# EPIDURAL SPINAL CORD STIMULATION FOR SENSORY RESTORATION AND PHANTOM LIMB PAIN REDUCTION IN UPPER-LIMB AMPUTEES

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## BRIEF DESCRIPTION

It is estimated that by 2020, over 2.2 million people in the United States will be living with limb loss [1]. Upper extremity amputations are predominantly traumatic injuries occurring in relatively young and active individuals and can lead to significant decreases in function and impairment in activities of daily life [2]. Additionally, phantom limb pain after amputation can lead to further impairment and withdrawal from social activities [3]. While there have been important improvements in prosthetic limb technology over the last decade, the control of these limbs remains non-intuitive and the lack of sensory feedback results in the requirement of significant visual attention during use of these devices. Further, treatment of phantom limb pain with pharmaceuticals is often ineffective and can result in significant side effects [4].

The long-term goals of this project are to provide sensory information to amputees and reduce phantom limb pain via electrical stimulation of the cervical spinal cord and spinal nerves as part of an integrated system that provides high degree-of-freedom, naturalistic control of a prosthetic limb. The spinal nerves convey sensory information from peripheral nerves to higher order centers in the brain. These structures remain intact after amputation, and electrical stimulation of the dorsal spinal nerves in individuals with intact limbs has been demonstrated to generate paresthetic sensory percepts referred to portions of the distal limb [5]-[7]. These results have yet to be extended to amputees. Further, there is recent evidence that careful modulation of stimulation parameters can convert paresthetic sensations to more naturalistic ones when stimulating peripheral nerves in amputees [8]. However, it is currently unclear whether it is possible to achieve this same conversion when stimulating the spinal nerves, and if those naturalistic sensations can have positive effects on phantom limb pain. As a first step towards those goals, in this study, we will quantify the sensations generated by electrical stimulation of the spinal nerves, study the relationship between stimulation parameters and the qualia of those sensations, and quantify the effects of that stimulation on the perception of the phantom limb and any associated pain.

During the study, two FDA-cleared spinal cord stimulator leads (Infinion 16; Boston Scientific; PMA P030017) will be placed in the cervical epidural space of ten upper-limb amputees and steered laterally towards the dorsal spinal roots under fluoroscopic guidance. This approach is essentially identical to the FDA-cleared procedure in which these devices are placed in the epidural space for treatment of intractable low back and leg pain. In that procedure, it is common clinical practice to place 2-3 leads temporarily in the epidural space through a percutaneous approach and perform a multi-day trial to determine if the patient experiences any pain reduction from spinal cord stimulation. Following the trial, the percutaneous leads are

typically removed by gently pulling on them, and the patient is referred to a neurosurgeon for permanent surgical implantation. Similarly, in this study, the device will be tunneled percutaneously through the skin and secured in place with tape. Using the stylet included with the spinal cord stimulator leads, the devices will be steered laterally under fluoroscopic guidance to target the dorsal spinal nerves. During lab experiments, the leads will be connected to an external stimulator. In clinical practice, the devices are typically left in the epidural space for one week or more, in order to determine whether patients experience any benefits from stimulation, including those with delayed onset. In this study, the devices will remain in the epidural space for less than 30 days and will be removed by gently pulling on the external portion. This extended testing period will have multiple benefits, as it will allow us: 1.) to quantify changes in the response to stimulation over time, 2.) to thoroughly explore the sensations that occur during electrical stimulation, 3.) to explore the effects of those sensations on functional use of a prosthetic limb, and 4.) to observe any delayed effects of stimulation on phantom limb pain. Throughout the study, we will perform a series of psychophysical evaluations to characterize the sensory percepts evoked by epidural stimulation, along with functional evaluations of the effects of stimulation on the ability to control a prosthetic limb. In addition, we will perform a survey to characterize changes in phantom limb sensation and pain that occur during stimulation.

Recruitment for the study will focus on trans-humeral and trans-radial amputees that are at least one year post-amputation. Subjects will have varying levels of phantom limb sensation and pain, but should have no other significant neurological disorders. It is important that these experiments be performed in amputees rather than patient-subjects, for multiple reasons, including: 1.) although the procedure for placing the leads is nearly identical to standard clinical practice, the anatomical target (spinal roots vs. dorsal columns) is slightly different, andwe believe it is unlikely that we could achieve focal percepts referred to the distal limb when stimulating the dorsal columns, which have a thick region of subdural cerebrospinal fluid, 2.) individuals with intact limbs will have ascending sensory information from the limb that may interfere with the perception of naturalistic sensations during electrical stimulation, 3.) there is recent evidence that electrical stimulation of peripheral nerves in amputees can produce naturalistic sensations referred to focal areas of the amputated limb [8]-[11], and 4.) the neurological conditions that have caused patient-subjects to seek out spinal cord stimulation may mask or interfere with the sensations that would otherwise be evoked during electrical stimulation. The risks associated with epidural spinal cord stimulation are low, and it has been estimated that these devices are placed in as many as 24,000 people per year [12]. We have included Tables I and II in the References and Other Attachment sections, which describe the most common complications of the procedure. Nearly all of those complications occur at a rate

of 5% or lower, with the exception of lead migration, which occurs at a rate of 16.6%. Quantifying the effects of lead migration on the stability of sensory percepts will be one of the endpoints that we will document throughout this study.

**PROTOCOL – Research Activities**

If an individual contacts us and is interested in this research study, we will provide that individual with information about the study (brochure, recruitment letter and/or consent form). We may conduct a phone screening to assess some of the inclusion and exclusion criteria. The initial screening can be conducted over the phone, in person, or using face-to-face video conference software, such as Skype or Facetime, for the individual's convenience. A physician-investigator will participate in this pre-screening to ensure that the subject fully understands the study procedures and risks. The purpose of this screening is to potentially eliminate the burden of travel on a potential participant who may not be eligible for the study. If any of the phone script screening questions indicate exclusion of that individual, the screening questions will stop at that point and the individual will be kindly told that they are not eligible for the study. If none of the phone script questions indicate exclusion from the study, then the individual will be asked to consider enrolling in the study. Written informed consent will be obtained after the individual has had sufficient time to consider the study procedures.

We will also use Brief Symptom Inventory 18 (BSI-18) to screen all potential participants. Given the known increased prevalence of anxiety and depressed mood in individuals with amputation and chronic pain it is our intent to use the BSI-18 to screen for mood symptoms as part of the consent process. The presence of symptoms, as reported on the BSI-18, will not exclude individuals from participating in the study - rather responses given during the BSI-18 survey will be used as a tool to guide discussion between the Principal Investigator, the study physician, and the potential subject. If an individual expresses severe depressed or anxious mood, resources will be provided to assist the individual in seeking appropriate mental health treatment.

SCREENING (after consent, prior to surgical procedures):
Once written informed consent is obtained, the subject is enrolled in the study and is assigned a unique subject ID. A physician-investigator/sub-investigator will verify the eligibility of the subject by assessing most of the eligibility criteria after consent via self-report. This will be documented on an "Eligibility Checklist" form, included in Section 2.8 of this protocol in OSIRIS.

After informed consent and after the participant's verbal self-report of eligibility criteria, an in person clinical evaluation will be performed, including a detailed history and physical examination, including a detailed musculoskeletal and neurologic examination of the arm, shoulder, and neck. Additionally, medical records may be accessed if additional information is required to perform pre-operative planning and review pertinent medical history, allergies, medications and radiology images.

- Pre-surgical procedures and device placement will occur within 6 months after the subject undergoes screening procedures. We will work with each individual to determine the optimal testing schedule. The schedule will be designed to meet study goals, and complete specific study tasks which will change over the duration of the study. The participants' engagement, and training preferences will also be considered in this process. We will photograph or videotape portions of the experimental session. Appropriate UPMC permission will be obtained as needed for any photographs or videotaping of participants. Female participants will be encouraged to avoid getting pregnant throughout the duration of the research study. Experimental procedures are described below.

- Demographic and Medical History Questionnaire:
The subject will be asked to provide basic demographic information (age, weight, height, etc.) via self-report. We will also ask questions about their medical history including the date of amputation and their current level of function, prosthetic usage, as well as recent history and current status of phantom limb sensations and pain. The subject will be asked to rate their current phantom limb pain on a scale from 0-10 using a visual analog scale. We will also ask questions related to improvement of quality of life and neuroprosthetic technology. A complete copy of the questionnaire is included in Section 2.8.

- Pre-operative labs and screening:
We will obtain pre-operative complete blood count with differential, prothrombin time and international normalized ratio (PT/INR), and partial thromboplastin time (PTT) within two weeks prior to the device placement procedure. Lab work can be performed at any UPMC facility.

-Pre-operative structural MRI with contrast:
We will perform a pre-operative MRI of the spine with contrast, to image the region where we will be placing the stimulator lead. If MR images of the region of interest already exist in the subject's medical record, these may be used instead. The MRI can be performed at any UPMC facility or at the Magnetic Resonance Research Center at UPMC Presby.

-Pre-operative high resolution structural MRI without contrast:
We may perform a second pre-operative MRI of the spine without contrast, to generate a high resolution scan of the spinal cord and spinal roots. This scan will be co-registered with a post-operative high-resolution CT scan of the neck so that we can accurately visualize the location of the leads with respect to neural tissue. This MRI will be performed at the Magnetic Resonance Research Center at UPMC Presby. We may use a neck brace during this MRI and the CT scan to ensure the subject's neck is in a similar position for both scans.

-Pre-operative antibiotics:
We will follow the standard clinical procedures to minimize the risks associated with surgical implantation or removal of electrodes. For example, antibiotic prophylaxis administration is usually initiated for the patient approximately 30 minutes before the surgery and will be maintained as directed by the study physiatrist and their clinical team. We have excluded pregnant females and those with renal failure as they may be at an increased risk for complications resulting from administration of the antibiotics. Complications or side effects usually result from prolonged dosing, rather than the single dosing that will be administered in this study. Antibiotic ointment and sterile dressings will be applied to the implantation site to minimize the risk of infection. Standard sterile surgical techniques will be followed for this study. These procedures will greatly minimize the risk of infection.

- Fluoroscopically guided lead placement procedure:
Between one and three leads will be placed in the cervical epidural space near the spinal roots. Clinical practice commonly includes placement of two or three of these leads in the epidural space. Leads will be placed in the cervical epidural space by Dr. Helm at UPMC Mercy. He will follow the following procedures, although, based on his professional judgement, he may make slight modifications to the surgical procedure to improve targeting and outcomes. A 22 gauge IV will be placed and a pre-operative antibiotic (1 mg Cefazolin) will be given 30 minutes prior to the procedure. A different appropriate broad spectrum antibiotic may be used if the subject is allergic to cefazolin. The subject will be fully awake throughout the procedure, and 1% preservative-free lidocaine will be used for local anesthesia. The subject will be taken to a fluroscopy suite, placed in a prone position with a pillow under the abdomen to decrease the normal lumbar lordosis. Each staff member involved in the procedure will sterilely scrub in with sterile gowns and gloves. The skin overlying the thoracolumbar area will be prepped and draped in aseptic fashion with Hibiclens and betadine. 1% lidocaine on a 22-gauge 3.5 inch spinal needle will be used in the skin and subcutaneous tissue for local anesthesia. For each of the leads, a 14 gauge epidural tuohy needle will be advanced through the T1-T2 space or a nearby intervertebral space to the epidural space via loss-of-resistance technique. Needle location will

be confirmed in anteroposterior (AP), lateral, and contralateral oblique fluoroscopy views. Either an 8- or 16-contact stimulator lead, which is designed to span 2-3 spinal segments, will then be advanced into the C6-C8 posterior epidural space and steered laterally using the accompanying stylet under live fluoroscopic guidance in the AP, lateral, and contralateral oblique fluoroscopy views. The lead may be connected to an additional extension lead that is included in the approved epidural stimulation system (under PMA P030017). The external portion of the lead will be connected to one of three external stimulators: 1) a Boston Scientific External Trial Stimulator included in PMA P030017 that covers the SCS system, 2) a bp Optical Isolator (manufactured by FHC, Inc), which is commonly used for clinical evaluation of neural stimulation, such as during intraoperative testing of deep brain stimulation implants, or 3) a current-controlled 32-channel neural stimulator (manufactured by Ripple, LLC), a device which, according to the manufacturer "...meets safety standards for human research studies through IRB approval for both recording and stimulation" [25]. During a brief volley of stimulation, the subject will be asked to report the region of their body over which they feel any evoked sensations. The lead placement will be iteratively adjusted based on subject feedback until the evoked sensations are referred appropriately to the amputated limb. The stylet will then be removed under live fluoroscopic guidance to ensure the lead does not move. At the discretion of Dr. Helm, sterile suture may be used to secure the lead to the skin, and a sterile dressing will be placed over the percutaneous sites. The entire procedure is expected to take approximately two hours. Immediately following lead placement and up to 5 times a week for the following 29 days, the following experimental procedures will be performed. Each testing session will be limited to no more than 8 hours, and will include breaks. Meals will also be provided.

-Post-operative antibiotics
We will follow the standard clinical procedures to minimize the risks associated with surgical implantation or removal of electrodes. For example, patients are often treated with antibiotics for the duration of the time that the leads are implanted. These procedures will greatly minimize the risk of infection.

- Psychophysical testing:
We will conduct a series of psychophysical tests to establish the relationship between epidural spinal root stimulation and sensory perception. All experiments will occur either in a patient examination room at UPMC Mercy, in testing space within the Rehab Neural Engineering Lab at the University of Pittsburgh, or in the subject's home, with trained researchers present. During psychophysical stimulation trials, an external stimulator will be connected to the SCS lead, a volley of stimulation will be performed, and the subject will be asked to respond to a set of standard psychophysical questions, as well as to provide any additional comments. Stimulus

parameters to vary include:
• Pulse amplitude (maximum of 12.7 mA per electrode; 20 mA for all electrodes simultaneously; based on guidelines in PMA P030017)
• Pulse width (maximum of 1000 us; based on guidelines in PMA P030017)
• Pulse frequency (maximum of 1200 pulses per second; based on guidelines in PMA P030017)
• Spatial effects: groups of electrodes will be stimulated simultaneously to investigate the effects of spatial summation
• Temporal effects: the pattern of stimulus pulses will be varied to model naturally occuring neural patterns (e.g. rapidly adapting or slowly adapting neurons) or engineering patterns (e.g. sinusoidal modulation)
In clinical practice, these devices are typically used throughout the day, with the exception of while driving or sleeping. As such, we do not expect that we will need to impose any upper limits on the total duration of stimulation applied throughout any experimental session or the entire study. As subjects will not be provided with a take-home stimulator, there is no risk that subjects will drive or sleep during stimulation.

Participants will be asked to identify where on their body any consciously perceived sensations were referred to, and will be asked to rate and describe various perceptual qualities of stimulation, such as naturalness, location, painfulness, and modality of sensation.

Participants may also be asked to compare two or more successive stimulus trains and describe or compare the effects of stimulation. Examples of the kinds of comparisons that participants may be asked to make include:
• Was the frequency of stimulus 1 higher or lower than stimulus 2?
• Did stimulus 2 feel stronger or weaker than stimulus 1?
• Which of stimuli 1, 2, or 3 felt like it came from the tip of the index finger?

-Mechanical and/or electrical stimulation of the limbs
In order to provide a comparison between electrical stimulation at the DRG to natural sensations, we may impart mechanical or electrical stimulation to either the residual limb or the contralateral limb, and ask subjects to document the perceived sensations.
Examples of stimulation include:
• Vibration of the skin using a mechanical tactor
• Skin indentation using von Frey hairs
• Passive movement of the limb
• Electrical stimulation of peripheral nerve or skin using adhesive gel electrodes
• Imagined or observed somatosensory stimulation

Any responses from participants about sensations they may consciously experience during these peripheral stimuli will be recorded.

-Post-operative High Resolution CT to Document Lead location:
Within one week after lead placement, we may perform a high-resolution CT scan of the cervical spine to document the 3-dimensional location of the leads with respect to bony landmarks. This scan will be co-registered with the pre-operative high resolution MRI to determine the location of the leads with respect to the spinal cord and spinal roots. We may use a neck brace during this CT and the MRI without contrast to ensure the subject's neck is in a similar position for both scans. This scan can be performed at any UPMC facility.

- Weekly X-Ray to Document Lead Migration:
Once per week, two X-ray images (AP and lateral views) of the cervical spine will be captured to document the location of the leads and any movement that may have occurred. We will attempt to correlate movement of the electrodes with any documented changes in stimulation thresholds or the types of sensory percepts that are evoked by stimulation.

- EEG and EMG studies:
Non-invasive electroencephalography (EEG) and electromyography (EMG) may be used during the study to measure neural and muscular responses to electrical stimulation. For EEG studies, electrodes will be placed on the surface of the scalp and, for EMG studies, electrodes will be placed on the surface of the skin on both the residual and contralateral limbs. Stimulation will be applied as described above.

- Effects on Phantom Limb Sensation and Pain:
Periodically throughout the experimental sessions, we will ask each subject to rate their current phantom limb pain from 0-10 on a visual analog scale, and to describe any subjective effects of stimulation on their phantom limb sensations and pain. We will also administer the pain portion of the Trinity Amputation and Prosthesis Experience Scales [26] before device placement, at least once during the <30 day testing portion of the study, and again within a month after device removal. We may also administer the McGill Pain Questionnaire before device placement, during testing, or within a month after device removal [27]. Other similar questions may be developed to best capture the effect of stimulation.

- Closed-loop Control of a Prosthesis:
During some sessions, participants will be asked to control a prosthesis with and without sensory stimulation. The prosthesis may be their own device, a device provided by the lab, or a

virtual reality hand. When physical devices are used, they will be instrumented with sensors that measure force and joint angle, and signals from those sensors will be used to modulate stimulation. Any sensors placed on the participants prosthesis will be easily attached and removed from the device (e.g. small electrogoniometers, thin strain gauges), and will be removed at the end of the session. EMG signals will be recorded from the muscles in the residual limb using surface electrodes, and participants will be asked to perform tasks that test their ability to utilize sensory stimulation such as manipulating blocks, opening a jar, or identifying the stiffness and size of various objects.

- Initial Stimulation Parameters:
When stimulation commences on an electrode that has not been previously used, stimulation parameters will be set conservatively in order to minimize the chance for eliciting an undesired response. Pulse train duration and then pulse frequency will be increased as these are the least likely to modify electrical recruitment of neurons in the vicinity of electrodes, yet may increase the detectability of the stimulus due to synaptic integration at downstream neural pathways. Pulse amplitude will be the last parameter increased as this is expected to have the most significant effect on neural recruitment and detectability.

- Electrode Impedance:
Periodically during the experimental session, we may measure the impedance of the SCS leads as a means to ensure that the device is functioning properly. This functionality is included in the Boston Scientific External Trial Stimulator and the Ripple stimulator.

- Removal of SCS Leads:
After completion of testing and no later than 29 days after device placement, the SCS leads will be removed at UPMC Mercy. To remove these devices, the subject will be positioned prone on an examination table, and using sterile technique, the lead will be gently pulled until it is removed. Visual inspection of the leads will confirm that they are intact and that no portion of the device remains under the skin. The skin will be cleaned with hibiclens and dried with sterile 4x4s, and a sterile bandage will be placed on the site. A follow-up telephone call will be made to the patient within 48 hours of their discharge to make sure they are asymptomatic. After this follow-up call no further follow up will be required after device removal unless the subject had significant reduction in pain during stimulation. In that case, the subject will be referred to a neurosurgeon for consultation on permanent implantation of a SCS device.

- After device removal, subjects will be instructed on care of the wound and provided with a list of symptoms that may occur (e.g. headache as a result of CSF leak, elevated temperature as a

result of infection). Within two days after removal, a member of the study team will contact the subject to check for any relevant symptoms. Within one month after removal, a member of the study team will contact the subject to document any long-lasting effects of stimulation on phantom limb sensations and pain.

-Possible Second Lead placement:
If excessive lead migration or premature lead breakage occurs during the study, it may be necessary to remove the leads. In this case, the subject may be offered the opportunity to undergo a second lead placement procedure, followed by an additional 29 days of testing. At a study physician's discretion, we may repeat pre-operative testing (e.g. bloodwork) before device replacement. All testing procedures will be repeated as described above and the devices will be removed within 29 days after device replacement. The replacement procedure can happen a maximum of one time per subject.

## STUDY AIMS

1. The proposed study is a pilot study to examine the perceived sensations evoked in upper-limb amputees during electrical stimulation of the spinal nerves, the effect of sensory feedback on control of a prosthetic limb, and the effect of stimulation on phantom limb pain. Results of this study will provide the foundation for future development of a neuroprosthesis to restore sensory function to individuals with upper-limb amputation, thereby increasing the functionality of prosthetic limbs and improving quality of life.

   Specific Aim 1: Characterize the sensations evoked by cervical epidural spinal nerve stimulation in upper-limb amputees, and quantify changes in those sensations over time.

   Specific Aim 1a: Quantify the threshold (minimum charge and pulse rate) stimulus required to evoke sensory percepts and neurophysiological responses (e.g. reflexive EMG responses, somatosensory evoked potentials) during epidural spinal nerve stimulation, and monitor changes in those percepts and responses over time. These results will provide insight into the design requirements for future implantable epidural spinal nerve stimulators, as well as a point of comparison among subjects and with other studies in the scientific literature. Additionally, the stability of the responses will provide

insight into the feasibility of long-term use of the device.

Specific Aim 1b: Evaluate the relationship between stimulation parameters (e.g. pulse width, pulse amplitude, stimulus location, etc) and the modality and naturalness of perceived sensations. Based on results from the literature and anecdotal experience of co-investigators on this study, we expect that cervical spinal nerve stimulation can evoke paresthesias referred to the amputated limb, but our goal is to produce meaningful (non-paresthetic) sensations. As we expect the stimulation parameters to have significant effects on the evoked sensations, we will perform standardized psychophysical examinations to determine the relationship between stimulation parameters and the perceived sensations. These tests will be repeated at multiple points throughout the study to observe any changes that occur over multiple days of use.

Specific Aim 1c: Document the subjective perception of upper-limb amputees of cervical epidural spinal nerve stimulation for restoration of sensation. To achieve widespread adoption of a sensory neuroprosthesis, it will be crucial for amputees to perceive significant value from the device. As such, we will ask each subject to provide subjective feedback on their perceived utility of the sensory feedback provided by the device.

Specific Aim 2: Characterize the effects of cervical epidural spinal nerve stimulation on phantom limb sensations and phantom limb pain in upper-limb amputees. This aim is secondary to the primary study goal in Aim 1, and as such, we will not exclude individuals that do not experience phantom limb pain. A recent study reported that as many as 85% of amputees experience phantom limb sensations and/or pain, and as such, we still believe we will encounter enough amputees with these sensations to collect preliminary data to address this aim.

Specific Aim 2a: Document changes in phantom limb sensation during and shortly after cervical epidural spinal nerve stimulation in amputees. Before placement of the spinal cord stimulator leads, we will document the subject's description of their history of perceived phantom limb. If subjects report a history of phantom limb pain, we will ask them to periodically update their perception of the limb throughout each experimental session, as well as within a month after the device has been removed.

Specific Aim 2b: Document changes in phantom limb pain during and shortly after cervical epidural spinal nerve stimulation in amputees. Before placement of the spinal cord stimulator leads, we will ask subjects about their history of perceived phantom limb

pain, and will use a visual analog scale to assess the subject's phantom limb pain. If subjects report a history of phantom limb pain, we will ask them to periodically update their pain level throughout each experimental session, as well as within a month after the device has been removed.

Specific Aim 3: Characterize changes in control of a prosthetic hand in the presence of sensory feedback. The long-term goal of this line of research is to provide sensory feedback that can be used in the control of a prosthetic hand. In this study, we will test the subject's ability to use a myoelectric prosthetic hand with and without sensory feedback provided by electrical stimulation of the spinal roots. Using either a virtual prosthetic limb or an instrumented prosthesis, stimulation of the spinal roots will be modulated based on signals recorded from the limb such as pressure at the finger tips or joint angles. In both the presence and absence of stimulation, subjects will be asked to perform tasks such as manipulating blocks, opening a jar, or identifying the stiffness and size of various objects.

2. *** Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**
   It is estimated that by 2020, over 2.2 million people in the United States will be living with limb loss [1]. Upper extremity amputations are predominantly traumatic injuries occurring in relatively young and active individuals, and can lead to significant decreases in function and impairment in activities of daily life [2]. Additionally, phantom limb pain after amputation can lead to further impairment and withdrawal from social activities [3]. While there have been important improvements in prosthetic limb technology over the last decade, the control of these limbs remains non-intuitive and the lack of sensory feedback results in the requirement of significant visual attention during use of these devices. Further, treatment of phantom limb pain with pharmaceuticals is often ineffective and can result in significant side effects [4].

   Restoration of sensory function is a crucial step in the further development of truly integrated prosthetic devices. Without provisions for sensory feedback, even the most advanced limbs, even those under ‘neural control’ will remain as numb, extracorporeal ‘tools’, rather than fully integrated functional limbs. In the upper extremity, body powered prostheses have remained the preferred choice for many amputees, in part

because users receive proprioceptive feedback from the control cable [13].

A number of recent studies have demonstrated that it is possible to restore sensation in long-term amputees by electrically stimulating the spared peripheral nerves that no longer innervate the amputated limb [8]–[11]. In these individuals, electrical stimulation has produced meaningful sensory percepts that are referred to specific locations on the amputated limb and can be modulated by varying stimulation parameters. These studies suggest that, even in the case of long-term amputation (20+ years), the neural sensory pathways remain intact and can be activated by electrical stimulation. Additionally, these studies have demonstrated that sensory restoration can improve functional control of a prosthetic limb, and allow a user to identify properties of manipulated objects (e.g. stiffness, size) without any visual feedback. The approach proposed in this study builds on these results, but aims to improve the potential for clinical translation by using FDA-cleared spinal cord stimulator leads in an off-label manner, and targeting the dorsal spinal nerves rather than the distal peripheral nerves. We believe this approach will facilitate clinical translation for the following reasons:
1) Placement of spinal cord stimulator leads is a widely accepted clinical treatment for intractable pain with very strong clinical outcomes [12], [14]. The process for placing the devices is well understood and minimally invasive. It has been estimated that over 24,000 spinal cord stimulator systems are implanted each year [12]. It is common clinical practice for patients to undergo a multi-day percutaneous trial phase, which includes 2-3 leads providing coverage for multiple vertebral segments, to determine if there is sufficient benefit to warrant a fully implanted system. In the US, this percutaneous phase typically lasts approximately 7 days [15], while in Europe, it is often extended to multiple weeks [16]. Summary of the rates of complications in the use of these devices from the Boston Scientific PMA (P030017) as well as in the cervical spine is included in Tables I and II in the References and Other Attachments section of this protocol. The rates are generally below 5% for all complications (e.g. CSF leak, infection). The most common complication, lead migration, happens in 16.6% of patients and does not add additional clinical risk to the patient, although it may reduce or eliminate the benefits of stimulation. As such, we will focus on documenting changes in the response to stimulation, and the effects of those changes on sensory perceptions and phantom limb pain over multiple days during this study. Additionally, through the use of current steering techniques, in which combinations of anodic and cathodic electrodes are combined, it may be possible to generate "virtual electrodes" that can achieve activation at regions of the nerve where no physical electrode exists. Eric Helm, the physician-coinvestigator responsible for placing these devices in this study has performed

approximately 100 spinal cord stimulator cases, with one instance of lead migration and no other significant complications.
2) The spinal nerves provide a unique target for sensory restoration in that they provide the only location in the peripheral nervous system where there is complete segregation of both cutaneous and proprioceptive afferents from motor axons, enabling activation of sensory pathways without causing muscle contractions. Unlike with stimulation of more distal peripheral nerve targets, stimulation of the DRG will not cause contamination of the myoelectric signals often used to control prosthetic limbs.
3) The cervical spinal roots provide access to primary afferents with anatomical selectivity for specific regions of the hand and arm in a compact physical volume. Unlike with peripheral nerve stimulation, which typically requires extensive dissection of the residual limb to wrap cuff electrodes around the nerves, spinal cord stimulator leads can be placed in the epidural space via minimally invasive outpatient procedures.
4) The vertebral bones provide mechanical protection that may improve neural interface stability over what is currently achieved when stimulating peripheral nerves, which undergo significant stretching and movement during limb manipulations [17], [18].

Additionally, we believe there is significant evidence that electrical stimulation of the dorsal spinal roots with spinal cord stimulator leads will produce naturalistic sensations of touch and proprioception along with a reduction in phantom limb pain. There have been multiple studies that describe the use of spinal cord stimulation for treatment of phantom limb pain [4], [19]–[22], and other pilot studies that have demonstrated that electrical stimulation of the dorsal spinal roots, including the cervical roots, with spinal cord stimulator leads can reduce limb pain from complex regional pain syndromes [5]–[7]. During these studies, electrical stimulation produced paresthesias (unnatural electrical buzzing sensations) that could be targeted to specific regions of the distal limb, and those paresthesias resulted in significant decreases in distal limb pain. In another recent study that relied on electrical stimulation of peripheral nerves to restore sensation in amputees, during initial testing of stimulation parameters, subjects consistently reported paresthesias [23]. Importantly, when stimulus trains were modulated in specific ways, such as sinusoidal modulation of pulse width, those paresthesias were converted to naturalistic sensations of touch and proprioception. These important results have encouraged us that: 1) it may be possible to use dorsal spinal root stimulation to generate paresthetic sensations referred to the amputated limb, 2) that careful modulation of stimulation parameters can convert those paresthetic sensations into more naturalistic perceptions of touch and proprioception, and 3) that stimulation of the dorsal spinal roots will result in a reduction in phantom limb pain.

Many of the techniques and technologies currently under investigation for restoration of sensory function, such as targeted sensory reinnervation [24], or implantation of penetrating electrodes in peripheral nerves [25], require extensive surgery and may have challenges with respect to maintenance of a stable interface with the nerve. While these approaches have demonstrated important preliminary examples of the potential for restoring sensation in individuals with limb amputation, they require extensive surgeries, and, in the case of electrodes that penetrate the epineurium, have yet to demonstrate a long-term stable interface with the nerve. Based on the important advantages described above (see Background section), we believe the dorsal spinal roots are a highly attractive target for restoring sensation in amputees while avoiding the limitations of these other approaches. Through minimally invasive medical procedures, and building on results of studies to treat pain via spinal cord stimulation, we believe stimulation of the dorsal spinal roots will lead to production of multiple channels of meaningful sensory restoration referred to distinct locations on the amputated limb, and will also reduce phantom limb pain.

Successful completion of these experiments will be the first steps in development of a neuroprosthesis that will have important impacts on the quality of life of individuals with upper-limb amputation (e.g. improved control of the prosthesis, heightened embodiment, increased prosthetic adoption). Additionally, restoration of sensory function may lead to a reduction in phantom limb pain. These improvements in prosthetic function may lead to significantly increased use of prosthetic devices for performance of activities of daily living. Further, the results of this study will likely be applicable to other applications such as lower-limb sensory neuroprostheses, and treatment of peripheral neuropathies that occur with diabetes and aging.

**3.** The proposed study is a pilot study to examine the perceived sensations evoked in upper-limb amputees during electrical stimulation of the spinal nerves, the effect of sensory feedback on control of a prosthetic limb, and the effect of stimulation on phantom limb pain. Results of this study will provide the foundation for future development of a neuroprosthesis to restore sensory function to individuals with upper-limb amputation, thereby increasing the functionality of prosthetic limbs and improving quality of life.

Specific Aim 1: Characterize the sensations evoked by cervical epidural spinal nerve stimulation in upper-limb amputees, and quantify changes in those sensations over time.

Specific Aim 1a: Quantify the threshold (minimum charge and pulse rate) stimulus required to evoke sensory percepts and neurophysiological responses (e.g. reflexive EMG responses, somatosensory evoked potentials) during epidural spinal nerve stimulation, and monitor changes in those percepts and responses over time. These results will provide insight into the design requirements for future implantable epidural spinal nerve stimulators, as well as a point of comparison among subjects and with other studies in the scientific literature. Additionally, the stability of the responses will provide insight into the feasibility of long-term use of the device.

Specific Aim 1b: Evaluate the relationship between stimulation parameters (e.g. pulse width, pulse amplitude, stimulus location, etc) and the modality and naturalness of perceived sensations. Based on results from the literature and anecdotal experience of co-investigators on this study, we expect that cervical spinal nerve stimulation can evoke paresthesias referred to the amputated limb, but our goal is to produce meaningful (non-paresthetic) sensations. As we expect the stimulation parameters to have significant effects on the evoked sensations, we will perform standardized psychophysical examinations to determine the relationship between stimulation parameters and the perceived sensations. These tests will be repeated at multiple points throughout the study to observe any changes that occur over multiple days of use.

Specific Aim 1c: Document the subjective perception of upper-limb amputees of cervical epidural spinal nerve stimulation for restoration of sensation. To achieve widespread adoption of a sensory neuroprosthesis, it will be crucial for amputees to perceive significant value from the device. As such, we will ask each subject to provide subjective feedback on their perceived utility of the sensory feedback provided by the device.

Specific Aim 2: Characterize the effects of cervical epidural spinal nerve stimulation on phantom limb sensations and phantom limb pain in upper-limb amputees. This aim is secondary to the primary study goal in Aim 1, and as such, we will not exclude individuals that do not experience phantom limb pain. A recent study reported that as many as 85% of amputees experience phantom limb sensations and/or pain, and as such, we still believe we will encounter enough amputees with these sensations to collect preliminary data to address this aim.

Specific Aim 2a: Document changes in phantom limb sensation during and shortly after cervical epidural spinal nerve stimulation in amputees. Before placement of the spinal cord stimulator leads, we will document the subject's description of their history of perceived phantom limb. If subjects report a history of phantom limb pain, we will ask them to periodically update their perception of the limb throughout each experimental session, as well as within a month after the device has been removed.

Specific Aim 2b: Document changes in phantom limb pain during and shortly after cervical epidural spinal nerve stimulation in amputees. Before placement of the spinal cord stimulator leads, we will ask subjects about their history of perceived phantom limb pain, and will use a visual analog scale to assess the subject's phantom limb pain. If subjects report a history of phantom limb pain, we will ask them to periodically update their pain level throughout each experimental session, as well as within a month after the device has been removed.

Specific Aim 3: Characterize changes in control of a prosthetic hand in the presence of sensory feedback. The long-term goal of this line of research is to provide sensory feedback that can be used in the control of a prosthetic hand. In this study, we will test the subject's ability to use a myoelectric prosthetic hand with and without sensory feedback provided by electrical stimulation of the spinal roots. Using either a virtual prosthetic limb or an instrumented prosthesis, stimulation of the spinal roots will be modulated based on signals recorded from the limb such as pressure at the finger tips or joint angles. In both the presence and absence of stimulation, subjects will be asked to perform tasks such as manipulating blocks, opening a jar, or identifying the stiffness and size of various objects.

4. *** Describe the relevant prior experience and gaps in current knowledge including preliminary data. Provide for the scientific or scholarly background for, rationale for, and significance of the research based on existing literature and how it will add to existing knowledge:**
   It is estimated that by 2020, over 2.2 million people in the United States will be living with limb loss [1]. Upper extremity amputations are predominantly traumatic injuries occurring in relatively young and active individuals, and can lead to significant decreases in function and impairment in activities of daily life [2]. Additionally, phantom limb pain after amputation can lead to further impairment and withdrawal from social activities [3]. While there have been important improvements in prosthetic limb technology over the last decade, the control of these limbs remains non-intuitive and the lack of sensory feedback results in the requirement of significant visual attention during use of these devices. Further, treatment of phantom limb pain with pharmaceuticals is often ineffective and can result in significant side effects [4].

   Restoration of sensory function is a crucial step in the further development of truly integrated prosthetic devices. Without provisions for sensory feedback, even the most advanced limbs, even those under ‘neural control’ will remain as numb, extracorporeal ‘tools’, rather than fully integrated functional limbs. In the upper extremity, body powered prostheses have remained the preferred choice for many amputees, in part because users receive proprioceptive feedback from the control cable [13].

   A number of recent studies have demonstrated that it is possible to restore sensation in

long-term amputees by electrically stimulating the spared peripheral nerves that no longer innervate the amputated limb [8]–[11]. In these individuals, electrical stimulation has produced meaningful sensory percepts that are referred to specific locations on the amputated limb and can be modulated by varying stimulation parameters. These studies suggest that, even in the case of long-term amputation (20+ years), the neural sensory pathways remain intact and can be activated by electrical stimulation. Additionally, these studies have demonstrated that sensory restoration can improve functional control of a prosthetic limb, and allow a user to identify properties of manipulated objects (e.g. stiffness, size) without any visual feedback. The approach proposed in this study builds on these results, but aims to improve the potential for clinical translation by using FDA-cleared spinal cord stimulator leads in an off-label manner, and targeting the dorsal spinal nerves rather than the distal peripheral nerves. We believe this approach will facilitate clinical translation for the following reasons:

1) Placement of spinal cord stimulator leads is a widely accepted clinical treatment for intractable pain with very strong clinical outcomes [12], [14]. The process for placing the devices is well understood and minimally invasive. It has been estimated that over 24,000 spinal cord stimulator systems are implanted each year [12]. It is common clinical practice for patients to undergo a multi-day percutaneous trial phase, which includes 2-3 leads providing coverage for multiple vertebral segments, to determine if there is sufficient benefit to warrant a fully implanted system. In the US, this percutaneous phase typically lasts approximately 7 days [15], while in Europe, it is often extended to multiple weeks [16]. Summary of the rates of complications in the use of these devices from the Boston Scientific PMA (P030017) as well as in the cervical spine is included in Tables I and II in the References and Other Attachments section of this protocol. The rates are generally below 5% for all complications (e.g. CSF leak, infection). The most common complication, lead migration, happens in 16.6% of patients and does not add additional clinical risk to the patient, although it may reduce or eliminate the benefits of stimulation. As such, we will focus on documenting changes in the response to stimulation, and the effects of those changes on sensory perceptions and phantom limb pain over multiple days during this study. Additionally, through the use of current steering techniques, in which combinations of anodic and cathodic electrodes are combined, it may be possible to generate "virtual electrodes" that can achieve activation at regions of the nerve where no physical electrode exists. Eric Helm, the physician-coinvestigator responsible for placing these devices in this study has performed approximately 100 spinal cord stimulator cases, with one instance of lead migration and no other significant complications.

2) The spinal nerves provide a unique target for sensory restoration in that they provide the only location in the peripheral nervous system where there is complete segregation of both cutaneous and proprioceptive afferents from motor axons, enabling activation of sensory pathways without causing muscle contractions. Unlike with stimulation of more distal peripheral nerve targets, stimulation of the DRG will not cause contamination of the myoelectric signals often used to control prosthetic limbs.

3) The cervical spinal roots provide access to primary afferents with anatomical

selectivity for specific regions of the hand and arm in a compact physical volume. Unlike with peripheral nerve stimulation, which typically requires extensive dissection of the residual limb to wrap cuff electrodes around the nerves, spinal cord stimulator leads can be placed in the epidural space via minimally invasive outpatient procedures.
4) The vertebral bones provide mechanical protection that may improve neural interface stability over what is currently achieved when stimulating peripheral nerves, which undergo significant stretching and movement during limb manipulations [17], [18].

Additionally, we believe there is significant evidence that electrical stimulation of the dorsal spinal roots with spinal cord stimulator leads will produce naturalistic sensations of touch and proprioception along with a reduction in phantom limb pain. There have been multiple studies that describe the use of spinal cord stimulation for treatment of phantom limb pain [4], [19]–[22], and other pilot studies that have demonstrated that electrical stimulation of the dorsal spinal roots, including the cervical roots, with spinal cord stimulator leads can reduce limb pain from complex regional pain syndromes [5]–[7]. During these studies, electrical stimulation produced paresthesias (unnatural electrical buzzing sensations) that could be targeted to specific regions of the distal limb, and those paresthesias resulted in significant decreases in distal limb pain. In another recent study that relied on electrical stimulation of peripheral nerves to restore sensation in amputees, during initial testing of stimulation parameters, subjects consistently reported paresthesias [23]. Importantly, when stimulus trains were modulated in specific ways, such as sinusoidal modulation of pulse width, those paresthesias were converted to naturalistic sensations of touch and proprioception. These important results have encouraged us that: 1) it may be possible to use dorsal spinal root stimulation to generate paresthetic sensations referred to the amputated limb, 2) that careful modulation of stimulation parameters can convert those paresthetic sensations into more naturalistic perceptions of touch and proprioception, and 3) that stimulation of the dorsal spinal roots will result in a reduction in phantom limb pain.

Many of the techniques and technologies currently under investigation for restoration of sensory function, such as targeted sensory reinnervation [24], or implantation of penetrating electrodes in peripheral nerves [25], require extensive surgery and may have challenges with respect to maintenance of a stable interface with the nerve. While these approaches have demonstrated important preliminary examples of the potential for restoring sensation in individuals with limb amputation, they require extensive surgeries, and, in the case of electrodes that penetrate the epineurium, have yet to demonstrate a long-term stable interface with the nerve. Based on the important advantages described above (see Background section), we believe the dorsal spinal roots are a highly attractive target for restoring sensation in amputees while avoiding the limitations of these other approaches. Through minimally invasive medical procedures, and building on results of studies to treat pain via spinal cord stimulation,

we believe stimulation of the dorsal spinal roots will lead to production of multiple channels of meaningful sensory restoration referred to distinct locations on the amputated limb, and will also reduce phantom limb pain.

Successful completion of these experiments will be the first steps in development of a neuroprosthesis that will have important impacts on the quality of life of individuals with upper-limb amputation (e.g. improved control of the prosthesis, heightened embodiment, increased prosthetic adoption). Additionally, restoration of sensory function may lead to a reduction in phantom limb pain. These improvements in prosthetic function may lead to significantly increased use of prosthetic devices for performance of activities of daily living. Further, the results of this study will likely be applicable to other applications such as lower-limb sensory neuroprostheses, and treatment of peripheral neuropathies that occur with diabetes and aging.

## Power Analysis

This is the first study to evaluate sensory perceptions during spinal cord stimulation in amputees. Because this is a pilot study, we feel that it is appropriate to begin with a small sample size in this initial investigation.

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