulation for Two Weeks in Patients Using Tonic Stimulation: Results From a Small Clinical Study. Neuromodulation 2015;18(5):361–6.
8. Tjepkema-Cloostermans MC, de Vos CC, Wolters R, Dijkstra-Scholten C, Lenders MWPM. Effect of Burst Stimulation Evaluated in Patients Familiar With Spinal Cord Stimulation. Neuromodulation 2016;19(5):492–7.
9. de Vos CC, Bom MJ, Vanneste S, Lenders MWPM, de Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic

neuropathy. Neuromodulation 2014;17(2):152–9.
10. Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJPM. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and placebo-controlled crossover trial. Eur J Pain 2016;(August):1–13.
11. Chaturvedi A, Butson CR, Lempka SF, Cooper SE, McIntyre CC. Patient-specific models of deep brain stimulation: Influence of field model complexity on neural activation predictions. Brain Stimul [Internet] 2010;3(2):65–77. Available from: http://dx.doi.org/10.1016/j.brs.2010.01.003
12. Lempka SF, McIntyre CC, Kilgore KL, Machado AG. Computational Analysis of Kilohertz Frequency Spinal Cord Stimulation for Chronic Pain Management. Anesthesiology [Internet] 2015;122(6):1362–76. Available from: http://insights.ovid.com/crossref?an=00000542-201506000-00029
13. Gunalan K, Chaturvedi A, Howell B, et al. Creating and parameterizing patient-specific deep brain stimulation pathway-activation models using the hyperdirect pathway as an example. PLoS One 2017;12(4):e0176132.
14. Price DD, Hayes RL, Ruda M, Dubner R. Neural representation of cutaneous aftersensations by spinothalamic tract neurons. Fed Proc 1978;37(9):2237–9.
15. Yarnitsky D, Arendt-Nielsen L, Bouhassira D, et al. Recommendations on terminology and practice of psychophysical DNIC testing. Eur. J. Pain. 2010;14(4):339.
16. Shealy CN, Mortimer JT, Reswich JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg 1967;46(4):489–91.
17. Melzack R, Wall PD. Pain Mechanisms: A New Theory. Science (80-) 1965;150:971–9.
18. Moffitt MA, Lee DC, Bradley K. Spinal Cord Stimulation: Engineering Approaches to Clinical and Physiological Challenges [Internet]. In: Implantable Neural Prostheses 2. New York: Springer; 2009. p. 155–94.Available from: http://link.springer.com/10.1007/978-0-387-98120-8
19. Guan Y. Spinal cord stimulation: Neurophysiological and neurochemical mechanisms of action. Curr Pain Headache Rep 2012;16(3):217–25.
20. Linderoth B, Foreman RD. Conventional and Novel Spinal Stimulation Algorithms: Hypothetical Mechanisms of Action and Comments on Outcomes. Neuromodulation 2017;20(6):525–33.
21. North RB, Ewend MG, Lawton MT, Piantadosi S. Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. Pain 1991;44(2):119–30.
22. Taylor RS, Desai MJ, Rigoard P, Taylor RJ. Predictors of pain relief following spinal cord stimulation in chronic back and leg pain and failed back surgery syndrome: a systematic review and meta-regression analysis. Pain Pract 2014;14(6):489–505.
23. Ross E, Abejõn D. Improving patient experience with spinal cord stimulation: Implications of position-related changes in neurostimulation. Neuromodulation 2014;17(SUPPL. 1):36–41.
24. Deer T, Slavin K V., Amirdelfan K, et al. Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. Neuromodulation [Internet] 2018;21:56–66. Available from: http://doi.wiley.com/10.1111/ner.12698
25. De Ridder D, Vanneste S. Burst and Tonic Spinal Cord Stimulation: Different and Common Brain Mechanisms. Neuromodulation 2016;19(1):47–59.
26. Kapural L, Yu C, Doust MW, et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain. Anesthesiology 2015;123(4):851–60.
27. Kilgore KL, Bhadra N. Reversible Nerve Conduction Block Using Kilohertz Frequency

Alternating Current. 2014;17:242–55.
28. Song Z, Viisanen H, Meyerson BA, Pertovaara A, Linderoth B. Efficacy of kilohertz-frequency and conventional spinal cord stimulation in rat models of different pain conditions. Neuromodulation 2014;17(3):226–34.
29. Crosby ND, Janik JJ, Grill WM. Modulation of activity and conduction in single dorsal column axons by kilohertz-frequency spinal cord stimulation. J Neurophysiol [Internet] 2017;117(1):136–47. Available from: http://jn.physiology.org/lookup/doi/10.1152/jn.00701.2016
30. Shechter R, Yang F, Xu Q, et al. Conventional and Kilohertz-frequency Spinal Cord Stimulation Produces Intensity- and Frequency- dependent Inhibition of Mechanical Hypersensitivity in a Rat Model of Neuropathic Pain. Anesthesiology 2013;2:422–32.
31. De Carolis G, Paroli M, Tollapi L, et al. Paresthesia-Independence: An Assessment of Technical Factors Related to 10 kHz Paresthesia-Free Spinal Cord Stimulation. Pain Physician [Internet] 2017;20(4):331–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28535555
32. Vallejo R, Bradley K, Kapural L. Spinal Cord Stimulation in Chronic Pain. Spine (Phila Pa 1976) 2017;42(14):S53–60.
33. Zannou AL, Khadka N, Truong DQ, et al. Temperature increases by kilohertz frequency Spinal Cord Stimulation. Brain Stimul [Internet] 2018;Available from: https://doi.org/10.1016/j.brs.2018.10.007
34. Thomson SJ, Tavakkolizadeh M, Love-Jones S, et al. Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial. Neuromodulation 2018;21(1):67–76.
35. Kumar K, Rizvi S, Nguyen R, Abbas M, Bishop S, Murthy V. Impact of Wait times on Spinal Cord Stimulation Therapy Outcomes. Pain Pr 2014;14(8):709–20.
36. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: The neuromodulation appropriateness consensus committee. Neuromodulation 2014;17(6):515–50.
37. Levy RM. Anatomic considerations for spinal cord stimulation. Neuromodulation 2014;17(SUPPL. 1):2–11.
38. Al-Kaisy A, Palmisani S, Pang D, et al. Prospective, Randomized, Sham-Control, Double Blind, Crossover Trial of Subthreshold Spinal Cord Stimulation at Various Kilohertz Frequencies in Subjects Suffering From Failed Back Surgery Syndrome (SCS Frequency Study). Neuromodulation 2018;21(5):457–65.
39. Perruchoud C, Eldabe S, Batterham AM, et al. Analgesic efficacy of high-frequency spinal cord stimulation: A randomized double-blind placebo-controlled study. Neuromodulation 2013;16(4):363–9.
40. Sankarasubramanian V, Harte SE, Chiravuri S, et al. Objective Measures to Characterize the Physiological Effects of Spinal Cord Stimulation in Neuropathic Pain : A Literature Review. Neuromodulation 2018;Epub ahead of print.
41. Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. Neuromodulation 2014;17(5):443–50.
42. Mogil JS. Animal models of pain: Progress and challenges. Nat Rev Neurosci 2009;10(4):283–94.
43. Burma NE, Leduc-Pessah H, Fan CY, Trang T. Animal models of chronic pain: Advances and challenges for clinical translation. J Neurosci Res 2017;95(6):1242–56.
44. Noecker AM, Choi KS, Riva-posse P, Gross RE, Mayberg HS, Mcintyre CC. StimVision Software : Examples and Applications in Subcallosal Cingulate Deep Brain Stimulation for

Depression. Neuromodulation 2018;2:191–6.
45. Huang Y, Datta A, Bikson M, Parra LC. Realistic vOlumetric-Approach to Simulate Transcranial Electric Stimulation – ROAST – a fully automated open-source pipeline. bioRxiv 2017;
46. Lempka SF, Zander H, Anaya CJ, Wyant A, Ozinga JG, Machado AG. Model-Based Analysis of Spinal Cord Stimulation for Chronic Pain. In: Masia L, Micera S, Akay M, Pons J, editors. Converging Clinical and Engineering Research on Neurorehabilitation III. ICNR 2018. Biosystems & Biorobotics. Cham: Springer; 2019. p. 39–43.
47. Elzahaf RA, Tashani OA, Unsworth BA, Johnson MI. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: A systematic review without meta-analysis. Curr Med Res Opin 2012;28(7):1221–9.
48. Nahin RL. Estimates of Pain Prevalence and Severity in Adults: United States, 2012. J Pain 2015;16(8):769–80.
49. Turk DC, Audette J, Levy RM, Mackey SC, Stanos S. Assessment and treatment of psychosocial comorbidities in patients with neuropathic pain. Mayo Clin Proc 2010;85(3 Suppl):S42-50.
50. Berger A, Dukes EM, Oster G. Clinical Characteristics and Economic Costs of Patients With Painful Neuropathic Disorders. J Pain 2004;5(3):143–9.
51. Ballantyne JC, Mao J. Opioid Therapy for Chronic Pain. N Engl J Med 2003;1943–53.
52. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann. Intern. Med. 2007;146(2):116–27.
53. Kemler MA, Barendse GA, van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343(9):618–24.
54. North RB, Kidd DH, Piantadosi S. Spinal Cord Stimulation Versus Reoperation for Failed Back Surgery Syndrome: a Prospective, Randomized Study Design. Acta Neurochir 1995;64:106–8.
55. Youn Y, Smith H, Morris B, Argoff C, Pilitsis JG. The Effect of High-Frequency Stimulation on Sensory Thresholds in Chronic Pain Patients. Stereotact Funct Neurosurg 2015;93(5):355–9.
56. Sdrulla AD, Guan Y, Raja SN. Spinal Cord Stimulation: Clinical Efficacy and Potential Mechanisms. Pain Pract 2018;Epub ahead of print.
57. Marchand S, Kupers RC, Bushnell MC, Duncan GH. Analgesic and placebo effects of thalamic stimulation. Pain 2003;105(3):481–8.
58. Eide PK. Wind-up and the NMDA receptor complex from a clinical perspective. Eur J Pain 2000;4:5–15.
59. Lempka SF, Patil PG. Innovations in spinal cord stimulation for pain. Curr Opin Biomed Eng [Internet] 2018;8:51–60. Available from: https://doi.org/10.1016/j.cobme.2018.10.005
60. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983;67(6):361–70.
61. Schuh-Hofer S, Fischer J, Unterberg A, Treede R, Ahmadi R. Spinal cord stimulation modulates descending pain inhibition and temporal summation of pricking pain in patients with neuropathic pain. Acta Neurochir 2018;160(12):2509–19.
62. Harte SE, Mitra M, Ichesco EA, et al. Development and validation of a pressure-type automated quantitative sensory testing system for point-of-care pain assessment. Med Biol Eng Comput 2013;51:633–44.
63. Eisenberg E, Backonja M-M, Fillingim RB, et al. Quantitative sensory testing for spinal cord stimulation in patients with chronic neuropathic pain. Pain Pract 2006;6(3):161–5.
64. Meier K, Nikolajsen L, Sørensen JC, Jensen TS. Effect of spinal cord stimulation on sensory characteristics: a randomized, blinded crossover study. Clin J Pain 2015;31(5):384–92.

65. Campbell CM, Buenaver LF, Raja SN, et al. Dynamic Pain Phenotypes are Associated with Spinal Cord Stimulation-Induced Reduction in Pain: A Repeated Measures Observational Pilot Study. Pain Med (United States) 2015;16(7):1349–60.
66. Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJPM. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: A multicentre, double-blind, randomized and placebo-controlled crossover trial. Eur J Pain [Internet] 2017;21(3):507–19. Available from: http://doi.wiley.com/10.1002/ejp.944
67. Melzack R. The short-form McGill Pain Questionnaire. Pain 1987;30(2):191–7.
68. Tait RC, Chibnall JT, Krause S. The Pain Disability Index: Psychometric properties. Pain 1990;40(2):171–82.
69. Cleeland CS. Brief Pain Inventory (BPI). Cleel CS MD Anderson Cancer Cent 1982;1100:6.
70. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: A modification of the ACR preliminary diagnostic criteria for fibromyalgia. J Rheumatol 2011;38(6):1113–22.
71. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22(10):1911–20.
72. Swartzman LC, Gwadry FG, Shapiro AP, Teasell RW. The factor structure of the Coping Strategies Questionnaire. Pain 1994;57(3):311–6.
73. Gabriel C, Gabriel S, Corthout E. The dielectric properties of biological tissues: I. Literature survey. Phys Med Biol [Internet] 1996;41(11):2231–49. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8938024
74. Gabriel S, Lau RW, Gabriel C. The dielectric properties of biological tissues: II. Measurements in the frequency range 10 Hz to 20 GHz. Phys Med Biol 1996;41(11):2251–69.
75. Gabriel S, Lau RW, Gabriel C. The dielectric properties of biological tissues: III. Parametric models for the dielectric spectrum of tissues. Phys Med Biol 1996;41:2271–93.
76. Holsheimer J. Which neuronal elements are activated directly by spinal cord stimulation. Neuromodulation 2002;5(1):25–31.
77. Lee D, Hershey B, Bradley K, Yearwood T. Predicted effects of pulse width programming in spinal cord stimulation: a mathematical modeling study. Med Biol Eng Comput [Internet] 2011;49(7):765–74. Available from: http://link.springer.com/10.1007/s11517-011-0780-9
78. Todd AJ. Neuronal circuitry for pain processing in the dorsal horn. Nat Rev Neurosci 2010;11(12):823–36.
79. Carpenter MB. Core Text of Neuroanatomy. Fourth. Baltimore, MD: Williams & Wilkins; 1991.
80. Feirabend HKP, Choufoer H, Ploeger S, Holsheimer J, van Gool JD. Morphometry of human superficial dorsal and dorsolateral column fibres: significance to spinal cord stimulation. Brain 2002;125:1137–49.
81. Niu J, Ding L, Li JJ, et al. Modality-Based Organization of Ascending Somatosensory Axons in the Direct Dorsal Column Pathway. J Neurosci [Internet] 2013;33(45):17691–709. Available from: http://www.jneurosci.org/cgi/doi/10.1523/JNEUROSCI.3429-13.2013
82. Struijk JJ, Holsheimer J, van der Heide GG, Boom HBK. Recruitment of Dorsal Column Fibers in Spinal Cord Stimulation: Influence of Collateral Branching. IEEE Trans Biomed Eng 1992;39(9):903–12.
83. Struijk JJ, Holsheimer J, Boom HBK. Excitation of Dorsal Root Fibers in Spinal Cord Stimulation - A Theoretical Study. IEEE Trans Biomed Eng 1993;40(7):632–9.

84. Hines ML, Andrew P, Muller E. NEURON and Python. Front Neuroinform 2009;3(January):1–12.
85. Rall W, Burke RE, Holmes WR, Jack JJB, Redman SJ, Segev I. Matching Dendritic Neuron Models to Experimental Data. Physiol Rev 1992;72(4):S159–86.
86. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol 1952;117:500–44.
87. Choi J-S, Waxman SG. Physiological interactions between Nav1.7 and Nav1.8 sodium channels: a computer simulation study. J Neurophysiol [Internet] 2011;106(6):3173–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21940606
88. Herzog RI, Cummins TR, Waxman SG. Persistent TTX-Resistant Na+ Current Affects Resting Potential and Response to Depolarization in Simulated Spinal Sensory Neurons. J Neurophysiol [Internet] 2001;86(3):1351–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11535682
89. Law JD. Spinal Stimulation: Statistical Superiority of Monophasic Stimulation of Narrowly Separated, Longitudinal Bipoles having Rostral Cathodes. Appl Neurophysiol 1983;46:129–37.
90. Yearwood TL, Hershey B, Bradley K, Lee D. Pulse Width Programming in Spinal Cord Stimulation: A Clinical Study. Pain Physician 2010;13:321–35.
91. Wilson HR, Cowan JD. Excitatory and Inhibitory Interactions in Localized Populations of Model Neurons. Biophys J [Internet] 1972;12(1):1–24. Available from: http://dx.doi.org/10.1016/S0006-3495(72)86068-5
92. Crodelle JA, Piltz SH, Booth V, Hagenauer MH. Investigating circadian rhythmicity in pain sensitivity using a neural circuit model for spinal cord processing of pain. bioRxiv 2017;
93. Simone DA, Sorkin LS, Oh U, et al. Neurogenic hyperalgesia: Central neural correlates in responses of spinothalamic tract neurons. J Neurophysiol [Internet] 1991;66(1):228–46. Available from: http://www.scopus.com/scopus/inward/record.url?eid=2-s2.0-0025827277&partnerID=40
94. Foreman RD, Beall JE, Applebaum AE, Coulter JD, Willis WD. Effects of dorsal column stimulation on primate spinothalamic tract neurons. J Neurophysiol 1976;39(3):534–46.
95. Linderoth B, Foreman RD, Meyerson BA. Mechanisms of Action of Spinal Cord Stimulation. In: Textbook of Stereotactic and Functional Neurosurgery. New York: McGraw-Hill; 2009. p. 2331–2348.
96. Zhang TC, Janik JJ, Grill WM. Modeling effects of spinal cord stimulation on wide-dynamic range dorsal horn neurons: influence of stimulation frequency and GABAergic inhibition. J Neurophysiol 2014;112(3):552–67.
97. Purves ED, Augustine GJ, Fitzpatrick D, Katz LC, Mcnamara JO, Williams SM, editors. Neuroscience. 2nd ed. Sunderland: Sinauer Associates; 2001.
98. Le Bars D, Gozariu M, Cadden SW. Animal Models of Nociception. Pharmacol Rev 2001;53(4):597–652.
99. Harper AA, Lawson SN. Conduction velocity is related to morphological cell type in rat dorsal root ganglion neurones. J Physiol 1985;359:31–46.
100. Liu X, Eschenfelder S, Blenk K-H, Jänig W, Häbler H-J. Spontaneous activity of axotomized afferent neurons after L5 spinal nerve injury in rats. Pain 2000;84:309–18.
101. Wall PD, Gutnick M. Ongoing activity in peripheral nerves: The physiology and pharmacology of impulses originating from a neuroma. Exp Neurol 1974;43(3):580–93.
102. Kajander KC, Bennett GJ. Onset of a Painful Peripheral Neuropathy in Rat : A Partial and Differential Deafferentation and Spontaneous Discharge in Aβ and Aδ Primary Afferent Neurons. J Neurophysiol 1992;68(3):734–44.
103. Slugg RM, Meyer RA, Campbell JN. Response of Cutaneous A- and C-Fiber Nociceptors in the Monkey to Controlled-Force Stimuli. J Neurophysiol 2000;83(4):2179–91.
104. Herrero JF, Laird JMA, Lopez-Garcia JA. Wind-up of spinal cord neurones and pain

sensation: Much ado about something? Prog Neurobiol 2000;61(2):169–203.
105. Schouenborg J, Sjölund BH. Activity Evoked by A- and C-Afferent Fibers in Rat Dorsal Horn Neurons and Its Relation to a Flexion Reflex. J Neurophysiol 1983;50(5):1108–21.
106. Woolf CJ, King AE. Physiology and morphology of multireceptive neurons with C-afferent fiber inputs in the deep dorsal horn of the rat lumbar spinal cord. J Neurophysiol [Internet] 1987;58(3):460–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/3655877
107. Woolf CJ, Wall PD. Chronic peripheral nerve section diminishes the primary afferent A-fibre mediated inhibition of rat dorsal horn neurones. Brain Res 1982;242(1):77–85.
108. Schoen CJ, Ablin JN, Ichesco E, et al. A novel paradigm to evaluate conditioned pain modulation in fibromyalgia. J Pain Res 2016;9:711–9.