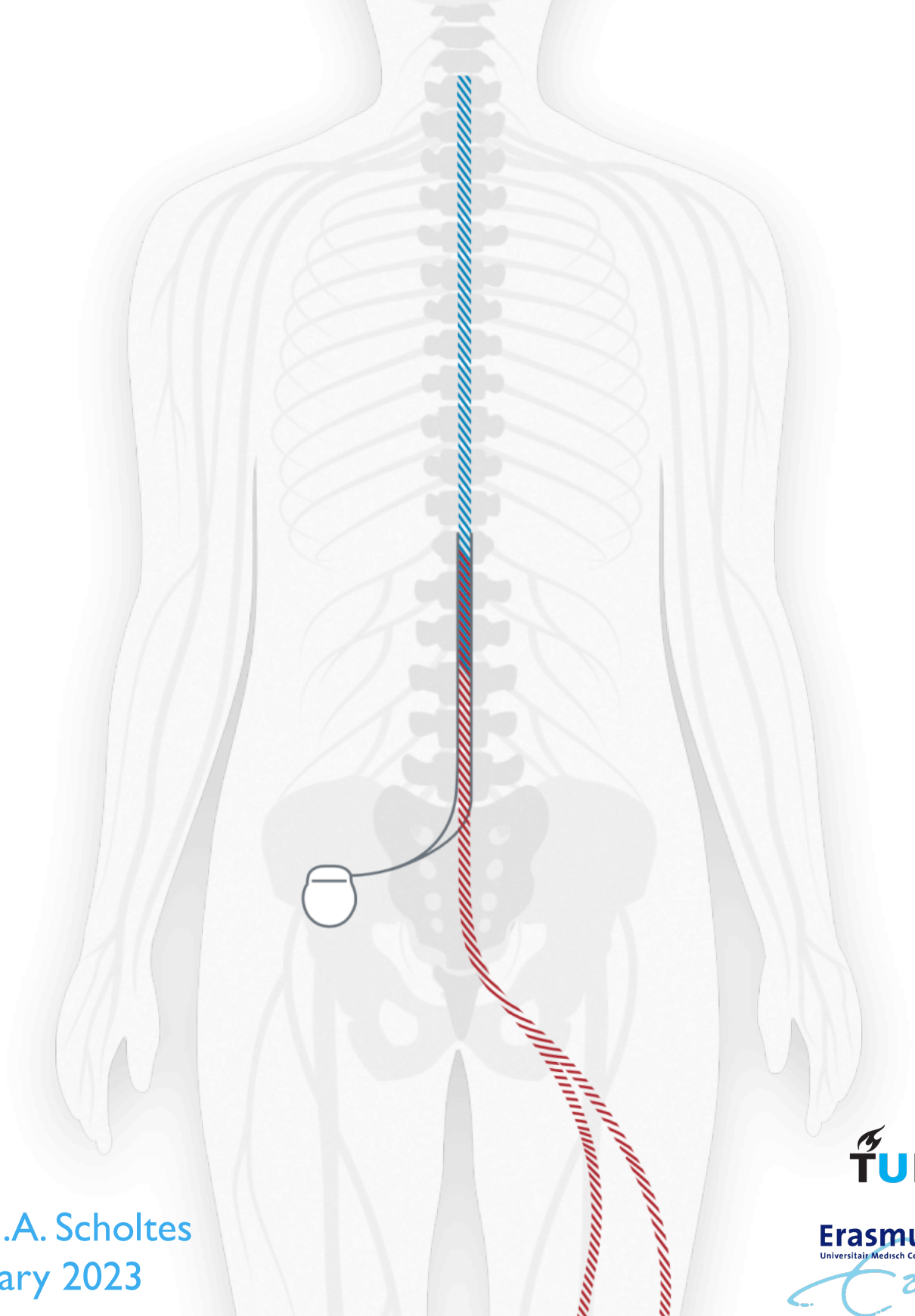
Intraoperative **evoked compound action potential** measurements in the **dorsal column** to guide **spinal cord stimulation** lead placement: a feasibility study



M.M.A. Scholtes
January 2023

TU Delft
Erasmus MC
Universitair Medisch Centrum Rotterdam

INTRAOPERATIVE EVOKED COMPOUND ACTION POTENTIAL MEASUREMENTS IN THE DORSAL COLUMN TO GUIDE SPINAL CORD STIMULATION LEAD PLACEMENT: A FEASIBILITY STUDY

M.M.A. Scholtes

Student number: 4448448

25 January 2023

Thesis in partial fulfilment of the requirements for the joint degree of Master of Science in

Technical Medicine

Leiden University | Delft University of Technology | Erasmus University Rotterdam

Master thesis project (TM30004; 35 ECTS)

Dept. of Pain Medicine, Erasmus MC

March 2022 – December 2022

Supervisor(s):

Dr. ir. C.C. de Vos

Prof. dr. F.J.P.M. Huygen

Thesis committee members:

Prof. dr. F.J.P.M. Huygen, Erasmus MC (chair)

Dr. ir. C.C. de Vos, Erasmus MC

Dr. ir. W. Mugge, TU Delft

Universiteit Leiden

TU Delft Delft University of Technology

Erasmus Universiteit Rotterdam

1 Preface

Graduating from high school, ideal choice would be studying Medicine in Delft. When I learned this was not possible, I discovered that Clinical Technology could combine my interest for medicine and technique in the city of my choice. This seemed to be the ideal study for me.

When starting the bachelor, it felt as if the Technical and Medical part were always quite separated. However, after choosing the minor Pain Medicine at the Center for Pain Medicine in the Erasmus University Medical Center, the technical and medical parts came together when learning about neurostimulation for the treatment of chronic pain. This completely confirmed the study Clinical Technology as the right choice for me.

A natural choice was to select the Sensing and Stimulation Master. During the first year I followed courses into the specifics of signal acquisition and signal processing, sensing and stimulation of neurophysiological systems, and sensing and stimulation of circulation and ventilation. I was happy to return to the Center for Pain Medicine to do my first TM2 internship there under the great tutorship of Cecile de Vos. I followed my interests in other internships, at the department of Otolaryngology, Head- and Neck Surgery researching electroencephalography, and at the department of neurosurgery focused on Deep Brain Stimulation. I did my company internship at Saluda Medical, a neurostimulation company, following my clear interest in neurostimulation/modulation.

This master's thesis is therefore focused on improving patient experience of neurostimulation of the spinal cord for patients with chronic pain, finding a way to perform lead placement while patients are under sedation. I was happy to finalize my education via this graduation project at the Center for Pain Medicine.

Most importantly, I would very much like to thank my supervisor Cecile de Vos for supporting and guiding me through this project. I have very much appreciated working with you, and hope to continue collaboration. I would also like to thank Marjolein Thijssen from Saluda Medical for her guidance with the experiments and interpretation of results. I have also felt very supported by the team at the Center for Pain Medicine and I would like to thank the full team for their help.

Mathilde Scholtes
Rotterdam, January 2025

2 Abstract

Introduction The positioning of spinal cord stimulation (SCS) leads in the epidural space to deliver therapy for chronic pain currently relies on intraoperative feedback from the patient. This feedback is not always reliable due to sedation, discomfort, and prone positioning of the patient. Excluding the need for patient feedback by performing objective intraoperative measurements to guide lead placement could be possible using the recording capabilities of closed loop SCS leads.

Objective Assess the feasibility of performing intraoperative evoked compound action potential (ECAP) measurements in the spinal cord using stimulation on the dorsal root ganglion (DRG) corresponding to the painful area of the patient to guide SCS lead placement.

Methods Intraoperative measurements were performed during placement of the SCS leads. The L3, L4 or L5 DRG was stimulated with a RF-needle and a recording electrode on the lead measured the neural activity in the dorsal column. The reference electrode was either on a subdermal needle or on one of the electrodes on the lead. The DRG was stimulated with a frequency of 10 Hz, a pulse width of 300 µs and a biphasic pulse type with negative polarity. By increasing the stimulation amplitude until ECAPs are visible, the activation threshold was determined, and by recording on different electrodes on the lead, propagation of the signal was validated. All data gathered during the measurements was processed and analyzed in MATLAB, and conduction velocities were calculated.

Results We included eight patients, and in two out of eight patients it was possible to measure ECAPs in the epidural space when stimulating on the DRG. A measured signal was deemed an ECAP if certain characteristics were met. The morphology should match that of an ECAP. Also, an increase in the stimulation amplitude on the DRG should lead to a linear increase in the ECAP amplitude. Lastly, an ECAP propagates along the dorsal column. In many patients, the stimulation on the DRG did not activate enough fibers to create an ECAP that was measurable in the epidural space.

Discussion There is no clear common denominator in the patients or stimulation parameters in the measurements where ECAPs were successfully measured in the epidural space, making specific improvements to the measurement protocol difficult. Age, gender or medication use seemed unrelated to whether the measurements succeeded. The experimental set-up could be improved by validating the distance between RF-needle and the DRG. Also, the use of sedation allows for an increased stimulation amplitude use, which could increase the amount of fibers activated to elicit an ECAP.

Conclusion Stimulating the DRG with a RF-needle can lead to measurable ECAPs in the dorsal column, which could help guide lead placement without the need for feedback. However, the measurement protocol as it is now does not produce predictable results and should be improved if to continue with this study. Also, the need for this intraoperative procedure should be reevaluated since experienced surgeons estimate the lead localization quite accurately. In combination with 12 electrode leads covering 3 vertebrae, the rest of the coverage overlap can often be achieved during postoperative programming of the stimulation.

Contents

3 Abbreviations

CMAP - Compound muscle action potential

DRG - Dorsal root ganglion

ECAP - Evoked compound action potential

ECG - Electrocardiogram

eCLS - External closed loop stimulator

EMG - Electromyography

IONM - Intraoperative neuromonitoring

PSPS - Persistant Spinal Pain Syndrome

RF - Radiofrequency

SSEP - Somatosensory evoked potentials

SCS - Spinal cord stimulation

4 Introduction

4.1 Spinal cord stimulation for chronic neuropathic pain

Chronic pain is defined as "pain that persists or recurs for more than three months" [1]. While acute pain is provoked by a specific disease or injury and serves a useful biological purpose like pulling back from a dangerous hot object, chronic pain can be caused by a disease or injury but outlasts the normal time of healing and thereby loses its biologic purpose [2]. Chronic pain is a problem affecting at least 10% of the population world-wide [3], and as much as 19% of the European population [4]. Of the chronic pain patients 30-40% experience neuropathic pain [5], which is defined as pain caused by a lesion or disease of the somatosensory nervous system. Symptoms include pain perceived as burning, electrical or shooting, often in combination with paresthesias.

Treatment of chronic neuropathic pain starts with non-surgical options as pharmacotherapy, physical therapy, and psychological counseling. Most relevant pharmacotherapy includes antidepressants, anti-epileptics and opioids [6]. However, lack of adequate efficacy of these medications and high risk of side effects can result in failure to provide sufficient pain relief. Additionally, minimally invasive procedures for neuropathic pain can be used, like nerve blocks, epidural steroid injections, radio-frequency ablations and other types of injection-based procedures. Injections may stop or lessen pain for a certain period of time, but are not intended as long-term solutions and should not be used solitarily. Surgical treatments like spinal cord stimulation (SCS) work well for pain syndromes like persistent spinal pain syndrome (PSPS) (also known as failed back surgery syndrome or postlaminectomy syndrome), complex regional pain syndrome, peripheral vascular disease, refractory angina and diabetic neuropathy [7, 8]. The term PSPS was recently proposed to replace the term failed back surgery syndrome as it is deemed inadequate, misleading and misrepresents causation [9]. According to Christelis et al. [9], PSPS encompasses chronic pain of spinal origin and its associated neurological symptoms, most commonly, but not exclusively, lumbar. PSPS-type 1 applies when there was no spinal surgery; type 2 applies when surgery has occurred.

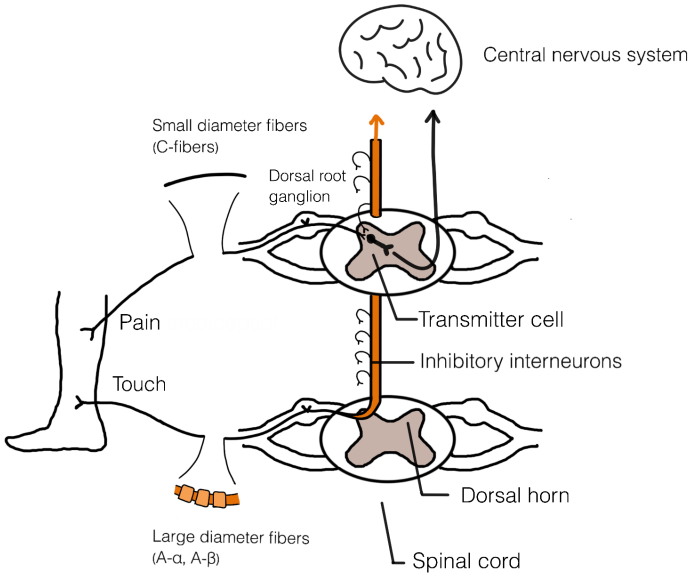


Figure 1: Pain activates small diameter fibers, which in turn excite a transmitter cell in the dorsal horn. This information is sent to the central nervous system. Touch activates large diameter fibers which activate inhibitory interneurons to reduce the excitability of the transmitter cell. This results in pain inhibition.

Traditionally, the mechanism of action of SCS is based on the concept of the gate control theory by Melzack and Wall in 1965 [10]. They described a revolutionary model that explained the origin of pain. As visualized in Figure 1, nociceptive stimuli from small-diameter afferent fibers (C fibers), excite a transmitter cell in the dorsal horn of the spinal cord to transmit this potentially harmful information to the central nervous system (CNS). However, activation of large diameter primary afferent fibers (A-α and A-β fibers) originating from the peripheral nervous system can in turn activate inhibitory interneurons which reduce the excitability of the transmitter cell transmitting the noxious stimuli to the CNS, leading to a reduced pain perception at the central level. Therefore, the large diameter input "controls the gate" by which small diameter input transmits nociceptive stimuli to higher pain centres [11, 12].

In general, SCS devices consist of an implantable pulse generator which is connected to one or two leads that are implanted in the epidural space of the spinal cord. The leads contain multiple electrodes with the ability to electrically stimulate the primary afferent fibers in the dorsal column of the spinal cord. This leads to “closing of the gate” and a decrease in perceived pain. There are two groups of SCS paradigms: paresthesia inducing SCS or sub-threshold SCS. Paresthesias mask the pain while sub-threshold stimulation is not felt by the patient. For this thesis, SCS with paresthesias is used.

4.2 The current implantation procedure

Implantation of SCS devices is usually divided in two steps. First, the leads are implanted and connected to an external battery for approximately 10 days. During this trial period, the efficacy of stimulation in relieving pain is tested. If the pain reported by the patient has decreased with at least 50%, the trial is deemed successful. Second step of the implantation procedure is implanting the pulse generator in a subcutaneous pocket, commonly on the buttock. The already implanted leads are also connected to the generator.

When the leads are implanted, the patient is usually under conscious sedation so they can give direct feedback about where paresthesias are perceived when the stimulation is activated. This is called paresthesia mapping, and the goal is to elicit satisfactory paresthesia coverage in the painful area. Based on the outcome of paresthesia mapping, the leads can either be repositioned or secured. However, the responses of patients under conscious sedation are often unreliable due to several reasons like sedative-related confusion, miscommunication because of prone position and patient discomfort [13].

The current implantation procedure could be improved by excluding the need for patient feedback during lead placement, and replacing it with a more objectively substantiated method. This would also make the procedure less uncomfortable for the patient.

4.3 Intraoperative testing procedures

To improve the current implantation procedure, there is a need for an intraoperative testing procedure like paresthesia mapping which relies on objective measurements to guide lead placement. I conducted my literature review into this topic and found that using intraoperative neuromonitoring allows for an objective placement of leads without feedback from the patient. Therefore, these surgeries can also be performed under general anesthesia. Benefits of the use of intraoperative neuromonitoring techniques include patient safety by monitoring critical neurological structures and increased patient comfort, as they are not awakened during surgery. Two intraoperative testing procedures based on intraoperative neuromonitoring stand out in literature. They are called the compound muscle action potential (CMAP) technique and the collision technique.

- The CMAP technique uses electromyography (EMG) to monitor motor activity in the patient. The testing procedure consists of dorsal column stimulation with SCS-leads to elicit CMAPs in the muscles where paresthesias are warranted. Because CMAPs and SCS activate the same primary afferent fibers, CMAPs are a substitute for feedback by the patient and thus can confirm that the lead is placed correctly. Four studies into this technique all described a successful lead placement with a postoperative paresthesia coverage, defined as the overlap between painful area and area where paresthesias are experienced, between 85 and 96% [14, 15, 16, 17]. One study compared the CMAP technique to traditional paresthesia mapping, and reported a postoperative

coverage of 80% after using the CMAP technique to guide lead placement and a postoperative coverage of 45% when paresthesia mapping was performed [18].

- The collision technique requires somatosensory evoked potential (SSEP) testing, which is a way of monitoring the sensory pathway, consisting of the primary afferent fibers. A distal nerve is stimulated and measured at the cortex, and when the sensory nerves are in distress or damaged, this can be sensed cortically. The intra-operative testing procedure is based on the principle that SCS and SSEP activate the same primary afferent fibers. Therefore, when the dorsal column is stimulated at the same time as the distal nerve of the muscle in the painful area, the signals collide and a decrease in amplitude can be measured cortically. Meaning the SCS is reaching the painful area and the leads are placed correctly. Balzer et al. [19] described a 100% success rate and 100% postoperative paresthesia coverage, but three other studies comparing the collision technique with the CMAP technique found the CMAP technique more successful in correctly placing the SCS leads without patient feedback [20, 21, 22].

Both intraoperative testing procedures have been proven successful. Today, both techniques are mostly implemented in the United States. There, EMG or SSEP are often already part of the standard implantation procedure. However, in the Netherlands EMG or SSEP are not commonly used during standard SCS implantation surgeries, making the implementation of these methods increasingly challenging, costly and time-consuming. An intraoperative testing procedure without the need of intraoperative neuromonitoring could be more suitable for implementation in the Netherlands.

4.4 New method for intraoperative testing

Closed-loop SCS is a new SCS paradigm which differs from conventional SCS in that closed-loop SCS can record evoked compound action potentials (ECAPs) while stimulating in the dorsal column. The ECAP morphology consists of a positive P1 peak followed by a negative N1 and another positive P2 peak (Figure 2). The N1-P2 peak-to-peak amplitude increases with the amount of fibers in the dorsal column activated. The ECAPs are recorded directly from the dorsal columns of the spinal cord, using the contacts on the leads. The Evoke system (Saluda Medical, Sydney, Australia) has 12 contacts per lead, capable of recording and stimulating. It uses ECAPs recorded from the spinal cord to drive a feedback (ECAP) controlled stimulation therapy. As a result, the stimulation is improved according to the measured ECAPs, leading to a more constant stimulation for the patient in every posture. By utilizing the recording capabilities of the Evoke system, it may be possible to use objective electrophysiological recordings and ECAP morphology to guide lead placement without the need for patient feedback or intraoperative neuromonitoring.

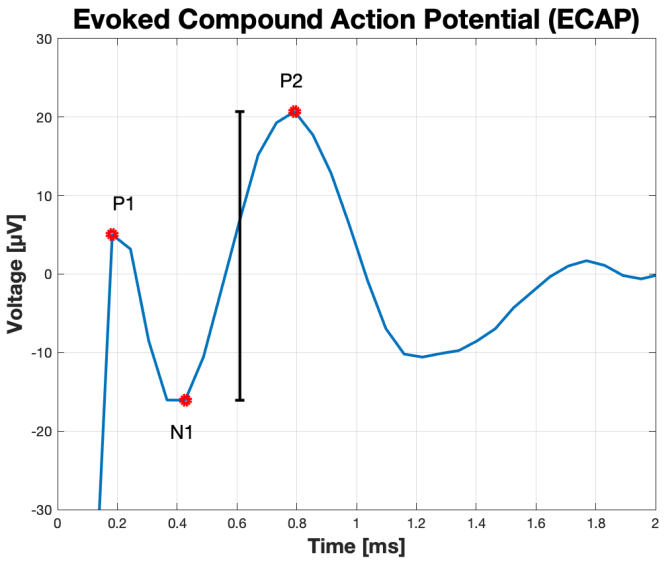


Figure 2: Example of an evoked compound action potential (ECAP) with a first positive peak (P1), first negative peak (N1) and a second positive peak (P2). This shape is characteristic of the potentials generated from depolarising nerve fibres. The ECAP amplitude is commonly expressed using the N1-P2 amplitude.

Chronic low back pain caused by PSPS usually results in large affected painful areas. SCS leads with 12 electrodes cover approximately three vertebrae, making it possible to stimulate the entire painful area. As a rule of thumb, lower back coverage is best obtained at T8, buttock and leg coverage at T9 or T10, and foot coverage below T10 [13]. However, this is an estimation and anatomical differences in patients occur. As mentioned before, a minimally invasive procedure like radio-frequency (RF) ablation can target specific nerves or dorsal root ganglions (DRGs). Since the DRG houses the primary sensory neurons transmitting afferent nociception of a specific dermatome, stimulation of the DRG can target painful areas more specifically. However, for patients with a painful area running from low back to toes, this is not the best solution as you would need to target up to 10 dermatomes, as you can see in Figure 3. Still, the dermatomal distribution can be used to translate the painful area of the patients to corresponding dermatomes and DRGs. The hypothesis of this new intraoperative testing procedure is that when you stimulate the DRGs matching the painful area using an RF needle, the antidromic activation can be measured by the SCS leads as an ECAP on the dorsal column, and the optimal placement of the lead can be determined based on where the activation of the DRGs is recorded best. If successful, the procedure could replace the need for patient feedback, and RF ablations are commonly performed by anesthesiologist and thus more easily implemented into the standard SCS implantation procedure compared to intraoperative neuromonitoring.

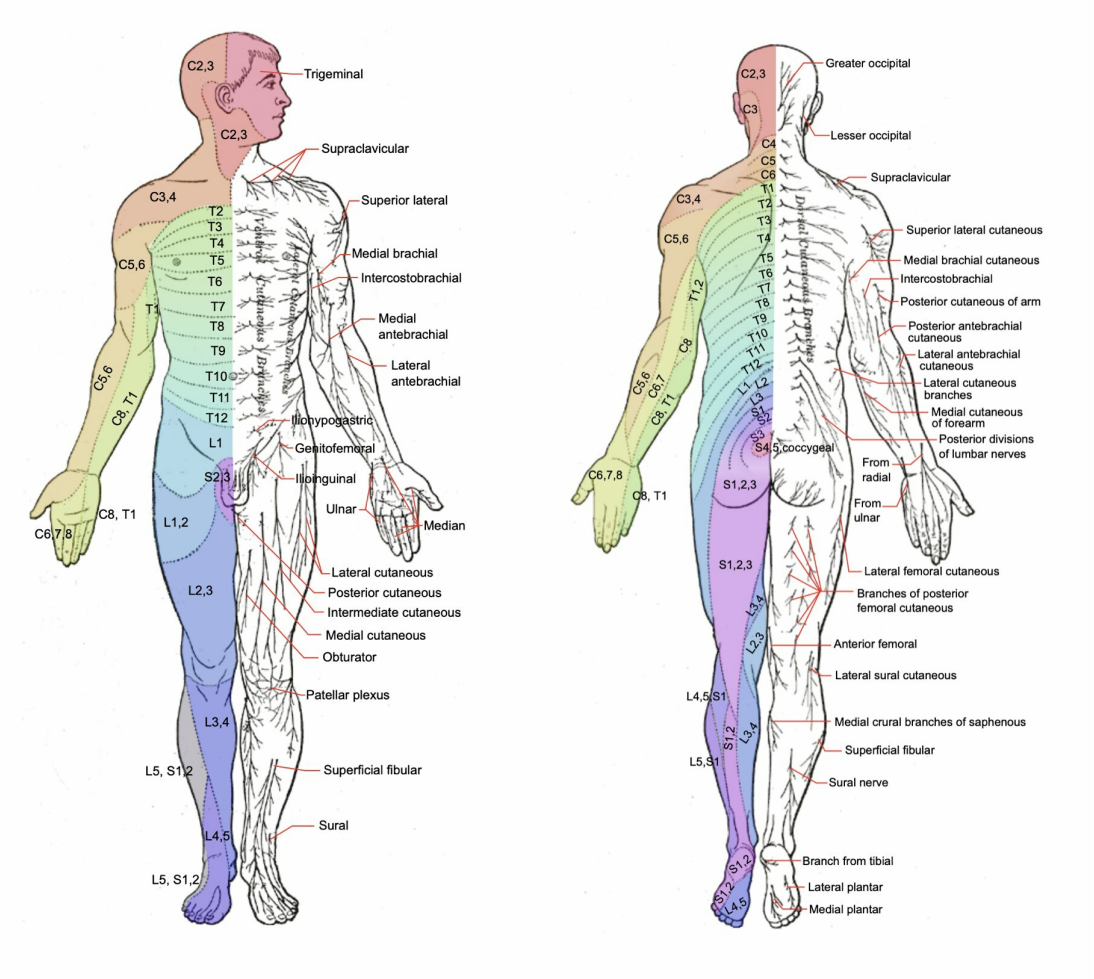


Figure 3: The dermatomal distribution shows each part of the body supplied by afferent nerve fibres from the dorsal root of any given spinal nerve. The dermatomal distribution can be used to translate the painful area as communicated by the patient to the corresponding dermatomes to objectively place the SCS leads. [23]

4.5 ECAP Guided SCS Lead Implantation study

The ECAP Guided SCS Lead Implantation study (NL69419.100.19) is an interventional feasibility study accepted by the medical ethical committee of Erasmus University Medical Centre, Rotterdam in July 2019. This study was designed to test the new intra-operative testing procedure described in section 4.4. The study consists of three phases of which a flowchart can be seen in Appendix A. Phase 1 includes 10 patients who will undergo paresthesia mapping to verify a correct lead placement. When the lead is placed correctly based on patient feedback, the ECAP measurements will be performed to test the hypothesis that DRG stimulation using an RF-needle can be recorded in the dorsal column. After every phase there is an interim analysis that states whether to proceed to the next phase. Phase 1 is deemed successful if ECAPs are recorded corresponding with the final lead position in $\geq$50% of the study population. Phase 2 would include 10 more patients whose leads would be implanted using the proposed intra-operative testing procedure first, and validated through paresthesia mapping afterwards. If the leads of $\geq$50% of subjects are successfully implanted based on the new testing procedure, the study will continue to phase 3. In phase 3 lead placements are only performed using the new testing procedure.

4.6 Aim of this thesis

The aim of my thesis research is to complete phase 1 of the study and perform the corresponding interim analysis. During phase 1, the included patients will be stimulated on the L3, L4 or L5 DRG and measurements are performed on the lead in the epidural space. Phase 1 is focused on the feasibility of the measurements, so a measurement protocol is developed, but the measurements will also be explorative to optimize the protocol.
My hypothesis is that stimulating the DRG will cause measurable neural activity in the dorsal column, which could (eventually) help SCS lead placement without the need for patient feedback.

5 Methods

5.1 Study population

Patients under treatment for PSPS at the department of Anesthesiology-Pain Medicine in St. Antonius Hospital, Nieuwegein were recruited for the study after a multidisciplinary approach accepted that a SCS trial would be performed. In order to be eligible to participate in the study, patients had to meet all inclusion criteria listed:

1. Patient will be included for implantation according to standard criteria from the Dutch Neuromodulation Society.
2. Patient will be implanted with the Evoke system.
3. Patient suffers from chronic neuropathic pain as a result of PSPS for at least 6 months.
4. Patient is 18 to 80 years old.
5. Patient is able and willing to comply with the protocol and follow-up.
6. Patient is fluent in the Dutch language.
7. Patient is able to provide written informed consent.

5.2 Intraoperative method

5.2.1 Preparation and anesthetics

All included patients undergo a general preparation for surgery conform protocol. Patients are placed in prone position and brought to a conscious sedated state while maintaining local anesthetics. A member of the anesthesiology team continually monitors the patient. An incision is made, the epidural needle is inserted into the epidural space and the lead(s) are guided into the epidural space under fluoroscopy to an estimated desired position. The patient is then woken from sedation to undergo intraoperative paresthesia mapping. The leads are connected to an external stimulation device and clinical staff asks the patient to provide verbal feedback regarding the paresthesia coverage in the painful area when testing different stimulation intensities and electrodes. The stimulation parameters used during paresthesia mapping are described in Table 1. All settings and recorded ECAPs are saved for data analysis . If insufficient paresthesias are elicited in the painful area, the leads are repositioned by the operating anesthesiologist and tested until a satisfactory lead position is attained. During phase 1, the leads are fixated prior to the experimental measurements.

5.2.2 Experimental set-up

The experimental set-up can be seen in Figure 4. The external closed loop stimulator (eCLS - CE marked product) is connected to the break-out box (a modified lead adapter), which is connected to the leads that are implanted. The eCLS is a non-implantable external version of the implantable CLS. It has all the capabilities of the implantable CLS including the ability to record ECAPs. It is designed to be used by clinical staff to perform the intraoperative paresthesia mapping, and by the patient during the SCS trial period. The break-out box is a research tool that is able to take over functions like stimulating, recording and referencing functions, normally occurring on the electrodes on the lead, and perform them externally. This way the external stimulation device that is also used for paresthesia mapping, can be used to stimulate or record on the DRG. The break-out box has 24 contacts in relation to the 24 contacts on the two leads implanted. The L3, L4 or L5 DRG is selected for stimulation. A standard radiofrequency (RF) needle is used to place near the nerve root's DRG and functions as the cathode. A diathermy pad is placed on the side of the torso and functions as an anode. The subdermal needle functions as a reference electrode, which means it should measure constant activity in the body, that can be subtracted from the recording electrode so activity that is not constant stands out. The subdermal needle is placed diagonally in the dermis to make sure no motor activity is recorded. The function of reference electrode can also be fulfilled by an electrode internally on the lead. The recording electrode moves along the lead placed at the side where the DRG is stimulated.

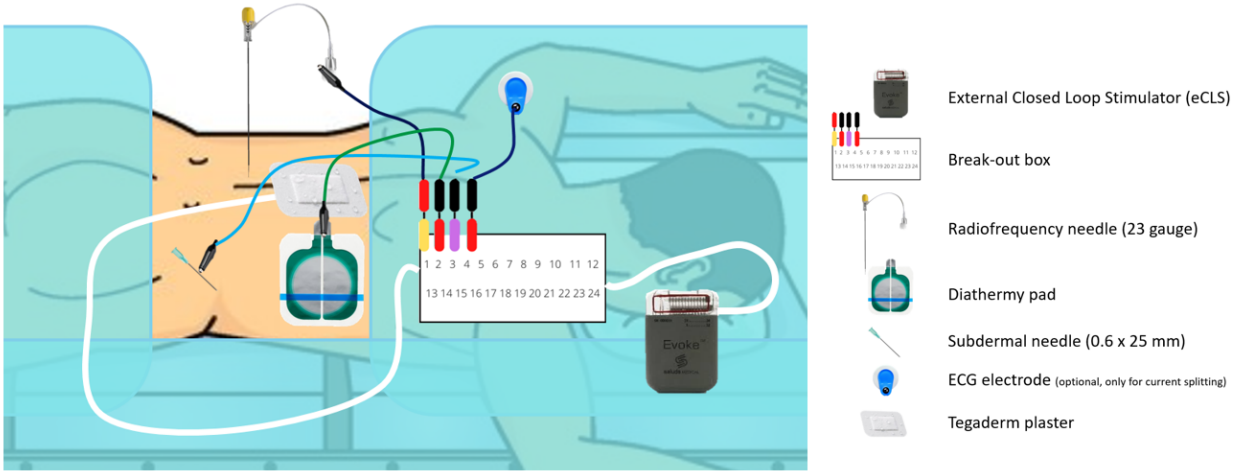


Figure 4: Schematic representation of the experimental set-up. The patient is placed in prone position for the placement of the spinal cord stimulation leads. When the leads are implanted, fixated and covered with a Tegaderm plaster, a radiofrequency (RF) needle is placed in the dorsal root ganglion (DRG) where the needle will function as a cathode. A diathermy pad is placed on the side of the torso to function as anode. A small needle is placed subdermally to function as reference electrode. Lastly, an electrocardiogram (ECG) electrode can be placed when current splitting is used, meaning that a part of the stimulation give will go to the RF needle, and the rest to the ECG electrode. All parts are connected with crocodile clips to the break-out box, which is connected to the external closed loop stimulator.

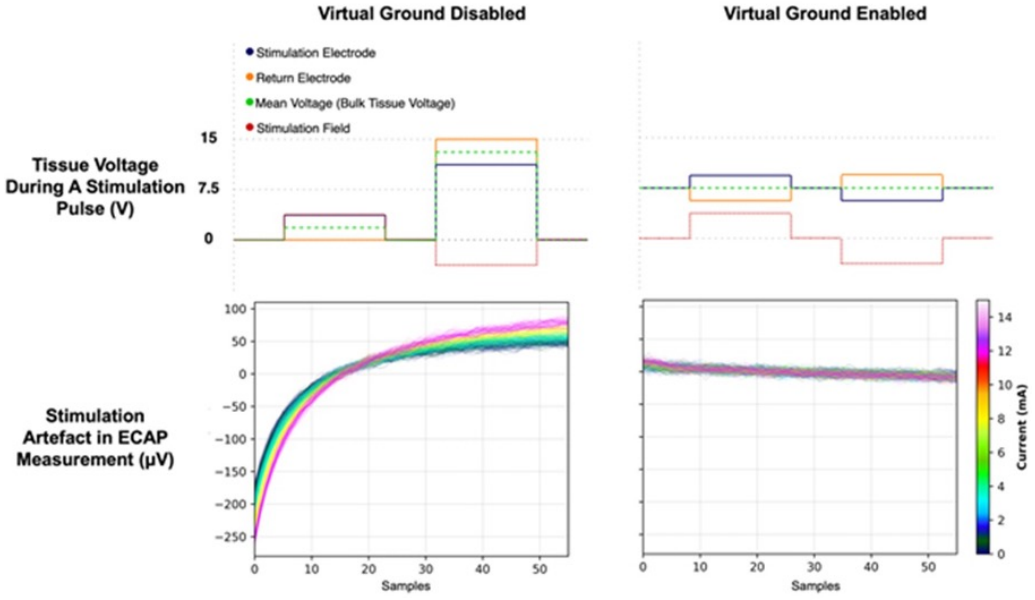


Figure 5: This schematic visualization shows how Virtual Ground works. The stimulation field given to the dorsal column is the difference between the stimulation on the stimulation electrode and return electrode. To create the desired stimulation field with Virtual Ground disabled, there is a high voltage swing at the recording electrode (the mean voltage in the tissue) which causes artifact. When Virtual Ground is enabled, the mean voltage in the tissue is more constant and thus no voltage swing at the recording electrode which results in less artifact. Figure from Saluda Medical, Sydney, Australia

Virtual Ground Virtual Ground is a setting developed by Saluda Medical to reduce the amount of artifact recorded. As is shown in Figure 5, with Virtual Ground disabled the stimulation artifact is distinctively present over all stimulation currents. With Virtual Ground enabled the artifact is only present at the baseline 0 uV at all currents.

5.2.3 Intraoperative testing procedure

With the leads implanted and the experimental set-up in place, the measurements can start. The aim is to record an electrical signal stimulated in the DRG as an ECAP in the dorsal column, using the recording function of the leads implanted in the epidural space. Via the same programming tablet as used with the intraoperative paresthesia mapping and the break-out box, an electrical signal was sent to the DRG via the RF needle using standard settings for sensory stimulation on the DRG [24] (see Table 1). Some of the included patients were awake during the measurements, and were asked to provide verbal feedback again regarding any sensations felt while the stimulation was turned on. All signals recorded in the spinal cord were saved for later data analysis.

Table 1: Stimulation parameters

	Paresthesia mapping	**Stimulation on DRG**
Frequency	30 Hz	10 Hz
Pulse width	300 µs	300 µs
Interphase gap	200 µs	200 µs
Pulse type	Triphasic	Biphasic
Polarity pulse	Positive	Negative

Stimulation parameters during paresthesia mapping and stimulation on the dorsal root ganglion (DRG). Paresthesia mapping is performed by clinical staff, and the settings are usually as described here but small changes in the frequency (40 Hz) or pulse width (250-350 µs) can be made because of individual preference of the staff or optimization of the procedure and is deemed negligible. If there were changes in the settings for stimulation on the DRG, they are mentioned in the results.

5.3 Data analysis

5.3.1 ECAP characteristics

To perform a systematic data-analysis of the results from the measurements, the measurements should firstly be performed systematically. The leads in the dorsal column can record different activities like noise, artifact, motor activity, non evoked potentials and the ECAPs we would like to measure. To be able to state that something is an ECAP instead of the aforementioned activities, we should look at the characteristics of an ECAP. ECAPs are the results of a summation of evoked action potentials in the dorsal column, generally the A-β fibers. The conduction velocity of A-β fibers is between 33-75 m/s, dependent on age, gender and various medical conditions [25]. This provides a certain window in which we would expect to measure neural activity in the form of ECAPs, based on the distance between the place of stimulation and recording. Neural activity (as compared to artifact or noise) has several distinctive characteristics that can be tested [26]. First, when there is no stimulation amplitude, there can be no signal measured except for noise. Secondly, the stimulation amplitude will be increased in steps. The expectation is that first a certain activation threshold should be overcome to form an ECAP, and after that the ECAP amplitude should increase linearly with the increase in stimulation amplitude. Thirdly, neural activity propagates along the dorsal column, which can be validated by recording on multiple electrodes subsequently. Fourthly, the measured signal is the difference between the recording electrode and the reference electrode. By moving the reference electrode between locations, the measurements can be validated to an extent.

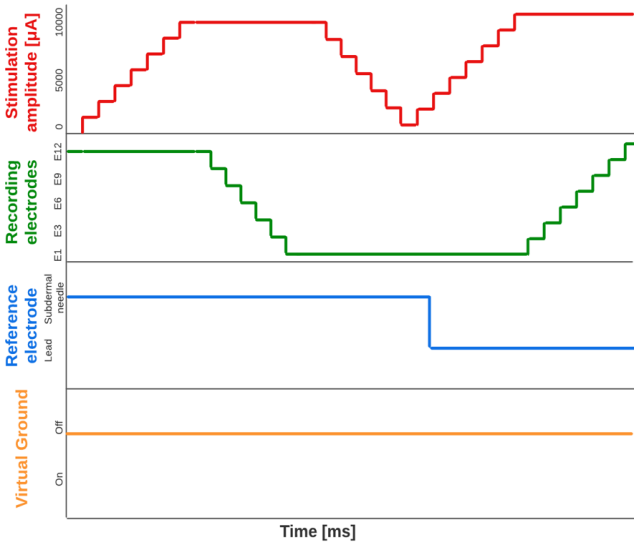


Figure 6: Visualization of how the measurements were performed. While increasing the stimulation, the recording electrode, reference electrode and Virtual Ground setting were kept constant. When at a certain stimulation amplitude ECAPs would appear, the recording electrode was moved along the lead to prove propagation of the signal. The stimulation amplitude would be decreased and turned off, to change settings like the reference electrode or Virtual Ground.

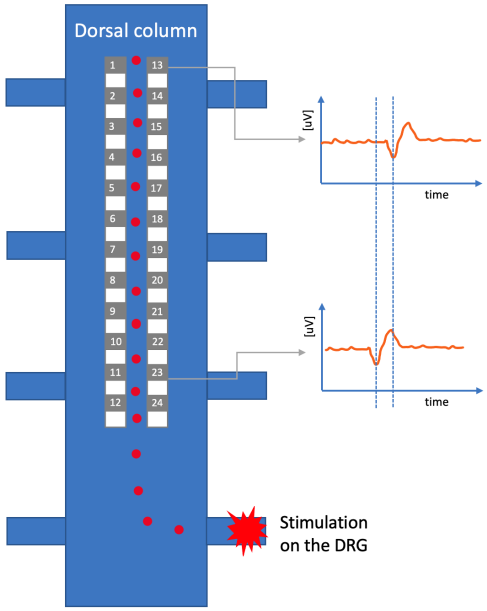


Figure 7: Schematic visualization of propagation of the signal. When stimulation is given on the dorsal root ganglion (DRG), an evoked compound action potential (ECAP) travels along the dorsal column. Electrode 12 and 24 are the first to record the action potential, visualized next to the dorsal column. Electrode 1 and 13 are the last to record the action potential, and a shift in the peak latency shows propagation of the signal.

5.3.2 Measurement protocol

These characteristics lead to the systematic measurement protocol I developed, which can be found in Appendix B. An indication of how they are performed can be seen in Figure 6. The measurements start with no stimulation amplitude, to see if there is no signal measured except for spontaneous activity. Next, the stimulation amplitude is increased in small steps of 50 μA to determine the stimulation threshold, and after that validate that the increase in amplitude proceeds linearly. During this period of increasing the stimulation amplitude, the recording electrode is constantly the same. When the patient communicates that the stimulation amplitude exceeds a comfortable level, or when there are clear ECAPs measurable, the propagation of the ECAP is tested. This is done by moving the recording electrode along the SCS lead. Propagation can be proved as visualized in Figure 7. When recordings are made on every available electrode, the process of increasing the stimulation is repeated at another electrode. Other settings can be changed as well, like Virtual Ground or changing the reference electrode from subdermally to internally on the lead.

5.3.3 Clinical Data Viewer: data collection

All data gathered during the measurements was saved in H5-files and can be visualized in Clinical Data Viewer, a program especially for Saluda data. The data was viewed in Clinical Data Viewer, filtered with a triple exponential filter across all 160 samples, and averaged over five consecutive samples, meaning the signal is the result of the two samples before and after the selected sample. Averaging the samples increases the signal-to-noise ratio. I chose to average over five samples because while increasing the stimulation, there were often only a few samples recorded during that stimulation amplitude. When the number of averages would be 10 or 15, it could become an estimation of the result of stimulation amplitude 100, 150 and 200 μA. The filtered and averaged data was downloaded to process further in Matlab, and included in data-file was the raw data.

5.3.4 MATLAB: data analysis

The data was processed and analyzed in MATLAB. Firstly, the conduction velocity was estimated based on the ECAPs measured during paresthesia mapping. Based on the amount of samples before the first peak of the ECAP, the sample time and the traveled distance of the signal, the velocity can be estimated. The absolute distance between the recording electrode and the stimulus on the L4 DRG was measured to be minimally 15 cm. Taking into account the internal anatomy, a range of 15 to 25 cm was used for conduction velocity calculations. The estimated conduction velocity gives an indication in which time window an ECAP elicited in the DRG would appear in the dorsal column. In this window of interest, the relation between the stimulation and measured signal was analyzed. This was done by increasing the stimulation amplitude to find the activation threshold of the signal. After the threshold was overcome, the N1-P2 peak-to-peak ECAP amplitudes would increase linearly (to a certain extent). To visualize the linear increase of the ECAP amplitudes, they were plotted against the stimulation amplitude. The ECAP amplitudes were calculated with peak detection function in Matlab. Lastly, the propagation of the signal was tested by comparing the recordings on different electrodes, like in Figure 7.

6 Results

6.1 Patient characteristics

Eight patients were included in this research, of which two were pilot measurements and six were included in Phase 1 of the study. The pilot measurements were performed prior to my role in this study, but during the next six inclusions I contributed to the measurements. The planned number of ten included patients during this thesis research (and Phase 1) was not met due to a lack of time. The characteristics are shown in Table 2. The average age was 63 years and the distribution of male/female was 50/50.

Table 2: Patient characteristics

	Age	Gender	Pain duration	Pain area	Medication	Pre-surgery NRS	End of trial NRS	3-month NRS	Coverage
Pilot 1	50	M	42	Low back	P, N	8	2	2	Extra: ribs
Pilot 2	57	F	47	Left leg, low back	P, N, O, AD, AE	8	0	1	Unknown
Patient 1	78	F	60	Low back, left upper leg	AD	8	3	6	Missing: low back
Patient 2	51	M	15	Right front leg	N	7	3	4	Correct
Patient 3	76	M	240	Buttock, back of both legs	WO, AE	8	3*	2	Correct
Patient 4	55	M	288	Both calves and feet	O, AD, AE	7	10	-$\circ$	Unknown
Patient 5	71	F	48	Left low back until calve	O, B	9	4	-$\oplus$	Unknown
Patient 6	65	F	300	Low back, left back leg	P, O, AD, AE	8	1	-$\oplus$	Missing: low back

Pain duration in months, medication: P = paracetamol, N = NSAIDs, WO = weak opioids, O = opioids, AD = antidepressants, AE = anti-epileptics, B = benzodiazepines, * = Patient 3 had an all-in-one implantation because of increased risk of infection, so there was no trial, $\circ$ = Trial failed no 3-month NRS available, $\oplus$ = 3-month NRS in the future.

6.2 Pilot measurement 1

6.2.1 Paresthesia mapping

The stimulation parameters during paresthesia mapping were as described in Table 1 in the Methods. The stimulation configuration and the resulting ECAPs are shown in Figure 8. Both leads were successfully implanted and positioned based on the feedback during paresthesia mapping.

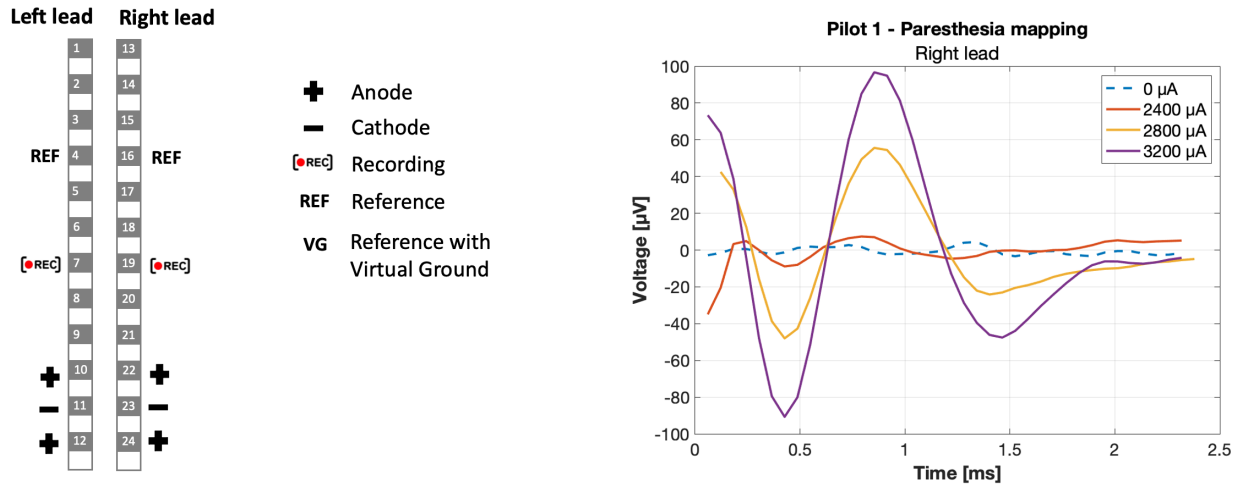


Figure 8: Left figure: Settings on the leads during paresthesia mapping. On E10-E11-E12 and E22-E23-E24 is a guarded cathode visualized. The recording electrodes are placed on E7 and E19, and the reference electrode is placed on E4 and E16. Right figure: Evoked compound action potentials (ECAPs) recorded on the right lead in Pilot 1.

Conduction velocity and window of interest Based on paresthesia mapping ECAPs an estimation of the conduction velocity was made. Based on that conduction velocity, a window of interest can be determined. The absolute distance between the DRG and the lead was measured externally and was 15 cm. To account for the anatomical distance internally, the window of interest assumes a distance between 15 and 25 cm.
Estimated conduction velocity: 50 - 60 m/s
Window of interest: 2.5 - 5 ms

6.2.2 Stimulation on the DRG, recording on the lead

Set-up measurements Patient was under sedation. The L4 DRG on the patient's right side was stimulated. The set-up is visualized in Figure 9. The stimulation parameters were as described in Table 1 in the Methods.

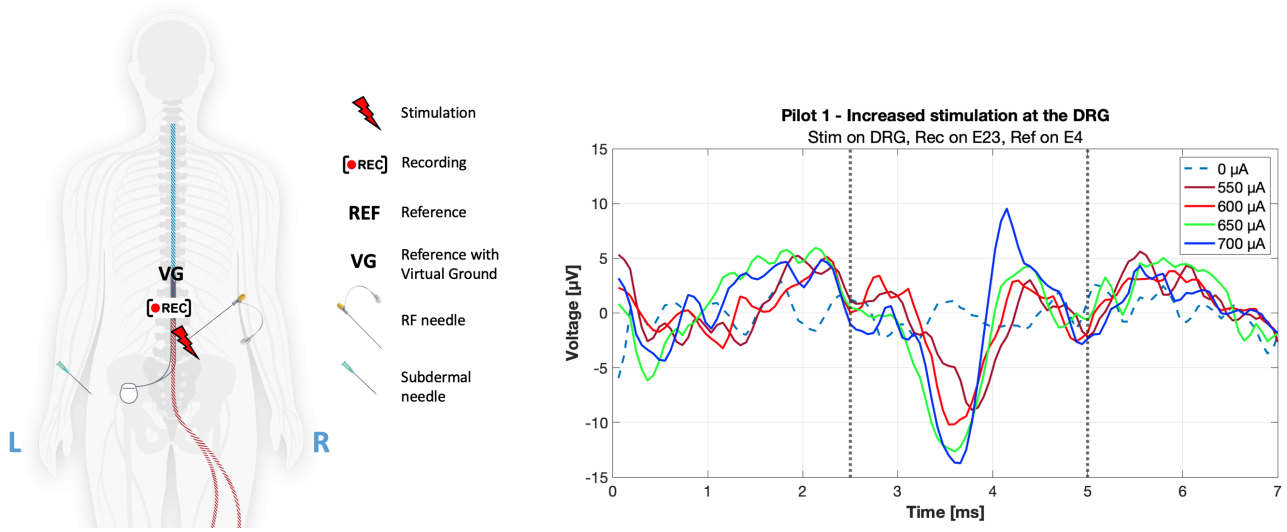


Figure 9: Left figure: Posterior view of the settings during stimulation on the L4 DRG, recording on the lead (E23) and reference with Virtual Ground turned on (E4). Right figure: Recordings on the lead of increased stimulation at the DRG. The black dotted lines show the window of interest. An ECAP is visible, and the ECAP amplitude increases with increased stimulation amplitude.

Increasing the stimulation The stimulation on the DRG was increased from 0 µA until 700 µA, at which amplitude an apparent ECAP was visible. The stimulation was increased in steps of 50 µA. Figure 9 shows several stimulation amplitudes in one plot, visualizing an increase in ECAP amplitude with increased stimulation amplitude. In Figure 10 all individual stimulation amplitudes are plotted, showing the ECAP forming at 550 µA, which would mean that the threshold to elicit enough fibers to form an ECAP was between 500 and 550 µA. Plotting the ECAP amplitude against the stimulation amplitude results in Figure 11. This figure shows a linear increase in ECAP amplitude after the activation threshold is reached.

Measuring on different electrodes When the stimulation was increased to 700 µA, the stimulation was kept at a constant to record the ECAPs on different electrodes to prove propagation of the signal. This is shown in Figure 12. The latency of the negative peak is marked with a single black line, to visualize the propagation. Note that the stimulation of the L4 DRG is occurring below E24, meaning that the ECAP is first measured at E24 and last at E13. This is supported by the increasing peak latency the further away from the stimulation you record. Also notable is the change in polarity of the signal at E15-E13, which can be explained by the reference electrode at E4 (across from E16). As mentioned in the Methods, the measured signal is always the difference between the recording electrode and the reference electrode, resulting in a change in polarity at E15.

Conduction velocity The conduction velocity can be calculated based on the latency difference between E24 and E13, and the distance across the lead the signal travels. This results in a conduction velocity of approximately 90 m/s, which is very fast for A-β fibers. Calculating the conduction velocity based on the latency of the negative peak at E24 and the distance between E24 and the L4 DRG results in a conduction velocity of approximately 75 m/s.

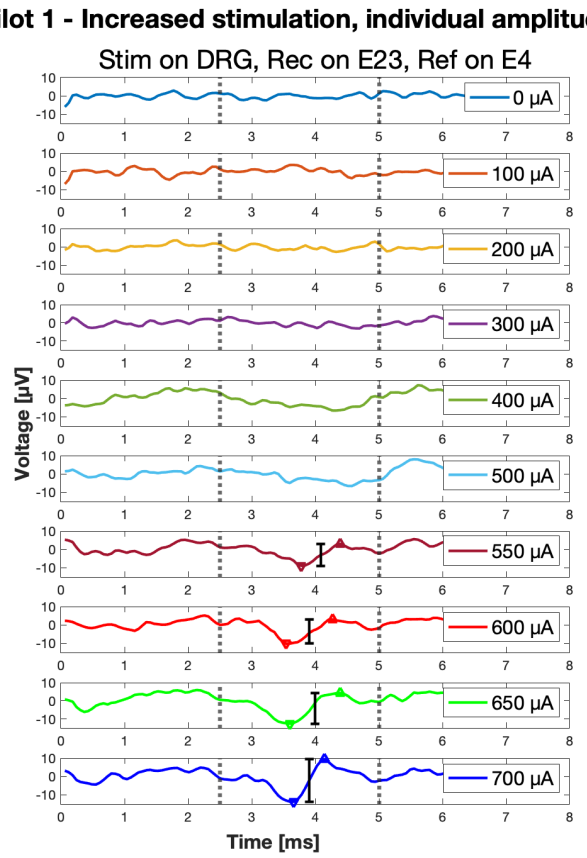


Figure 10: Recordings on E23 as a result of stimulation on the dorsal root ganglion (DRG) in Pilot 1. All individual stimulation amplitudes are shown. At 550 µA we see an evoked compound action potential (ECAP) amplitude forming that increases with an increasing stimulation amplitude at the DRG. The black dotted line shows the window of interest.

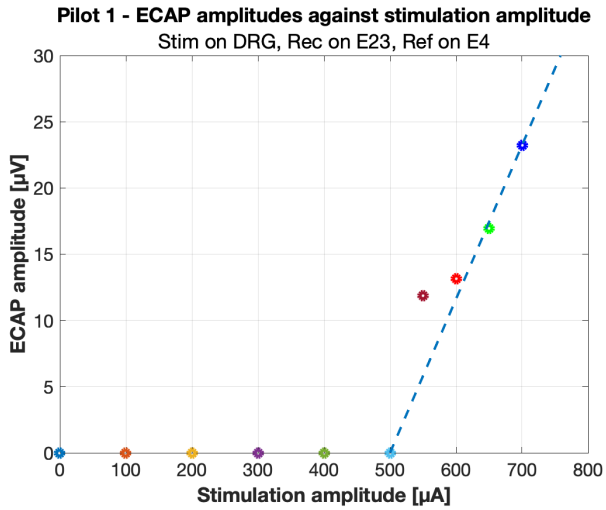


Figure 11: The evoked compound action potential (ECAP) amplitudes are plotted against the stimulation amplitudes at the dorsal root ganglion, to visualize a linear increase in ECAP amplitude.

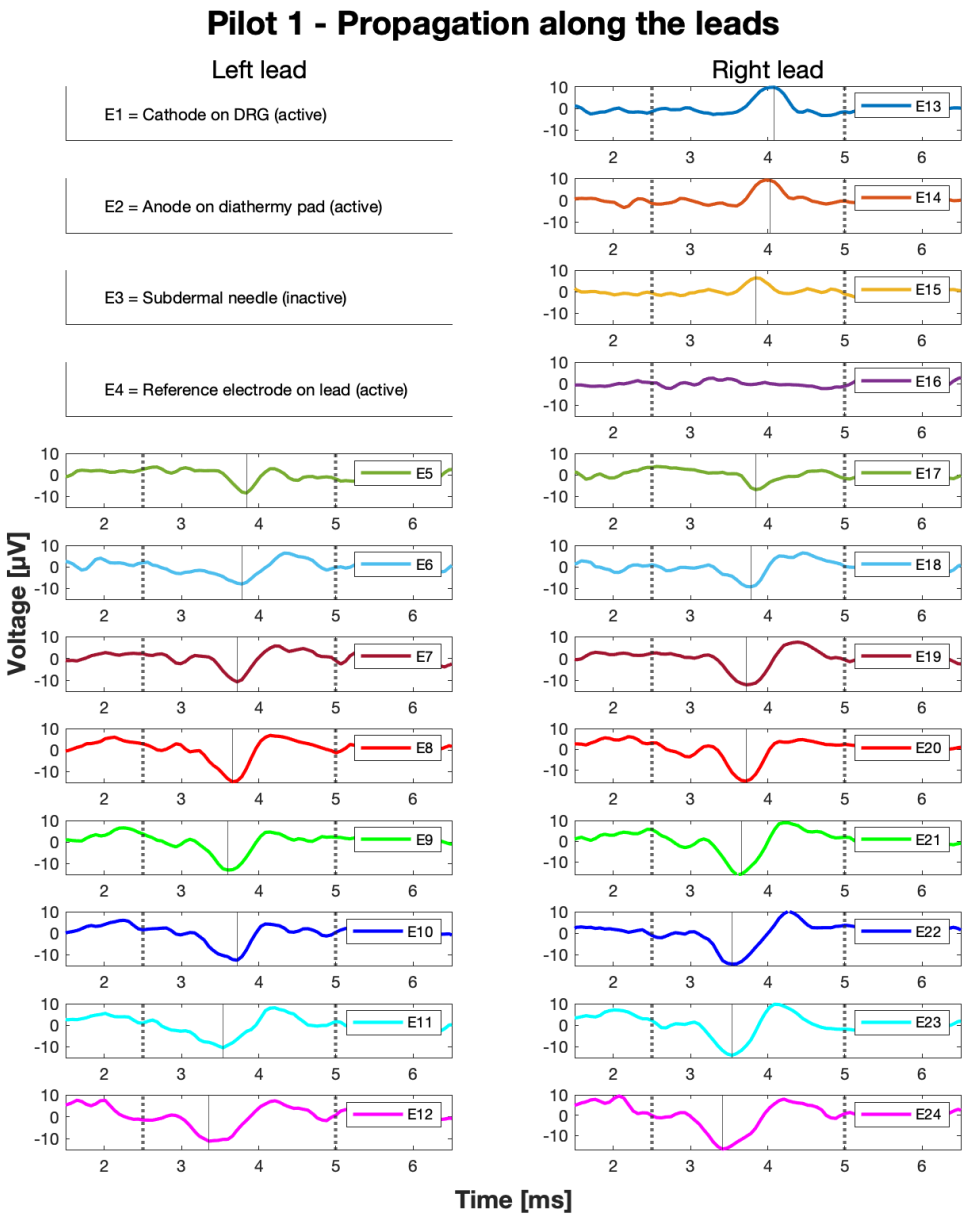


Figure 12: Individual measurements on all electrodes of the two leads show propagation of the ECAP along the dorsal column. The result of L4 DRG stimulation "enters" the recording electrodes at E12 and E24, and the latency of the first negative peak is approximately 3.3 ms. Furthest away from the stimulation is E13, where the peak latency is 4.1 ms. Polarity in E13-E15 positive because the reference electrode is located at E4. Black dotted line = window of interest, black line refers to peak latency.

6.3 Pilot measurement 2

6.3.1 Paresthesia mapping

The stimulation parameters during paresthesia mapping were as described in Table 1 in the Methods. The stimulation configuration and the resulting ECAPs are shown in Figure 13. Both leads were implanted, but the right lead was not stimulated for paresthesia mapping

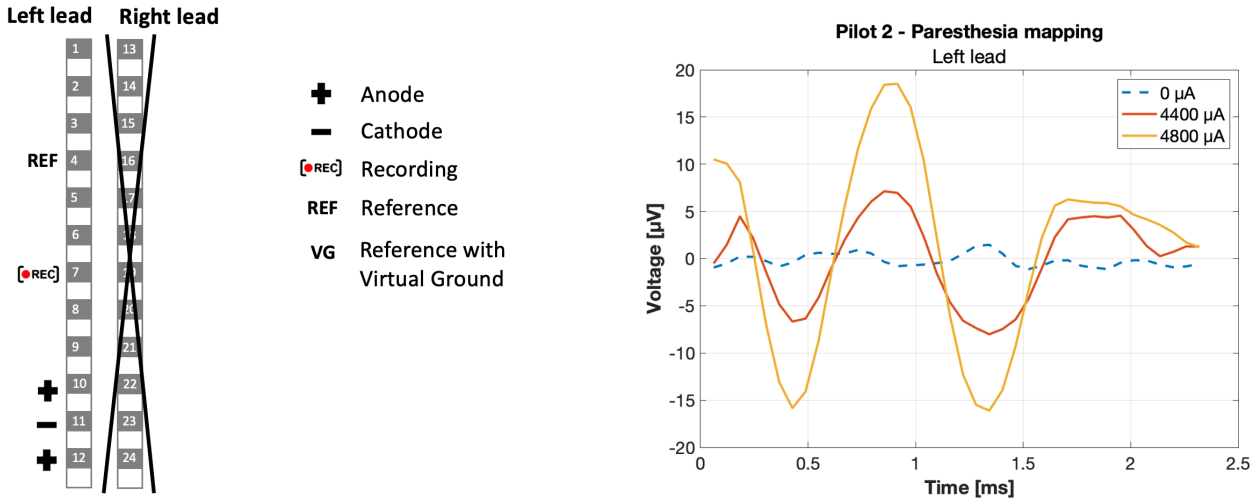


Figure 13: Left figure: Settings on the leads during paresthesia mapping. On E10-E11-E12 is a guarded cathode visualized. The recording electrode is placed on E7 and the reference electrode is placed on E4. Right figure: Evoked compound action potentials (ECAPs) recorded on the left lead in Pilot 2.

6.3.2 Conduction velocity and window of interest

Paresthesia mapping was performed successfully, and an estimation of the conduction velocity was made based on the ECAPs measured. Next, a window of interest was determined.
Estimated conduction velocity: 50 - 60 m/s
Window of interest: 2.5 - 5 ms

6.3.3 Stimulation on the DRG, recording on the lead

Set-up measurements Patient was under sedation. The L4 DRG on the patient's left side was stimulated. The set-up is visualized in Figure 14. The stimulation parameters were as described in Table 1 in the Methods, except for the pulse width which was also 220 µs, 300 µs or 800 µs at times for comparison.

Increasing the stimulation Increasing the stimulation on the DRG while recording on the lead did not have the same effect as in Pilot measurement 1. As can be seen in Figure 14, there is no ECAP visible of which the amplitude increases with the stimulation. The measurements were performed multiple times, with Virtual Ground on the reference electrode or with Virtual Ground turned off. The effect of Virtual Ground is mostly visible in the first 0.5 ms when comparing the stimulus artifacts (see Figure 39 in Appendix C).

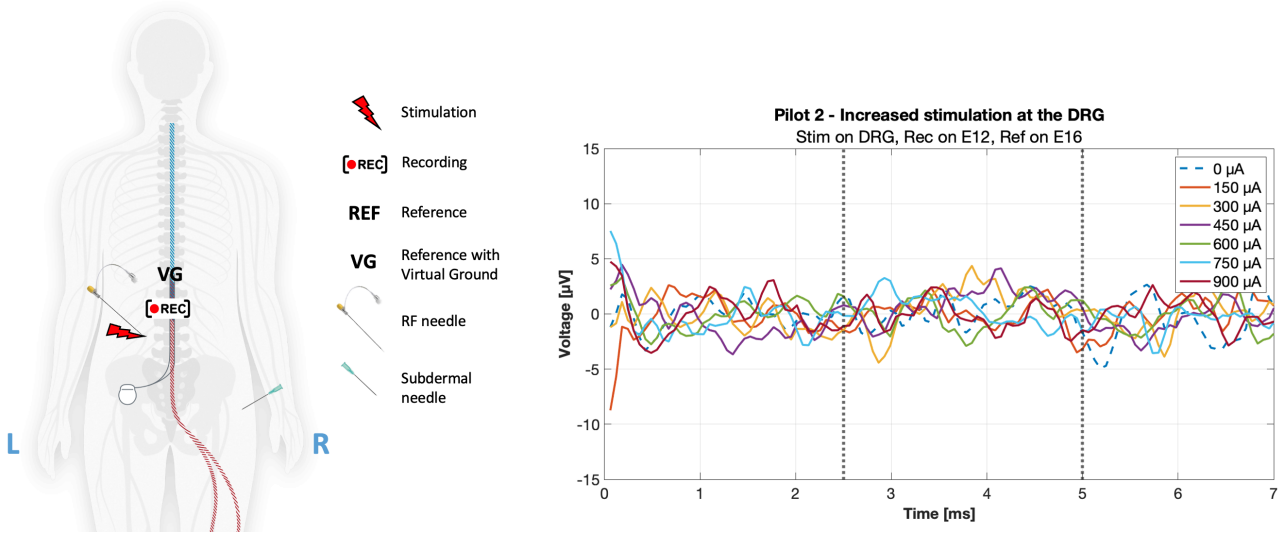


Figure 14: Left figure: Posterior view of the settings during stimulation on the L4 DRG, recording on the lead (E12) and reference with Virtual Ground turned on (E16). Right figure: Recordings on the lead of increased stimulation at the DRG. The black dotted lines show the window of interest. No ECAPs are visible, only noise between -5 µV and 5 µV.

Measuring on different electrodes There were no measurements performed on different electrodes.

Changing the pulse width Measurements were performed with 220 µs, 300 µs and 800 µs, but none of the settings elicited any measurable ECAPs.

6.4 Patient 1

6.4.1 Paresthesia mapping

The stimulation parameters during paresthesia mapping were as described in Table 1 in the Methods. The stimulation configuration and the resulting ECAPs are shown in Figure 15. Both leads were implanted, but the right lead was not stimulated for paresthesia mapping

Conduction velocity and window of interest Paresthesia mapping was performed successfully, and an estimation of the conduction velocity was made based on the ECAPs measured. Next, a window of interest was determined. The estimated conduction velocity was higher because N1-ECAP peak occurred faster than in Pilot 1 & 2, but across the same distance.
Estimated conduction velocity: 60 - 70 m/s
Window of interest: 2.1 - 4.2 ms

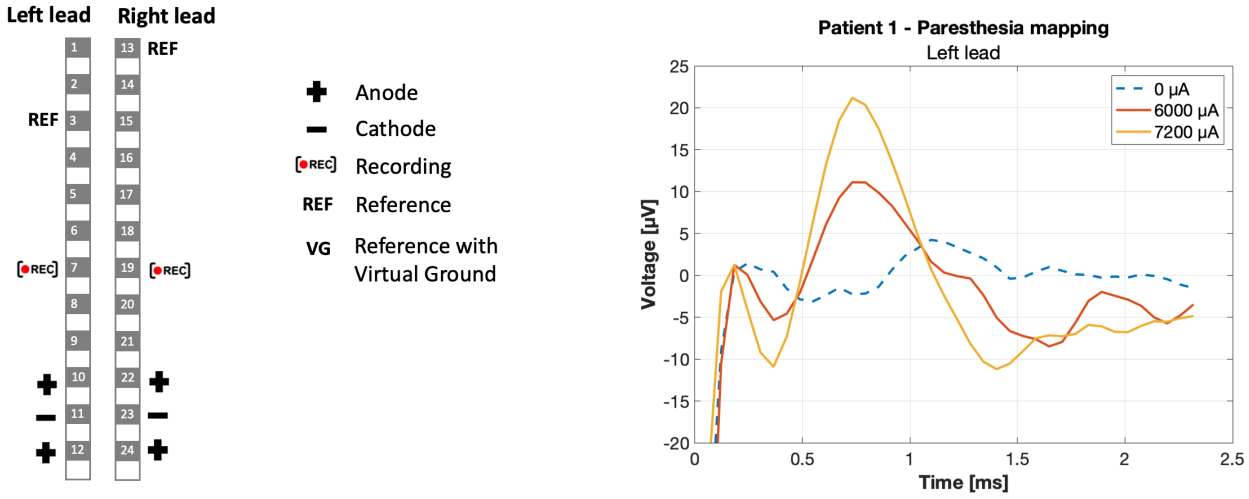


Figure 15: Left figure: Settings on the leads during paresthesia mapping. On E10-E11-E12 and E22-E23-E24 is a guarded cathode visualized. The recording electrodes are placed on E7 and E19, and the reference electrode is placed on E4 and E13. Right figure: Evoked compound action potentials (ECAPs) recorded on the left lead in Patient 1.

6.4.2 Stimulation on the DRG, recording on the lead

Set-up measurements Patient was not under sedation. The L3 DRG on the patient's left side was stimulated. The set-up is visualized in Figure 16. The stimulation parameters were as described in Table 1 in the Methods, except for the pulse width which was also 200 µs or 310 µs at times for comparison.

Increasing the stimulation The stimulation on the DRG was increased from 0 to 1100 µA and recorded on E1, and again on E12 until 800 µA, as can be seen in Figure 16. At 1100 µA the patient communicated that she perceived the stimulation as maximal. Measurements on E1 did not show any neural activity. Measurements on E12 showed several different kinds of signals. At stimulation amplitude 200 µA and 600 µA artifact can be seen. At 400 µA an almost sine-like wave can be seen, with a frequency of 700 Hz. As the stimulation at the DRG is only 10 Hz, it is not likely that multiple ECAPs are measured in the same sample window. This type of interference was quite common, also in other measurements. So while there is much activity, there is no evoked neural activity visible of which the amplitude increases with increased stimulation amplitude.

Coverage Since the patient was awake during the measurements, the patient could communicate where she felt the DRG stimulation, similar to paresthesia mapping. The patient stated that she felt the stimulation on the DRG in the same area as during paresthesia mapping, so it matched her painful area. The only area that was missing compared to paresthesia mapping was the front of the shin.

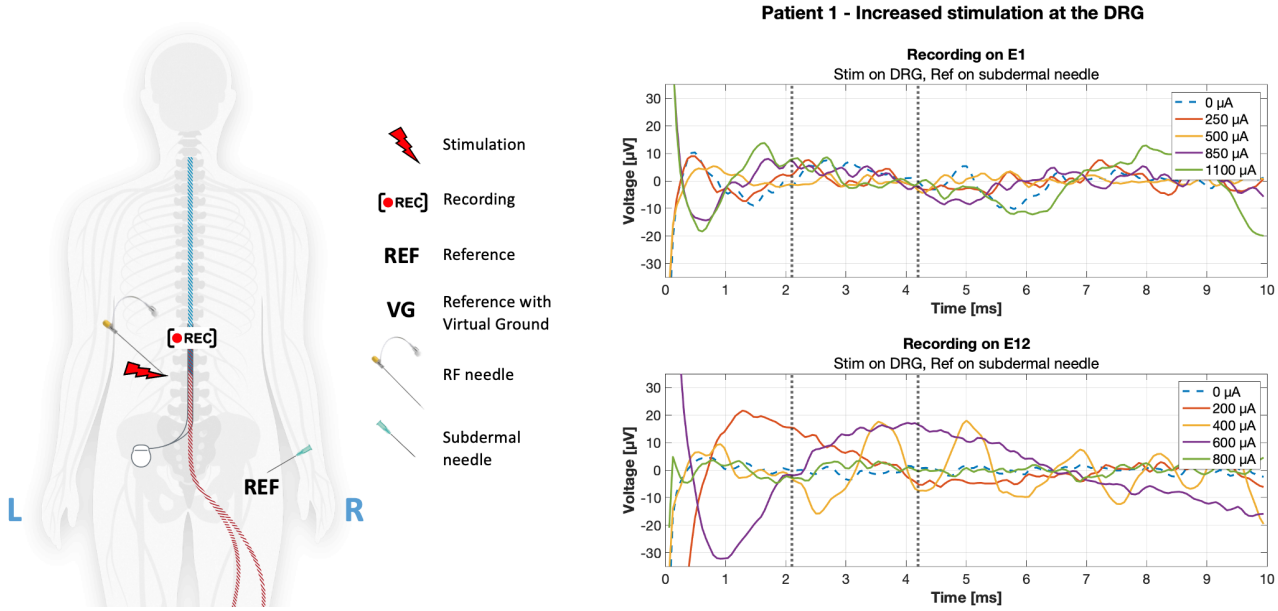


Figure 16: Left figure: Posterior view of the settings during stimulation on the DRG, recording on the lead (E1 and E12) and reference on the subdermal needle. Right figure: Recordings on the lead of increased stimulation at the DRG. The black dotted lines show the window of interest. In neither of the two figures is elicited neural activity visible, only noise and artifact.

Measuring on different electrodes The reference was changed from the subdermal needle to E13 on the right lead. The measurements at a constant stimulation of 1100 µA on different electrodes can be seen in Figure 17. There is no visible difference between the measurements on E7 as compared to E12, on all electrodes there are only small oscillations around baseline 0 µV.

Changing the pulse width Measurements were performed with a pulse width of 200 µs and 310 µs, but neither resulted in activation of ECAPs or any measurable neural activity.

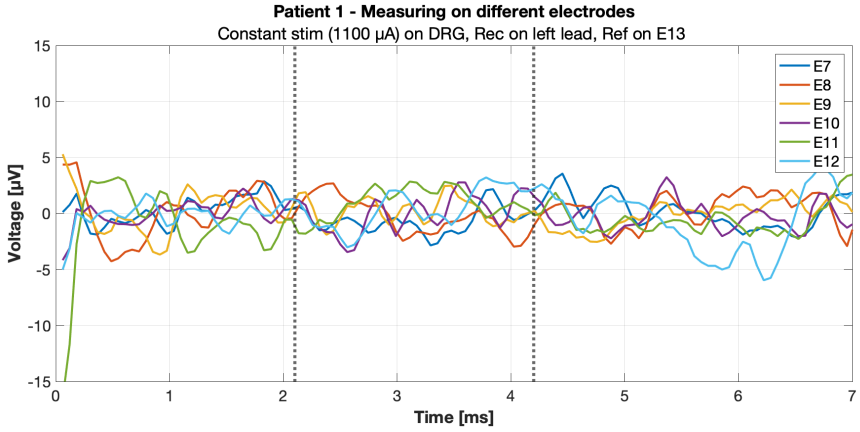


Figure 17: Measuring on different electrodes at constant stimulation of 1100 µA did not result in any neural activity or visible difference between the recording electrodes.

6.5 Patient 2

6.5.1 Paresthesia mapping

The stimulation parameters during paresthesia mapping were as described in Table 1 in the Methods. The stimulation configuration and the resulting ECAPs are shown in Figure 18. Both leads were successfully implanted and positioned based on the feedback during paresthesia mapping.

Conduction velocity and window of interest Paresthesia mapping was performed successfully, and an estimation of the conduction velocity was made based on the ECAPs measured. Next, a window of interest was determined.
Estimated conduction velocity: 50 - 60 m/s
Window of interest: 2.5 - 5 ms

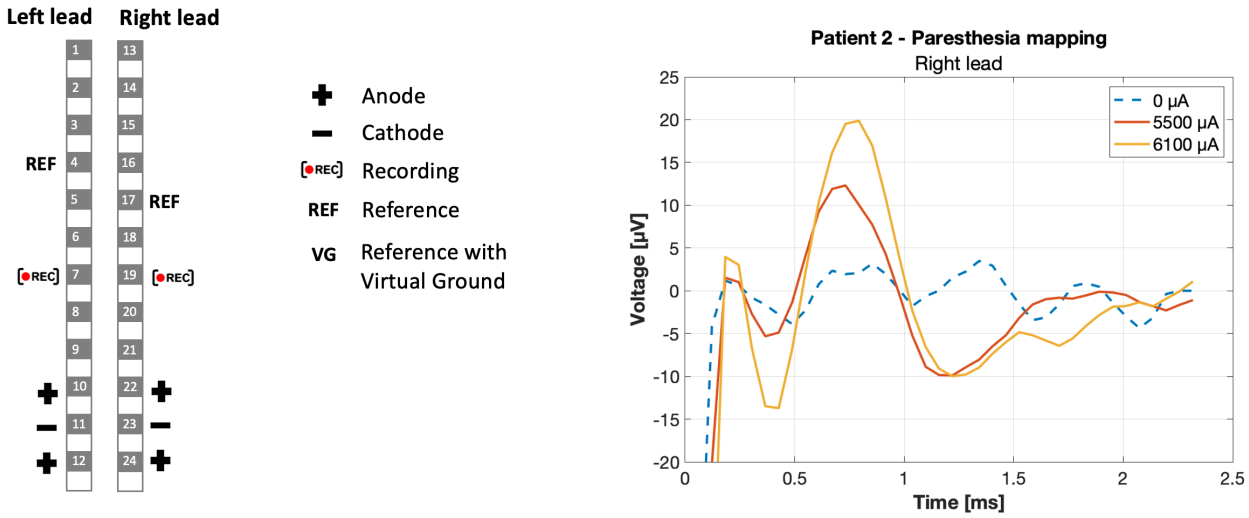


Figure 18: Left figure: Settings on the leads during paresthesia mapping. On E10-E11-E12 and E22-E23-E24 is a guarded cathode visualized. The recording electrodes are placed on E7 and E19, and the reference electrode is placed on E4 and E17. Right figure: Evoked compound action potentials (ECAPs) recorded on the right lead in Patient 2

6.5.2 Stimulation on the DRG, recording on the lead

Set-up measurements Patient was not under sedation. The L4 DRG on the patient's right side was stimulated. The set-up is visualized in Figure 19A. The stimulation parameters were as described in Table 1 in the Methods.

Increasing the stimulation The stimulation amplitude was increased from 0 µA to 2650 µA, which is more than double the amplitude used in previous measurements, but again this did not lead to any visible activity outside of the -5 µV to 5 µV range.

Coverage Patient felt the stimulation in the back of his leg and foot, but not the front of his leg.

Measuring on different electrodes Measuring on different electrodes did not show any evoked neural activity.

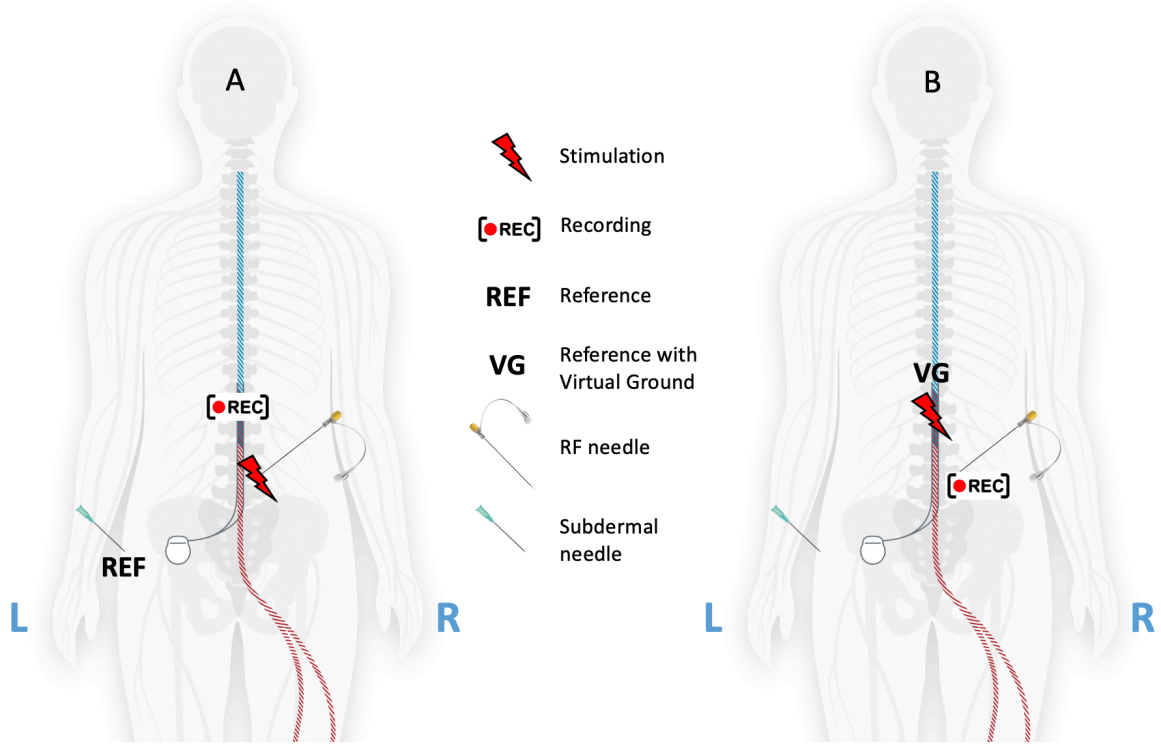


Figure 19: Figure A: Settings during stimulation on the dorsal root ganglion (DRG), recording on the lead. Figure B: Settings during stimulation on the bottom right lead (E23) and top right lead (E14), recording on the DRG. Virtual Ground was placed on the left lead (E3).

6.5.3 Stimulation on the lead, recording on the DRG

After the measurements on Patient 1, the idea was formed to perform the measurements both ways, so not only stimulating on the DRG and measuring on the lead, but also stimulating on the lead to record on the DRG. Since the experimental set-up would not change, only the settings on the programming tablet, this was deemed a good addition to the measurement protocol. Also, for the intra-operative procedure described to replace paresthesia mapping it would not matter which way the measurements were performed because either way, all DRGs corresponding to the painful area would need to have been stimulated to confirm the paresthesia coverage of the lead.
The settings for stimulating on the lead and recording on the DRG were the same as during paresthesia mapping (see Table 1). Because the same programming settings were used as paresthesia mapping without increasing the sample length, all recording were cut short at 4 ms. This can be seen in Figure 20.

Increasing the stimulation When stimulating on the lead and recording on the DRG, the steps of increasing the stimulation do not have to be as small as when stimulating on the DRG. During paresthesia mapping, the sensation threshold and also the activation threshold have been determined. During the measurements in patient 2, the stimulation was increased until a maximum of 5300 µA. As you can see in Figure 20, with increasing the amplitude there is a clear ECAP forming between 0 - 1.5 ms. When taking into account the distance the signal has to travel to the DRG before it can be measured, it makes it unlikely that this signal is recorded at the DRG. Estimating the conduction velocity based on the distance (15-25 cm), it would have to travel at a velocity between 300-500 m/s. It is also not likely stimulus artifact, because that is commonly restricted to the first 0.5 ms. Also, the signal has an activation threshold and before that threshold there is no signal amplitude, but stimulus artifact does not have an activation threshold. Lastly, the morphology looks more like a depolarization than artifact. The recording electrode is the RF needle in the DRG, but the reference electrode is placed internally on the top left lead. As mentioned before, a measurement is always the difference between the recording and reference electrode, and in this case it is more likely that the reference electrode is the one recording the signal instead of the DRG. This would mean the

signal is evoked by the stimulation on the bottom right lead, even though the reference electrode is located on the top of the left lead, meaning this signal is a 'regular ECAP' activated and recorded in the dorsal column.
Because a measurement is always the difference between the recording and reference electrode, the signals in the top two figures of Figure 20 are actually mirrored around the x-axis. Comparing an ECAP measured during paresthesia mapping mirrored around the x-axis gives almost exactly the same result (see bottom figure of Figure 20, supporting the statement that this signal is an ECAP activated and recorded in the dorsal column.
Remembering the characteristics of an ECAP, we have seen that there is an activation threshold after which the ECAP amplitude increases, the morphology fits the morphology of an ECAP. What we have not been able to prove is propagation of the signal. The difference in latency between stimulation on E23 and E14 is not clearly visible. This could be proven by moving the reference electrode on the left lead to prove the latency shifts and propagation along the lead is visible.

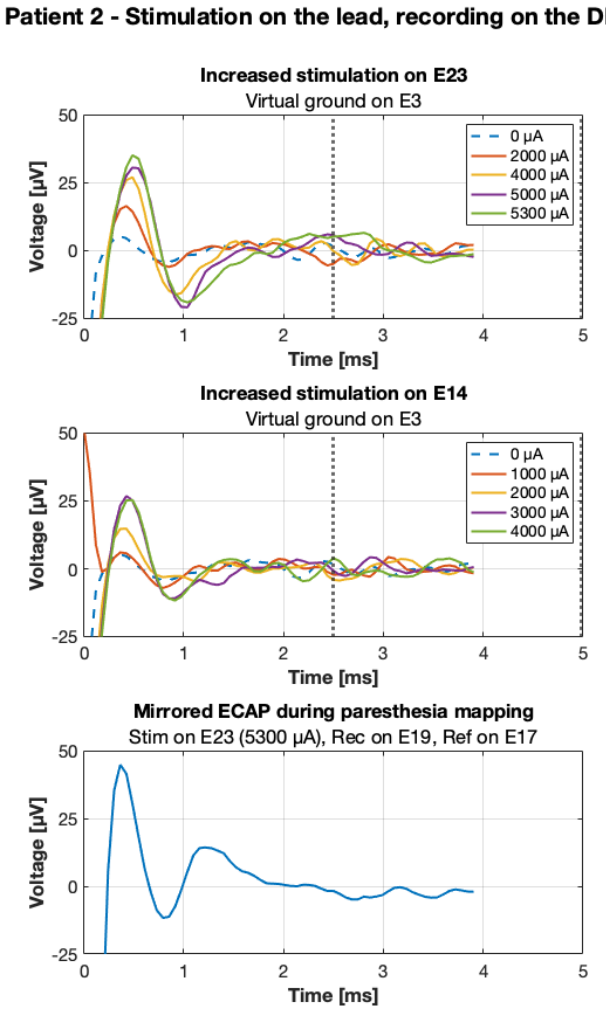


Figure 20: Top figure: Increased stimulation on E23, recording on the dorsal root ganglion (DRG). Window of interest half empty because sample length was wrongly set. Middle figure: Increased stimulation on E14, recording on DRG. Bottom figure: mirrored evoked compound action potential (ECAP) to compare to measurement on DRG.

6.6 Patient 3

6.6.1 Paresthesia mapping

The stimulation parameters during paresthesia mapping were as described in Table 1 in the Methods. The stimulation configuration and the resulting ECAPs are shown in Figure 21. Both leads were successfully implanted and positioned based on the feedback during paresthesia mapping.

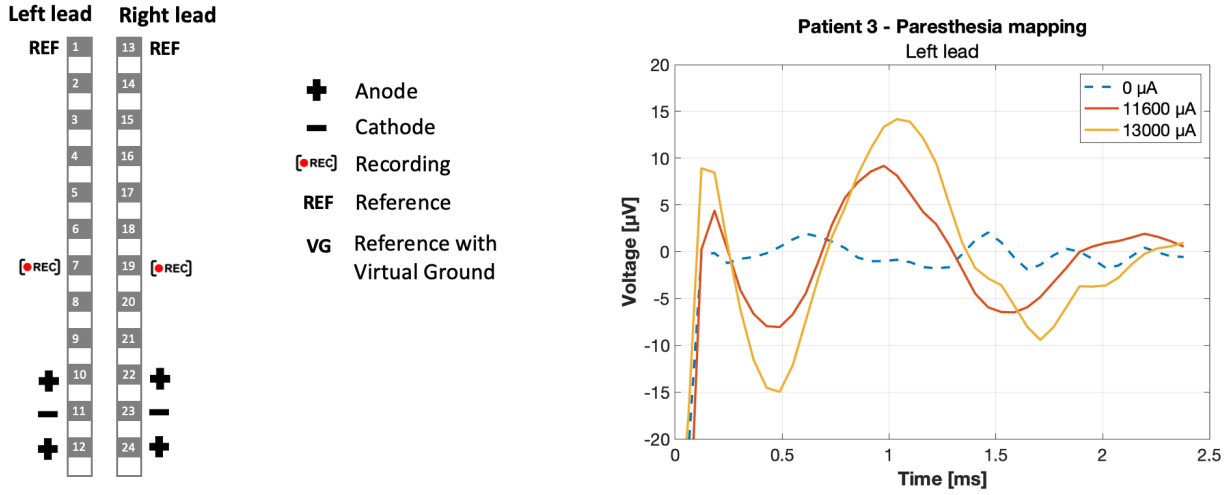


Figure 21: Left figure: Settings on the leads during paresthesia mapping. On E10-E11-E12 and E22-E23-E24 is a guarded cathode visualized. The recording electrodes are placed on E7 and E19, and the reference electrode is placed on E1 and E13. Right figure: Evoked compound action potentials (ECAPs) recorded on the left lead in Patient 3

Conduction velocity and window of interest Paresthesia mapping was performed successfully, and an estimation of the conduction velocity was made based on the ECAPs measured. Next, a window of interest was determined.
Estimated conduction velocity: 50 - 60 m/s
Window of interest: 2.5 - 5 ms

6.6.2 Stimulation on the DRG, recording on the lead

Set-up measurements Patient was not under sedation. The L4 DRG on the patient's left side was stimulated. The set-up is visualized in Figure 22A. The stimulation parameters were as described in Table 1 in the Methods.

Increasing the stimulation Nothing to see, comparable to Pilot 2 (Figure 14) and Patient 2.

Coverage Left L4 DRG stimulation covered the low back, left buttock and left backside of the knee.

Measuring on different electrodes Nothing to see, comparable to Patient 1 (Figure 17) and Patient 2.

6.6.3 Stimulation on the lead, recording on the DRG

Set-up measurements Patient was not under sedation. The set-up is visualized in Figure 22B. The stimulation parameters were the same as for paresthesia mapping (see Table 1).

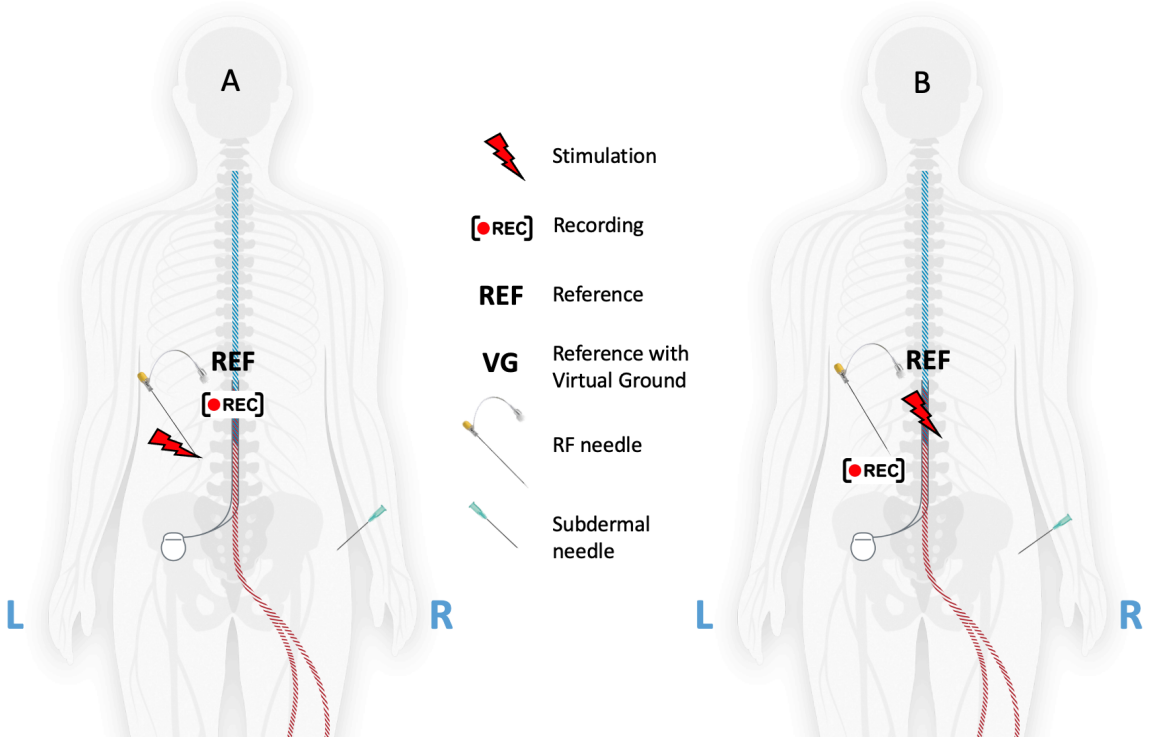


Figure 22: Figure A: Settings during stimulation on the dorsal root ganglion (DRG), recording on the lead, reference on the lead. Figure B: Settings during stimulation on the bottom left lead (E11), recording on the DRG. Reference was placed on the left lead (E2)

Increasing the stimulation To prevent that the reference electrode on the lead measures an ECAP formed by stimulation on the lead, like with Patient 2, the reference electrode was placed on the subdermal needle for Patient 3. The measurements were performed with both Virtual Ground turned on and off on the reference electrode, of which the results are visualized in Figure 23. The effects of Virtual Ground in reducing stimulation artifact are visible in the first 0.5 ms.

Moving the reference electrode As mentioned in Section 6.5.3, to prove the propagation of the ECAP activated and recorded on the lead in Patient 2, the reference electrode should be moved around to show a shift in latency. During the measurements in Patient 3, we moved the reference from E1 to E7 at same stimulation level. We also performed measurements with the reference with Virtual Ground turned on on E1, and at constant stimulation of 8100 µA we moved the reference from E1 to E7 (see Figure 24). The signals in the first 2 ms are clearly distinguishable from the rest of the time window, looking more like depolarizations or sinuses in different phases, while the rest looks more like noise. Zooming in on the first 3 ms (see Figure 25), the propagation of the signal can clearly be seen. The peak latency is marked with a black line. Keep in mind that the stimulation is given on E11 (bottom left lead), so when the reference is on E7 (middle left lead) the negative peak is closest compared to when the reference is on E1 (top left lead). By taking into account the conduction velocity needed to elicit an ECAP that fast on the DRG, and proving that the ECAPs propagate, in combination with an increasing ECAP amplitude by increased stimulation amplitude as seen in Patient 2, it can be concluded that when stimulating on the lead, recording on the DRG with the reference internally on the lead, the signals you measure are more the result of what is measured on the reference than what is measured on the DRG.

Conduction velocity The conduction velocity based on the latency shift in Figure 25 is approximately 90 m/s. Based on the peak latency at E7 and the distance between E11 and E7 the velocity is approximately 60 m/s, and based on the peak latency at E1 and the distance between E11 and E1 the velocity is 80 m/s. These velocities differ considerably.

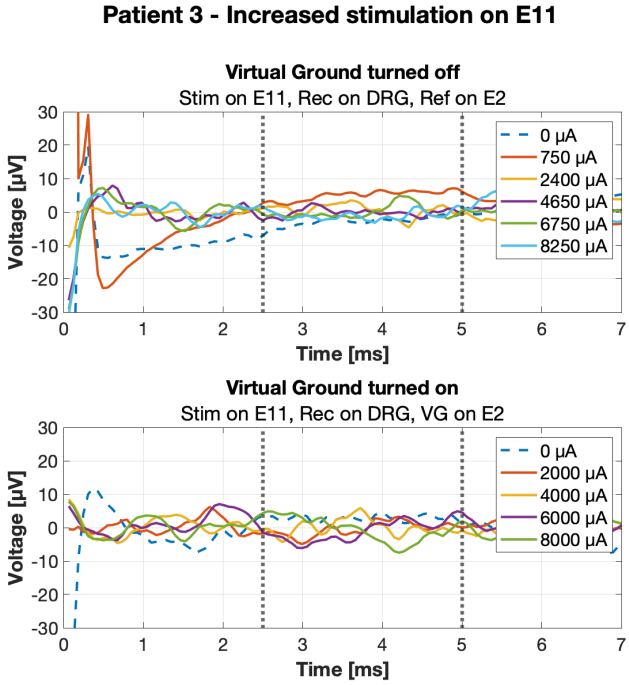


Figure 23: Result of increased stimulation on E11, recording on the dorsal root ganglion (DRG). There is no evoked neural activity visible in the window of interest. The comparison between Virtual ground turned off/on shows the effect of Virtual Ground in reducing artifact, where it is most visible in the first millisecond.

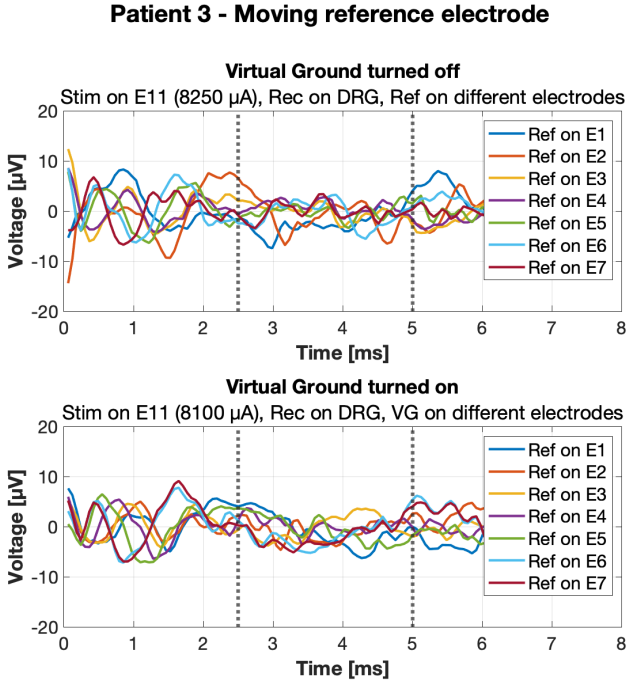


Figure 24: Result of constant stimulation on E11, recording on the dorsal root ganglion (DRG). The reference electrode is moved along the lead. In the window of interest there is no activity, but in the first two milliseconds there are some depolarizations visible.

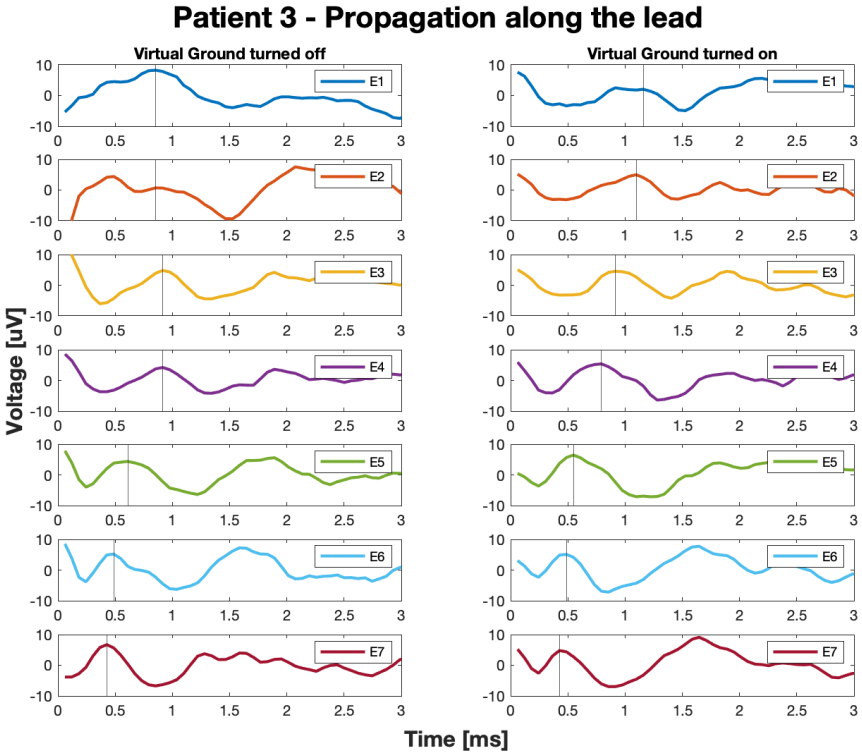


Figure 25: Zooming in on the first 3 milliseconds of Figure 24, a propagating evoked compound action potential (ECAP) is visible. The peak latency is marked with a single black line. It is clearly visible the peak latency shifts comparing the measurement on E7 and E1.

6.7 Patient 4

6.7.1 Paresthesia mapping

The stimulation parameters during paresthesia mapping were as described in Table 1 in the Methods. The stimulation configuration and the resulting ECAPs are shown in Figure 26. Both leads were successfully implanted and positioned based on the feedback during paresthesia mapping.

Conduction velocity and window of interest Paresthesia mapping was performed successfully, and an estimation of the conduction velocity was made based on the ECAPs measured. Next, a window of interest was determined.
Estimated conduction velocity: 50 - 60 m/s
Window of interest: 2.5 - 5 ms

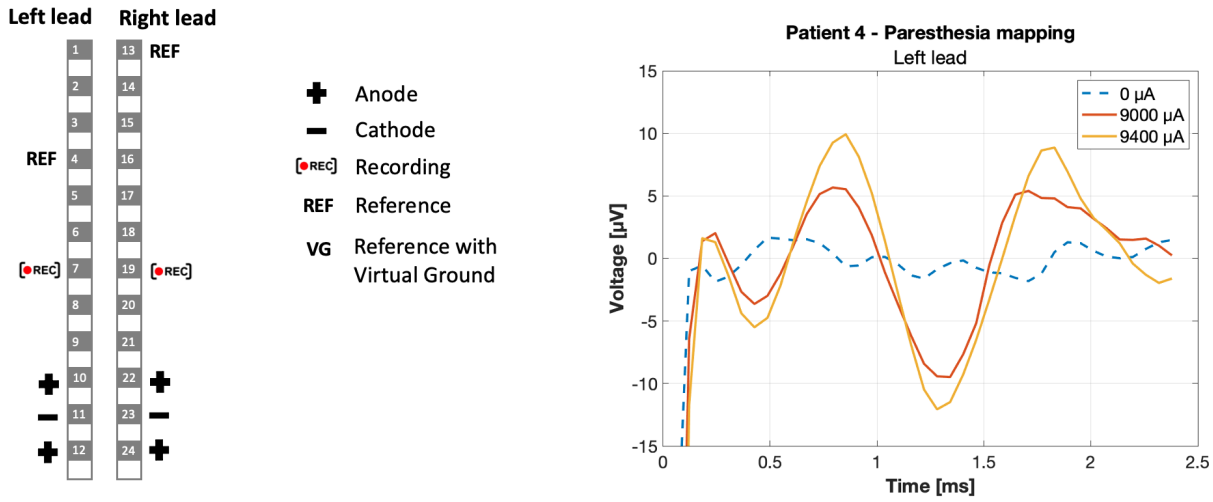


Figure 26: Left figure: Settings on the leads during paresthesia mapping. On E10-E11-E12 and E22-E23-E24 is a guarded cathode visualized. The recording electrodes are placed on E7 and E19, and the reference electrode is placed on E4 and E13. Right figure: Evoked compound action potentials (ECAPs) recorded on the left lead in Patient 4

6.7.2 Stimulation on the DRG, recording on the lead

Set-up measurements Patient was not under sedation. The L5 DRG on the patient's left side was stimulated. The set-up is visualized in Figure 27A. The stimulation parameters were as described in Table 1 in the Methods. During the measurements on Patient 4, we also performed automatic conduction velocity measurements with a fixed reference (subdermal needle) and with fixed distance, meaning the distance between the recording and reference electrode is always two electrodes on the lead.

Increasing the stimulation The stimulation amplitude was increased until 2700 µA while recording on E1 and until 2500 µA while recording E12. Looking at the recording on E1 in Figure 28, the first thing that stands out is that there is a very broad depolarization-like looking signal, of which the amplitude increases with an increased stimulation amplitude. There is also an activation threshold at around 1500 µA. The window where the signal occurs is not entirely explainable, since the first peak is already present at 1.5 ms, which would mean the conduction velocity is between 100 and 160 m/s. When looking at the recording on E12, the same signal is present at a stimulation amplitude of 2500 µA and 2400 µA, but not at 2150 µA or lower, which would mean the activation threshold is different at E1 compared to E12. This could be because of differences in the impedance at the electrode. The stimulation was not increased any more after 2700 µA so it is not verifiable that the increase in amplitude after reaching the threshold is linear. Also, the maximum peak-to-peak amplitude of the signal is approximately 80 µV, while the amplitude during paresthesia mapping at a stimulation amplitude of 9400 µA is only 25 µV (Figure 26). Another notable thing is that you would expect a certain propagation in the signal when comparing the measurements on E12 (closest to stimulus on DRG) to E1. This all makes it unlikely we are measuring neural activity elicited in the DRG and recorded on the lead in the dorsal column.
The same measurements were performed with Virtual Ground turned on on the reference electrode. In Figure 44 in the Appendix, the plots are nearly identical to the graph seen as in Figure 28.

Measuring on different electrodes Propagation is a requisite for neural activity and can be proved by measuring on different electrodes. From the recordings on E1 and E12 while increasing the stimulation it did not seem as though there was any propagation occurring and in the top figure in Figure 29 this is assumption is further solidified. The signal is nearly identical for all recording electrodes on the left lead. This leads to the question if this is again the reference electrode recording activity instead of the recording electrode. This can be verified by changing the reference electrode from the subdermal needle to internally on the lead, just as the recording electrode. This is shown in the bottom figure of Figure 29 where the reference is placed on a fixed distance from the recording electrode on

the lead. Here we can see that there is nothing left of the ECAP-like signal measured when the reference electrode was on the subdermal needle. This suggest that we were not measuring neural activity, but motor activity picked up by a subdermal needle wrongly placed in the underlying muscle.

Coverage Left L5 DRG stimulation provided paresthesias in the left calve.

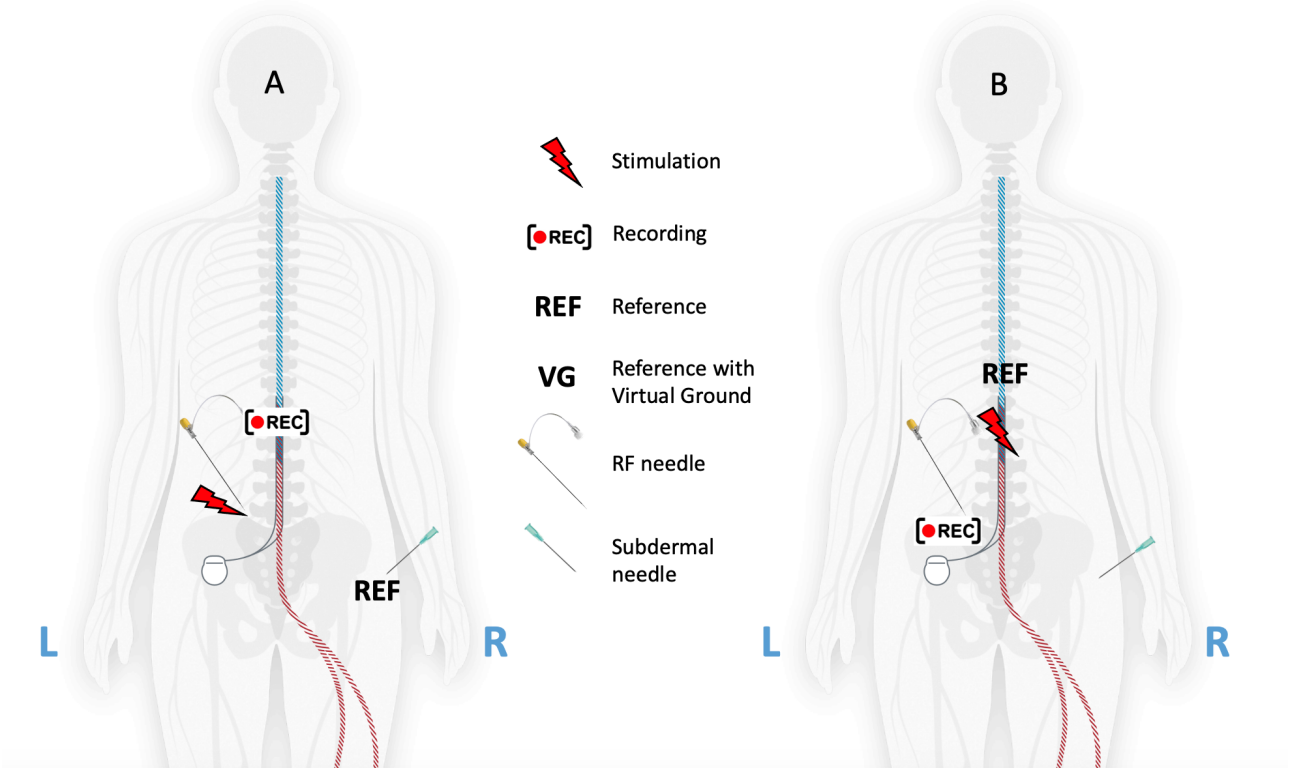


Figure 27: Figure A: Settings during stimulation on the dorsal root ganglion (DRG), recording on the lead (E1 and E12), reference on the subdermal needle. Figure B: Settings during stimulation on the lead, recording on the DRG and reference on the lead.

6.7.3 Stimulation on the lead, recording on the DRG

Set-up measurements Patient was not under sedation. The set-up is visualized in Figure 27B. The stimulation parameters were the same as for paresthesia mapping (see Table 1).

Increasing the stimulation Nothing to see, comparable to Figure 14.

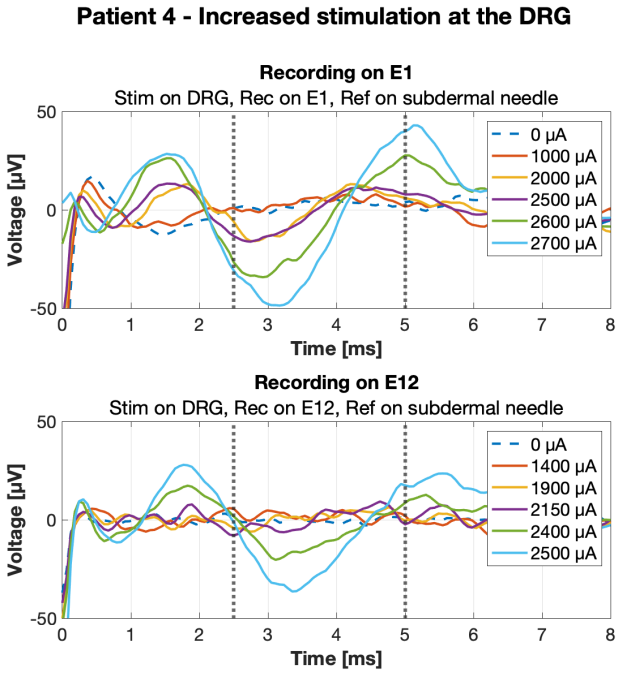


Figure 28: Result of increased stimulation on the dorsal root ganglion (DRG), recorded on E1 and E12. A broad signal that looks like a depolarization is clearly visible, inside and outside the window of interest. The signal amplitude also increases with an increased stimulation amplitude.

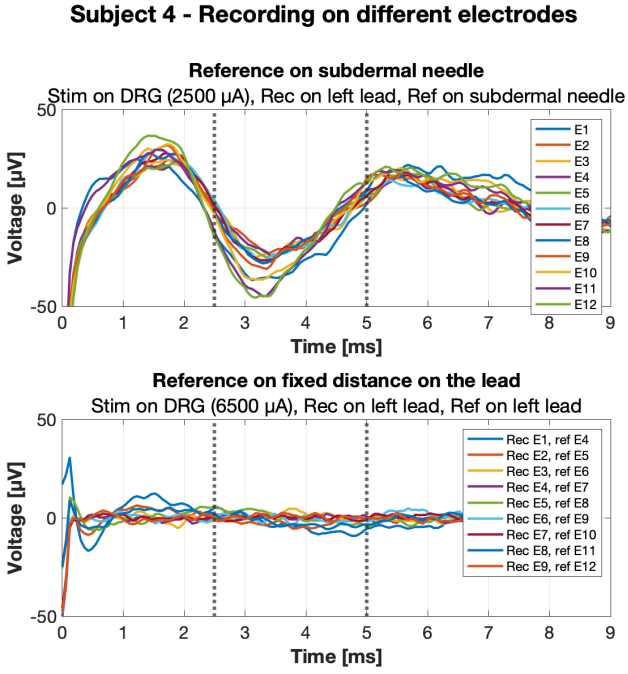


Figure 29: Result of recording on different electrodes to verify propagation of the signal. Top figure shows recordings on different electrodes with fixed reference on the subdermal needle. Bottom figure repeats the measurements with a fixed distance on the lead. These results show there is no propagation of the signal, but actually the subdermal needle recording motor activity.

6.8 Patient 5

6.8.1 Paresthesia mapping

The stimulation parameters during paresthesia mapping were as described in Table 1 in the Methods. The stimulation configuration and the resulting ECAPs are shown in Figure 30. The left lead was successfully implanted and positioned based on the feedback during paresthesia mapping. Paresthesia mapping on the right side failed, the lead was implanted but not connected very well.

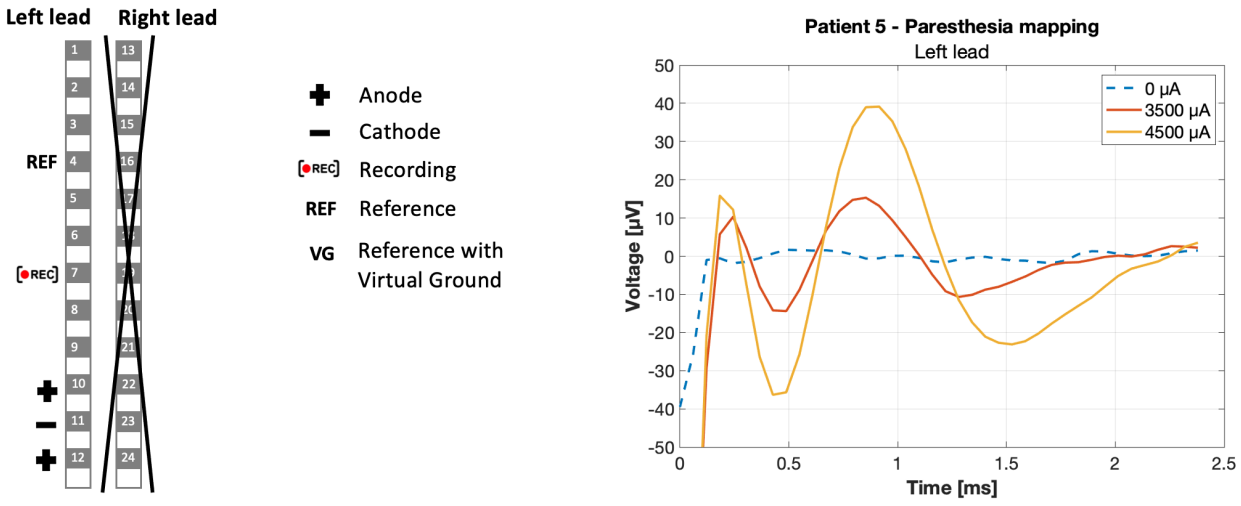


Figure 30: Left figure: Settings on the lead during paresthesia mapping. On E10-E11-E12 is a guarded cathode visualized. The recording electrode is placed on E7, and the reference electrode is placed on E4. Right figure: Evoked compound action potentials (ECAPs) recorded on the left lead in Patient 5.

Conduction velocity and window of interest Paresthesia mapping was performed successfully, and an estimation of the conduction velocity was made based on the ECAPs measured. Next, a window of interest was determined.
Estimated conduction velocity: 50 - 60 m/s
Window of interest: 2.5 - 5 ms

6.8.2 Stimulation on the DRG, recording on the lead

Set-up measurements Patient was under sedation. The L4 DRG on the patient's left side was stimulated. The set-up is visualized in Figure 31A. The stimulation parameters were as described in Table 1 in the Methods, except for the pulse width which was 120 µs or 190 µs at times for comparison.

Current splitting Because the measurements up to Patient 5 have not been very successful, we considered improvements to the protocol. The distance between the RF needle and the DRG has not been quantified between patients, and it is possible that the activation threshold was never met to elicit ECAPs in the DRG. For these reasons we decided to perform the measurements under sedation again, to be able to increase the stimulation amplitude more without hurting the patient since it became clear that we were not harming the DRG with the stimulation amplitudes used until now. Also, the RF needle was now placed under guidance of fluoroscopy with contrast, to decrease the distance between the tip of the RF needle and the DRG. To make sure the stimulation given to the DRG was not harmful, current splitting was used. This setting enabled us to split the current over different electrodes, so only 6% of the complete stimulation amplitude was given to the RF needle, and the remaining 94% was given to an ECG electrode on the shoulder (see the set-up in Figure 31A. The stimulation on the shoulder was not harmful.

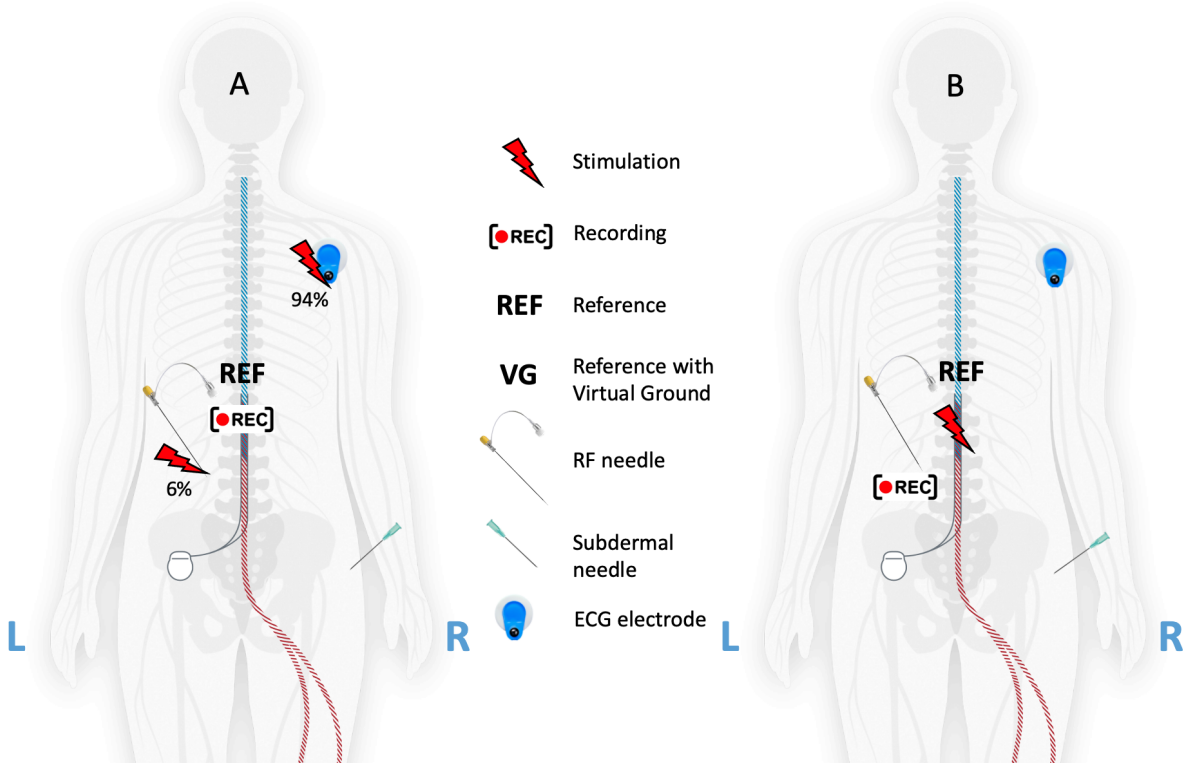


Figure 31: Figure A: Settings during stimulation on the dorsal root ganglion (DRG) with current splitting, 6% on the DRG and 94% on a ECG electrode on the shoulder, recording on the lead, reference on the lead. Figure B: Settings during stimulation on the lead, recording on the DRG. Reference was placed on the lead.

Increasing the stimulation Unfortunately, the placement of the RF needle using fluoroscopy did not improve the results. During increased stimulation, there was again nothing to see, comparable to Patient 3, Patient 2 and Pilot 2. Notable is amount of artifact before 10 samples (before 0.5 ms), see Figure 46 in Appendix C.

Coverage It was not possible to communicate the coverage because the patient was under sedation.

Measuring on different electrodes Nothing to see.

Changing the pulse width Measurements were performed with 120 µs and 190 µs, but none of the settings elicited any measurable ECAPs.

6.8.3 Stimulation on the lead, recording on the DRG

Set-up measurements Patient was under sedation. The set-up is visualized in Figure 31B. The stimulation parameters were the same as for paresthesia mapping (see Table 1).

Increasing the stimulation Only artifact, no ECAPs. See Figure 48 in Appendix C.

Moving the reference electrode When moving the reference electrode around on the lead contacts, while stimulating on the lead and recording at the DRG, you can see the propagating ECAPs again caused by the stimulation on the lead and recorded on the reference, like in Patient 3 (see Figure .. in the Appendix).

6.9 Patient 6

6.9.1 Paresthesia mapping

The stimulation parameters during paresthesia mapping were as described in Table 1 in the Methods. The stimulation configuration and the resulting ECAPs are shown in Figure 32. Both leads were successfully implanted and positioned based on the feedback during paresthesia mapping.

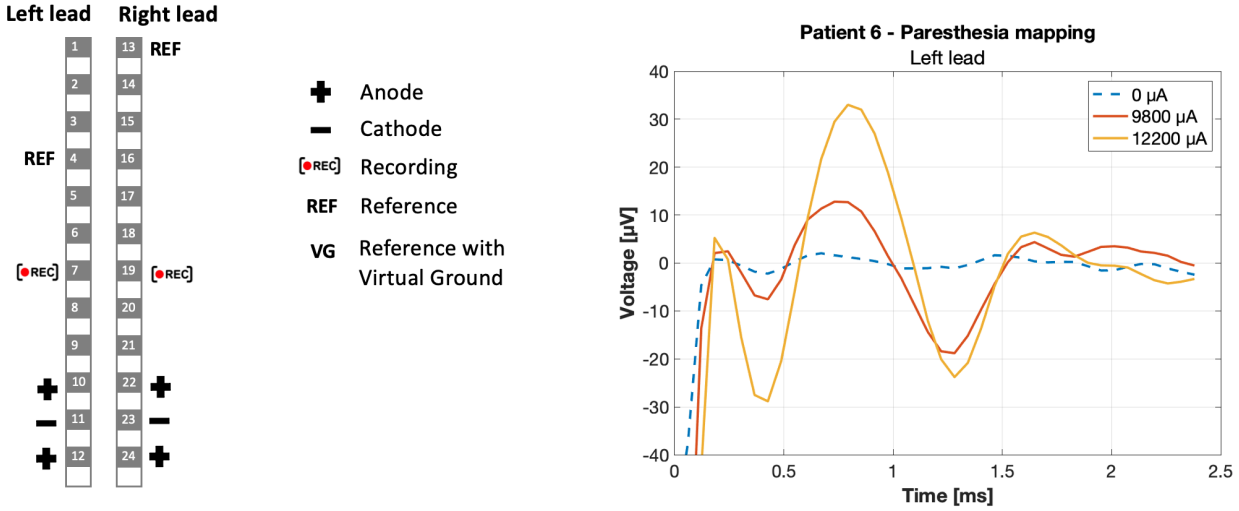


Figure 32: Left figure: Settings on the leads during paresthesia mapping. On E10-E11-E12 and E22-E23-E24 is a guarded cathode visualized. The recording electrodes are placed on E7 and E19, and the reference electrode is placed on E4 and E13. Right figure: Evoked compound action potentials (ECAPs) recorded on the left lead in Patient 6.

Conduction velocity and window of interest Paresthesia mapping was performed successfully, and an estimation of the conduction velocity was made based on the ECAPs measured. Next, a window of interest was determined.
Estimated conduction velocity: 50 - 60 m/s
Window of interest: 2.5 - 5 ms

6.9.2 Stimulation on the DRG, recording on the lead

Set-up measurements Patient was under sedation. The L4 DRG on the patient's left side was stimulated. The set-up is visualized in Figure 33A. The stimulation parameters were as described in Table 1 in the Methods. The RF needle was placed under fluoroscopy guidance with contrast and the stimulation was given via current splitting again.

Increasing the stimulation When looking at Figure 34, it appears like the increase of stimulation current results in an increased ECAP amplitude with the activation threshold between 64 and 96 µA. The low current is remarkable however. A recurring problem alert during the measurements forced us to stop stimulating using current splitting. After current splitting, 100% stimulation was given in smallest possible steps (see Figure 35. No other settings changed, so very remarkable that noting happened at current 100 µA or even 150 µA. Current was increased even more, and at 1800 µA an ECAP started showing. When we saw the ECAP, the stimulation was kept at constant 2400 µA and different electrodes were measured. The patient became restless which made us believe the stimulation was painful so the current was not increased.

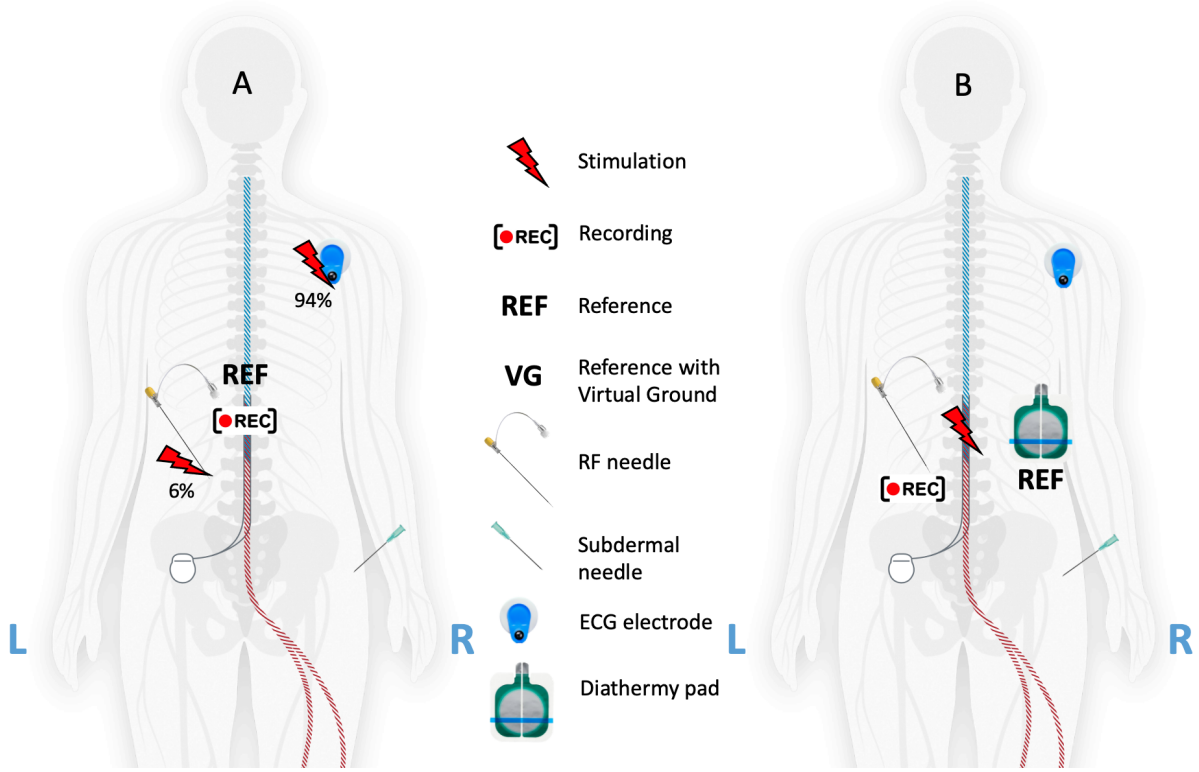


Figure 33: Figure A: Settings during stimulation on the dorsal root ganglion (DRG), with current splitting, 6% on the DRG and 94% on a ECG electrode on the shoulder, recording on the lead (E12), reference on the lead (E17). Figure B: Settings during stimulation on the left lead (E11), recording on the DRG, and the reference was placed on the diathermy pad.

Coverage Not possible to communicate because patient was under sedation.

Measuring on different electrodes Measurements on different electrodes on the left lead show the propagation of the ECAP along the lead. The peak latency is marked with a single black line. The peak latency shifts from approximately 2.5 ms at E12 to 3.3 ms at E2

Conduction velocity The conduction velocity calculated based on the latency shift and the distance between E12 and E2 is approximately 75 m/s. Based on the peak latency at E12 and the distance between DRG and E12 (15-25 cm), the conduction velocity would be between 60 and 100 m/s. Based on the distance between DRG and E2 (22-32 cm), the conduction velocity would be between 65 and 100 m/s.

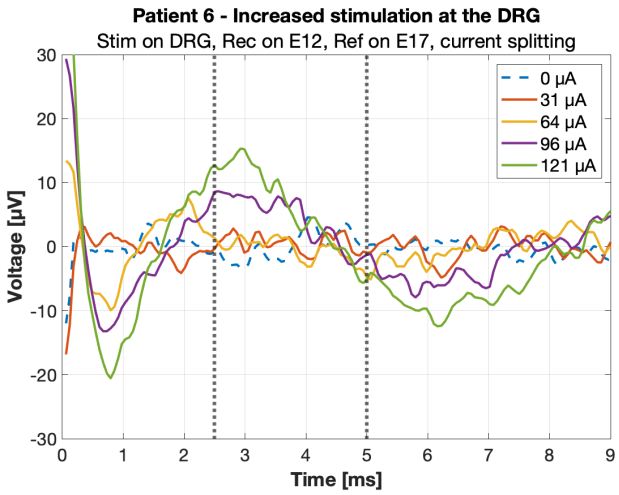


Figure 34: Results of increased stimulation using current splitting on the dorsal root ganglion (DRG), recorded on E12 with reference electrode on E17. A broad signal that looks like a depolarization appears after 60-90 µA, of which the amplitude increases with increased stimulation amplitude. The signal appears inside and outside the window of interest. Remarkably low current to elicit any neural activity.

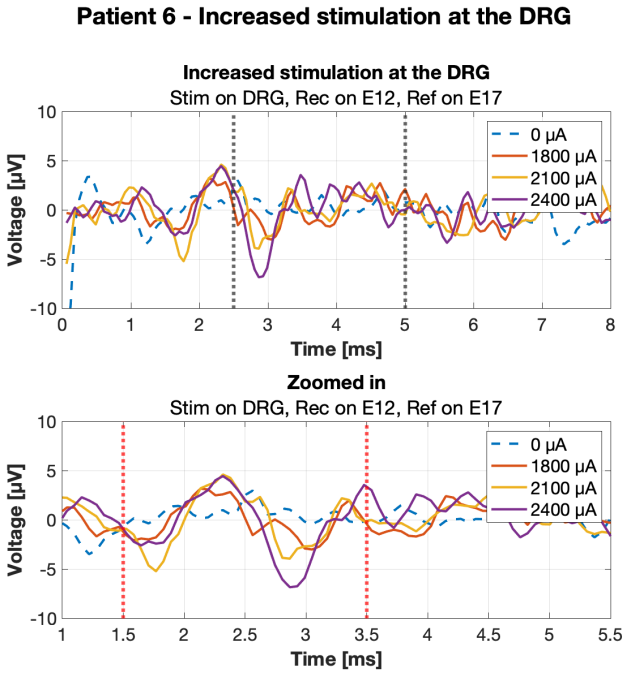


Figure 35: Results of increased 100% stimulation on the dorsal root ganglion (DRG). Settings are not changed compared to Figure 34, except percentage of stimulation on the DRG. At 1800 µA a depolarization appears, of which the amplitude increases with increased stimulation amplitude. Bottom figure zooms in on the window 1 to 5.5 ms, to show the depolarization more clearly.

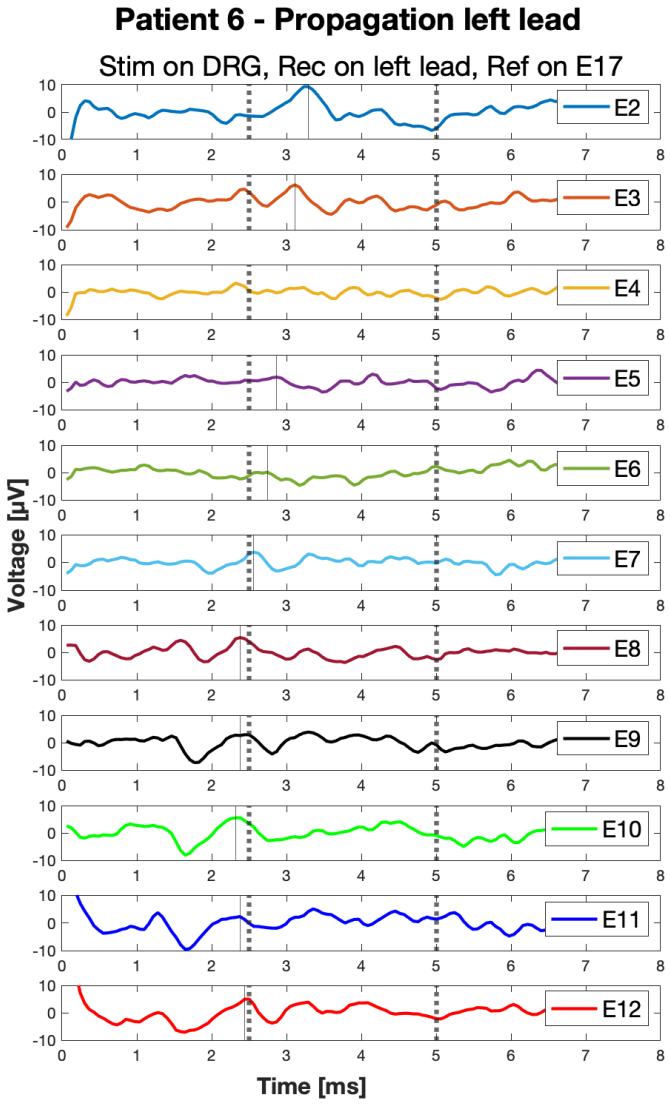


Figure 36: Individual measurements on all electrodes of the left lead shows propagation of the evoked compound action potential (ECAP) along the dorsal column. The result of L4 DRG stimulation "enters" the recording electrodes at E12, and the latency of the first negative peak is approximately 2.5 ms. Furthest away from the stimulation is E2, where the peak latency is approximately 3.3 ms. Black dotted line = window of interest, black line refers to peak latency.

6.9.3 Stimulation on the lead, recording on the DRG

Set-up measurements Patient was under sedation. The set-up is visualized in Figure 31B. During these measurements, we also attempted to use the diathermy pad as the reference electrode. The stimulation parameters were the same as for paresthesia mapping (see Table 1), except for the pulse width which was 250 µs.

Increasing the stimulation The measurements with the reference electrode on the subdermal needle or internally on the lead did not result in any measurable activity, but when we switched to the diathermy pad the result was Figure 37. No measurements were made at 0 µA, but at 6000 µA there is no activity visible so the activation threshold was not yet overcome. At around 8000 µA a depolarization starts showing, of which the peak-to-peak amplitude increases with increased stimulation amplitude. The ECAP does form outside of the window of interest. The corresponding conduction velocity is between 80 and 130 m/s.

Propagation Not possible to prove propagation of the signal because the RF needle on the DRG is only one contact.

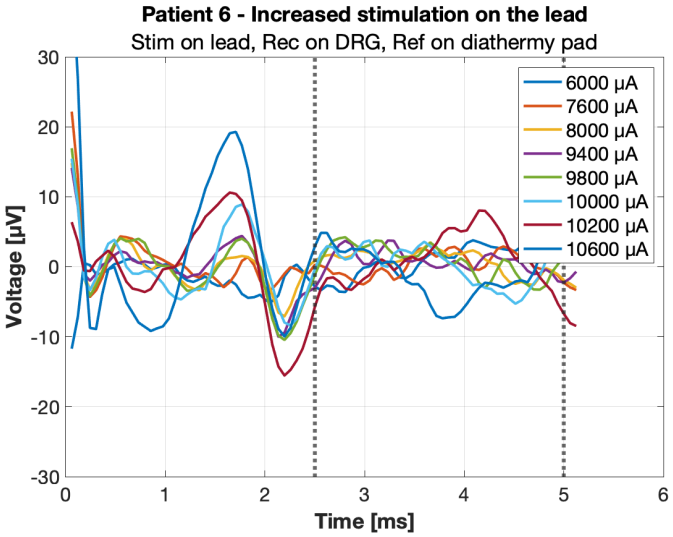


Figure 37: Results of increased stimulation on the lead, recorded on the dorsal root ganglion (DRG). An evoked compound action potential (ECAP) starts appearing at approximately 8000 µA, and the ECAP-amplitude increases with the increased stimulation amplitude on the lead. The black dotted line shows the window of interest, so the ECAP does appear outside of this window.

7 Discussion

7.1 Intraoperative measurements

Intraoperative testing procedures to objectively place SCS leads without the need for patient feedback have been widely researched, but all make use of intraoperative neuromonitoring [8, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22]. In the Netherlands, intraoperative neuromonitoring is reserved for operations like the removal of a spinal cord tumor, scoliosis surgery, carotis endarterectomy, and not commonly present for routine SCS implantations. This complicates the implementation of these intraoperative testing procedures, and indicates that a procedure without the need for intraoperative neuromonitoring would be better suited for use in the Netherlands.
Closed loop SCS stimulates the dorsal column and records the evoked neural activity. In this thesis I aimed to evaluate whether neural activity caused by DRG stimulation was also measurable in the dorsal column. The exploratory measurement protocol enabled us to investigate different stimulation parameters, stimulation and recording targets and materials. By evaluating every completed measurement, we changed or added components to the protocol in order to improve the measurement protocol. As described in the Results, this led to two successful measurements of neural activity out of the eight measurements performed, so the measurements turned out predominantly unsuccessful. In this discussion I will elaborate on similarities and differences between the successful and unsuccessful measurements, improvements for the experimental set-up and protocol and provide recommendations for the future.

7.2 Successful measurements

Pilot 1 Pilot 1 was a 50-year old male with primarily low back pain. The medication he used was limited to paracetamol and NSAID's and his pre-implantation NRS was 6. The measurements were performed while the patient was under sedation. The stimulation on the DRG was performed with a frequency of 10 Hz, pulse width of 300 µs, interphase gap of 200 µs and a biphasic pulse type with negative polarity. The recording electrode was E23 during the increasing stimulation phase, and when constant stimulation was given, all electrodes on the lead were used for recording.
As presented in the Results, the measurements in Pilot 1 were successful in proving that stimulation on the DRG can be recorded as ECAPs in the dorsal column. When there was no stimulation, no signal appearedin the dorsal column. When the stimulation increased, there was an activation threshold to overcome and after that threshold the ECAP amplitude increased linearly (Figure 9, 11). Lastly, when recording on different electrodes, propagation was visible (Figure 12).

Patient 6 Patient 6 was a 65-year old female with low back pain and pain at the back of the left leg. Her medication included paracetamol, NSAID's, opioids, antidepressants and anti-epileptics, and her pre-implantation NRS was 8. All measurements were performed under sedation. The stimulation on the DRG was performed with the same stimulation parameters as with Pilot 1, with the only difference that current splitting was used for some measurements. The stimulation on the lead while recording on the DRG was performed with the following stimulation parameters: frequency of 30 Hz, pulse width of 250 µs, interphase gap of 200 µs and a triphasic pulse with positive polarity. The reference electrode was placed on the diathermy pad.
Stimulation on the DRG, recording on the lead: In Figure 34 it appeared that increasing the stimulation amplitude resulted in an ECAP forming at 100 µA, and the ECAP amplitude increased with increased stimulation amplitude. However, the current at which this is occurring is remarkably low. For dorsal column stimulation this would not suffice, but it could be that the RF needle was placed so close to the DRG that a stimulation amplitude of 100 µA is enough to elicit an ECAP measurable on the lead. Unfortunately, the measurements using current splitting resulted in a recurring problem alert, preventing us from increasing the stimulation further and forcing us to switch to stimulating with 100% on a single electrode. This resulted in Figure 35, where at a stimulation of 100 µA or even 150 µA no neural activity occurred. The stimulation was increased and only at a stimulation amplitude of 1800 µA a depolarization started showing. The patient became restless and groaned through her sedation, leaving us with the assumption that that the stimulation was painful, so the stimulation amplitude was not increased. The stimulation amplitude of 2400 µA on the DRG in Patient 6 resulted in clear ECAPs, and the propagation of the signal also clearly visible in Figure 36.

The fact that the activation threshold increased almost 20 fold between the measurements using current splitting and 100% on the DRG, without changing the settings makes our previous measurement using current splitting less credible. It is possible that the stimulation on the ECG electrode on the shoulder disturbed the measurements, but the morphology of the two measurements also differs a lot. It could also be that the RF-needle was repositioned slightly by accident between the measurements, resulting in an increased distance between the RF-needle tip and DRG.
Stimulation on the lead, recording on the DRG: Increased stimulation on the lead was measurable on the DRG. No measurements were made at 0 µA, but at 6000 µA there is no activity visible so the threshold was not yet overcome. At around 8000 µA a depolarization starts showing, of which the peak-to-peak amplitude increases with increased stimulation amplitude. The conduction velocity was relatively fast (80 - 130 m/s). Proving propagation when recording on the DRG is slightly more difficult because there are not multiple measuring contacts possible on the DRG. However, the propagation could be proved by stimulating on the top & bottom of the lead while recording the reaction on the DRG, but unfortunately this was not performed at that time. The measurements in Patient 6 on the DRG while stimulating on the lead were the only ones in this direction that were successful, which could be due to the diathermy pad being the reference electrode.

Similarities and differences Age and gender differed between the two successful measurements. Their pre-surgery NRS differed slightly, but the pain medication of Patient 6 was a lot heavier than Pilot 1. Both measurements were performed under sedation, while many of the unsuccessful measurements were not performed under sedation. The similarities between the successful measurements are limited because in Pilot 1 only measurements were only performed in the direction of stimulation on the DRG, and not in the other direction. In Patient 6 the results after stimulation on the DRG were not as distinctive as in Pilot 1, but still apparent. It is remarkable how the stimulation amplitude on the DRG differs between Pilot 1 and Patient 6. A stimulation amplitude of 700 µA resulted in an ECAP amplitude of 25 µV in Pilot 1, but in Patient 6 a stimulation amplitude of 2400 µA barely resulted in an ECAP amplitude of 15 µV. The proximity of the RF needle to the DRG could have played a role in this.

Conduction velocity The conduction velocity calculations in this research can differ substantially between measurements, even using the exact same settings. This is causes by several factors. The distance between the stimulating/recording electrode is unknown, and therefore a range of 15-25 cm is used for calculations. This is a wide range, resulting in differences in velocities of up to 50 m/s. Also, literature states that SCS involves mostly A-beta fibers, but this is based on stimulation and recording in the epidural space. When the DRG is directly stimulated via a RF needle, it could be possible A-alfa fibers in the DRG are activated which travel with a velocity of 80-120 m/s [25]. Activation of A-alfa fibers would increase the peak latency of the ECAP, because an ECAP is the summation of all action potentials measured together. This would only occur in measurements performed in the direction of stimulation on the DRG and recording on the lead.

7.3 Unsuccessful measurements

Patient 2 Patient 2 was a 51-year old male with pain in his entire front right leg. These measurements were unsuccessful, but notable because in this patient we changed the direction of the measurements first time. Surprisingly, very distinctive ECAPs were measurable, and the amplitude increased with stimulation, but outside of the window of interest. It became clear that the reference electrode internally on the lead was measuring the ECAPs caused by stimulation on the lead, instead of the DRG measuring ECAPs caused by stimulation on the lead.
Also, comparing Patient 2 with Pilot 1, who had a shorter pain duration (15 months compared to 42), less medication, similar NRS, but still unsuccessful measurements.

Patient 4 Patient 4 was a 55-year old male with pain in his calves and feet on both sides. These measurements were unsuccessful but notable because ECAPs were measured, and again the amplitude increased with stimulation. The morphology was the problem, much broader than expected, which also resulted in the expected window being much smaller than where the activity happened. It became clear that there was no propagation which led to the belief that the reference on the subdermal needle was measuring motor activity. When repeating the measurements with the reference on the subdermal needle at a fixed distance from the recording electrodes, nothing remained of the 80 µV ECAP amplitude.

Pilot 2, Patient 1, 3 and 5 Comparing the successful measurements to the unsuccessful measurements, gender is not a discriminating factor, in both groups half is male, half is female. Effect of medication on conduction velocity, propagation, signal transduction etc. could play a role. However, all patients with unsuccessful measurements received high doses of medication except for Patient 2. But again, successful Patient 6 was also prescribed a lot of medication but still successful measurements and Pilot 1 almost no medication and also successful measurement so not a clear denominator.

7.4 Experimental set-up and measurement protocol

7.4.1 Materials

RF needle When stimulating the DRG using the RF needle, a stimulation field is formed to recruit fibers in the DRG. The distance from the RF needle to the DRG and stimulation amplitude determine how many fibers will be recruited. The stimulation amplitude can be controlled, but the distance of the RF needle to the DRG is variable between patients. This can be caused by patient anatomy, especially in PSPS-type 2 patients with previous surgeries in the same area. With the needle tip closer to other tissues near the DRG, the stimulation can be harmful to that tissue and painful for the patient. During the last two measurements in this study, we tried to verify the needle placement with contrast fluid and fluoroscopy. Still, the distance between the needle tip and DRG was difficult to verify because even with contrast fluid and fluoroscopy, the DRG is not clearly visible. When the distance between RF needle and DRG is unknown, determining which stimulation amplitude is necessary to recruit fibers is hard to predict and to reproduce between patients.
Also, an RF needle is developed and used for stimulation. In this study we have also used the RF needle as a recording electrode, which is a function outside of the scope of the needle. Only one out of eight recordings on the DRG resulted in a successful measurement, which could be partly the result of the RF needle not being sensitive enough to measure activity in the DRG.
Recommendation: Using a percutaneous RF ablation lead, much like a DRG stimulation lead, designed for stimulating the DRG on multiple contacts at once could improve the amount of fibers activated by stimulation [source]. Or a regular DRG stimulation lead could be used because they are developed to elicit neural activity and paresthesias in the corresponding dermatomes. Or a DRG stimulation lead with directional current, that way you can direct the current to the DRG and not stimulate other tissues, making the stimulation less painful. Or even a lead with stimulating and recording capabilities, like the Evoke lead, would also solve the problem of the RF needle not being suitable for using as measuring electrode. All interesting options for research but very expensive since the DRG stimulation in the intraoperative testing procedure described in this study is only used for the guidance of SCS lead placement, and would thus be removed after the SCS lead was placed correctly.

Subdermal needle The needle that was used as a reference electrode was placed in the dermis, and connected via a crocodile clip to the break-out box. The impedance of the first needle tested was very high (2,4 KOhm), and trying different sizes of needles improved the impedance only slightly (1,8 KOhm). The crocodile clip connecting the needle to the break-out box could also contribute to the impedance, but it is a common functionality to connect components to an electrical circuit [wikipedia].
Recommendation: the diathermy pad was used in Patient 6 as the reference electrode when depolarizations were measured. The impedance of this pad during the measurements was ...

7.4.2 Dorsal root ganglion as target

Fibers in DRG A possible explanation for the failure to recruit enough fibers in the DRG to produce a measurable ECAP in the dorsal column could be the amount of fibers in the DRG. In the dorsal column, all afferent fibers converge and travel to the central nervous system. In a single DRG only the afferent fibers of that dermatome are present, which could be an insufficient amount to produce a ECAP that is measurable in the dorsal column.
Recommendation: In this research we have stimulated one DRG at a time, and we have only recorded an ECAP activated in the DRG twice. But since the eventual goal of this intraoperative testing procedure is to stimulate the dermatomes matching the patient's painful area to guide lead placement, we could stimulate multiple DRGs simultaneously. The ECAP is a summation of action potentials, so if the L4 and L5, or bilateral L4's are stimulated simultaneously, it is possible this would lead an ECAP better measurable in the dorsal column.

7.4.3 Changes in protocol

Reference electrode The function of a reference electrode, measuring constant activity in the body, that can be subtracted from the recording electrode so activity that is not constant stands out, was fulfilled by different objects. The subdermal needle, the electrodes on the SCS leads and also the diathermy pad. The location and placement of the reference electrode was critical, as noticed in the measurements in Patient 2 and Patient 4. At first sight seemingly successful measurements turned out unsuccessful as a result of recordings on the reference electrode perceived as neural activity measured on the recording electrode. The reference electrode internally on the lead can record ECAPs as a result of stimulation on the lead, when the recording electrode is the RF needle in the DRG. When this occurred, we decided to measure with the reference on the subdermal needle and again with the reference internally on the lead. However, if the subdermal needle is placed too sharply into the dermis it can reach the muscle and thus record motor activity. The role of the reference electrode was more important than I anticipated before starting the measurement.
Recommendation: We should carefully consider what can function properly as a reference electrode, and in what location can it be used. In a perfect situation you would measure just outside the reach of the recording electrode, so you record the same constant background activity, but not the evoked activity that the recording electrode should measure. In Patient 6, when stimulating on the lead and recording on the DRG, the diathermy pad was used as the reference and so far this was the only measurement in that direction that was successful. The diathermy pad as a reference electrode is worth investigating further.

Sedation The protocol stated that the measurements were to be performed under sedation, since the goal of the intraoperative testing procedure is to be able to place the leads without patient feedback. However, after the two pilot measurements were performed under sedation, we received feedback from one patient that the dermatome where stimulation was given was numb for the rest of the day. With the inclusion of Patient 1 and 2, we decided that we wanted to make sure no potential damage was done to the DRG so we performed the measurements while the patient was awoken from sedation to alert us of any pain or damage. The measurement procedure was new and we wanted first to get familiar with the amount of stimulation that was acceptable without harming the DRG. However, increasing the stimulation turned painful very fast for the patient, but we never received feedback again that the numbness lasted after the procedure. When the measurements turned out unsuccessful multiple times, we had the idea that we were not stimulating hard enough to overcome the activation threshold so we decided to sedate the patients again during the measurements. Since one out of two pilot measurements was successful and they were performed under sedation, we wanted to exactly simulate those settings again for the last patients.
Recommendation: Proceed to sedate patients during the measurements, also because both successful measurements in this study were under sedation during the measurements. To prevent harmful stimulation of other tissue around the DRG, the placement of the RF needle tip could be optimized.

7.4.4 Stimulation parameters

Pulse type Biphasic pulse type with negative polarity is commonly used for RF stimulation [24], so these settings are mimicked for this experiment. For stimulation on the dorsal column, triphasic pulses with positive polarity first is preferred because it reduces artifact [27]. However, Chakravarthy et al.[27] also describe that the decrease in artifact could be at the expense of higher activation thresholds, which is problematic in this intraoperative testing procedure where we believe the stimulation we provide is not sufficient to elicit neural activity. In a guarded cathode setting, the negative part of the triphasic pulse is the part that excites fibers to elicit an ECAP.
Recommendation: stimulation on the lead with biphasic pulse to compare the activation thresholds and artifact to measurements using triphasic pulses.

Pulse width and frequency The pulse width and frequency was previously determined for the measurement protocol based on common settings for stimulation on the lead and DRG. However, we also experimented with changes in the pulse width and frequencies, of which the results can be seen in Appendix C.
With longer pulse widths you would expect more fibers activated in the same pulse, so a larger ECAP amplitude and broader ECAP because the fibers differ in size and thus conduction velocity. This leads to a broadened out ECAP

because it is the summation of all action potentials. This also leads to an increase in latency.
It is commonly known that the difference between paresthesia-inducing SCS and sub-threshold SCS is due to the difference in stimulation frequency, with low-frequency resulting in paresthesias and high-frequency in impalpable stimulation. The Evoke system uses low-frequency stimulation, but in the low frequency range (0-250 Hz) there is still an effect on the strength of the perceived paresthesia and even the ECAP amplitude [28]. Higher frequencies generate smaller ECAPs but a stronger stimulation-induced paresthesia, which would mean for this study that the lower the frequency, the larger the ECAP amplitude.
Recommendation: the use of longer pulse widths and lower frequency could result in larger ECAP amplitudes, and larger ECAP amplitudes are better measurable in both the dorsal column or at the DRG.

7.5 Data-analysis

Triple exponential filter in Clinical Data Viewer The triple exponential filter is a function in Clinical Data Viewer that is commonly used to filter out artifact and hereby make ECAPs more clearly visible. It automatically uses parameters from the data it filters to optimize the filter for ECAP detection, but this is not transparent. Because the filter is optimized for standard ECAP data, stimulated and recorded on the lead, the filter could be disturbing the signal when the stimulating and recording electrode are divergent.

Automatic ECAP detection With a script that automatically detects ECAPs, time is saved and bias is prevented. Hand-picking which signals in Clinical Data Viewer do or do not show ECAPs is very time consuming and prone to bias.
Naturally, creating an automatic ECAP detection script is also very time consuming. Clinical Data Viewer also has some features of ECAP detection and conduction velocity calculations, but all implemented in the program which makes it hard to know for researchers what is actually done with the data. Also, Clinical Data Viewer is not made for elaborate analyses and therefore freezes a lot, making the whole data analysis part even more time consuming.

7.6 Interim analysis

Since phase 1 is not yet completed, only six out of ten patients were included in the time of my involvement in the study, the interim analysis cannot officially be performed. The interim analysis states that phase 1 is deemed successful if ECAPs are recorded corresponding with the final lead position in $\geq$50% of the study population. However, out of the six included patients (pilot measurements not included) there was only one successful ECAP measurement. This means the following four measurements would all have to be successful in capturing ECAPs for the interim analysis to be positive. I deem this outcome unlikely, also because the condition for continuation of the study as stated in the interim analysis is not met when applying it to my patient group. Out of the eight patients in my thesis, two measurements can be deemed successful. Therefore, my preliminary recommendation would be to discontinue the study after phase 1, conform protocol.

8 Conclusion

The ECAP Guided SCS lead placement study proposed a new method of utilizing the recording capabilities of the closed loop SCS leads. The hypothesis was that by stimulating the DRGs corresponding to a patient's pain area, the evoked neural activity could be measured in the dorsal column and help guide lead placement. The study was divided into three consecutive phases, of which I performed phase one for my thesis. In this thesis I tested the feasibility of the measurements; whether neural activity elicited in the DRG could actually be measured in the dorsal column. I helped develop and optimize the measurement protocol based on the characteristics of the neural activity we aimed to record, within the boundaries of the accepted study protocol.

In two out of eight experiments, we were successful in recording neural activity elicited in the DRG in the dorsal column. In the other six experiments we were not able to measure any neural activity. Age, gender or medication use seemed unrelated to whether the measurements succeeded. The proximity of the stimulating RF needle to the DRG could have been a determining factor since many experiments were ceased when the stimulation became painful before the activation threshold was overcome. Unfortunately, we have not been able to precisely determine the distance between the needle tip and DRG in any of the measurements in the current set-up. Also, the need for this intraoperative procedure should be reevaluated since experienced surgeons estimate the lead localization quite accurately. In combination with 12 electrode leads covering 3 vertebrae, the rest of the coverage overlap can often be achieved during postoperative programming of the stimulation.

Recommendations for improvements to the measurement protocol for future use are described in this thesis. Whether these recommendations will be used to proceed with this study protocol is uncertain since the requirements of the interim analysis to proceed to phase 2 were not met.

References

[1] Joachim Scholz, Nanna B Finnerup, Nadine Attal, Qasim Aziz, Ralf Baron, Michael I Bennett, Rafael Benoliel, Milton Cohen, Giorgio Cruccu, Karen D Davis, et al. The iasp classification of chronic pain for icd-11: chronic neuropathic pain. *Pain*, 160(1):53, 2019.

[2] KP Grichnik and FM Ferrante. The difference between acute and chronic pain. *The Mount Sinai journal of medicine, New York*, 58(3):217–220, 1991.

[3] Tracy P. Jackson, Victoria Sutton Stabile, and K.A. Kelly McQueen. The Global Burden Of Chronic Pain. *ASA Newsletter*, 78(6):24–27, 06 2014. ISSN 0270-5877.

[4] Harald Breivik, Beverly Collett, Vittorio Ventafridda, Rob Cohen, and Derek Gallacher. Survey of chronic pain in europe: prevalence, impact on daily life, and treatment. *European journal of pain*, 10(4):287–333, 2006.

[5] OASKR van Hecke, Sophie K Austin, Rafi A Khan, BH Smith, and N Torrance. Neuropathic pain in the general population: a systematic review of epidemiological studies. *PAIN®*, 155(4):654–662, 2014.

[6] Monique van Velzen, Albert Dahan, and Marieke Niesters. Neuropathic pain: challenges and opportunities. *Frontiers in Pain Research*, 1:1, 2020.

[7] Raj N Parekh. Clinical indications for spinal cord stimulation. In *Seminars in Spine Surgery*, volume 29, pages 147–149. Elsevier, 2017.

[8] Steven M Falowski, Amanda Celii, Anthony K Sestokas, Daniel M Schwartz, Craig Matsumoto, and Ashwini Sharan. Awake vs. asleep placement of spinal cord stimulators: a cohort analysis of complications associated with placement. *Neuromodulation: Technology at the Neural Interface*, 14(2):130–135, 2011.

[9] Nick Christelis, Brian Simpson, Marc Russo, Michael Stanton-Hicks, Giancarlo Barolat, Simon Thomson, Stephan Schug, Ralf Baron, Eric Buchser, Daniel B Carr, et al. Persistent spinal pain syndrome: a proposal for failed back surgery syndrome and icd-11. *Pain Medicine*, 22(4):807–818, 2021.

[10] Ronald Melzack and Patrick D Wall. Pain mechanisms: A new theory: A gate control system modulates sensory input from the skin before it evokes pain perception and response. *Science*, 150(3699):971–979, 1965.

[11] Yun Guan. Spinal cord stimulation: neurophysiological and neurochemical mechanisms of action. *Current pain and headache reports*, 16(3):217–225, 2012.

[12] FJPM Huygen, M van Kleef, KCP Vissers, and WWA Zuurmond. *Handboek Pijngeneeskunde*. De Tijdstroom, 2014.

[13] Jay L Shils and Jeffrey E Arle. Neuromonitoring for spinal cord stimulation lead placement under general anesthesia. *Journal of Clinical Neurology*, 14(4):444–453, 2018.

[14] Ellen L Air, Greg R Toczyl, and George T Mandybur. Electrophysiologic monitoring for placement of laminectomy leads for spinal cord stimulation under general anesthesia. *Neuromodulation: Technology at the Neural Interface*, 15(6):573–580, 2012.

[15] Antonios Mammis and Alon Y Mogilner. The use of intraoperative electrophysiology for the placement of spinal cord stimulator paddle leads under general anesthesia. *Operative Neurosurgery*, 70(suppl_2):ons230–ons236, 2012.

[16] Roy Hwang, Nicholas Field, Vignessh Kumar, Steven Paniccioli, Rachel Grey, Michael Briotte, Vishad Sukul, and Julie G Pilitsis. Intraoperative neuromonitoring in percutaneous spinal cord stimulator placement. *Neuromodulation: Technology at the Neural Interface*, 22(3):341–346, 2019.

[17] José F Paz, Maria del Mar Santiago Sanz, María Victoria Paz-Domingo, María Luisa Gandía-González, Susana Santiago-Pérez, and Jose Maria Roda Frade. The use of transcranial motor-evoked potentials, somatosensory-evoked potentials and free-run electromyography for proper placement of paddle leads in chronic pain. *British Journal of Neurosurgery*, 34(4):465–469, 2020.

[18] Steven M Falowski, Ashwini Sharan, James McInerney, Darren Jacobs, Lalit Venkatesan, and Filippo Agnesi. Nonawake vs awake placement of spinal cord stimulators: a prospective, multicenter study comparing safety and efficacy. *Neurosurgery*, 84(1):198–205, 2019.

[19] Jeffrey R Balzer, Nestor D Tomycz, Donald J Crammond, Miguel Habeych, Parthasarathy D Thirumala, Louisa Urgo, and John J Moossy. Localization of cervical and cervicomedullary stimulation leads for pain treatment using median nerve somatosensory evoked potential collision testing. *Journal of neurosurgery*, 114(1):200–205, 2011.

[20] Jin-gyu Choi, Sang-woo Ha, and Byung-chul Son. Multimodal, intraoperative monitoring during paddle lead placement for cervicothoracic spinal cord stimulation. *Stereotactic and Functional Neurosurgery*, 93(4):271–281, 2015.

[21] Steven G Roth, Steven Lange, Jessica Haller, Priscilla De La Cruz, Vignessh Kumar, Meghan Wilock, Stephen Paniccioli, Michael Briotte, and Julie G Pilitsis. A prospective study of the intra-and postoperative efficacy of intraoperative neuromonitoring in spinal cord stimulation. *Stereotactic and Functional Neurosurgery*, 93(5): 348–354, 2015.

[22] Arvydas A Tamkus, Andrew F Scott, and Fahd R Khan. Neurophysiological monitoring during spinal cord stimulator placement surgery. *Neuromodulation: Technology at the Neural Interface*, 18(6):460–464, 2015.

[23]

[24] Suleyman Deniz, Omer Bakal, and Gokhan Inangil. Application of radiofrequency in pain management. *Pain Management; IntechOpen: London, UK*, page 95, 2016.

[25] Allan Siegel and Hreday N Sapru. *Essential neuroscience*. Lippincott Williams & Wilkins, 2006.

[26] John L Parker, Dean M Karantonis, Peter S Single, Milan Obradovic, and Michael J Cousins. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain*, 153(3):593–601, 2012.

[27] Krishnan Chakravarthy, Hank Bink, and David Dinsmoor. Sensing evoked compound action potentials from the spinal cord: novel preclinical and clinical considerations for the pain management researcher and clinician. *Journal of Pain Research*, 13:3269, 2020.

[28] Gerrit Eduard Gmel, Rosana Santos Escapa, John L Parker, Dave Mugan, Adnan Al-Kaisy, and Stefano Palmisani. The effect of spinal cord stimulation frequency on the neural response and perceived sensation in patients with chronic pain. *Frontiers in Neuroscience*, page 10, 2021.

Appendices

A Study flowchart

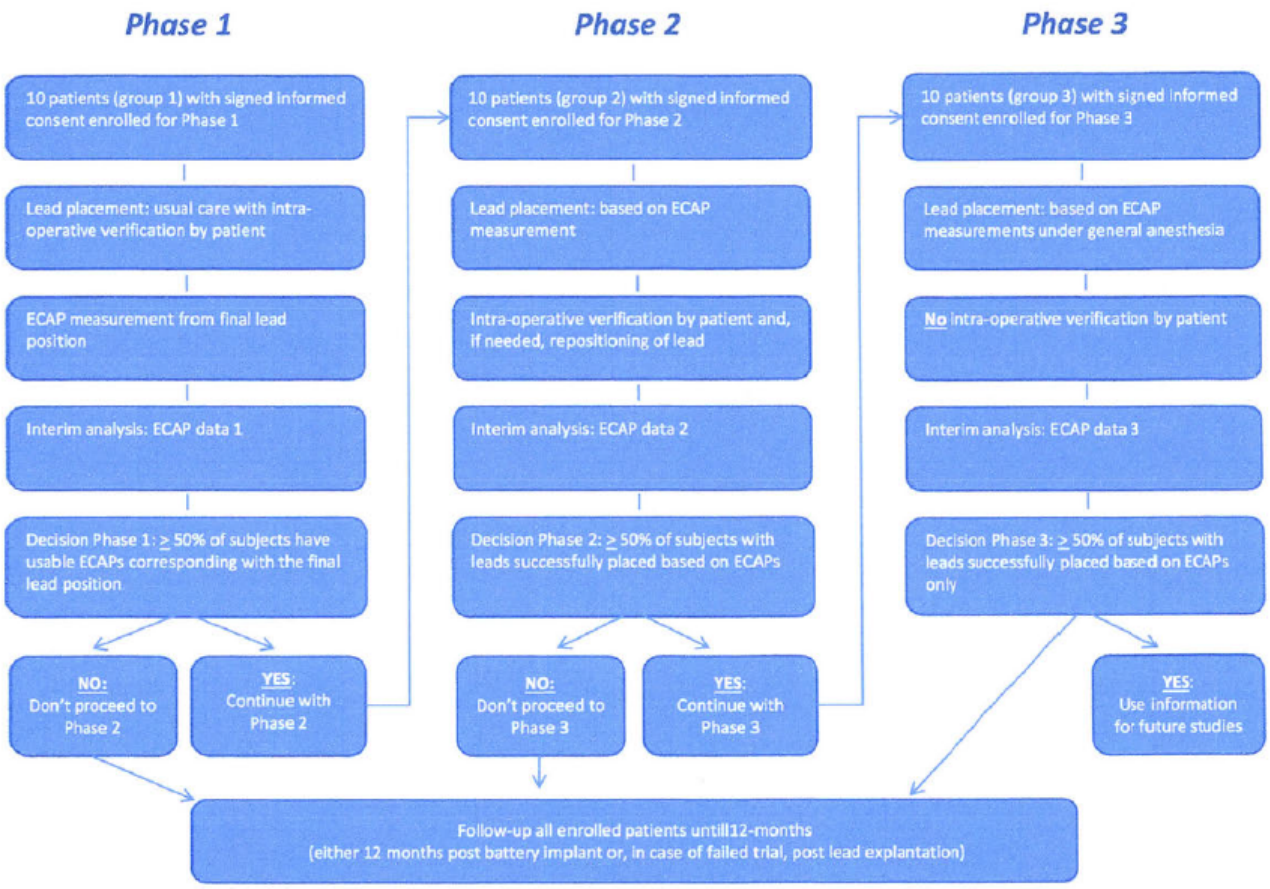


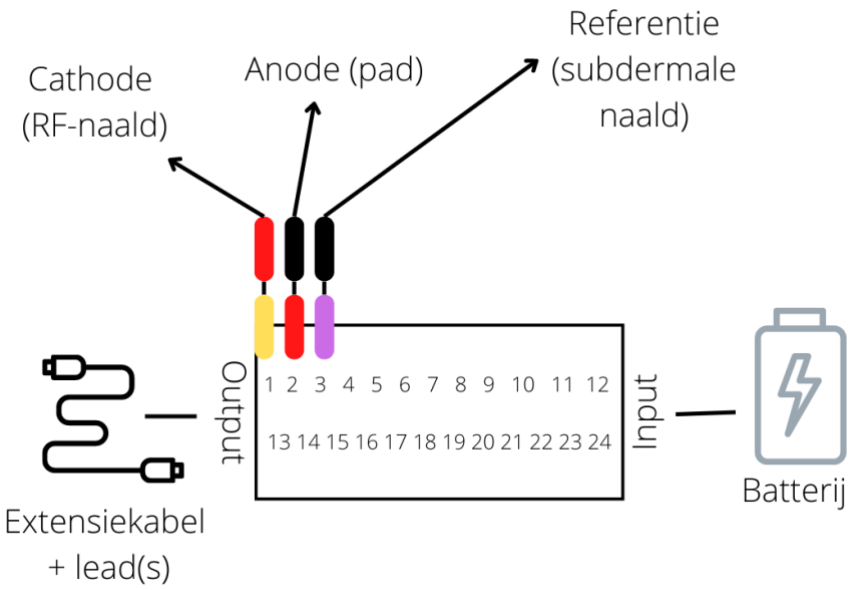
Figure 38: Flowchart of the three phases of ECAP Guided SCS Lead Implantation study

B Measurement protocol

Meetprotocol ECAP studie

Voorbereiden

Schematische meetopstelling:



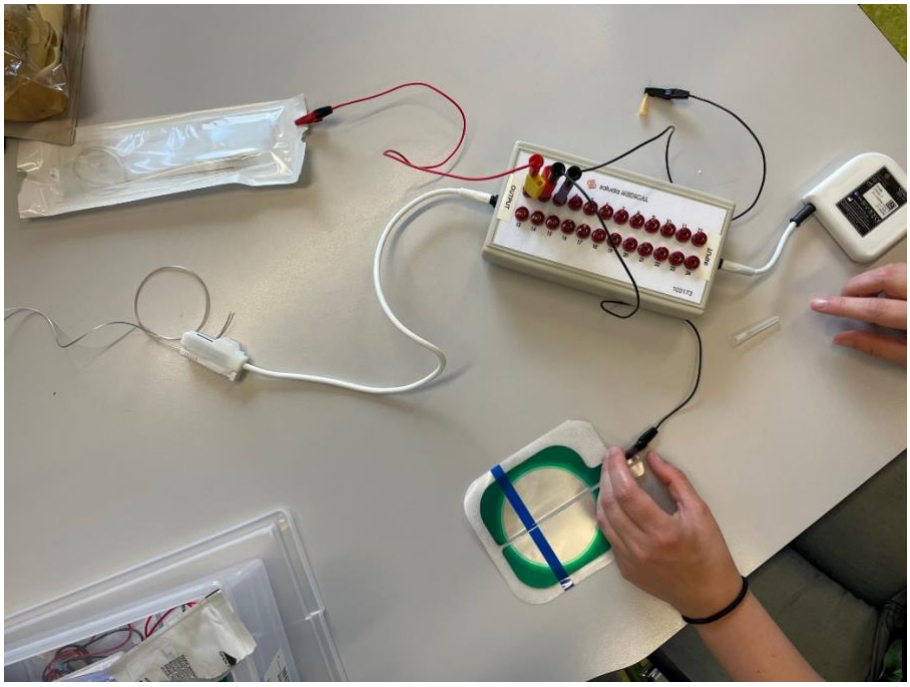
Let op:

Subdermale naald moet echt schuin in de huid, niet verticaal anders ga je spieractiviteit meten. Probeer verschillende naaldjes en kijk welke de minste impedantie geeft.

Het krokodillenbekje van de pad kan aan beide kanten van het lipje, maakt geen verschil. Plak de pad niet te dicht bij een spier. Buiten operatiegebied in ieder geval.

Als we de linker DRG stimuleren wil je de hele linker lead gebruiken om metingen op te doen. Daarom is het handig om dan de 3 kabels op 13, 14 en 15 (rechts) te zetten, anders mis je 3 electrodes om op te meten.

Foto opstelling:



Voor de meting

1. **Maak foto's van de lead en plaatsing van de RF naald in de DRG.**

Meten

Startsituatie: Stimulatie op DRG, meten op de lead, referentie subdermaal (cathode op RF naald, anode op de pad)

1. Connect de extensiekabel met de leads die net geïmplanteerd zijn.

De RF naald wordt nu in de DRG geplaatst.

2. Zet de instellingen als volgt:
    a. 10 Hz
    b. 300 µs
    c. Bipolar
    d. Negative first
    e. Sampling max
    f. Virtual Ground **UIT**
3. Begin met stimuleren op de DRG vanaf de laagst mogelijke intensiteit, en ga ook omhoog met de kleinst mogelijke stapjes.
4. Sensatie uitvragen en noteren.
5. Maak screenshots van het signaal en loop alle electroden op de lead af met je recording.
6. Wijzig de referentie van subdermaal naar intern op de lead. Hiervoor hoeft de stimulatie niet uit.
7. Maak screenshots van het signaal en loop alle electroden op de lead af met je recording.
8. Zet de stimulatie uit.
9. Zet nu Virtual Ground **AAN**, laat de referentie intern op de lead
10. Begin weer met stimuleren op de DRG vanaf de laagst mogelijke intensiteit. Je weet nu tot hoe hard je kunt stimuleren.
11. Maak screenshots van het signaal en loop alle electroden op de lead af met je recording.
12. Wijzig nu de referentie weer van intern op de lead naar subdermaal. Hiervoor hoeft de stimulatie niet uit.
13. Maak screenshots van het signaal en loop alle electroden op de lead af met je recording.
14. Zet de stimulatie uit.

Startsituatie: Stimulatie op de lead, meten op de DRG (recording = RF-naald), referentie intern op de lead

Standaard guarded cathode op lead (of electrode die bij sensation testing de beste coverage gaf).

1. Zet de instellingen als volgt:
    a. 10 Hz
    b. 300 µs
    c. Tripolair
    d. Positive first
    e. Sampling max
    f. Virtual Ground **UIT**
2. Begin met stimuleren op de lead. Hoeft niet zo laag als bij stim op DRG. Stimuleer op zowel sterk maar comfortabel en maximaal.
3. Sensatie uitvragen en noteren.
4. Maak screenshots van het signaal.
5. Wijzig de referentie van intern op de lead naar subdermaal. Hiervoor hoeft de stimulatie niet uit.
6. Maak screenshots van het signaal.
7. Zet de stimulatie uit.
8. Zet nu Virtual Ground **AAN**, laat de referentie subdermaal.
9. Begin weer met stimuleren. Je weet nu tot hoe hard je kunt stimuleren. Stimuleer op zowel sterk maar comfortabel en maximaal.
10. Maak screenshots van het signaal.
11. Wijzig nu de referentie weer van subdermaal naar intern op de lead. Hiervoor hoeft de stimulatie niet uit.
12. Maak screenshots van het signaal.
13. Zet de stimulatie uit.
14. De extensiekabel kan blijven zitten voor de trial.

C Extra figures

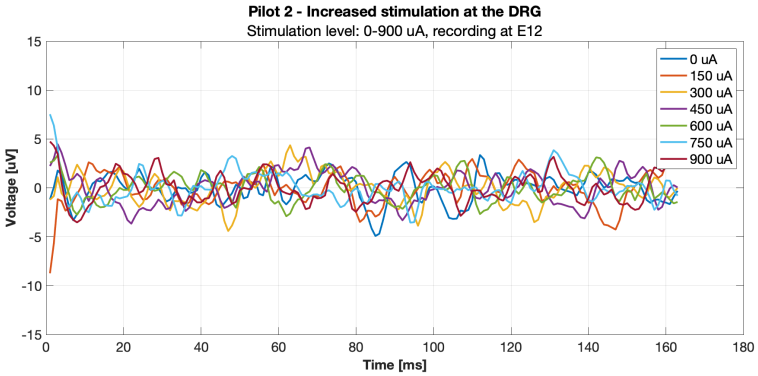


Figure 39: Effect of Virtual Ground on increased stimulation in Pilot 2

C.1 Patient 2

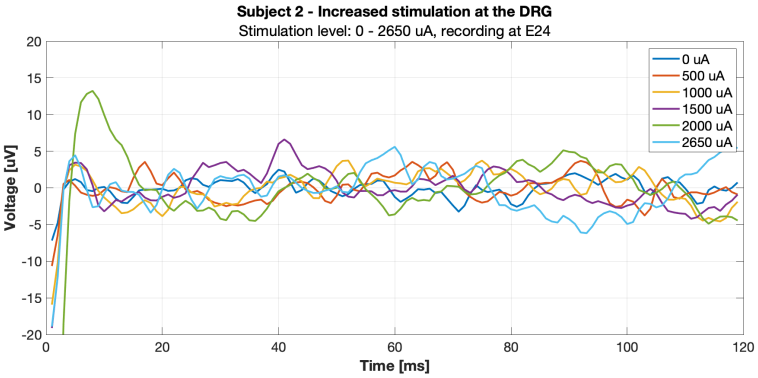


Figure 40: Increased stimulation on the DRG, recorded on E24

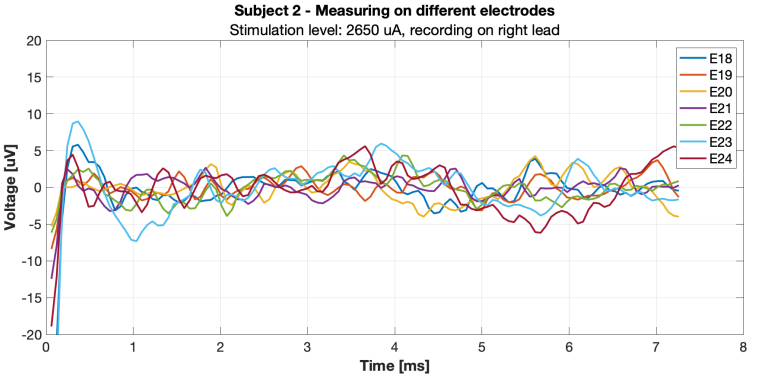


Figure 41: Stimulation on the DRG, recording on different electrodes

C.2 Patient 3

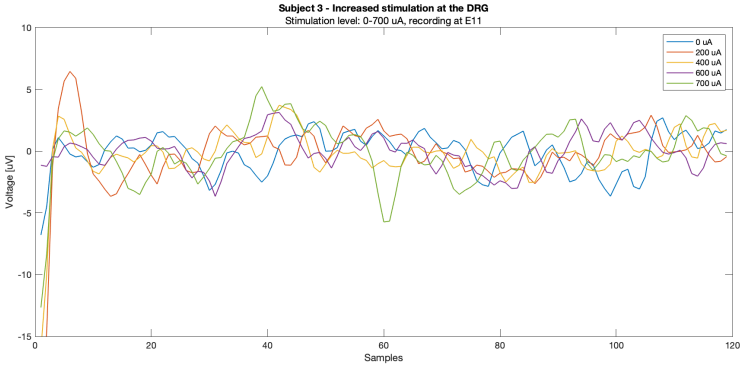


Figure 42: Increased stimulation on the DRG, recording on E11

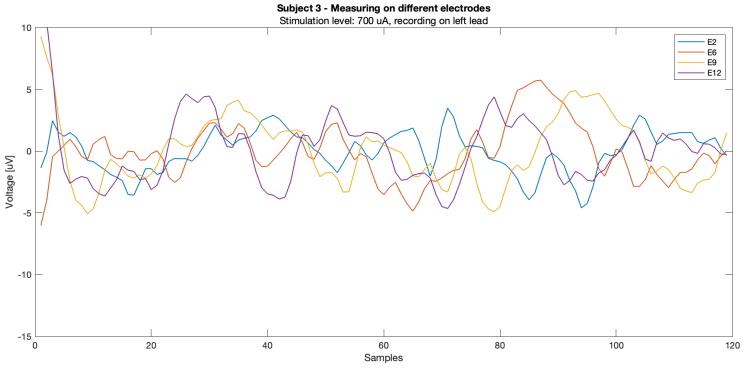


Figure 43: Stimulation on the DRG, recording on different electrodes

C.3 Patient 4

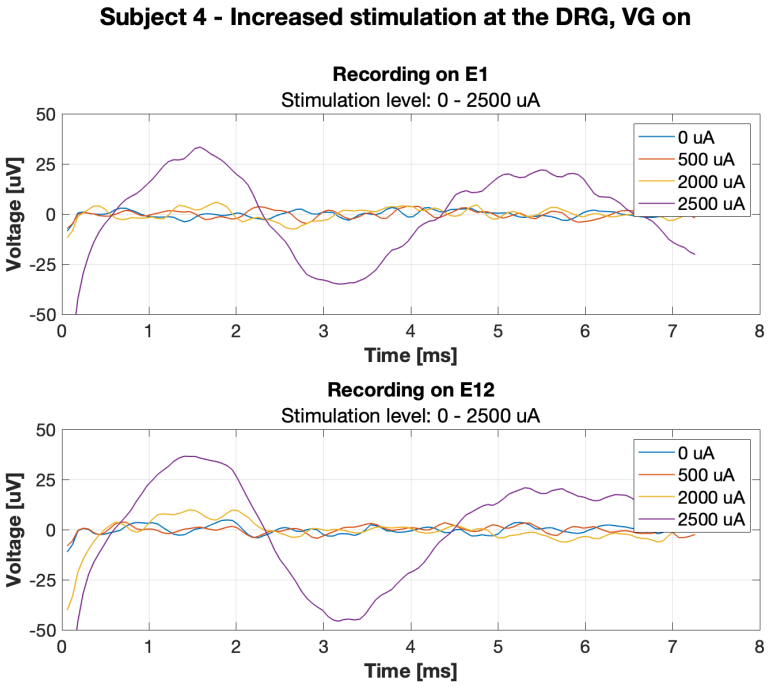


Figure 44: Effect of Virtual Ground on increased stimulation in Patient 2

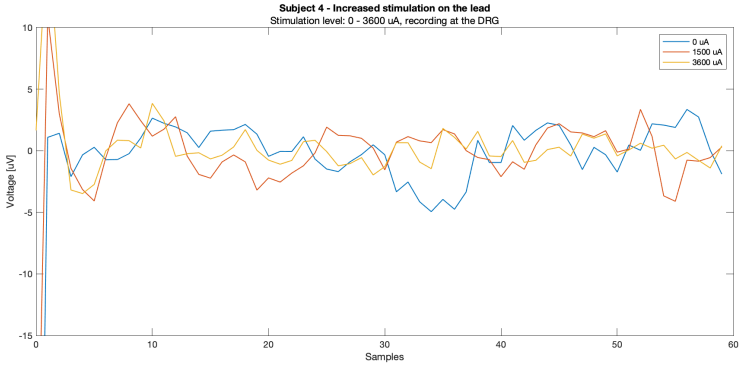


Figure 45: Increased stimulation on the lead, recording on the DRG

C.4 Patient 5

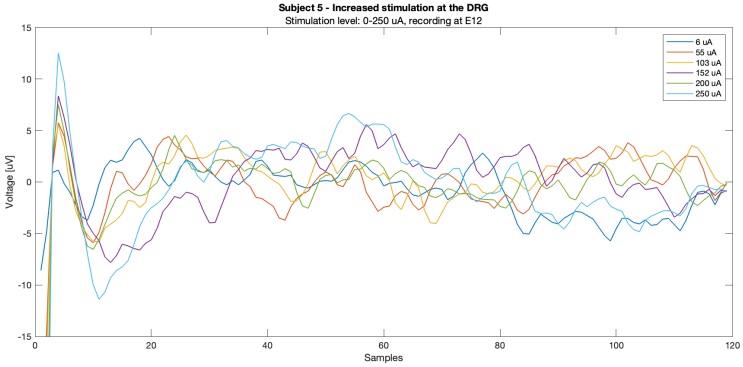


Figure 46: Increased stimulation on the DRG, recording on E12

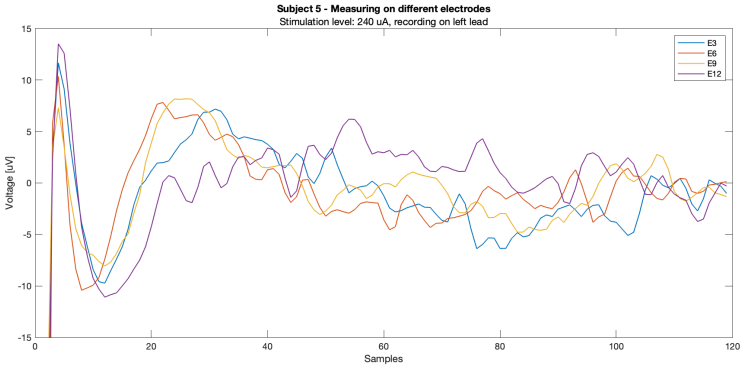


Figure 47: Stimulation on the DRG, recording on different electrodes

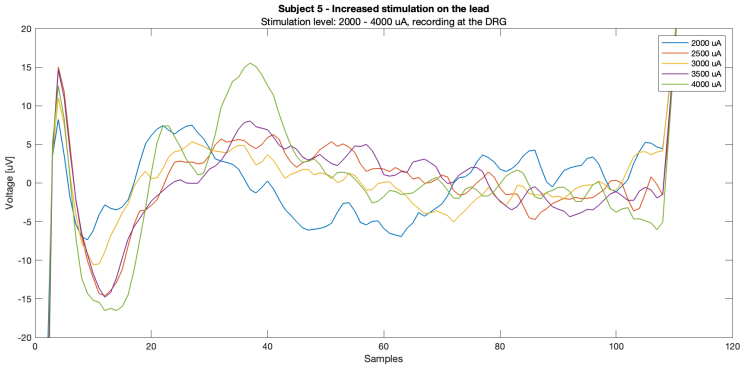


Figure 48: Increased stimulation on the lead, recording on the DRG

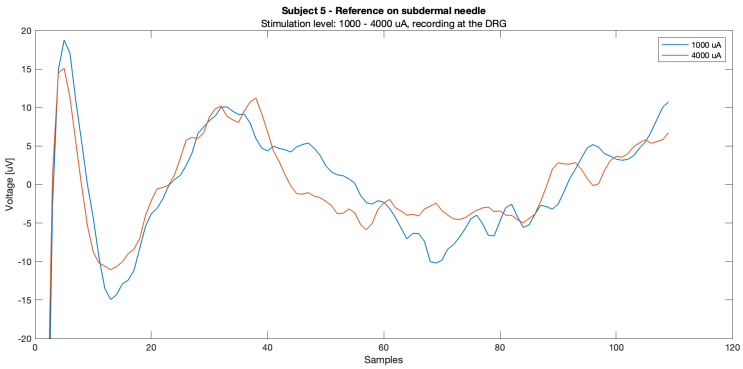


Figure 49: Reference on the subdermal needle

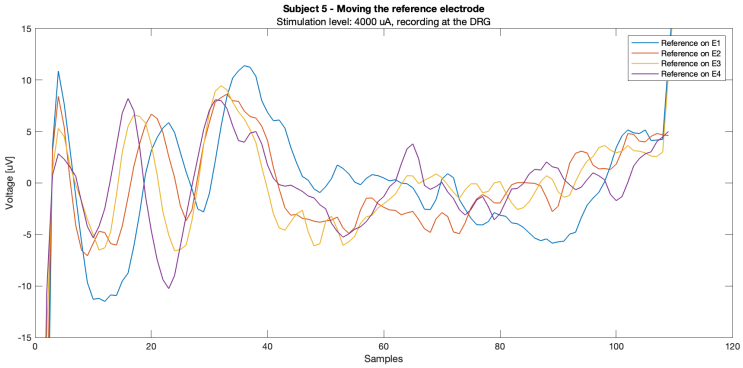


Figure 50: Moving the reference electrode