Investigating mechanisms underlying spinal cord stimulation efficacy using virtual reality and full body illusion

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Abstract

Epidural spinal cord stimulation (SCS) is an approved treatment for truncal and extremity neuropathic pain. The mechanisms underlying the efficacy of SCS are unknown. Recent advances in cognitive neuroprosthetics using virtual reality allow for modulation of body perception and bodily experience, which has also been shown to modulate pain perception. The present research proposal plans to merge expertise in cognitive neuroprosthetics from the laboratory of cognitive neuroscience of Prof. Blanke with neuromodulation techniques from the Center for Neuromodulation directed by Prof. Rezai, in order to test the analgesic properties of the combination of epidural spinal cord stimulation with a new system of multisensory stimulation based on virtual and enhanced reality (i.e., neuro-visual stimulation). We propose to study this hypothesis prospectively in 25 patients with implanted SCS systems for the treatment of chronic neuropathic pain. Primary outcomes will be pain reduction (based on subjective, functional and physiological measures) and changes in body perception (based on subjective and objective measures). The present study will generate a proof-of-concept for the application of neuro-visual stimulation for the treatment of chronic pain and will form the basis for future NIH funding application.

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Study hypothesis

We hypothesize that SCS combined with virtual leg illumination (provided through a wearable headset (OculusRift, OculusVR, Irvine, CA) and a custom-designed virtual reality leg scenario) will lead to controlled analgesia induction, boosting analgesic effects obtained with standard SCS treatments and will further be associated with changes in the perception of the affected body part.

Specific Aims and predictions

1. To quantify pain reduction induced by the combination of SCS and neuro-visual stimulation (using virtual reality) in a significant cohort of patients with implanted SCS for the treatment of chronic neuropathic pain.
2. To quantify changes in body perception.

To achieve these aims, we will compare the effects of 3 different experimental conditions of neuro-visual stimulation on different pain and body perception measures (see below): Condition 1 - SCS ON and visual illumination via virtual reality of the body part where patients perceive paresthesia due to SCS (congruent neuro-visual stimulation); Condition 2 - SCS ON and visual illumination of a another sector of the visual field without paresthesia (incongruent neuro-visual stimulation); Condition 3 – SCS OFF and illumination of the congruent body part (baseline condition). We predict stronger effects in Condition 1, properly combining SCS and virtual reality stimulation. The comparison between condition 1 and 3 will measure the effect of SCS, while controlling for visual stimulation; the comparison between condition 1 and condition 2 will measure the additional benefit induced by multisensory stimulation in virtual reality. Primary outcomes of the treatment will be pain reduction, as quantified by means of subjective (visual analogue scales and questionnaires), functional (scales and assessments) and physiological measures (changes in heart rate variability) measures. Secondary outcomes will be changes in body perception, as assessed by questionnaires and behavioral tasks.

Significance of problem

Chronic pain is a major public health problem with implications for high health care costs, lost productivity and an estimated financial burden of $500 billion.[1,2] It leads to deterioration in overall health of individual suffering from pain.[3] Epidural SCS is an FDA approved therapy for patients with refractory neuropathic pain associated with failed back syndrome (FBS) and complex regional pain syndrome type-1 (CRPS-1).[4,5] Conventionally 40-60 Hz stimulation frequency is used for producing paresthesias in the affected body region ('coverage'). Initially paresthesias were thought to be critical for pain control (Gate control theory).[6] However pain control can also be achieved with the non-paresthesia producing kilohertz frequency stimulation (1-10 KHz).[7] Overall the mechanisms underlying SCS therapy are unclear.[8] Investigations into the mechanisms underlying SCS efficacy are desirable to optimize outcomes and guide stimulation parameters (electrode contacts, amplitude, pulse width etc.) and integration with other technologies.

Chronic pain is often frequently associated with a distorted representation of one's own body and of the painful body parts in particular. Current accounts in neuroscience posit that a congruent perception of one's body, including the feeling of owing and controlling the body, depends on the constant integration of online multisensory and motor information from the body [9,10]. Accordingly, research in cognitive neuroscience has developed powerful approaches to experimentally modulate body perception and experience (i.e. bodily self-consciousness (BSC)) through the administration of multisensory or sensorimotor stimulation regarding the appearance and location of a body part, for example a hand in the rubber hand illusion (RHI[11]), legs in the virtual leg illusion (VLI[12]), face in the enfacement illusion [13,14] or whole body in the full body illusion (FBI[15,16]). These paradigms, especially if implemented into VR and robotic set-ups [28], are efficient at transiently inducing

illusory tactile perceptions and ownership for artificial or virtual body parts or the whole body, and have shown efficacy in neurorehabilitation [17], for example improving the sense of ownership for hand prosthesis in amputees [18], restoring tactile awareness on the hand in patients with tetraplegia [19], and, crucially for the present project, inducing selective analgesic effects [20-24].

Innovations

In the present research proposal, we propose to link expertise from École Polytechnique Fédérale de Lausanne (EPFL) on analgesic effects of experimentally induced alterations of body perception based on virtual and enhanced reality technology with neuromodulation expertise at OSU in treating pain in patients with implanted SCS. The aim is to develop novel technological solutions for pain management in patients with neuropathic leg pain. The virtual reality technology we propose to use comes from EPFL's latest innovations with the *Reality Substitution Machine* **(**RealiSM; http://lnco.epfl.ch/realism). This technology involves recording and immersion in 360° stereoscopic video environment using a commercially available headset (Oculus Rift, Oculus,VR, Irvine, CA). This headset has stereoscopy, depth integration, visual blending capabilities. The RealiSM software enables the integration of one's own body as seen in a first person perspective through a. Compared to more classical virtual reality systems, RealiSM allows sophisticated experimental control of meaningful real-life scenarios in which users are dynamically and seamlessly integrated. Of particular interest for the present project, the visual feedback over subjects' trunk, legs, arms and hands can be manipulated experimentally with special effects and overlays. This study might have tremendous clinical and translational implications for advancing future patient care. If successful, the paradigm tested here will 1) offer new technical approach to modulate body perception 2) to increase patient's life quality by restoring own body perception and 3) potentially to lead to new analgesic treatments that might be used to treat different chronic pain disorders.

Approach

This pilot prospective cohort study will enroll patients (n=25) who have already undergone implantation of SCS electrode and internal pulse generator (IPG) for the treatment of chronic pain due to FBS or CRPS-1. All eligible patients will undergo a one-day visit for the VR session. We will investigate leg embodiment and leg analgesic effects during SCS integrated with different patterns of virtual leg illumination (see Figure 1A-B-C). Expected duration of this visit is approximately 5 hours (including an intervening 2 hour washout period).

Methods

Population

Participants in this study will be adults who have already undergone implantation of SCS for the treatment of their pain conditions. The study involves no further treatment or intervention. Subjects will be approached for participation in this study during their routine postoperative clinical visit to the Center for Neuromodulation at the Ohio State University (OSU). Patients will be informed about the scope of this study and our aim of investigating basic brain functions in patients who have undergone SCS implantation. Patients will be informed about the study procedures, duration of participation. We wish to enroll 25 patients for this study. Although a power calculation for this type of observational study is not feasible, collecting data on 25 participants will allow us to investigate several patient populations and be able to capture heterogeneity reasonably well.

Inclusion Criteria

1. Age 18–and older at the time of enrollment
2. patients experiencing lower extremity pain e.g. neuropathy, CRPS type-1, neuropathic leg pain following FBS etc.'[4,25]
3. Patients who have implanted epidural SCS
4. The SCS implantation for at least three months prior to enrollment

5. Patients willing and able to provide informed consent

Exclusion criteria

1. Patients who are unable to effectively or efficiently communicate for example patients suffering from speech deficits (dysarthria, aphasia) or are non-English speaking.
2. Patients with history of prior cranial surgery, significant brain lesions for example intracranial tumors, strokes etc.
3. Evidence of untreated psychiatric disorders or drugs/alcohol abuse.
4. History of seizures

Equipment: **(Figure 1.)**

The VR system includes a head mounted display (Oculus Rift development Kit 2 (DK-2), Oculus VR, Irvine, CA),. Patients will be comfortably seated while concurrently observing in first person perspective their own legs through the head-mounted display and captured on line via a camera. The RealiSM interface will allow for the integration of online recording of one's own body and virtual illumination of different parts of the visual field, depending on the different experimental conditions, as well as the presentation of the different outcomes measures. Device specifics are included with this submission.

Study Procedures **(Figure 2)**

Consent

Research physicians or coordinators at the Center for Neuromodulation, OSU, other than the treating physician, will obtain consent from patients during clinical evaluation after implantation of SCS system. The patient will have the opportunity to be able to have time beyond the routine clinical visit to consider participation, and can provide consent upon his/her return for the subsequent standard of care clinical follow-up. Refusal to participate will not change the care of these patients at the Center of Neuromodulation, OSU.

Study visits

This study involves a total of 2 visits.

Baseline Clinical Evaluation

Upon obtaining informed consent, the patients will undergo clinical evaluation prior to receiving neuro-visual stimulation. During this evaluation the following variables will be determined -

1. Confirm 'optimal' stimulation efficacy by performing clinical evaluation with ON and OFF SCS conditions. This is done to ensure participants are receiving optimal pain control. This also ensures participants are all receiving equivalent amounts of pain control as they begin the virtual reality sessions.
2. Assess the rapidity of stimulation-induced clinical improvement
3. Assess the wash out period of stimulation-induced clinical improvement
4. Identify the location (accuracy and reliability) of parasthesias induced by SCS.

Patients will be requested to turn the SCS OFF the at least 2 hours before their arrival for the clinical visit. The dose and frequency of the pain medications will be left unchanged (SCS OFF, meds ON state). The clinical condition will be assessed with the 10-point Visual Analogue Scale (VAS). The SCS will then be switched to the optimal stimulation parameters (SCS ON, meds ON state) and the clinical condition evaluated at 5 and 10 minutes. The efficacious stimulation parameters (electrode contacts, pulse width, frequency and amplitude) will be noted for future reference. The 'optimal' stimulation efficacy is defined as maximal improvement improvement between the SCS OFF and SCS ON state achieved. The SCS will then be switched

to OFF state and the wash-out period will be assessed using VAS. Once this baseline clinical evaluation is completed, patients will be switched to efficacious stimulation paradigm.

VR session (Figure 2)

Similar to the baseline clinical visit, patients will be requested to turn off their SCS at least 2 hours before experiment. The evaluation battery will include the following –

1. Visual Analogue Scale
2. Oswestry Disability Index
3. Vital signs including pulse, blood pressure, respiratory rate, oxygen saturation, temperature and heart rate variability
4. Peri-personal space task
5. Embodiment questionnaire

Modulation of leg embodiment will be performed using a simple block design to study the SCS ON states with leg illumination paradigm in the following three conditions:

Condition 1: SCS ON and congruent leg illumination (neuro-visual)

Condition 2: SCS ON and incongruent leg illumination (SCS only)

Condition 3: SCS OFF and congruent leg illumination (vision only)

Condition 1 represents the target condition, combining SCS and virtual reality stimulation, i.e. neuro-visual stimulation. Condition 2 represents the effects of SCS stimulation only, while condition 3 represents the effects of visual stimulation only. The comparison between condition 1 and 3 will measure the effect of SCS, while controlling for visual stimulation; the comparison of condition 1 and condition 2 will measure the additional benefit induced by multisensory stimulation in virtual reality.

Overall each condition will be about 1 hour in duration. Taking into account the washout period (2 hours) between ON and OFF conditions, the whole experiment will be approximately 5 hours long, which will be distributed along a whole day visit, to avoid fatigue and between conditions carry-over effects. The patient will be encouraged to report the development of any discomfort or symptoms (dizziness, headache etc.) after and during each session. If a patient reports discomfort, the VR session will be immediately stopped.

Data management

Data from source documents will be de-identified and stored in the CranialCloud™. CranialCloud™ is a "cloud-based" data capture platform developed by Neurotargeting, Inc. Through a rigorous risk assessment process, it has been approved by the OSUWMC Office of Information Technology and its Security Team, for the capture of clinical and/or research data inclusive of Protected Health Information (PHI) fields. A Business Authorization Agreement has been fully executed between the OSU Wexner Medical Center and Neurotargeting, Inc., regarding the clinical data management services, use and governance of CranialCloud™. All data is stored in a HIPAA compliant database system, is encrypted and is not visible to the administering team. The system automatically deidentifies all data entered and links it to an identification value. A separate database within the CranialCloud system is mantained with patient identifiers and the associated key.

Access to individual patient data within the database can be done through a secure login linked to the person's qualifications to access PHI. The list of persons authorized to view PHI (for example, treating

physicians, members of the surgical team, and specific research associates) will be determined by the study PIs. Once in the database, patient identifiers will be codified and not accessible for any queries outside of those listed above. Non-patient specific information can be analyzed, sorted or queried in response to specific statistical questions related to this protocol only by any investigator of the research team or other authorized person for this protocol. If subjects no longer wish to have their data tracked within the atlas, they can call the study team and have their name removed from any further data collection from the time of notification forward. All previously collected data will still be accessible and not expunged from the database.

Outcomes analysis

Analysis of the data obtained during different study conditions will be done offline, and will involve a wide variety of analytical and computation techniques to determine the best method/technique that can robustly detect the statistical differences.

Outcome measures

Analgesic effects

We will assess the analgesic effects of neuro-visual stimulation using 1) subjective pain perception (pain rating) (Huskisson 1974), 2) functional impact (Oswestry Disability Index)[26] 3) objective physiological heart changes (Heart rate variability, HRV)[27] measured by Visimobile monitoring system as described below.

Pain rating

Subjective pain perception will be measured by pain ratings on a 10cm visual continuous analog scale (VAS). Patients will be ask to rate their pain, ranging from “no pain” (bottom part of the scale) to “the worst imaginable pain” (upper part of the scale) (Huskisson 1974).

Functional impact

Oswestry Disability Index is a commonly used validated scale to quantify disability associated with back pain[26]. This scale measures the impact of back pain in ten different domains of life with 0 signifying no disability and 100 implying maximum disability.

Vital signs

The vital signs (pulse, blood pressure, respiratory rate, oxygen saturation, temperature) will be recorded using non-invasive monitoring with Visimobile monitoring system.

Heart rate variability (HRV)

HRV will be used as an objective physiological measure of analgesia, as low a HRV is associated with chronic pain and increase in HRV have been repetitively associated to pharmacologically-induced analgesia[27,28]. ECG signals will be acquired online during the whole duration of the treatment and Inter-beat intervals will be calculated as the time between two successive R spikes. For each subject and each condition, we will calculate the square root of the mean squared differences of successive beats intervals (RMSSD), which estimates the short-term components of HRV and is commonly used over short recording periods[29].

Body perception

We will use validated questionnaires from EPFL in order to investigate induced changes in leg perception and ownership. In particular, we will assess: 1) feeling of ownership towards the leg shown in the virtual reality set-up (leg ownership); 2) tactile sensations felt on the virtual legs, depending on the different conditions of SCS and visual stimulation. Patients will be asked to indicate how much they agreed with each item using a 7-point colored vertical Likert scale ranging from 0 (complete disagreement, the bottom extreme, red point) to +6 (complete agreement, the top extreme, green point).

Peri-personal space

The peripersonal space task will be used as an implicit measure of changes in body perception. We will use a dynamic visuo-tactile interaction task, implemented by means of the RealiSM technology, which measures the strength of multisensory integration within the space surrounding the leg. The rationale of the approach is that tactile stimuli on one's own body more effectively interact with external (visual) stimuli, when these are presented within the peripersonal space. Thus, the strength of multisensory interaction close to a part of the body can be considered on a measure of how much that body part is perceived as one's own[30,31]. Subjects will sit on a chair and wear the virtual reality headset through which they will be able to see their own legs. A virtual ball will be showed as approaching the participant's legs. Along with the visual stimulus, participants will receive a tactile stimulation on their leg, delivered by means of a tactile stimulator at different temporal delays from the virtual stimulus appearance. This way, tactile stimulation will be associated with visual stimulation, at a different distance from the body. Trials with tactile stimulation only, with no virtual objects, will be also administered as a baseline condition. Participants will be asked to respond by button press as quickly as possible to the tactile stimulus. RT to tactile simulation when the virtual stimulus is perceived at a different distance will be compared with RT to tactile stimulation only in order to measure visuo-tactile interaction and its modulation as a function of the spatial location of the visual stimulus.

Compensation

Patients will be compensated for participating $100 each visit for their participation in this study.

Ethics

None of the OSU investigators involved this study have any financial or academic conflicts of interest that influence their participation in this study. Patients will be carefully selected and all study procedures and protocols precisely in line with the final active protocol as approved by the OSU Biomedical IRB. Protected Health Information (PHI) of participants will be captured into the secure and password protected REDCap database but the final data set will be de-identified for statistical analysis and manuscript preparation.

Milestones

1. Clinical study – 24 months
2. Data analysis – 6 month
3. Report preparation – 3 month
4. Journal submission and publication – 3 months

Preliminary data regarding bodily self-consciousness in pain patients

EPFL has recently finished two clinical studies where we manipulated multisensory bodily signals to reduce chronic pain. In a first study with patients with thoracic spinal cord injury we found that analgesia can be induced in highly specific experimental conditions already following short periods of multisensory stimulation (Pozeg et al., in preparation). In a second experiment we exposed 24 patients suffering from CRPS to multisensory stimulation through a physiologically-enhanced virtual reality system, in which patients were presented with a virtual hand flashing in synchrony (or out of synchrony in the control condition) with their own online-detected heartbeat. Pain rating was significantly reduced following synchronous stimulation compared to asynchronous stimulation. Moreover, we used force strength and HRV, respectively, as functional and physiological measures of pain. Both increased with synchronous stimulation as compared to control condition (i.e. asynchronous), similarly as previously reported after analgesics administration[28,32]. Taken together, these results support the idea that multisensory modulation of bodily inputs might be used for new analgesic rehabilitation programs. The present research protocol is aimed at extending and boosting the beneficial effects of multisensory virtual reality treatments and spinal cord stimulation (SCS) in patients with chronic leg pain.

Safety considerations

There is no published data interfacing virtual reality device and Spinal cord stimulation. However, at the EPFL, there are two studies, approved by the Swiss Cantonal Ethical Committee involving the same virtual reality set up we aim to use in the present project and neural stimulation. The first project involves Transcranial Magnetic stimulation to the primary motor cortex (Ambitione Project from Swiss National Science Foundation to Dr Bassolino, Prof. Blanke), while the second project includes peripheral stimulation of the residual median nerve in amputee patients by means of intrafscicular electrodes (Raspopovic S, et al., Restoring natural sensory feedback in real-time bidirectional hand prostheses. Sci Transl Med. 2014 Feb 5;6(222):222ra19). No compatibility issues have been reported between the virtual reality device and the neural stimulation devices.

We believe that the use of VR setup in patients with implanted SCS poses non-significant risks. The spinal cord stimulator and the Oculus Rift Virtual Reality headset do not interact with each other. The SCS device will be activated and controlled manually via its standard and approved external controller. The signal will be recorded and stored in a computer and this signal will be used to control and trigger the stimuli for the virtual reality device. Physically these two systems are placed in two different body regions. The spinal cord stimulator is implanted in the thoraco-lumbar spine with the battery pack in the gluteal region. The VR headset is positioned on the head. Further the two systems are in different body compartments/spaces. The spinal cord stimulator electrode is in the epidural compartment while the extension and the battery is in the subcutaneous tissue. The VR headset is external to the body. The VR headset does not produce any electrical or magnetic stimulation during its use. In fact the skin interface of the VR headset contains insulated material. Also the outer covering of the implanted battery pack is insulated which does not allow interference from outside electrical equipment like cell phone, laptop computer and microwave. Overall the VR headset does not pose additional risk in patients with implanted SCS e.g. no more than using a cell phone in day today life.

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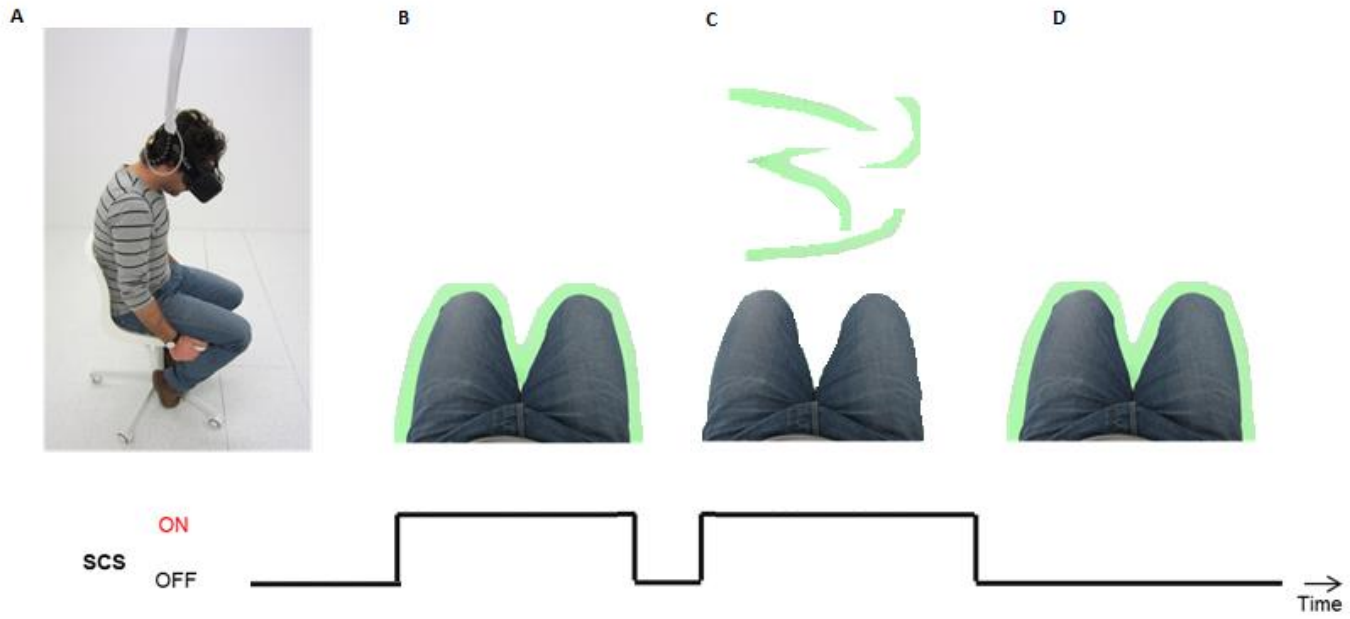

Figure 1. SCS mediated visuo-tactile stimulation. An illustration of the experimental setup is shown. During the experiment, SCS mediated tactile stimulation will be coupled with a visual stimulus on a head mounted display where he legs of the patients will be represented with the illumination of the same skin region where SCS mediated somatosensory sensation (induced-paraesthesia) will be experienced (A). Modulation of legs embodiment will be performed using a simple block design to study the SCS ON states with leg illumination paradigm in the following three conditions. Condition 1 represents the target condition, combining SCS and virtual reality stimulation, i.e. neuro-visual stimulation (B). Condition 2 represents the effects of SCS stimulation only (C), while condition 3 represents the effects of visual stimulation only (D).

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A.

Stimulator → / Illumination ↓	Paresthesia	No paresthesia
Congruent	Condition1	Condition 3
Incongruent	Condition 2	

Combined effect = Condition 1
Stimulation effect = Condition 2
Illumination effect = Condition 3

B.

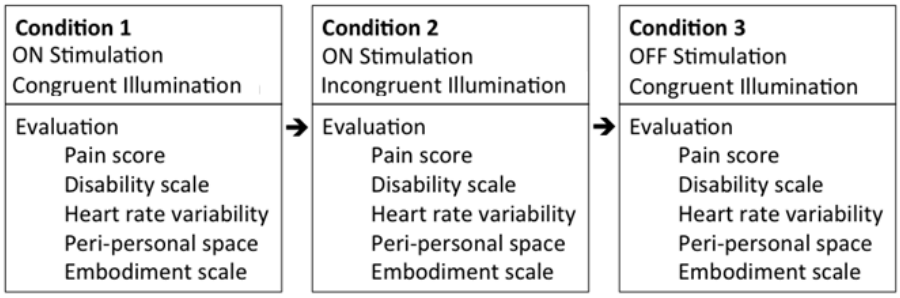

Figure 2. Study design and procedures. A. The conditions for combined stimulation and illumination. The condition 1 involves SCS ON and congruent leg illumination (target condition) while condition 2 is designed with SCS ON and incongruent leg illumination and condition 3 as SCS OFF and congruent leg illumination. B. The sequence of various study conditions. The patients will report with stimulator OFF and undergo evaluation for condition 1 followed by condition 2. A washout period of 2 hours will be allowed between condition 2 and 3.

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