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Assessment of chronic peripheral localized neuropathic pain during stimulation of the dorsal root ganglion using laser-evoked potentials

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“A person who never made a mistake, never tried anything new.”

Albert Einstein

Dedicated to my parents

Index

Abbreviations

APs	Action potentials
BPI	Brief Pain Inventory
CI	Confidence interval
CNS	Central nervous system
CRPS	Complex regional pain syndrome
DBS	Deep brain stimulation
DN4	Douluer Neuropatique en 4 questions
DNIC	Diffuse noxious inhibitory control
DREZ	Dorsal root entry zone
DRG	Dorsal root ganglion
DRGS	Dorsal root ganglion stimulation
EEG	Electroencephalogram
EFNS	European Federation of Neurological Societies
EOG	Electrooculography
EPs	Evoked potentials
EQ-5D	EuroQol five dimensions questionnaire
ERF	Emotional Role Functioning
FBSS	Failed back surgery syndrome
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GHP	General Health Perception
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IPG	Implantable power generator

LANNS	Leeds Assessment of Neuropathic Pain
LEPs	Laser-evoked potentials
M0	Baseline measuring time-point with DRGS turned OFF
M1	1-Month measuring time-point with DRGS turned ON
M6	6-Months measuring time-point with DRGS turned ON
MEG	Magnetoencephalography
MH	Mental Health
MRI	Magnetic resonance imaging
NeuPSIG	Neuropathic Pain Special Interest Group
NGFs	Nerve growth factors
NPQ	Neuropathic Pain Questionnaire
NRS	Numerical rating scale
NS	Nociceptive specific
P	Pain
PDI	Pain Disability Index
PeNS	Peripheral nerve stimulation
PET	Positron emission tomography
PF	Physical Functioning
PLP	Phantom limb pain
PNS	Peripheral nervous system
PRF	Physical Role Functioning
PSN	Primary sensory neurons
QoL	Quality of life
QST	Quantitative sensory testing
RIII reflex	Nociceptive flexion reflex
SCS	Spinal cord stimulation
SEP	Somatosensory evoked potentials
SF-36	Medical Outcomes Survey - Short Form
SI	Primary somatosensory cortex

SII	Secondary somatosensory cortex
SPECT	Single-photon emission computed tomography
SRF	Social Role Functioning
SSRs	Plantar sympathetic skin responses
TENS	Transcutaneous electrical nerve stimulation
TNF	Tumor necrosis factor
V	Vitality
VAS	Visual analog scale
VRS	Verbal rating scale
WDR	Wide dynamic range
WHO	World Health Organization
YAP	Yttrium - Aluminum - Perovskite

1 INTRODUCTION

In this study, we used laser-evoked potentials (LEPs) to assess the efficacy of dorsal root ganglion stimulation (DRGS) as a treatment for chronic peripheral localized neuropathic pain. LEPs are considered the gold standard for the assessment of the functional integrity of pain pathways (*Haanpaa, Attal et al. 2011*). The mechanisms behind pain relief via electrical stimulation are not fully understood, and to the best of our knowledge, no study to date has used neurophysiological measures of pain perception in patients treated with DRGS.

DRGS was introduced for clinical use in some European countries and in Australia in 2011. The therapy targets primary sensory neurons (PSN) within the dorsal root ganglion (DRG). Following peripheral nerve damage, glial cells, nerve growth factors (NGFs), ion channels, chemokines and specific genes in the DRG undergo several adaptive alterations (*Krames 2014*). How DRGS interferes with those mechanisms is still largely unknown.

To investigate this issue, we performed the current prospective open-label study. At baseline (prior to DRGS therapy) and at one and six months after DRGS onset, the following variables were measured: LEPs parameters, pain intensity (using the Numerical Rating Scale, NRS), neuropathic pain components (using PainDETECT), quality of life (using the Medical Outcomes Survey – short form, SF-36) and pain disability (using the Pain Disability Index, PDI). A total of seven patients with localized neuropathic pain were enrolled in this study. All patients gave proper informed consent and only those who understood the study methods, and were able to regularly attend the experimental sessions were included.

Therefore, this study had two main objectives: 1. To assess the efficacy of DRGS in pain management by measuring LEPs (taken to reflect pain pathways functional status) and NRS scores and 2. To correlate this treatment efficacy with

neuropathic pain components, quality of life and pain disability measurements, using the PainDETECT, SF-36 and PDI questionnaires, respectively.

2 BACKGROUND

2.1 Pain

2.1.1 Definition

Pain is defined by the International Association for the Study of Pain (IASP) as an "unpleasant sensory and emotional experience with actual or potential tissue damage, or described in terms of such damage" (*Loeser and Treede 2008*). Others have defined it as a complex phenomenon, multidimensional in nature, an individual and subjective experience related to the person´s early life experiences involving beliefs, emotions and thoughts (*Boos and Abebi 2008*). Furthermore, nociception or pain perception comprises "the neural process of encoding and processing the pain stimulus, which is defined as an actual or potential event of tissue damage" (*Loeser and Treede 2008*). Nociception therefore enables an individual to elicit an appropriate, life-preserving reaction to a harmful stimulus (*Thomas Cheng 2010*) and thus avoid further lesions while protecting homeostasis.

2.1.2 Pain classification

Pain may be categorized in several ways. For treatment and research purposes, it is always judicious to fit a particular pain diagnosis into a specific group. In this regard, the most important aspects of pain are time course and type of pain. Having access to this information can help clinicians reach individualized diagnoses, thus optimizing the choice of therapy and treatment efficacy.

2.1.2.1 Time course

Pain may be classified as acute or chronic. Acute pain is commonly associated with ongoing tissue damage or a specific noxious stimulus that may occur following different pathophysiological scenarios such as infection or soft tissue lesions. Acute pain typically lasts for less than 1 month (*Moore 2009*) and serves as a physiological warning to the body of a specific threat or disease.

The term "chronic pain" usually refers to pain that persists past the normal healing time (i.e. usually for more than 3 to 6 months; *Treede, Rief et al. 2015*) – in research, the most common standard is 6 months (*Merskey, Bogduk et al. 1994*).

During this longer time-period, pain has lost its function as a warning sign and becomes a disease.

2.1.2.2 Types of pain

Pain is commonly categorized into two main categories: nociceptive pain and neuropathic pain. Nociceptive pain arises from the activation of nociceptors (*Loeser and Treede 2008*) and can be subdivided into somatic and visceral nociceptive pain. Somatic nociceptive pain may in turn be categorized as either superficial or deep. Neuropathic, on the other hand, may be subdivided into central and peripheral neuropathic pain. Finally, the co-occurrence of nociceptive and neuropathic pain in the same patient is known as mixed pain (*Baron and Binder 2004, Pazzaglia and Valeriani 2009*).

2.2 Neuropathic pain

2.2.1 Definition

The IASP originally defined neuropathic pain in 1994 as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" (*Merskey, Bogduk et al. 1994*). Since then, this definition has been widely criticized for being too broad. In 2008, the definition was modified to "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (*Loeser and Treede 2008*), which remains the currently accepted definition.

2.2.2 Classification

The most accepted classification of chronic pain is the one proposed by the World Health Organization (WHO) through the International Classification of Diseases (ICD). However, the latest released version, which is the 10th revision, does not reflect the current epidemiology of chronic pain, including chronic neuropathic pain. Therefore, an IASP task force developed a classification that will be released in the ICD-11. According to this new revision, there are four categories of neuropathic pain (*Treede, Rief et al. 2015*):

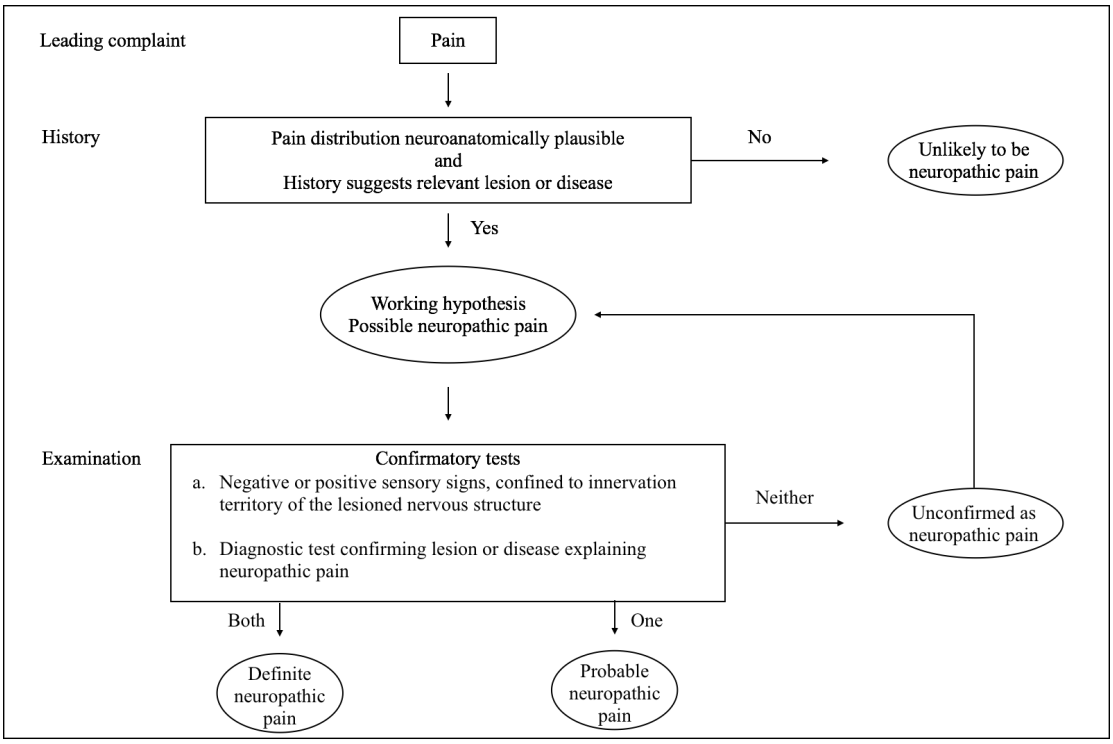
- Peripheral neuropathic pain
- Central neuropathic pain
- Other neuropathic pain
- Neuropathic pain not otherwise specified

In clinical practice, when a clear definition is not possible, one usually observes peripheral or central neuropathic pain. Peripheral neuropathic pain includes any disease or pathology affecting the peripheral nervous system (PNS; e.g. diabetic neuropathy), while central neuropathic pain comprises any disease or pathology involving the central nervous system (CNS; e.g. post-stroke pain) (*Gilron, Jensen et al. 2013*). Additionally, neuropathic pain is also classified as either spontaneous (stimulus-independent) or evoked (stimulus-dependent) (*Pazzaglia and Valeriani 2009*).

2.2.3 Diagnostic criteria

A grading system for neuropathic pain diagnosis was released in 2008. The system proposes three levels of certainty by which neuropathic pain can be present or absent in an individual patient (possible, probable and definite neuropathic pain) (Fig. 1). The use of such criteria helps stratify patients according to established methods of assessment and its use is recommended for clinical and research purposes.

Fig. 1 – Flow chart grading system for neuropathic pain (adapted from *Treede, Jensen et al. 2008*).



2.2.4 Somatic representation

In 2014, a screening tool based on the IASP grading system was developed to classify localized neuropathic pain and improve treatment strategies. When the area of maximum pain is circumscribed and smaller than a sheet of paper (A4 format), it was defined as localized neuropathic pain. If larger, it is considered neuropathic pain (*Mick, Baron et al. 2014*). However, sensitization mechanisms that typically occur in neuropathic pain are not accounted for in this screening tool.

Table 1 – Localized neuropathic pain screening questions (adapted from *Mick, Baron et al. 2014*).

Question	Observation
• Does the patient's history suggest a relevant nerve lesion or disease? • Is the pain distribution neuroanatomically plausible? • Does the neurological examination reveal any negative or positive sensory sign in the area of the presumably lesioned nerve?	3x yes = at least probable neuropathic pain
• Is the most painful area circumscribed and smaller than an A4 paper?	4x yes = at least probable localized neuropathic pain

2.3 Dorsal root ganglion stimulation

2.3.1 Background

The electrical stimulation of neural targets for the treatment of chronic pain has been established for several decades. However, only recently have key structures associated with the physiological processing of pain signals been tested as potential therapeutic targets for neuromodulation. As the site of the first synaptic modulation in the pain pathway, the DRG is a key structure in pain processing. Despite its relation to the development of chronic pain, the DRG was not explored as a target for neuromodulative pain treatments until recent years. The first to attempt this approach were Wright and Colliton, who showed pain reduction by stimulating the DRG in one patient diagnosed with refractory discogenic low back pain *(Wright and Colliton 1998*). In that case, the visual analog scale (VAS) score went from 8 to 2.5 after 8 months of stimulation targeting bilateral DRGs at the L2 nerve root level.

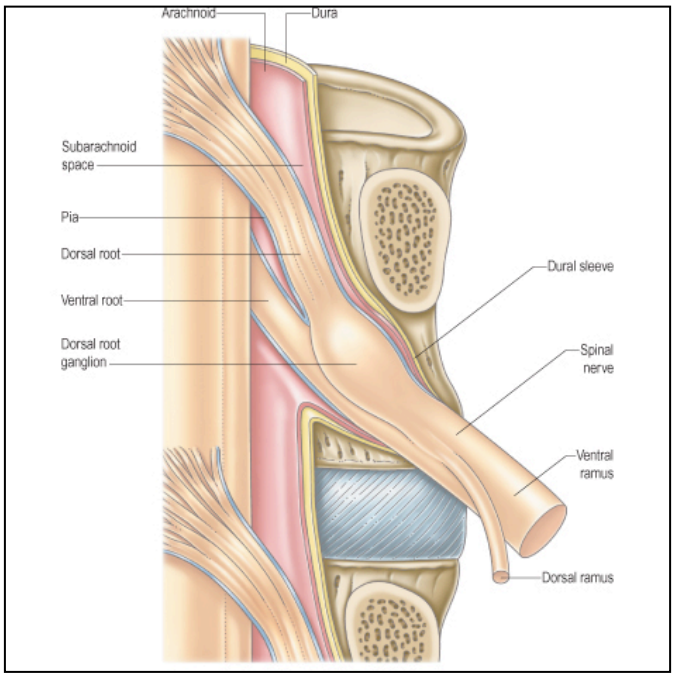
Nerve root stimulation attempting to recruit the DRG has also been shown to be beneficial (*Alo, Yland et al. 1999*), including stimulation using a transforaminal approach that resulted in effective pain relief (*Haque and Winfree 2006; Kellner, Kellner et al. 2011*). Additionally, a method for lead implantation with a curved stylet was shown to facilitate the procedure (*Haque and Winfree 2009*). In one case report, a

patient with post herpetic neuralgia in the left C2 dermatome did not require any medication following DRGS with an implanted peripheral nerve stimulation (PeNS) electrode (*Lynch, McJunkin et al. 2011*). No complications were described, and the stimulation effects remained stable over a 6-month follow-up period. Following the success of several single case reports and small series, DRGS should be further tested in larger groups of patients. With the recent design of a new specialized electrode, (*Deer, Grigsby et al. 2013*) DRGS has become more widespread.

2.3.2 Anatomy and physiology of the dorsal root ganglion

In humans, the dorsal root ganglia give rise to 31 pairs of nerves (8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal) (*Krames 2014*). Proximally, the spinal nerves are divided into ventral motor efferent roots and dorsal sensory afferent roots. The dorsal root ganglia are localized in the dorsal root, close to the zygapophyseal joints and intervertebral disc (Fig. 2) (*Hasegawa, An et al. 1993*). As one moves caudally along the intervertebral foramen, the DRG becomes longer and wider. The positioning of the DRG shows little variability across subjects, and is located between the medial and lateral borders of the pedicles in most healthy individuals (*Shen, Wang et al. 2006*). Disease in adjacent structures can potentially cause compression and radiculopathy (e.g. herniated disc).

Fig. 2 – DRG anatomy.



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The dorsal root ganglia contain almost all PSN cell bodies - as many as 15,000 (*Devor 1999*). Because of the small size of the somata and the usually long axon, 99.8% of the PSN cytoplasm is in the axon (*Hogan 2010*). The DRG therefore has high metabolic demand, with chemicals and proteins being transported over long distances.

In DRG neurons, a single axon arises from the cell body and then divides into two branches, making them 'pseudo-unipolar'. One branch extends peripherally and the other to the spinal cord, forming the so-called T-junction. This formation avoids information slowdown by the soma, thus ensuring fast action potentials (APs) transmission (*Hogan 2010*). The PSN in the DRG may also function as a low-pass filter to impulses coming from peripheral receptors (*Krames 2014*).

In humans, DRG neurons are round and range in size between 20-150 μm. They are divided into two distinct types according to their cytoplasmic neurofilament

domains: large-light (type A) and small-dark (type B). Large-light neurons consist of myelinated Aß fibers while small dark neurons have Aδ and C fibers (*Devor 1999*). Within each DRG, there are several different cell populations, including cells that control sensory modality (heat, mechanical, chemical), range of sensitivity responsiveness, conduction velocity capability and neurotransmitter release specificity. Thus, the DRG is a highly specialized structure with several different neurophysiological functions (*Hogan 2010*).

The surface of the DRG somata are covered by microvilli, which significantly increases the membrane surface (*Devor 1999*). Interestingly, the dorsal root ganglia have no blood-brain barrier, which allows the exchange of many small and large molecules, including drugs (*Hogan 2010*). However, although their surface membranes are permeable to many medications, they do not trap them within, thus lowering the chance of intoxication. Surrounding the soma are supporting satellite glial cells that regulate the neurons' internal environment and maintain electrical isolation (*Nedergaard, Ransom et al. 2003*). Satellite cells also communicate with their associated soma. This configuration also limits interactions between neighbouring neurons, leading to non-synaptic coupling mechanisms that are responsible for cross-excitation (*Devor 1999*). According to Hanani, the satellite glial cells are similar to astrocytes, with some additional unique functions. The spatial configuration around the DRG allow for those satellite cells to exert tighter extracellular control relative to other glial cells, which also explains the absence of a blood-nerve barrier (*Hanani 2005*).

The main function of PSNs is to conduct APs from the periphery to the CNS, but there is evidence that this also happens in the opposite direction (*Hogan 2010*).

Ultimately, the role of the DRG neurons is to maintain a balanced membrane resting state, allowing for the correct interpretation of stimuli and ensuring appropriate responses during sensory encoding. During the APs, Na^+, K^+ and Ca^{2+} ions flow across the membranes ionic channels, leading to cell depolarization followed by repolarization. Ca^{2+} plays a special depolarizing role in these signaling mechanisms by entering the soma. Ca^{2+} also acts as second messenger in neuronal development, gene expression, neurotransmitter release, kinase activity and apoptosis.

Therefore, the proper functioning of the Ca^{2+} channels that are extensively distributed across the DRG membrane is of utmost importance (*Abdulla and Smith 2001*).

2.3.3 Dorsal root ganglion stimulation - state of the art

The development of a novel electrode system, specifically engineered for DRGS, has facilitated the use of this technique for the clinical treatment of chronic neuropathic pain. The electrodes used for DRGS are more delicate, smaller, thinner and more flexible than traditional spinal cord stimulation (SCS) electrodes. They can be percutaneously inserted, thus making the procedure minimally invasive (*Bara and Deer 2016*).

One major potential advantage of DRGS is to complement traditional neuromodulation techniques such as SCS of the dorsal column. Initial observations indicate that DRGS is superior to conventional SCS for the treatment of localized pain, such as pain of the hand, individual fingers, the foot, the knee or the groin region. Moreover, SCS of the dorsal column commonly produces alterations in stimulation intensity or undesirable effects depending on body posture or movement pattern, which does not occur under DRGS (*Kramer, Liem et al. 2015*). Other problems related to traditional SCS include high lead migration rates with consequent loss of pain relief. SCS may also cause unpleasant stimulation-associated paresthesia, and because it cannot accurately target smaller painful regions, these sensations are frequently generated in broader areas than the specific area of pain (*Deer, Levy et al. 2013b*). DRGS may also help avoid such limitations.

The first human study conducted with DRGS on 10 patients was published in 2013 (*Deer, Grigsby et al. 2013*). In that study, DRGS was applied during a period of one week. Patients had been diagnosed with a neuropathic pain condition that was refractory to all previous therapies, either conservative or surgical. In this cohort, from the eight patients who completed the study, 75% experienced more than 50% pain relief relative to baseline, and all of them had anatomically specific relief over the painful region. Furthermore, medication intake was reduced by 78%. Also, pain ratings in the low back pain subgroup decreased by 84% after one week, a 34% higher rate than that observed in traditional SCS (*North, Kidd et al. 2005*). Finally, the authors were able to apply less electrical current with DRGS than is normally used for

SCS of the dorsal column, which saves battery life. The authors concluded that DRGS relieved pain in a satisfactory manner without any major safety concerns and highlighted the need for further corroborating studies.

That publication was followed by the first prospective phase I multicenter study using DRGS (*Liem, Russo et al. 2013*). The main goals of that study were to analyze the rates of adverse events and paresthesias, as well as to evaluate pain relief, quality of life (QoL), mood and physical functioning. A total of 70 adverse events occurred in 24 of the 32 patients tested. Paresthesias due to stimulation were properly localized over the painful area and did not vary significantly with changes in body position. The overall average pain relief was 66% during the test phase and 56.3% at the 6-month end-point evaluation, at which time significant improvements in QoL, mood and physical functioning were also observed. During this trial, electrode migration rate was 3%, considerably lower than that observed in traditional SCS. The rate of pain reduction during the ON-phase of stimulation was always higher than 50%. Foot pain, which is generally difficult to treat with traditional SCS, responded positively to DRGS. In conclusion, DRGS relieved chronic pain even in anatomical regions that are normally difficult to reach with SCS.

The same group then published a 12-month follow-up study of the same population showing significant improved status in pain relief, mood and QoL (*Liem, Russo et al. 2015*). Thus, DRGS seems to be a better option for treating some neuropathic pain states, especially in cases of localized pain. However, the population studied by this group was heterogeneous in terms of neuropathic pain etiologies, which warrants further studies addressing specific pain conditions.

Conventional SCS is a therapeutic option in patients with complex regional pain syndrome (CRPS) who do not respond to conservative clinical interventions (e.g. medication, physical therapy). However, Van Buyten et al. showed that DRGS can also be effective in treating this condition (*Van Buyten, Smet et al. 2014*).

It is estimated that 2-4% of all patients who underwent herniorrhaphy will develop neuropathic pain as a consequence of nerve damage during surgery *(Werner 2014)*. Schu et al. studied the effectiveness of DRGS for localized neuropathic pain of the groin in 12 patients diagnosed with post herniorrhaphy pain (*Schu, Gulve et al.*

2014). An additional 17 patients presented with diverse etiologies involving chronic pain. Twenty-five of the 29 patients had a positive test trial and 23 of those completed the study protocol. Of the 23 patients, 82.6% had pain relief greater than 50%, as reflected in their VAS score. Therefore, also in the case of groin pain, DRGS provides pain relief that conventional SCS usually does not.

The use of DRGS to treat phantom limb pain (PLP) was studied by Eldabe et al. (*Eldabe, Burger et al. 2015*). There is currently level IV evidence supporting the use of SCS to treat PLP, even though low rates of long-term pain relief have been reported (*McAuley, van Groningen et al. 2013*). SCS has been shown to be more effective against stump pain, which is often caused by a neuroma at the amputation nerve's ending, and less effective against phantom phenomena or myofascial stump pain. These other conditions affecting amputated patients are very often neglected or co-occur in a single patient, rendering treatment in these cases challenging. Eldabe et al. investigated eight phantom-pain patients who received DRGS and reported an average pain reduction of 52% (*Eldabe, Burger et al. 2015*). The effects of DRGS in conditions such as visceral pain, somatic trunk pain and upper limb have yet to be determined (*Liem 2015*).

2.4 Laser-evoked potentials

2.4.1 Evoked potentials - definition

Evoked potentials (EPs) reflect event-related electrical activity (i.e. the sum of excitatory and inhibitory post-synaptic potentials on cortical neurons) measured through electroencephalography (EEG) and represented as peaks and deflections. EPs are classified according to their time of occurrence in relation to the stimulus onset (latency), their polarity (negative or positive) and magnitude (amplitude). Thus, pain-related EPs represent the neuronal response to a painful stimulus and may be used to detect and analyze neuronal function (*Madsen, Finnerup et al. 2014*).

2.4.2 Background

The use of laser radiant heat to selectively activate pain fibers in research was first described in 1975 (*Mor and Carmon 1975*). The first reports of such research employed CO_2 laser, which is categorized in the infrared spectrum with a wavelength

of 10.6 μm. The total amount of energy delivered depends on the stimulus duration and laser beam diameter. The rate of CO_2 laser skin reflectance is less than 2%, which is needed to elicit a clear cortical evoked response (*Hardy 1980*).

In 1976, the same group used short laser pulses (in the ms range) that was locked to EEG recordings (*Carmon, Mor et al. 1976*). All subjects evoked highly similar responses after 20 to 50 averaged stimuli. The most prominent component was recorded from the Cz electrode linked to the earlobes and corresponded to a negative wave followed by a positive wave (*Carmon, Mor et al. 1976*). The greater the stimulus power, the larger the recorded peak-to-peak amplitudes. Notably, pain related potentials were produced only when individuals actually felt pain. Sensations of warmth that were not perceived as painful did not elicit a response.

In 1978, the first study addressing the clinical significance of LEPs was published (*Carmon, Dotan et al. 1978*). There was a significant correlation between referred pain intensity and LEPs parameters. In fact, the authors concluded that the LEPs measured pain intensity objectively. LEPs amplitude correlated significantly with individuals' pain rating scores. These results established LEPs as a neurophysiological correlate of pain experience (*Carmon, Friedman et al. 1980*).

CO_2 laser selectively activates thin and slow (C and Aδ) conduction fibers (*Bromm and Treede 1984*). A component analysis study showed that the late response originating from a stimulus on the left radial nerve dermatome elicited a negative-positive wave over Cz against the ear lobes with latencies of 235 and 380 ms respectively, and a peak-to-peak amplitude of 16 μV (*Bromm and Treede 1987*). An ultra-late positive wave with amplitude of 8 μV was also recorded at about 1300 ms using a pressure block paradigm for Aß fibers. This approach resulted in two independent responses for two distinct patterns of pain sensations. The late component represented Aδ fiber activation (fast and sharp pain), whereas the ultra-late component was related to C fiber activation (slow and dull pain). The late component was labeled N240/P370 and the ultra-late component was labeled N1050/P1250 (*Bromm and Treede 1987*). Yet another study identified four additional components: the N200, the P320, the N500, and the seldom-occurring P800 (*Kakigi, Shibasaki et al. 1989*). The greater the intensity of the subjective pain, the greater the amplitude of the P320 wave, which was maximal at the vertex. Tourniquet-induced

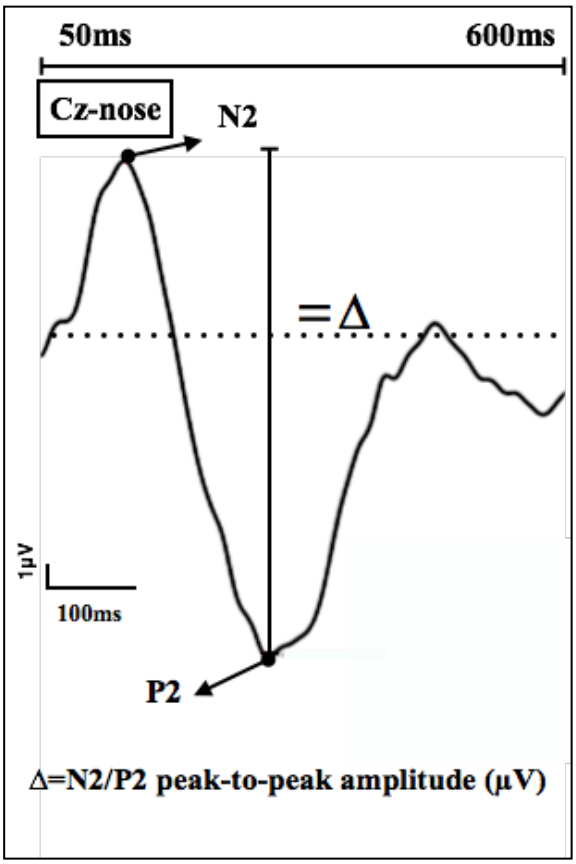
ischemia over the upper arm for 30 minutes gradually diminished the LEPs amplitude until it was no longer detectable. The lack of a signal correlated with the individual's inability to rate the stimulus as painful. Also, after an anesthetic block was applied to the ulnar nerve, no pain sensation was experienced and therefore no LEPs were recorded. In that study, only Aδ waves were clearly identified. Importantly, no EPs were elicited after electrical or mechanical tactile stimulation. Therefore, the authors concluded that P320 LEPs reflect an evoked response specific to pain (*Kakigi, Shibasaki et al. 1989*).

Arendt-Nielsen et al. tested healthy individuals to establish healthy thermal thresholds for use during laser stimulation. They considered skin thickness, temperature, color, sex and reflectance, as well as laser beam diameter and stimulus duration. Higher skin temperature was associated with lower pain thresholds. Increasing stimulus duration resulted in a logarithmic decrease in pain and sensory thresholds. Additionally, the smaller the beam diameter, the lower the pain or sensory threshold, as long as the power was kept constant. No pain threshold differences were observed for different skin pigmentations. Women had relatively lower pain thresholds, most likely due to their smaller skin thickness. Finally, intra-individual variability was low, suggesting robust results (*Arendt-Nielsen and Bjerring 1988*).

Skin type also affects the threshold, with glabrous skin having a higher pain threshold relative to hairy skin. Thresholds also varied more within and across subjects with glabrous skin. Moreover, an increase in temperature in either skin type reduced the amount of energy needed to elicit any sensation (painful or non-painful). In conclusion, CO_2 laser stimuli were found to selectively stimulate primary afferent fibers, including nociceptive receptors, thus eliciting painful as well as non-painful sensations (*Pertovaara, Morrow et al. 1988*).

Currently, two main laser-evoked components are reliably recorded: the N1, which is a small-amplitude negative wave recorded in the temporal regions contralateral to the site of stimulation, and the N2/P2 biphasic complex the most studied component, which is maximal at the vertex and is the most reliable and reproducible measure across studies (*Madsen, Finnerup et al. 2014*) (Fig. 3).

Fig. 3 – N2 and P2 LEPs components recorded in a healthy subject at our laboratory.



2.5 Study aims

It is known that the DRG plays a crucial role in pain processing. The DRG has traditionally been targeted to treat chronic neuropathic pain through ablative procedures, and has only recently been considered as a target for neuromodulation (*Pope, Deer et al. 2013*). Clinical results have shown that DRGS provides relief in some neuropathic pain conditions (*Forget, Boyer et al. 2015*). However, due to the recent introduction of this method, there is a need for new studies explaining these clinical effects.

The current work had two main goals: to determine 1) whether DRGS-induced pain reduction correlates with LEPs measurements and 2) whether DRGS influences neuropathic pain components, QoL and disability related to chronic pain, as measured by different standardized tests.

2.6 Scientific questions

Hypothesis 1: DRGS restores the N2/P2 peak-to-peak amplitude in chronic neuropathic pain.

Hypothesis 2: DRGS reduces chronic neuropathic pain and neuropathic pain components.

Hypothesis 3: DRGS improves QoL and disability related to chronic neuropathic pain.

3 MATERIAL AND METHODS

3.1 Study design

The study was performed prospectively and enrolled patients from the chronic pain outpatient clinic at the Department of Neurosurgery of the Eberhard-Karls University in Tuebingen, Germany. It was designed as a prospective, open-label non-placebo controlled study, with evaluation time-points at 1 and 6 months post DRGS. Patients were always aware of the stimulation of the painful area when DRGS was ON. DRGS produces paresthesia in the area corresponding to the specific nerve root dermatome. Medication intake was kept stable throughout the study.

Inclusion Criteria

- Patients > 18 years old
- Confirmed diagnosis of localized chronic neuropathic pain, affecting only one side of the body, warranted by abnormal LEPs
- Pain refractory to conventional medical treatment for at least 6 months
- Confirmation of peripheral nerve or nerve root lesion (sensory loss, allodynia or motor deficits)
- Normal cognition allowing understanding of the informed consent

Exclusion Criteria

- Prevalence of nociceptive pain
- Psychosomatic pain and/or severe depression
- Failure to comply with the study protocol or understand its terms
- Skin lesion or disease in the area to be stimulated by the laser

3.2 Dorsal root ganglion stimulation – surgical procedure

During the first consultation with each patient, we noted the painful area, we determined the level of DRG to be treated based on the dermatome affected and in cases of clinical uncertainty, we conducted a test block using fluoroscopy.

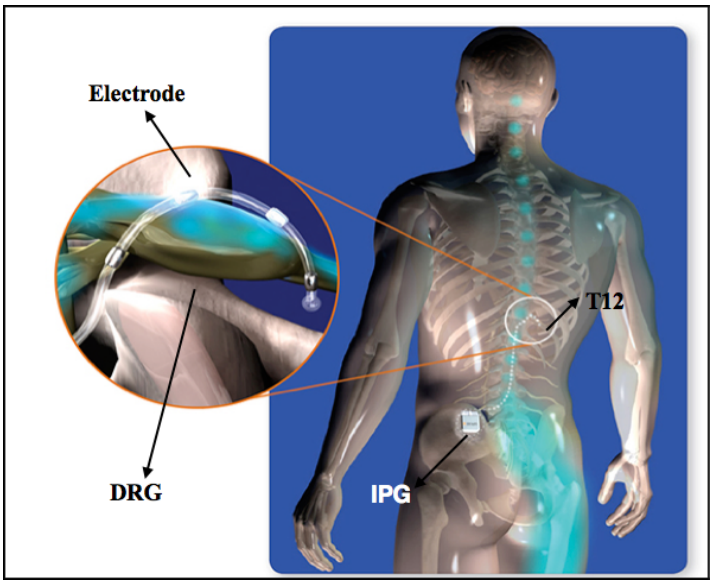
We also conducted routine pre-operative work-up assessments and patients were informed about surgical goals and risks in accordance with German Federal Law.

Surgical Procedure 1 – Lead implantation

The patient was taken to the operating room and the procedure was initiated under either general or local anesthesia. Local anesthesia is usually preferred because it allows patient's neurological monitoring with greater precision. Intraoperative assessment also permits more accurate targeting. The patients were positioned on the operating table in a prone position with arms and pressure points securely cushioned. Kyphosation of the lumbar spine was performed to facilitate puncture of the epidural space. Patients' skin was properly draped after iodine solution cleansing. Fluoroscopy in the antero-posterior view was then used to select the optimal needle entry point to best target the DRGS. We then placed the incision marks at the site designated for the implantable power generator (IPG), which is generally below the belt line around the buttock region. The needle entry point is located 1.5 to 2 levels below the intended interspinal space over the contralateral pedicle line. The needle tip should aim at the intended DRG at an angle of approximately 30 degrees relative to the anatomical spine midline. The epidural space was assessed using live-mode fluoroscopy guidance and the loss-of-resistance technique. After the puncture was made, its position was verified by inserting a flexible metallic guide-wire (*Bara and Deer 2016*).

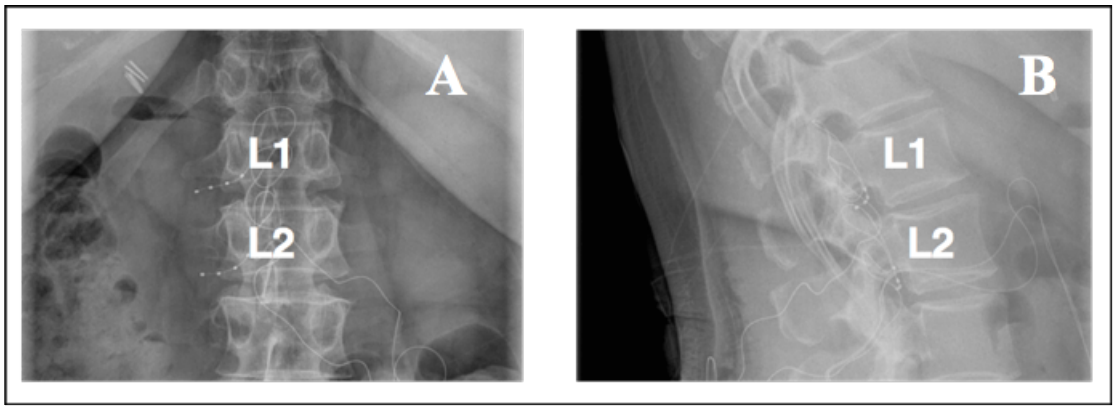
Then, a cylindrical quadripolar electrode (Spinal Modulation, Menlo Park, CA, USA) was prepared and introduced. This electrode is placed inside a sheath with a curved distal tip and secured to avoid sliding of the lead during navigation. The lead is navigated under fluoroscopy guidance into the neural foramen of interest. The optimal position is reached when the contacts are placed exactly below the pedicle, where the DRG is expected to be located. Lateral fluoroscopy is then performed to show the lead contacts, which are ideally located at the dorsal portion of the neuroforamen. Once optimal placement is achieved, the sheath is retracted carefully.

Fig. 4 – Schematic representation - DRGS at the thoracic (T12) DRG on the right side.



Modified from original picture. Courtesy of St. Jude Medical – all rights reserved.

Fig. 5 – Case example - DRGS leads placed at lumbar (L1 and L2) DRGs on the right side - postoperative radiographs in antero-posterior (A) and lateral (B) views.



A lead strain relief loop in the epidural space is performed to avoid lead dislocation. Before retracting the needle, a subcutaneous pocket around the puncture site is created and the lumbar fascia is exposed. Next, the needle is completely retracted. An anchor device is inserted and at least two stitches with non-absorbable sutures are sewn and fixed to the fascia in order to avoid lead migration. A strain loop is created and placed in the subcutaneous pocket. The distal portion of the electrode is

then tunneled through the subcutaneous tissue and externalized through the skin on the lateral portion of the lumbar region. An impedance check is performed to verify the integrity of the electrical circuit and results should ideally range between 600 and 1500 mΩ. Wound closure is performed on two layers. The externalized lead portion is secured to the skin with a suture and the wounds are draped with a sterile dressing.

Test phase

After surgery, the patient is taken to the ward and the leads are connected to an external power generator. Programming of the lead or leads is performed according to the patient's response to different stimulation parameters. The aim is to cover the maximal possible area of pain to ensure satisfactory results. After optimal settings are set, stimulation is set to ON and the patient is discharged from the hospital on the next day to test the stimulation at home. Test stimulations are conducted for one week, after which the patient is evaluated in the outpatient clinic. If the response is considered positive (average pain relief of 50% or more compared to baseline according to NRS scores) and the patient is satisfied, we proceed to the IPG placement. The externalized leads are cut off in a sterile fashion and a suture is performed on the site of lead externalization to decrease risk of infection.

Surgical procedure 2 – IPG implantation

The patient is taken to the operation theatre and the procedure is performed under general anesthesia. The previously planned pocket site for the IPG is re-opened with blunt dissection to avoid breakage of the lead, which is often lying underneath the wound. After localizing the lead's distal tips, an epifascial gluteal pocket is performed with blunt dissection, carefully controlling any bleeding with bipolar cautery. Once the opening is large enough to house the IPG, the leads are connected to the IPG ports and secured with a torque screwdriver system. Thereafter, the IPG is placed inside the pocket and two sutures are placed through the IPG fixation sites to the fascia in order to keep it in place, avoiding flipping or excess movement. The electrode impedances are re-checked through a remote controller. The closure is then performed in a three-layer fashion and the wound is draped with a sterile dressing.

Fig. 6 – IPG (Spinal Modulation, Menlo Park, CA, USA). Courtesy of St. Jude Medical – all rights reserved.

Postoperative assessment

After IPG implantation, the stimulation is turned to OFF. Two weeks after the termination of the test phase, chronic pain intensity has returned to baseline levels. At this time, the investigators explained the study to the patient and gave him/her the informed consent form to study and sign prior to enrollment.

3.3 Enrollment and ethics

The ethics committee of the University of Tuebingen approved the study under protocol number 096/2011BO2. Patients were enrolled in the study after understanding and signing the informed consent form and received no financial compensation for their participation. Participants were told that they could leave the study at any time without any consequences or alterations to their medical treatment.

3.4 Functional assessment

3.4.1 Clinical questionnaires

On postoperative day 1 (M0), while the stimulation was still OFF, patients were asked to complete three different clinical questionnaires: 1) PainDETECT (*Freynhagen, Baron et al. 2006*), a neuropathic pain screening tool developed and validated in German, 2) SF-36, a self-report survey of patient QoL (*Brazier, Harper et al. 1992*), and 3) PDI, a validated tool to assess disability in chronic neuropathic pain (*Tait, Pollard et al. 1987*). The patients were given detailed instructions on how to fill out the questionnaires and were given two sets of blank questionnaire forms to take

home after discharge and to fill them out one day before returning for the remaining neurophysiological measurements (after 1 and 6 months, i.e. at times M1 and M6).

3.4.2 Laser-evoked potentials

Pre-measurement assessment

On the morning of postoperative day 2, patients were recruited for LEPs recordings. Before leaving the ward, they were carefully instructed about the procedure, the risks, and the safety recommendations. The measurement workflow included the following steps, listed here in chronological order:

- Patients were always admitted to the laboratory laser room during the morning, between 10:00 and 11:00 a.m. Then, he/she was asked to expose both legs and groins with underwear left on. Thereafter, the patient was asked to relax in a comfortable reclinable armchair.
- The patient was then asked to indicate the site of maximal chronic pain, which we marked with a soft tip pen for the skin. This area was used throughout the study for all measurements and the contralateral homologous area was used as the control region.
- Before measurements were taken, we used the NRS to determine each patient's pain intensity. Next, we set up the EEG equipment, which is a 64 Channel EEG system (ActiCap, BrainProducts, Gilching, Germany). The pain-evoked potentials were recorded using 32 channels, two additional channels were used for electro oculographic (EOG) recordings, and one other channel for offline re-referencing at the nose, for a total of 35 channels.
- The equipment setup, which included two amplifiers, one power source, adequate cable connections, trigger port unit and a Microsoft Windows based EEG software - Brain Recorder version 2.0 (BrainProducts, Gilching, Germany), was mounted and set up following the manufacturer's guidelines.
- We measured the patient's head perimeter with a centimeter scaled tape at the glabella-inion level in order to choose the appropriate EEG cap size (54, 56 or 58 cm in diameter). This number was recorded and used in each patient's subsequent experimental sessions. The electrodes were placed into the cap

following the 32-channel 10/20 system, using code numbers on each electrode as a guide.

- We determined the Cz electrode's position, which was at the intersection of 2 lines: the glabella-inion and bitemporal line.
- The cap and electrodes were then positioned using the Cz electrode as a reference and secured with a chin strap.
- The three extra electrodes were placed using electrode-specific plastic holders and stickers to fix them appropriately: two on the epicanthal angle bilaterally for oculographic recordings and one at the nose.
- The electrode sites were injected with special EEG conducting gel using a syringe with a blunt tip needle. The EEG system was then turned on to check for impedance. A light indicator at each electrode turns green when impedance is below 5 kΩ, which is considered optimal for data recordings. Impedance values were double-checked with the computer software after all lights turned green.
- Patients and investigators wore laser protective goggles throughout the experiments.

LEPs protocol

- The measurements were performed with a CO_2 laser device (MCO25, KLS Martin, Tuttlingen, Germany). A room was especially prepared in accordance with German regulations for class IV laser devices. The laser settings selected during the study were determined after extensive test sessions with healthy volunteers. The beam diameter was set to 3.5 mm and the laser pulse duration to 15 ms. These parameters were found to elicit a sharp, pinprick pain sensation without causing undesirable skin burns.
- The first laser procedure was conducted to determine each subject's pain threshold. Before beginning that session, we re-checked the side of pain and whether the stimulator was turned OFF (M0 measurement). The pain threshold was determined on the control area contralateral to the painful region. We assumed that because the pain was unilateral, no disease affected the non-painful control region. Therefore, we were able to elicit normal LEPs from the control region, which functioned as a reference and internal control.

- Each participant received standardized instructions regarding the process of determining the pain threshold. They were told that the sensation should be similar to that of a drop of boiling water falling onto the skin (i.e. a sharp, fast, and slightly unpleasant painful sensation). We used an upward staircase design to detect each patient's pain threshold: starting at low intensity laser power values, 3 laser pulses of each increasing laser power were subsequently delivered to the skin of the control region. When the sensation of sharp pain was elicited, after 3 consecutive laser shots, we recorded the value and set this as our NRS 4 score. This laser power value was recorded as the patient's individual pain threshold and used throughout the whole experiment.
- We used noise-cancelling in-ear earphones playing white noise to protect patients' ears from the click produced by the laser device and to prevent any auditory-related potentials to create artifacts during the experiment. To this end, we performed three laser shots targeting the wall of the room while the white noise was playing. If the patient identified the click among the laser shots, we turned the volume up by 5% and retested until the white noise volume was loud so he/she could no longer perceive the clicks. That volume was then maintained constant during the whole experiment.
- Before starting the experiment, we instructed patients to stay relaxed and to fix their gaze on a fixed point on the wall in front of them. They were asked to avoid blinking and any body movement during the recording sessions. To ensure patients were paying attention, we asked them to mentally count the number of laser shots perceived as painful during each block session and told them we would ask them at the end of the block how many shots they were able to feel.
- The measurement session was designed in two parts. In the first part, we recorded LEPs from a dermatome on the control (non-painful) side to assure that the patient had understood the experiment and followed instructions. Whenever possible, LEPs were recorded from the L3 dermatome close to the medial portion of the skin next to the knee. If the L3 dermatome of the painful region was affected, we conducted the calibration on the dermatome above it. Twenty to 30 laser shots were delivered at this block session. During the measurement, the spot targeted by the laser beam was shifted slightly after

each shot to avoid habituation effects or repetitive stimulation of the same spot. We recorded the mean NRS score elicited by the whole set of laser shots.

- In the second part of the experiment, we delivered one run of 20 to 30 laser shots with the laser power value set to match the previously determined pain threshold. The NRS score of the laser evoked pain sensation on the control region should be 4. The laser beam was moved slightly in between shots. First, the LEPs were recorded from the non-painful control side. As described above, we recorded the number of laser shots. We also made sure the NRS score was 4. The same procedure was then conducted for the painful side.
- After the experiment, the DRGS was turned to ON. The patient was then released and instructed to keep the stimulation in the ON mode at all times.
- After 1 month (M1) and 6 months (M6) of DRGS, the patient came back and repeated the experiment with the DRGS on the ON mode.

Fig. 7 – Study design.

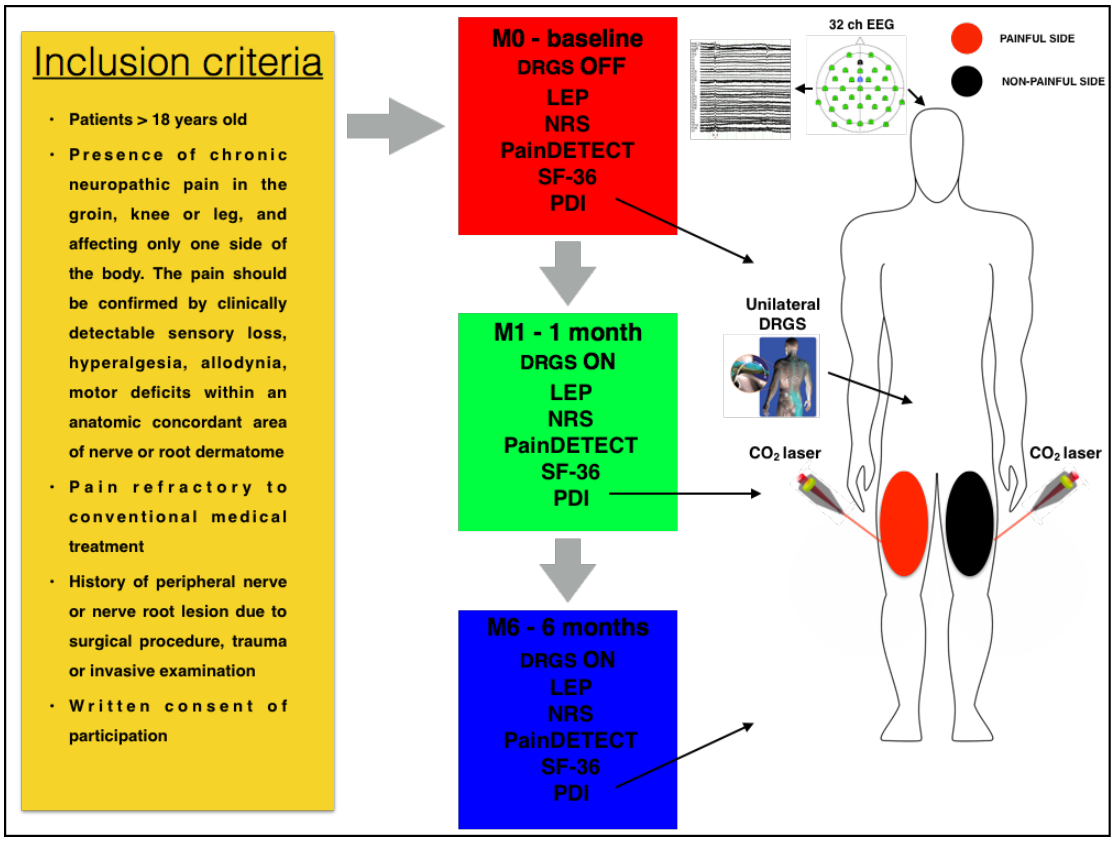
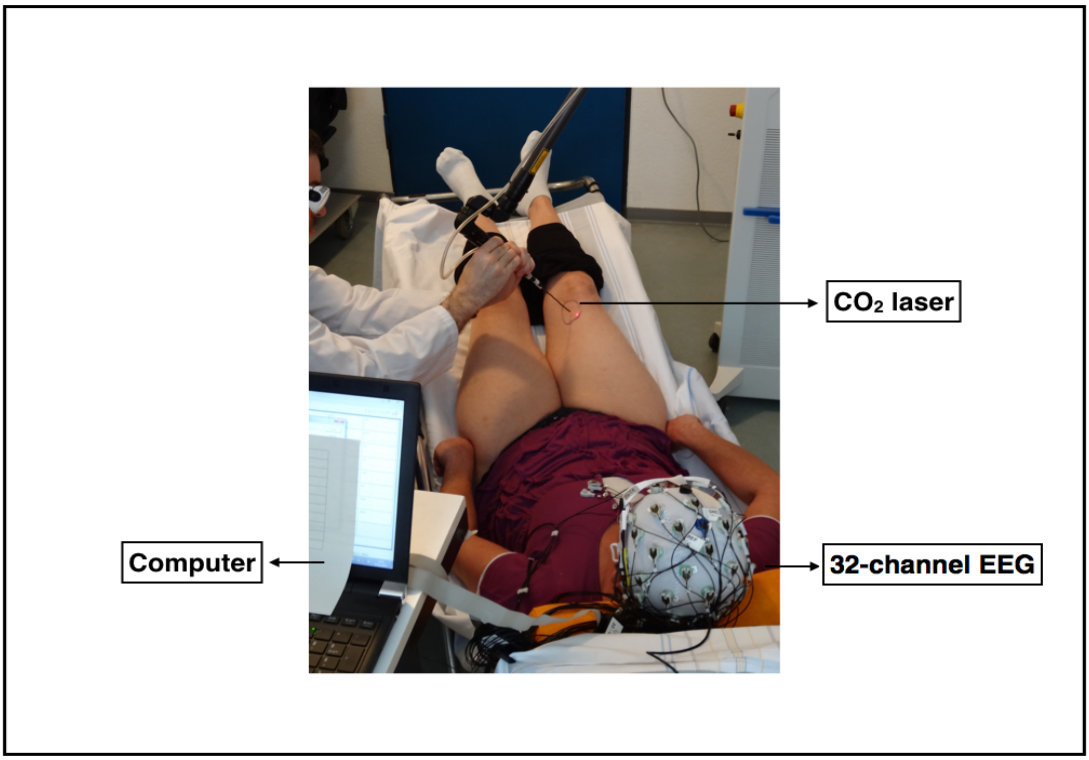


Fig. 8 – Experimental setup – LEPs protocol.



Data processing and analysis

EEG data were acquired at a 5000 Hz sampling rate and downsampled to 500Hz. Continuous data were then band-pass filtered from 0.3 to 30Hz, segmented into epochs (-100 ms to 700 ms) and re-referenced to the nose electrode. The EEG data were stored using codes created with Brain Recorder 2.0 (Brain Products, Gilching, Germany). Pre-processing was conducted using the Brain Analyzer version 2.1 (Brain Products, Gilching, Germany). The time window of interest was selected based on the target component, the N2/P2 complex, which usually appears between 150 and 450 ms after the onset of laser pulse. Baseline correction was performed from time window -100 ms to 0. We implemented an automatic artifact exclusion tool to discard epochs in the Cz channel exceeding ± 50 μV of amplitude. We then conducted a visual inspection and manually rejected any epochs contaminated with muscle or eye movement artifacts. Finally, the artifact free epochs from each trial were averaged and time-locked to the onset of the laser stimulus to measure Aδ-related LEPs. The N2 and P2 peaks in each curve were visually assigned according to the polarity, latency and scalp map. Whenever no evoked responses were detected from the painful side due to neuropathic pain, the N2 and P2 latencies of the LEPs recorded from the control side were used as references in the statistical analyses. The N2 and P2 peaks are maximal in amplitude at the vertex (Cz electrode) (*Madsen, Finnerup et al. 2014*). N2/P2 peak-to-peak amplitude from the Cz electrode data was measured using the Brain Analyzer 2.1 software. All data were recorded and stored in a Microsoft Excel worksheet file.

3.4.3 Statistical analysis

Background

Statistical analyses were performed with the SPSS software, version 22 (IBM, USA). Our first goal was to evaluate the peak-to-peak amplitude of the N2/P2 LEPs and NRS scores before and after DRGS implementation, while our secondary goal was to investigate the effect of DRGS on neuropathic pain components, QoL and disability related to chronic neuropathic pain, as measured by the PainDETECT, SF-36 and PDI clinical questionnaires. We used Friedman and Wilcoxon signed-rank tests for the first set of analyses (LEPs and NRS), and descriptive statistical methods

for the second set (PainDETECT, SF-36 and PDI). We used 95% confidence interval (CI) plots to show the peak-to-peak N2/P2 LEPs amplitude reproducibility on the control side. Data are summarized in box-plot and bar graphs. The significant alpha level was set at .05. Additionally, an alpha level Bonferroni correction was conducted before the first set of statistical analyses, for an alpha of .016. No further corrections were applied in the post-hoc analyses.

Hypothesis 1

We used the N2/P2 complex as a target for testing whether LEPs changes as a result of DRGS. We measured the N2/P2 complex's peak-to-peak amplitude values in μV from the painful dermatome receiving DRGS and the homologous dermatome on the control non-painful side. We conducted descriptive statistics using a 95% CI error plot on the control non-painful side to assess the reproducibility of repeated recording sessions for the group data. We used the two-tailed Friedman test for repeated measures to compare all three data points. The level of significance was set at .016 after Bonferroni correction. If the test showed statistically significant results, the Wilcoxon signed-rank test was implemented for post-hoc comparisons between the three paired conditions.

Hypothesis 2

To test whether DRGS reduces chronic neuropathic pain, we applied two validated and standardized pain scales: the NRS, an 11-point self-report scale of pain intensity, and the PainDETECT, a screening questionnaire to identify neuropathic pain components. Due to the dataset's small sample size and non-normal distribution, we compared scores at M0, M1 and M6 using the non-parametric Friedman test for repeated measures. The level of significance was set to .016 after Bonferroni correction. Whenever we observed statistically significant differences, we performed post-hoc analyses using the signed-rank Wilcoxon test to assess relationships between the three paired subgroups. PainDETECT questionnaire scores were descriptively assessed with box-plot charts. The graph depicts the mean scores that were classified according to the questionnaire's cut-off limits (Fig. 14).

Hypothesis 3

To assess whether DRGS affects QoL and disability related to chronic neuropathic pain, we used two validated and standardized clinical questionnaires: SF-36 and PDI. We scored the SF-36 using the RAND score version (*Hays, Sherbourne et al. 1993*). Here again, we used descriptive statistics with box-plot and bar graphs.

4 RESULTS

4.1 Demographic data

Of the 16 patients recruited to participate in the study, seven completed all three time-point measurements and one was excluded due to predominantly nociceptive pain. Table 2 shows patient demographics:

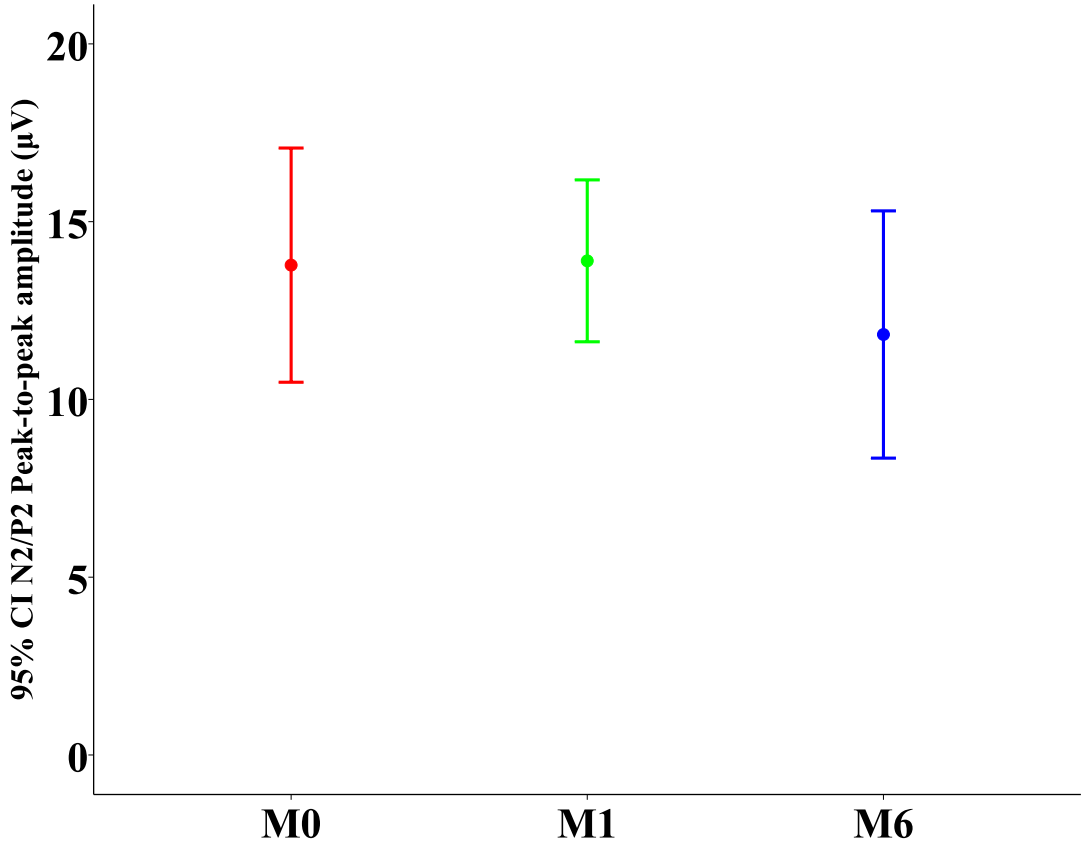
Table 2 – Study group demographics.

Id	Sex	Age	Pain duration (months)	Etiology	Area of Pain	Levels Stimulated	Side
1	F	57	36	Post femoral artery catheterism	Groin	L1 and L2	Right
2	M	47	40	Post lumbar discectomy	Groin and leg	L2, L3 and L4	Right
3	F	43	74	Post knee surgery	Knee	L3 and L4	Left
4	M	53	120	Post lumbar discectomy	Groin and leg	L1 and L2	Left
5	M	53	32	Post inguinal hernia surgery	Groin	L1 and L2	Right
6	M	50	84	Post fracture correction surgery	Leg	L4 and L5	Right
7	F	52	24	Post inguinal hernia surgery	Groin	L1 and L2	Right

4.2 Laser-evoked potentials

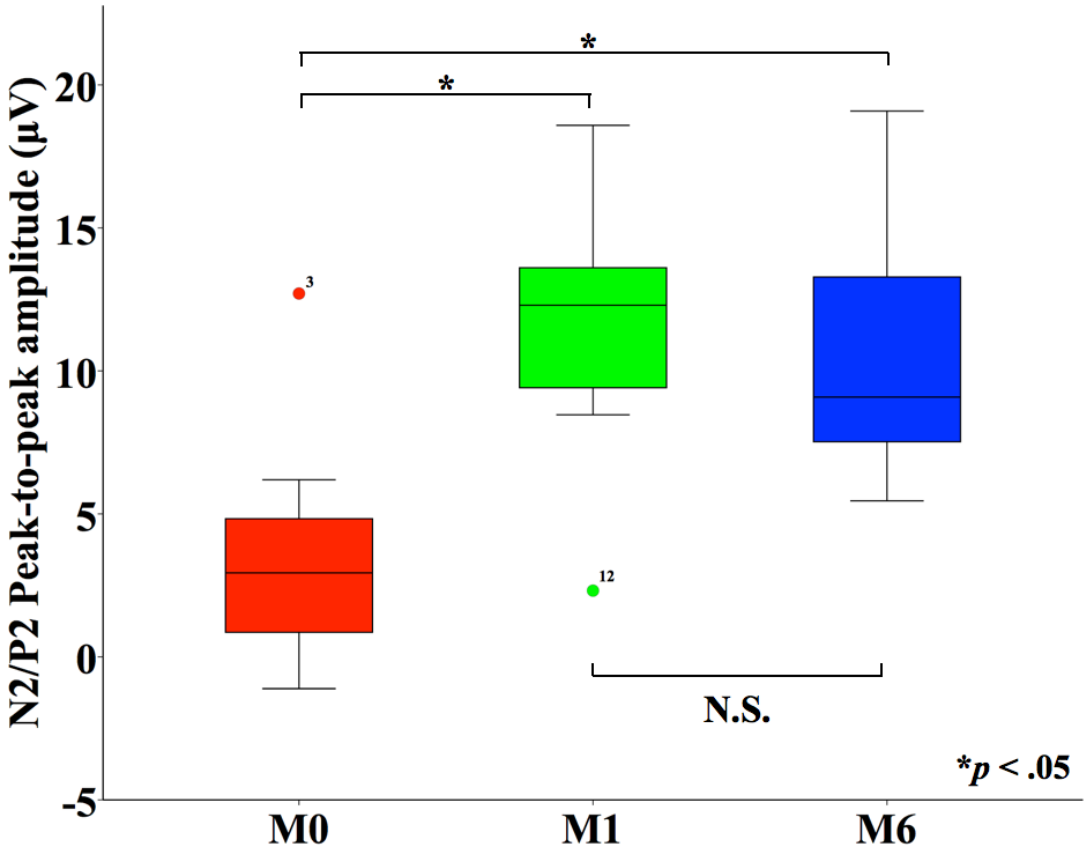
The N2/P2 peak-to-peak LEPs amplitudes were measured in μV at M0, M1 and M6. On the non-painful control side, we performed a 95% CI graphical representation of the study group's N2/P2 peak-to-peak amplitudes to show reproducibility (Fig. 9). On the graph one can observe that most amplitudes were between 10 and 17 μV across all measurements, with no statistical difference (Friedman Test, [$\chi^2(2) = 2.000$, $p = .368$]). The median values with interquartile ranges are 13.46 μV (11.61-16.33 μV), 14.16 μV (13.11-14.38 μV) and 13.59 μV (8.30-14.72 μV) at M0, M1 and M6, respectively.

Fig. 9 – 95% CI N2/P2 peak-to-peak amplitude (μV) from the non-painful control side, showing reproducibility across measurements at M0, M1 and M6.



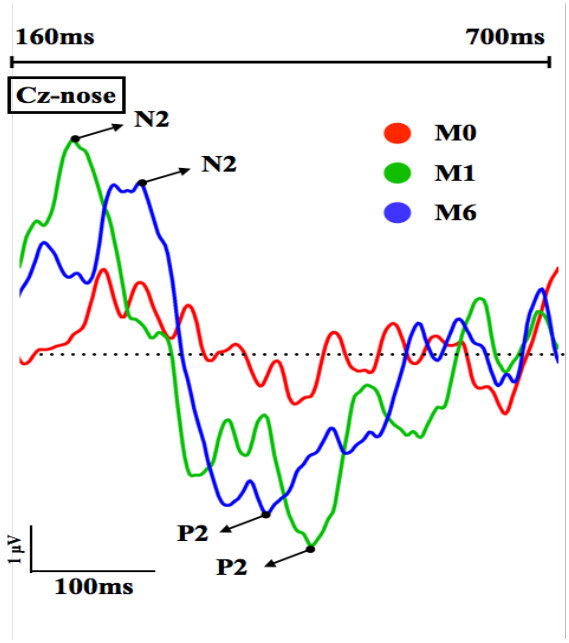
A two-tailed non-parametric Friedman test for repeated measures revealed a significant effect of DRGS on the N2/P2 peak-to-peak amplitudes [$\chi^2(2) = 10.571$, $p < .01$]. A Wilcoxon signed-rank test showed that the amplitudes at M0 were different from M1 [$Z = -2.366$, $p < .05$] and M6 [$Z = -2.366$, $p < .05$], showing a significant increase of the N2/P2 peak-to-peak amplitude after implementation of DRGS (Fig. 10).

Fig. 10 – N2/P2 peak-to-peak amplitude (µV) on the painful side significantly increased at M1 and M6 in comparison to M0.



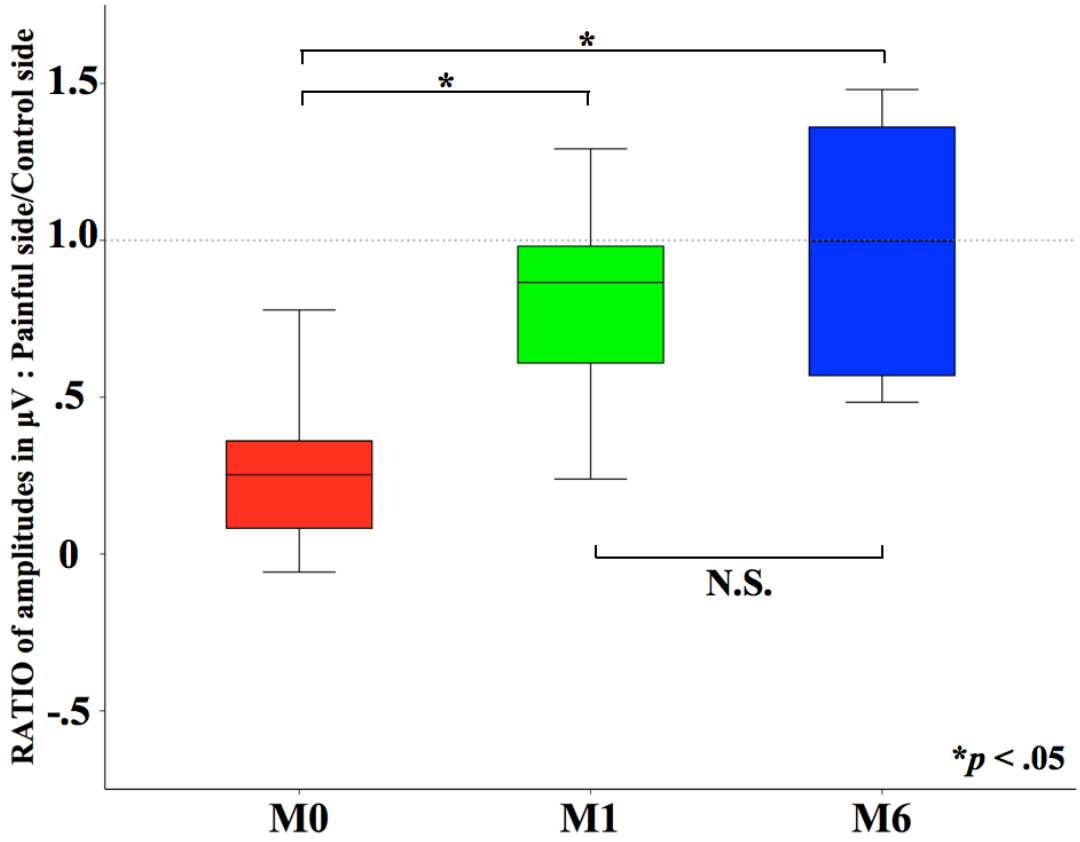
We then calculated the grand average of the seven patients' N2/P2 EEG curves. Figure 11 shows a graph with the data from all three time points overlayed, which shows restoration of the peak-to-peak amplitude after DRGS at M1 and M6 in comparison to M0.

Fig. 11 – Grand average LEPs curves (n=7), showing no LEPs at M0 and LEPs restoration at M1 and M6.



Next, a two-tailed non-parametric Friedman test for repeated measures revealed a significant effect of DRGS on the ratio of peak-to-peak amplitudes between the painful test side and the non-painful control side [χ^2 (2) = 11.143, p < .01]. The Wilcoxon signed-rank test showed that the ratio at M0 was different from M1 [Z = -2.366, p < .05] and M6 [Z = -2.366, p < .05]. The significant increase from M1 to M6 indicates LEPs restoration to near normal levels (Fig. 12).

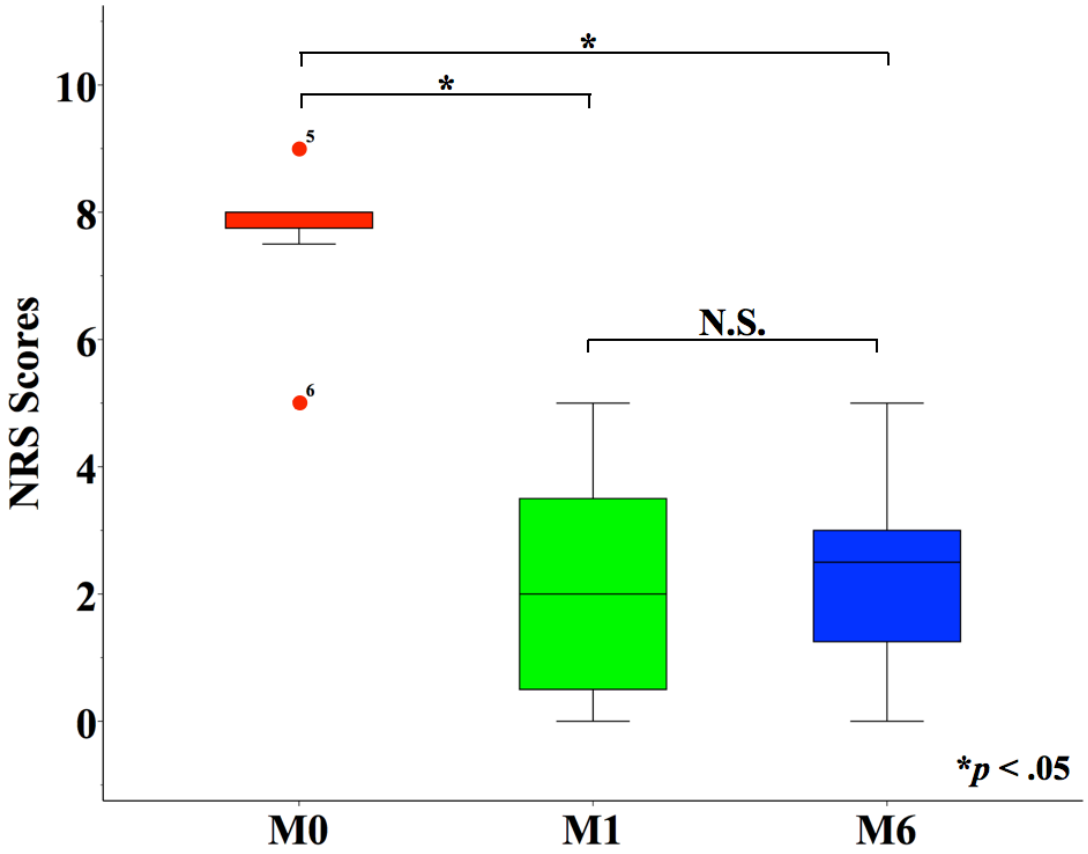
Fig. 12 – Ratios of the N2/P2 peak-to-peak amplitudes (µV) of the painful versus non-painful side, showing a significant increase in the M1 and M6 ratio relative to M0.



4.3 Pain intensity evaluation

NRS scores were significantly lower under DRGS (Friedman Test, [$\chi^2(2) = 11.385$, $p < .01$]): Scores at M1 [$Z = -2.371$, $p < .05$] and M6 [$Z = -2.371$, $p < .05$] differed significantly from those at M0 (Wilcoxon signed-rank test; Fig. 13).

Fig. 13 – NRS scores significantly decreased at M1 and M6 in comparison to M0.

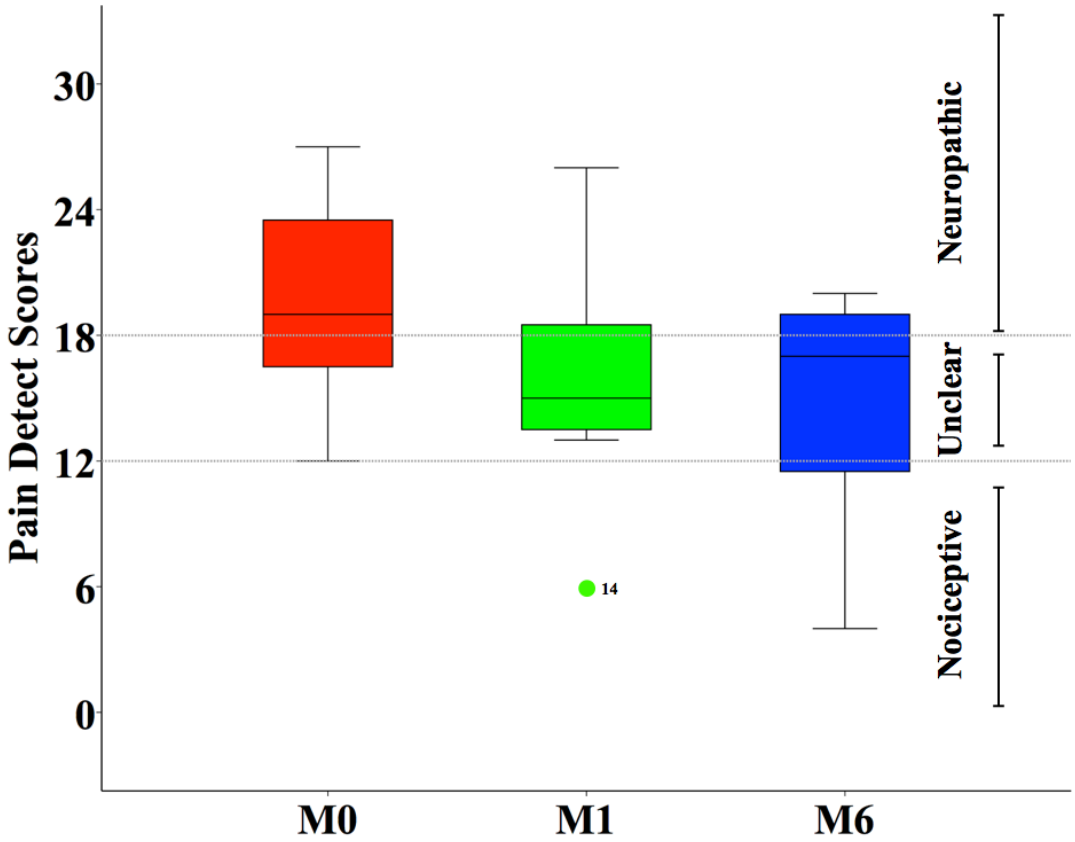


The mean values of spontaneous pain intensity in the affected area decreased from 7.6 at baseline to 2.1 at 1 month and 2.2 at 6 months after introduction of DRGS. This corresponds to an overall NRS pain score decrease of 73% at 1 month and 72% at 6 months.

4.4 Neuropathic pain components

Mean PainDETECT values decreased from 19.7 at M0 to 15.7 at M1 and 14.5 at M6. Interestingly, scores decreased in line with pre-defined cut-off values, which divide score ranges into 3 distinct intervals (neuropathic, unclear and nociceptive) (Fig. 14). This finding indicates neuropathic pain amelioration.

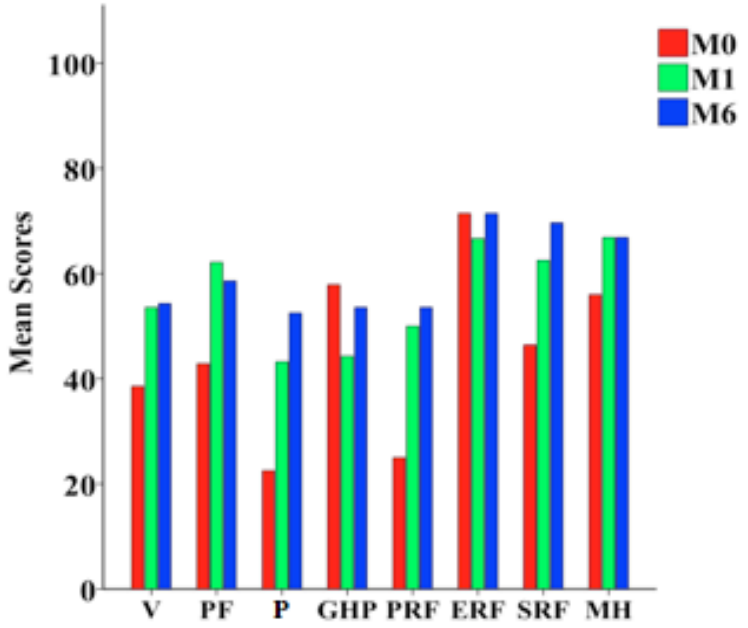
Fig. 14 – PainDETECT scores decreased at M1 and M6 relative to M0.



4.5 Quality of life assessment

The SF-36 is organized into eight different QoL dimensions: Vitality (V), Physical Functioning (PF), Pain (P), General Health Perceptions (GHP), Physical Role Functioning (PRF), Emotional Role Functioning (ERF), Social Role Functioning (SRF) and Mental Health (MH). Each dimension is scored on a scale of 0 (worst QoL) to 100 (best QoL) (Fig. 15).

Fig. 15 – SF-36 mean scores on 6 out of 8 items improved at M1 and M6 relative to M0.



Only two of the dimensions showed no improvement over time: General Health Perceptions and Emotional Role Functioning. By contrast, the mean score for Pain went from 22.5 at M0 to 43.2 at M1 and 52.5 at M6 (Table 3).

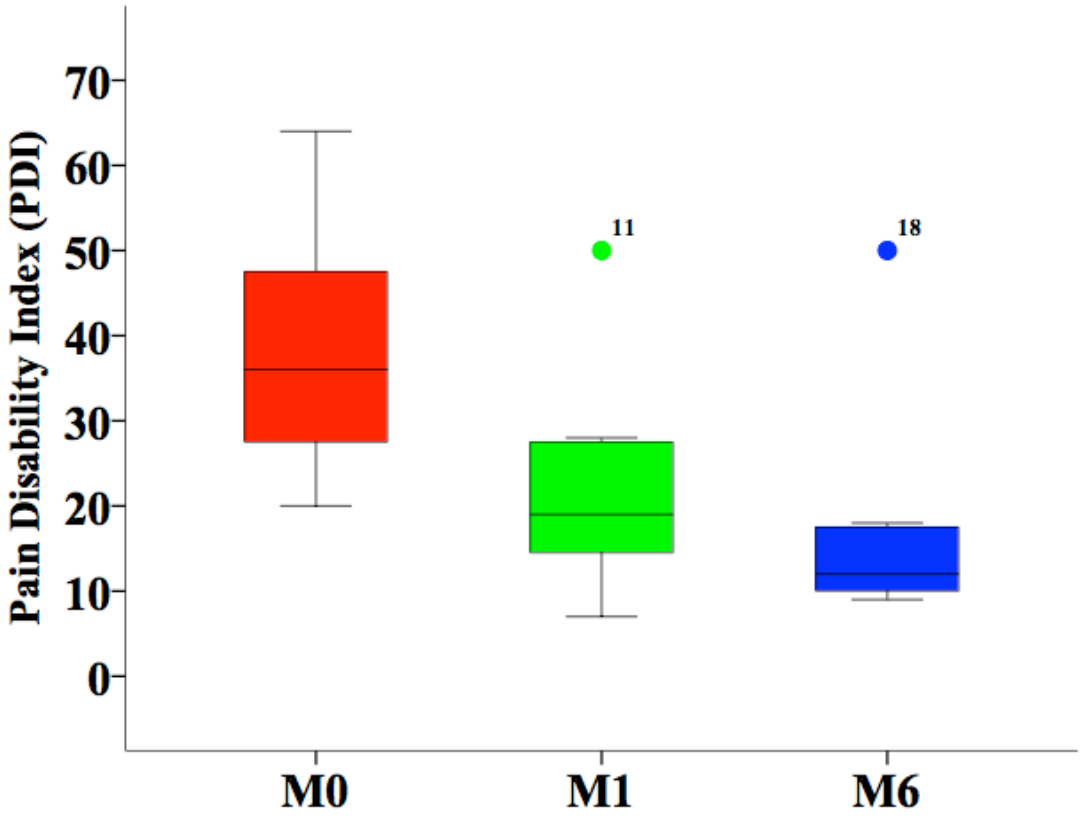
Table 3 – Mean SF-36 scores.

	M0	M1	M6
V	38.5	53.5	54.2
PF	42.8	62.1	58.5
P	22.5	43.2	52.5
GHP	57.8	44.2	53.5
PRF	25.0	50.0	53.5
ERF	71.4	66.6	71.4
SRF	46.4	62.5	69.6
MH	56	66.8	66.8

4.6 Pain-related disability assessment

PDI scores range from 0 (no disability related to pain) to 70. Scores decreased at M1 (22.8) and M6 (18) relative to M0 (38.5; Fig. 16).

Fig. 16 – PDI scores decreased at M1 and M6 in comparison to M0.



5 DISCUSSION

5.1 Neuromodulation for pain - background

The use of electrical stimulation to treat pain conditions dates to 15 A.D., when accidental contact with a torpedo fish resulted in relief from gout pain (*Goldenberg 2006*). In the modern era of medicine, pain neuromodulation arose after the publication of the gate control theory by Melzack and Wall in 1965 (*Melzack and Wall 1965*). Two years later, Shealy et al. published the first description of electrical stimulation of the spinal cord by insertion of a lead in the subarachnoid space of the dorsal column to treat a cancer pain patient (*Shealy, Mortimer et al. 1967*). Thereafter, the first commercially available spinal cord stimulator system was released in 1968 (*Kumar and Rizvi 2014*). Since then, the field of neuromodulation for pain, especially SCS, has evolved exponentially. Research in the area of neuromodulation continues to elucidate the mechanisms behind this technique and contribute to its improvement. Research using evidence-based together with mechanism-based medicine can contribute to the development of state-of-the-art treatments (*Levy 2012*).

Several studies addressing the effects of neuromodulation on different pain conditions have been published during the last decade (*Boswell, Shah et al. 2005, Airaksinen, Brox et al. 2006, Boswell, Trescot et al. 2007, Cruccu, Aziz et al. 2007, North, Shipley et al. 2007, Manchikanti, Boswell et al. 2009, Manchikanti, Abdi et al. 2013*). Most of those studies focused on SCS systems with the usual electrode design specifications engineered to be inserted into the dorsal column. In those studies, the frequency of stimulation was set at a regularly spaced, fixed rate of electrical spikes, mostly between 30 and 300 Hz (*Meier 2014*). This is typically called tonic SCS of the dorsal column.

In a recent review of neuromodulation for the treatment of chronic pain including SCS (*Deer, Krames et al. 2014*), the authors suggested that more randomized studies testing efficacy are needed, and also that efforts should be made to guarantee patients' access to such techniques. Furthermore, they recommended consensus meetings be held to determine the most appropriate use of neurostimulation

for pain. According to Meier, 25 to 50% of patients do not benefit from SCS (*Meier 2014*), and several authors have suggested ways of producing better outcomes (*Sindou, Mertens et al. 2003, Atkinson, Sundaraj et al. 2011, Campbell, Jamison et al. 2013*). Currently, the only clear positive level of evidence (I to II) for tonic low-frequency SCS of the dorsal column is for patients diagnosed with failed back surgery syndrome (FBSS) (*Grider, Manchikanti et al. 2016; Manchikanti, Falco et al. 2014*).

5.2 Innovative approaches using spinal cord stimulation

SCS has been used now for nearly half a century. However, there is still plenty of room for design innovations, system upgrades or hardware/software refinements. There have been several recent advancements in this area, particularly for SCS. These include rechargeable generators, multicolumn electrode leads, long-range telemetry, self-adjustable stimulation, magnetic resonance imaging (MRI) compatible systems, wireless rechargeable leads, novel programming waveforms, and electrodes for new stimulation targets. Some technologies expected to emerge in the near future are new stimulation paradigms, closed loop stimulation, optogenetic-based stimulation, the addition of neurochemicals to hybrid systems and miniaturization (*Slavin 2014*). The techniques with the greatest impact on clinical practice are most likely the two new waveform programming paradigms available for SCS, high frequency stimulation and burst stimulation, and DRGS (*Raja & Wallace 2015*).

5.2.1 Electrical properties of the stimuli

Relative to traditional (tonic) SCS, burst and high frequency SCS stimulation have been shown to offer better clinical outcomes (*De Ridder, Plazier et al. 2013, Kapural, Yu et al. 2015*). Burst stimulation is set to 40 Hz burst mode as a constant stimulus with 5 spikes at 500 Hz per burst and pulse width with interspike intervals of 1 ms, while high frequency stimulation consists of SCS at regular spaced spikes of stimulation with frequencies of up to 10 kHz (*Raja & Wallace, 2015*). Clinical trials using both techniques have shown preliminary positive results, including pain relief without paresthesia generation, particularly for lower back pain (*Tiede, Brown et al. 2013, Al-Kaisy, Van Buyten et al. 2014, de Vos, Bom et al. 2014, Schu, Slotty et al. 2014, Kapural, Yu et al. 2015*). A recent review article gave level of evidence IV for

burst stimulation and level of evidence II to III for high frequency stimulation. (*Grider, Manchikanti et al. 2016*).

5.2.2 Dorsal root ganglion stimulation

DRGS for the treatment of chronic pain is a relatively recent technique (*Deer, Grigsby et al. 2013*). Since 2011, DRGS is performed in some European countries and in Australia (*Deer, Kramer et al. 2014*). Some studies have referred to the technique with a different name: "spinal cord stimulation of the dorsal root ganglion" (*Liem, Russo et al. 2015*). Most authors agree that DRGS recruits the CNS (*Liem 2015*). A recent review highlights DRGS as an emerging management option for neuropathic pain (*Pessoa, Escudeiro et al. 2015*). Additionally, contemporary textbooks in the field of neuromodulation have already dedicated an exclusive chapter to DRGS for the treatment of chronic pain (*Kugler 2013, Knotkova and Rasche 2014, Deer and Pope 2015, Slavin 2015*).

A recent review suggested, that despite some evidence for the efficiency of DRGS, that more evidence is needed of its long-term efficacy and safety (*Forget, Boyer et al. 2015*). These authors further recommended the use of tools such as LEPs and quantitative sensory testing (QST) (*Forget, Boyer et al. 2015*). The ACCURATE study is a large ongoing clinical trial that aims to evaluate the safety and effectiveness of DRGS for patients diagnosed with CRPS I and II (*2016)*. In it, a group receiving DRGS is compared to a control group receiving traditional tonic SCS. Follow-up results at 12 months have been positive. Relative to the control group, more patients who received DRGS reported successful pain relief (74.2% vs. 53% of patients). Additionally, most DRGS patients had better stimulation targeting, enabling better coverage of the painful area. There was also a lower rate of paresthesia in the stimulated area among the DRGS patients (*2015*). As a result of these findings, in February 2016, the Food and Drug Administration (FDA) approved the treatment with DRGS for patients diagnosed with CRPS type I and II in the United States. It is important to note that this clinical trial was sponsored by the manufacturer of the neuromodulation system, raising a potential conflict of interest.

5.3 Mechanisms of action of neuromodulation

5.3.1 Background

Although neuromodulation was introduced several years ago, the mechanisms underlying the treatment of chronic pain through it have yet to be fully understood. But before understanding the mechanics behind SCS and even DRGS, one must fully understand neuropathic pain pathophysiology. In the following sections, we also consider the standardized methods used to quantify results, such as pain intensity scales, neuropathic pain assessment tools, and neurophysiological techniques.

5.3.2 Pathophysiology of chronic neuropathic pain

Chronic neuropathic pain is defined as maladaptive pain resulting from a lesion or disease affecting the somatosensory system. In contrast to regular pain, which plays a protective role in avoiding further tissue damage, chronic neuropathic pain offers no biological function. Neuropathic pain syndromes usually present a combination of negative symptoms or sensory deficits (e.g. loss of sensation), together with positive symptoms, which may include paresthesia or allodynia (*Woolf and Mannion 1999*). The diverse clinical presentation in neuropathic pain is directly related to the variety of mechanisms responsible for chronic pain development, including ectopic neuronal activity due to hyperexcitability, peripheral sensitization associated with a reduced activation threshold of the PSN, central sensitization due to increased excitability and synaptic efficacy of neurons in central nociceptive pathways, impaired inhibitory mechanisms of nociception, and activation of microglia and other non-neural cells in the CNS (Table 4) (*Gilron, Jensen et al. 2013, Gilron, Baron et al. 2015*).

Table 4 – Neuropathic pain mechanisms (modified from *Gilron, Baron et al. 2015*).

Neuropathic pain mechanisms
• Ectopic activity • Peripheral sensitization • Central sensitization • Impaired inhibitory modulation • Activation of microglia

Several chronic pain mechanisms are generated in the spinal cord, the first relay in the pain pathways from the periphery to the brain (*D'Mello and Dickenson 2008*). There are currently two possible distinct theories regarding chronic pain: central sensitization (i.e. neurogenic hyperalgesia), which manifests as slight sensory loss and partial nociceptive deafferentation (i.e. painful hypoalgesia), which presents as significant sensory deficits (*Baumgartner, Magerl et al. 2002*). Identifying the sensory profile of an individual's neuropathic pain can lead to better selection of therapy, which highlights the importance of a mechanism-based classification of neuropathic pain (*Baumgartner, Magerl et al. 2002, Cruccu and Truini 2009*).

5.3.3 Peripheral neuropathic pain

In this brief review, we focus on the pathophysiological mechanisms of peripheral neuropathic pain, which is defined as "pain arising as a direct consequence of a lesion or disease affecting the peripheral somatosensory system" (*Loeser and Treede 2008*). Peripheral neuropathic pain manifests as spontaneous, stimulus-independent pain and/or as stimulus-evoked pain (i.e. pain hypersensitivity) (Fig. 17) (*Woolf and Mannion 1999*). Peripheral nerve damage can lead to significant alterations in the neuron itself and/or in processes involved in nociception. Finally, a peripheral nerve lesion can lead to a number of pathophysiological alterations (*Kehlet, Jensen et al. 2006*).

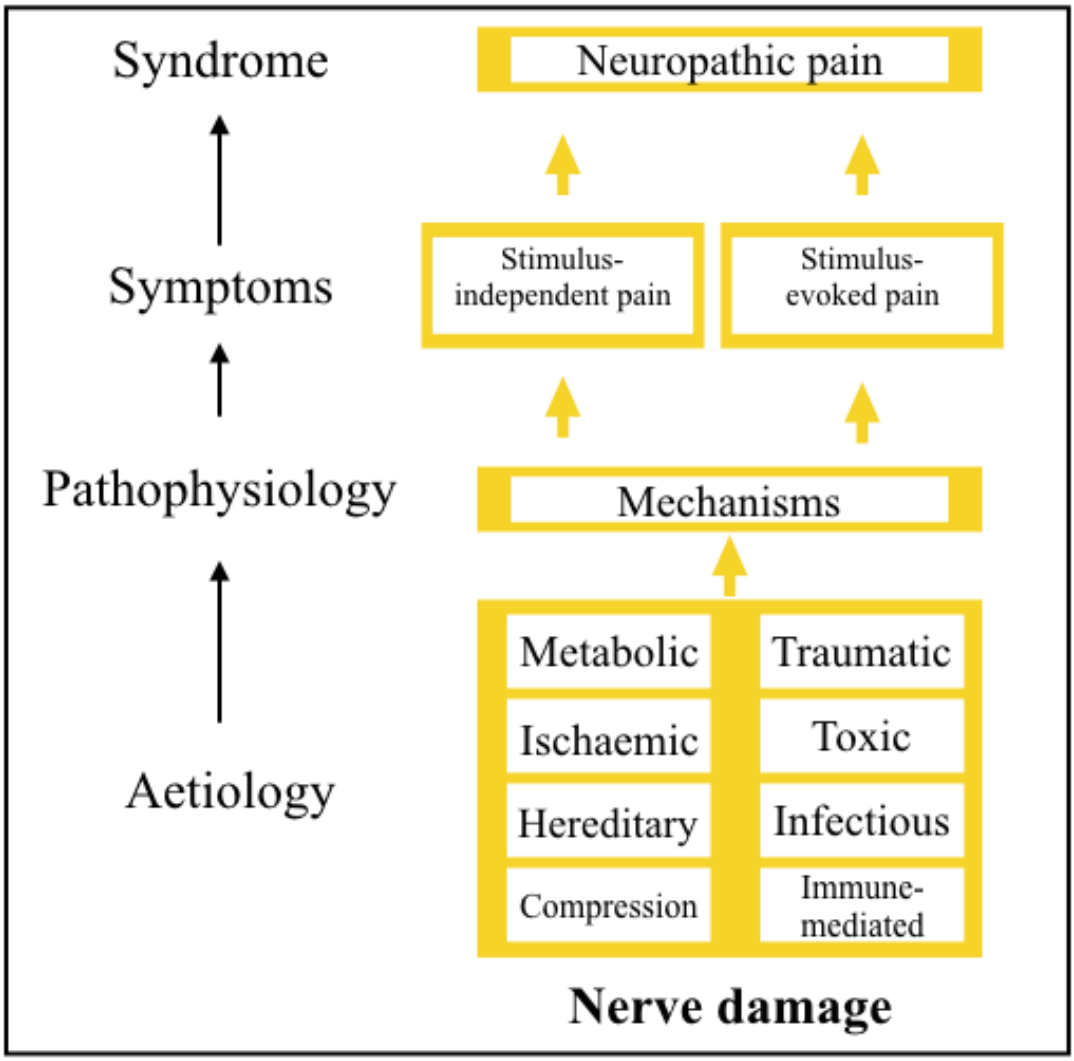
Spontaneous and evoked pain

Spontaneous pain is often described as shooting, lancinating or burning pain. It can be further divided into paroxysmal pain and constant pain. Paroxysmal pain is associated with high frequency bursts generated ectopically. Not only are the

peripheral terminals sensitized, but also the cell bodies and the region near the DRG, contributing to the generation of spontaneous bursts (*Truini and Cruccu 2006*). On the other hand, constant pain is the most typical form of neuropathic pain, and is attributed to either spontaneous firing of C fiber afferents due to excitation of C nociceptors in the skin, or as a consequence of central hyperactivity resulting from deafferentation.

Evoked pain is also a common outcome in peripheral neuropathic pain and may manifest as hyperalgesia or allodynia. Hyperalgesia is defined as "increased pain sensitivity" (*Loeser and Treede 2008*), generally resulting from abnormal processing of nociceptor input. Neuropathic hyperalgesia can be categorized as primary or secondary. Primary hyperalgesia is caused by the sensitization of the injured tissue after a peripheral nerve lesion, whereas secondary hyperalgesia is produced in an adjacent portion of unaffected tissue in response to CNS sensitization (*Cohen and Mao 2014*). Allodynia, on the other hand, is defined as "pain in response to a non-nociceptive stimulus" (*Loeser and Treede 2008*). It is believed that allodynia translates a pure sensitization of the peripheral receptors, with reduction of the mechanical threshold in the sensitized nociceptors *(Serra 1999)*. However, the most accepted explanation contends that central nociceptive neurons are sensitized to mechanically evoked input mediated by Aß fibers (*Truini and Cruccu 2006*).

Fig. 17 – Aetiology, mechanisms and symptoms of peripheral neuropathic pain (modified from *Woolf and Mannion 1999*).



5.3.4 Pathophysiology of the dorsal root ganglion in neuropathic pain

The DRG is a key structure in the processing of pain in chronic pain states, affecting intricate mechanisms in peripheral and central pain processing. The DRG participates in various pain-related pathophysiological modifications during inflammation, somatic pain and neuropathic pain. In a recent review, the authors suggest that the DRG is an important therapeutic target in the treatment of neuropathic pain and also the source of mechanisms associated with the development of neuropathic pain (*Sapunar, Kostic et al. 2012*). In the event of nerve injury, the PSN in the DRG start to generate ectopic discharges, contributing to neuropathic pain

and paresteshias (*Wall and Devor 1983, Amir, Michaelis et al. 1999, Sapunar, Ljubkovic et al. 2005*). Membrane potential oscillations at sub-threshold levels are increased in a chronic nerve injury and are associated to the ectopic discharges in the DRG (*Amir, Michaelis et al. 1999*). The ectopic activity is thought to be the source of pain producing signals after peripheral nerve lesions (*Truini, Biasiotta et al. 2010*). It is also known that the DRG starts to respond to blood-borne chemicals following a nerve lesion (*Burchiel 1984*).

One of the mechanisms responsible for hyperexcitability is thought to be the loss of Ca^{2+} influx into the somata (*Lirk, Poroli et al. 2008*). It has been shown that loss of Ca^{2+} current is related to the passage of high-frequency bursts from the periphery to the CNS. Furthermore, the low-pass filtering function that ensues in healthy DRG neuronal cells on the T-junction is impaired (*Luscher, Streit et al. 1994*). Some pathological conditions, such as neural injury and increased neural activity, may decrease the concentration of extracellular Ca^{2+}. This often happens following a nerve injury, which enhances hyperexcitability even when ion channel properties are not affected (*Lirk, Poroli et al. 2008*).

After a nerve lesion, the neural activity of the DRG is intensely modulated by a complex cascade of immune and glial cell responses (*Scholz and Woolf 2007*). The release of signaling inflammatory molecules from these cell types can lead to hypersensitivity of nociceptors in the periphery (*Julius and Basbaum 2001*). Following a peripheral nerve injury or inflammation, the glial cells surrounding the soma proliferate. Those cells produce cytokines and neurotropins, which in turn contribute to chronic pain states (*Znaor, Lovric et al. 2007*), and the release of neurotropic factors has been shown to exacerbate allodynia (*Zhou, Deng et al. 2000*). Nerve growth factor, a neurotropin that is elevated in inflammatory tissues, can modify PSN phenotype, altering sensory neuron function and leading to persistent pain (*Woolf 1996*).

Inflammatory cell proliferation surrounding the DRG after nerve injury involves macrophages and lymphocytes (*Hu and McLachlan 2002*). As these cells release excitatory cytokines, generation of ectopic neuron firing ensues, leading to neuropathic pain development (*Hu and McLachlan 2002*). It has been shown that tumor necrosis factor (TNF) alpha, a pro-inflammatory cytokine, can induce neuron

ectopic activity (*Sorkin, Xiao et al. 1997*). Additionally, inflammation at the level of the DRG is important in the development of neuropathic pain (*Li, Xie et al. 2011*).

Na^+ ion channels are associated with increased excitability in DRG C cells. An enhancement of C cell excitability has been shown after nerve injury in rats, which was most likely associated with a Na^+ channel mechanism (*Zhang, Donnelly et al. 1997*). Also, after axotomy, there is an up-regulation of type 3 sodium channel mRNA, which is not normally expressed by mature DRG neurons, and this may explain Na^+ channel involvement in hyperexcitable states after nerve injury (*Waxman, Kocsis et al. 1994*). Lower APs thresholds in DRG neurons with an increase in spontaneous APs were also observed in a study analyzing rats after ligation of the sciatic nerve, suggesting that the DRG cell body is the source of this abnormal activity (*Study and Kral 1996*). It is reasonable to assume that the pathological activity in the DRG may be associated with the initial phases of neuropathic pain (*Wall and Devor 1983*). Neuropathic pain hyperexcitability has also been linked to Na^+ channel hyper-expression (*Devor, Govrin-Lippmann et al. 1993*).

K^+ channels are also involved in neuropathic pain development, as seen in a rat model of sciatic nerve injury (*Kajander, Wakisaka et al. 1992*). Furthermore, alterations in K^+-channel function have been associated with chronic pain, including neuropathic pain (*Du and Gamper 2013*). Moreover, impairment of glial K^+ homeostasis may further contribute to pain (*Takeda, Takahashi et al. 2011*).

Norepinephrine, an excitatory neurotransmitter, can alter DRG physiology due to the DRG's sympathetic sensitivity in chronic pain states. Norepinephrine sensitivity can lead the PSN in the DRG to develop spontaneous firing. Moreover, after a nerve injury, norepinephrine appears to influence neuronal firing of sensitized A and C fibers via up-regulated alfa2-adrenoceptors, especially when there is ongoing spontaneous neuron activity. The abnormal sympathetic neuronal activity may be associated with cutaneous pain and hyperalgesia (*Xie, Zhang et al. 1995*). Finally, sympathetic innervation of the DRG after nerve lesions may play a role in sympathetically maintained neuropathic pain (*Chung, Lee et al. 1996*).

5.3.5 Spinal cord stimulation of the dorsal column - mechanisms of action

Gate control theory

The gate control theory proposed by Melzack and Wall was the most accepted theoretical framework explaining pain relief during SCS of the dorsal column (*Melzack and Wall 1965*). According to this model, a "gate" acts as an integrative center mediated by A fibers. The stimulation of the dorsal column leading to activation of A fibers can activate inhibitory interneurons in the dorsal horn. Interneuron activation, in turn, suppresses pain transmission by "closing" the gate to the afferent nociceptive inputs generated by small myelinated Aδ or unmyelinated C fibers. In order to validate this model as a mechanistic explanation, SCS must suppress the activity of wide dynamic range (WDR) neurons and SCS-mediated inhibitions must involve inhibitory interneurons (*Zhang, Janik et al. 2014*). Some evidence in rats points to a drastic reduction in the WDR neurons' spontaneous activity rate in the dorsal root following a conditioned stimulus in the dorsal column or in the posterior root (*Guan, Wacnik et al. 2010*). Additionally, pain suppression in animal models of neuropathic pain under SCS has been shown through suppression of WDR neurons, which requires activation of A-fibres originating from the pain area (*Guan 2012*). Dorsal horn WDR hyperexcitablity has been shown to normalize after SCS (*Yakhnitsa, Linderoth et al. 1999*).

Segmental mechanisms

With the publication of additional potential segmental mechanisms explaining pain relief during SCS, the gate control theory was considered to be insufficient on its own. The gate theory fails to fully explain SCS mechanisms of action (*Kumar, Toth et al. 1998*), and this view is corroborated by clinical findings of sustained pain relief even after cessation of stimulation (*Lindblom and Meyerson 1975*). For example, electrical stimulation of low-threshold afferents in an area surrounding the primary excitatory receptive field of a neuron results in inhibition of the neuron, similarly to stimulation of the dorsal column (*Hillman and Wall 1969*), and is therefore based on a mechanism similar to SCS. The influence of different cell populations, such as nociceptive-specific (NS) neurons and low-threshold neurons within the dorsal horn, can additionally influence pain relief during SCS. Distinct roles of these cells as well

as the interaction with the WDR neurons led to the development of the hypothesis of a microcircuit of pain perception (*Prescott and Rate 2012*). Furthermore, additional segmental effects include aberrant nerve sprouting into atypical laminae following a nerve lesion (*Woolf, Shortland et al. 1992*), excitatory synaptic receptor expression leading to hyperexcitability and sensitization of NS neurons (*von Hehn, Baron et al. 2012*), and loss of inhibitory mechanisms (*Woolf and Wall 1982*), all of which are also not accounted for by the gate theory (*Zhang, Janik et al. 2014*). The SCS-induced WDR neuron inhibition can occur to a greater extent if the electrode is positioned at the spinal level adjacent to the affected dermatome, and this suggests a segmental spinal site of action (*Smits, van Kleef et al. 2012*). Gamma-aminobutyric acid (GABA) mediated inhibition of local interneurons appears to be the driver of A-fiber mediated inhibition (*Zhang, Janik et al. 2014*), which also seems to be segmental. This GABA mediated effect was demonstrated in two clinical randomized trials through use of GABA B receptor agonist baclofen (*Lind, Schechtmann et al. 2008, Schechtmann, Lind et al. 2010*).

Supraspinal mechanisms

Supraspinal mechanisms appear to be independent of segmental mechanisms and may play a role in SCS (*Saade', Tabet et al. 1986, Foreman and Linderoth 2012*). Opioidergic (*Sato, King et al. 2013*), serotoninergic (5-HT) (*Song, Ultenius et al. 2009*), adenosinergic (*Cui, Sollevi et al. 1997*) and cholinergic (*Schechtmann, Song et al. 2008*) systems have also been shown to contribute to SCS, and recent evidence in rats suggests modulation of a spinal-supraspinal loop (*Song, Ansah et al. 2013*). The nucleous raphes magnus in the rostroventromedial medulla (*Song, Ansah et al. 2013*) and periaqueductal gray matter (*Sorkin, McAdoo et al. 1993*) appear to contribute to the descending antinociceptive system in SCS. Inhibition of neuropathic pain in rats has been shown to occur through dorsal column stimulation by activation of brainstem centers via rostral projections of the dorsal column nuclei (*El-Khoury, Hawwa et al. 2002*). It is possible that SCS pain relief may be a consequence of a complex interaction between ascending and descending fibers as well as due to direct root stimulation (*Yang, Carteret et al. 2011*). In fact, spinal and supraspinal mechanisms appear to be acting synergistically in pain relief through SCS (*Barchini, Tchachaghian et al. 2012*).

Finally, changes in the pain matrix (i.e. the network of brain areas involved in pain processing) also contribute to SCS-mediated pain relief (*Tracey and Mantyh 2007; Garcia-Larrea and Peyron 2013*). Researchers have identified areas of activation and/or inhibition of dorsal column nuclei which may function as a neural relay for SCS-induced alterations in the brain (*Qin, Yang et al. 2009*). Studies using functional magnetic resonance imaging (fMRI) showed increased activation of primary somatosensory cortex (SI) and secondary somatosensory cortex (SII) during neuropathic pain (*Kiriakopoulos, Tasker et al. 1997*), and pain reduction by SCS has been associated with reduced activity in prefrontal cortex, cingulate gyrus, thalamus, supplementary motor area, and postcentral gyrus (*Rasche, Siebert et al. , Moens, Sunaert et al. 2012*). Moreover, the effects of activation due to SCS in the contralateral insula and ipsilateral SII following unilateral painful heat stimulation were higher when measured during simultaneous stimulation (SCS + heat evoked pain) than when measured separately under either SCS or heat evoked pain. This finding raised the hypothesis that SCS interferes with pain processing by saturating neuronal circuits with neuronal impulses, which in turn reduces input to the pain matrix (*Stančák, Kozák et al. 2008*).

A positron emission tomography (PET) study in patients undergoing SCS for angina showed a number of regions (i.e. medial prefrontal cortex and cingulate gyrus) associated with nociception (*Hautvast, Ter Horst et al. 1997*). Another PET study showed significant simultaneous activation of the contralateral thalamus and bilateral parietal association area, as well as activation of the prefrontal cortex and cingulate gyrus during SCS, suggesting a strong influence of multiple supratentorial structures in pain processing (*Kishima, Saitoh et al. 2010*). And another PET study by Sufianov et al. showed that patients under SCS experience a normalization of brain metabolism and function (*Sufianov, Shapkin et al. 2014*). Further neuronal activation/deactivation patterns in multiple brain regions were also found in a Tc-99m-HMPAO single-photon emission computed tomography (SPECT) study (*Nagamachi, Fujita et al. 2006*). The identification of lateral and medial pain systems related to distinct noxious and innocuous CO_2 laser stimuli confirmed a major division of function within the pain matrix (*Kulkarni, Bentley et al. 2005*), and both may be affected by SCS, especially in the new waveform paradigm of burst (*De Ridder, Plazier et al. 2013*). Although studies have shown pain matrix effects after SCS, several authors

believe that few conclusions can be drawn and that more studies are necessary to assess the specific role of each particular brain area (*Meier 2014, Zhang, Janik et al. 2014*).

To conclude, there remains an incomplete understanding of SCS mechanisms of action and chronic neuropathic pain response to this technique. Thus, there is a wide opportunity for further research towards new experimental models and clinical investigation, as well as to explore novelty stimulation paradigms (*Meier 2014*, *Bentley, Duarte et al. 2016*).

5.3.6 Dorsal root ganglion stimulation - proposed mechanisms of action

Most studies on DRGS to date include PSN cultured cell techniques, neurophysiological assessment or animal models.

The neuronal somata of the first sensory neurons lie within the DRG, including those conveying Aδ and C fibers. Spontaneous or facilitated firing of lowered threshold neurons in the DRG can produce hyperexcitability, increasing pain signals towards the spinal cord. The mechanism behind pain alleviation through DRGS can be elucidated from research with electrical deep brain stimulation (DBS) (*McIntyre, Savasta et al. 2004*). Similarly to DBS, DRGS could potentially alter abnormal electrical activity of DRG neurons, decreasing pain by modulating ion channels through use of external electrical current (*Bradford 1970*). Specific genes that alter neuronal function are also expressed under electrical stimuli (*Klein, Tendi et al. 2003*). Evidence from cultured DRG cells show a direct correlation between electrical DRGS and neuronal somata activation (*Fuchs, Rigaud et al. 2007*). Yet another study recently showed that field electrical stimulation of DRG neurons can cause Ca^{2+} influx, triggering second messenger processes. Ca^{2+} enhanced influx has been associated to decreased excitability and restored the filtration of high-frequency action potentials (*Koopmeiners, Mueller et al. 2013*).

Electrical stimulation of neural tissue was shown to stimulate the synthesis of growth factors. There is evidence that electrical DRGS may release abnormal growth factors and/or inhibit the release of normal ones (*Aaron, Boyan et al. 2004*). Similar

mechanisms may be extended to immune response changes, which would lead to decreased pain following electrical DRGS.

As seen following dorsal column stimulation, autonomic effects are observed after electrical DRGS, which suggests that the dorsal root afferent fibers influence downstream autonomic effects (*Croom, Foreman et al. 1997*). Proposed mechanisms of DRGS based on this assumption include vasodilatory effects. Additionally, one may expect stabilization of nociceptors in the periphery, deactivation of WDR neurons in the dorsal horn and modulation of supraspinal brain regions involved in chronic pain (*Krames 2015*). Another hypothesis proposes that DRGS has a potential effect on DRG microglia, decreasing the release of chemokines associated to chronic pain, as seen in DBS (*Vedam-Mai, van Battum et al. 2012*). The decrease of the pro-inflammatory effect on microglia has been shown with electrical stimulation in a rat photic injury model (*Zhou, Ni et al. 2012*).

Table 5 – Hypothesized mechanisms of action - DRGS (modified from *Krames 2015*).

Hypothesized mechanisms of action - DRGS
• Modification of growth factor release • Reversal of cytokine release • Downstream and upstream effects • Rectification of electrical activity patterns • Reversal of genetic changes • Down-regulation of abnormal ion channels and restitution of normal ion flux • Filtering of electrical impulses

According to Yan et al., DRG electrical stimulation leads to nerve regeneration with neurite outgrowth via calcium influx that may result in stabilization of pain neurophysiology (*Yan, Liu et al. 2014*), a mechanism that has also been modeled computationally (*Adams, Willits et al. 2016*).

In sum, DRGS may function as a signal stabilizer of pain input coming from the periphery. Furthermore, it may reverse neural plasticity and sensitization of the CNS or even prevent maladaptative changes if initiated early in neuropathic pain patients (*Liem 2015*).

5.3.7 Neurophysiological assessment under neuromodulative therapies

Neurophysiological tools such as somatosensory evoked potentials (SEP), plantar sympathetic skin responses (SSRs), F-wave, H-reflex, nociceptive flexion assessment (RIII-reflex) (*de Andrade, Bendib et al. 2010*), have allowed investigators to further test SCS mechanisms of action in real clinical practice. In a study with FBSS patients, the authors assessed a variety of neurophysiological measurements during SCS ON and OFF conditions: segmental spinal integration was measured by means of sensorimotor reflexes for small fibers (RIII-reflex) and large fibers (H-reflex); spinal motorneuron excitability was assessed by recording F-waves; suprasegmental sensory pathways (dorsal columns) were examined by recording P40-SEP; and SSRs were assessed to evaluate SCS effects on sympathetic-related activity. Normalization of neurophysiological values during the ON condition were found in SSRs, F-wave persistence, reduced F-wave amplitude, increased F-wave latency and increased SEP latency. Significant differences between ON and OFF were found in SEP amplitude, H-reflex amplitude, RIII-reflex threshold and RIII-reflex area (*de Andrade, Bendib et al. 2010*).

Other studies have also found attenuation in RIII-reflex after SCS (*Garcia-Larrea, Sindou et al. 1989, Garcia-Larrea, Peyron et al. 2000*), which may be the strongest objective evidence of a real analgesic effect. A decrease in P40-SEP amplitude speaks in favor of supraspinal mechanisms effect (*de Andrade, Bendib et al. 2010, Larson, Sances et al. 1974, Doerr, Krainick et al. 1978*). A collision of action potentials travelling in opposite directions on peripheral large diameter fibers may explain such findings (*Buonocore, Bodini et al. 2012*). Antidromic action potentials as well as orthodromic activation of supraspinal systems may act simultaneously to relieve pain in SCS (*Weigel, Capelle et al. 2015*). Median and posterior tibial nerve SEP attenuation of abnormally enhanced responses was observed in patients under SCS for neuropathic pain (*Theuvenet, Dunajski et al. 1999*). The SEP amplitude decrease was also shown in a more recent study and was greater in SCS when compared to transcutaneuos electrical nerve stimulation (TENS) (*Wolter, Kieselbach et al. 2013*).

During SCS ON, attenuation of somatosensory processing in SI and SII was also observed during SEP of the tibial and sural nerve using a high density EEG dipole reconstruction method. The tonic increase of SI and SII cortical activity due to SCS-related lemniscal neuron activation or the inhibition of somatosensory afferent input at the segmental level is thought to diminish sensitivity to neuropathic pain (*Polacek, Kozak et al. 2007*). Enhancement of plantar SSRs reveals that there is also a sympathetic effect (*de Andrade, Bendib et al. 2010*). Bilateral decrease in pain threshold after cessation of SCS on a population diagnosed with unilateral pain speaks in favor of the supraspinal effects of SCS. Moreover, SCS appears to adjust the neurophysiological response of the neuropathic pain side to the unaffected side (*Weigel, Capelle et al. 2015*).

In conclusion, these findings suggest an inhibition of Aß and Aδ myelinated fibers either at a segmental or suprasegmental level, as well as provide objective evidence of pain relief during the SCS ON condition (*de Andrade, Bendib et al. 2010*). Taken together, the neurophysiological data suggest that SCS normalizes pathological pain processing in chronic pain patients to a more healthy state of cortical activity (*Bentley, Duarte et al. 2016*).

5.4 Laser-evoked potentials

Laser-evoked potentials (LEPs) are the gold standard assessment tool to evaluate pain physiology and pathophysiological mechanisms (*Bromm and Lorenz 1998, Haanpaa, Attal et al. 2011*). LEPs can be used to investigate specific diseases that affect the nociceptive system (*Treede, Meier et al. 1988, Kakigi, Shibasaki et al. 1990, Bromm, Frieling et al. 1991, Treede, Lankers et al. 1991, Kakigi, Kuroda et al. 1992, Agostino, Cruccu et al. 2000, Cruccu, Leandri et al. 2001, Garcia-Larrea, Convers et al. 2002, Spiegel, Hansen et al. 2003, Truini, Haanpaa et al. 2003*). Furthermore, solid-state lasers (e.g. Neodymium Yttrium - Aluminum – Perovskite (YAP)) facilitated application to any body region and also decreased unintended superficial skin burns (*Spiegel, Hansen et al. 2000, Cruccu, Pennisi et al. 2003*).

In 2004, the European Federation of Neurological Societies (EFNS) released guidelines for neuropathic pain assessment (*Cruccu, Anand et al. 2004*). At the time

of the publication, LEPs studies amounted to little more than 100 scientific articles in peer-reviewed journals. The expert panel review stated that LEPs were the most reliable neurophysiological tool to assess the functional integrity of nociceptive pathways and granted a grade B level of recommendation for use of Aδ LEPs to diagnose peripheral and central neuropathic pain. A grading system proposed to diagnose neuropathic pain in clinical and research scenarios has included LEPs as one of the principal tests, reinforcing its relevance in neuropathic pain investigation (*Treede, Jensen et al. 2008*). LEPs detect any functional conduction abnormality in the pain pathways, even when caused by minute somatosensory system lesions (*Cruccu, Aminoff et al. 2008*). LEPs should be included in the standard treatment of patients diagnosed with painful disorders, particularly in situations where the clinical sensory tests are inconclusive or the causative illness is unclear (*Haanpaa, Backonja et al. 2009, Pazzaglia and Valeriani 2009*).

A revision of the 2004 guidelines from the EFNS published in 2010 showed a substantial new number of high quality studies on LEP (*Lefaucheur and Creange 2004, Truini, Galeotti et al. 2008, Truini, Padua et al. 2009, Haanpaa, Attal et al. 2011*), upgrading the level of recommendation of LEPs to grade A (*Cruccu, Sommer et al. 2010*). LEPs were also shown to be a good option to monitor and evaluate pain-related conditions in the elderly who show degenerative changes in the nociceptive pathways (*Cruccu and Truini 2010*). A second separate revision published in 2011 by the Neuropathic Pain Special Interest Group (NeuPSIG) also issued a level A grade of recommendation for the use of LEPs to assess Aδ fiber pathways in neuropathic pain (*Haanpaa, Attal et al. 2011*).

More recently, Garcia-Larrea proposed that a "physiological photograph" with the use of neurofunctional methods such as LEPs is highly relevant, prompting optimized management strategies (*Garcia-Larrea 2012*). Definite diagnosis of neuropathic pain yields at least one objective confirmatory test proving existence of lesion or disease affecting the somatosensory system (*Treede, Jensen et al. 2008*); and LEPs can determine better than any other tool such an impairment. The author suggests that abnormal LEPs elicited from a painful region should be interpreted as an electrophysiological signature of neuropathic pain (*Garcia-Larrea 2012*). A study by Valeriani et al. also recently highlighted LEPs role in identifying the underlying

pathophysiological mechanisms of neuropathic pain subtypes (*Valeriani, Pazzaglia et al. 2012*).

In conclusion, the LEPs technique is to date the most advanced and reliable method to evaluate the functional integrity of pain pathways, and can also be used to study pain sensation and modulation (*Matre and Nilsen 2014, La Cesa, Tamburin et al. 2015, Mainka, Maier et al. 2015*).

5.4.1 Effects of dorsal root ganglion stimulation on laser-evoked potentials

LEPs precisely identify lesions in any portion of the nociceptive system. Laser pulses through CO_2 laser or solid-state lasers (thulium or neodymium-based) exclusively activate Aδ and C fibers while avoiding the activation of Aβ non-nociceptive related fibers.

Functional assessment of the nociceptive pathways is of utmost importance during the management of neuropathic pain patients (*Valeriani, Pazzaglia et al. 2012*). It is established that neuropathic pain arises from nociceptive pathway damage (*Truini, Garcia-Larrea et al. 2013*). In our study, we used the CO_2 laser, which is the most widely used in clinical investigation. The fact that we observed a clear LEP alteration in comparison to a control non-painful area in our study confirms that our patients had a definitive localized neuropathic pain (*Mick, Baron et al. 2014, Treede, Jensen et al. 2008*). When no pathologic condition affects the pain pathways, LEPs should reflect the functional integrity of the nociceptive system. Suppression, reduced amplitude or delayed latency of LEPs in comparison to a valid control is considered a hallmark in substantiating the diagnosis of neuropathic pain (*Valeriani, Pazzaglia et al. 2012*).

In this study, we selected patients with unilateral pain, thus allowing the internal control to be performed on the homologous contralateral non-painful region. Spontaneous pain is often associated to complete absence of LEPs, whereas provoked pain signs such as allodynia/hyperalgesia may show partially preserved LEPs (*Truini, Biasiotta et al. 2010*). In our study group, some patients showed complete abolition of LEPs at baseline, while others showed a decreased peak-to-peak amplitude response

compared to controls. Positive signs such as allodynia or hyperalgesia were not directly associated with partially preserved LEPs.

As mentioned above, LEPs reliably reflect Aδ fiber activation. The so-called N2/P2 complex, the component most frequently evaluated in clinical practice, represents activation of insular networks and the anterior cingulate cortex, with some contribution from prefrontal and parietal regions, reaching maximal amplitudes at the vertex. Aδ-related LEPs have also demonstrated good intra-subject reproducibility, making it an ideal tool for a repeated measures study design (*Bentley, Youell et al. 2002, Garcia-Larrea 2006*). In our group, we observed inter-session reproducibility in the control condition, which reinforces the findings of our test condition. The N2 response is considered to be a more reliable measure of the nociceptive volley, as it is less influenced by cognitive or attention effects (*Garcia-Larrea 2012*). In fact, LEPs are a mixture of sensory and attentional-cognitive responses and should be interpreted as such. To improve inter-session reproducibility, attentional levels should be kept stable across measurements (*Garcia-Larrea 2006*). In our study, we instructed patients to keep their eyes open and to count the stimuli to keep attentional levels as constant as possible.

When neuropathic pain affects only one or a few dermatomes, LEPs accurately detect the area of disease. These dermatome-guided LEPs facilitate measurements in localized neuropathic pain (*Lorenz, Hansen et al. 1996, Quante, Hauck et al. 2007*).

In our study group, we selected the most painful area inside a dermatome territory. This is important, since the stimulated area is also dermatome-guided, which ensures we are eliciting responses from the correct region. Paresthesia over the painful region also confirms that we have selected an appropriate region to test.

SCS of the dorsal column as well as DRGS alleviate pain. It is hypothesized that the DRG may be an extension of the CNS, and as a consequence a laterally displaced portion of the spinal cord (*Liem 2015*). In line with this theory, one may also hypothesize that some mechanisms by which DRGS decreases pain may be shared with those attributed to traditional SCS of the dorsal column. However, DRG is a promising target for modulation because it represents the first integration stage

along the pain pathways. Moreover, some mechanisms may be exclusive to DRGS (*Krames 2015*).

To the best of our knowledge, only one published article has studied LEPs in patients under SCS of the dorsal column and no study has reproduced such findings using DRGS (*Sestito, Lanza et al. 2008*). In that article, patients diagnosed with cardiac syndrome X and treated with SCS showed a significant increase in N2/P2 peak-to-peak LEP amplitudes during stimulation ON in comparison with stimulation OFF. This finding is in line with our results: after DRGS, we observed a significant increase in the N2/P2 peak-to-peak LEP amplitude elicited from the most painful area of chronic neuropathic pain after 1 and 6 months of ON stimulation in comparison with baseline (OFF).

One possible explanation for an increase in LEP amplitude is that just as in traditional SCS, DRGS removes the inhibition caused by sustained chronic pain, known as diffuse noxious inhibitory control (DNIC). DNIC can selectively inhibit the convergent neurons in the dorsal horn of the spinal cord during sustained noxious stimuli. This mechanism is even more pronounced when high frequency APs are fired (as occurs in the DRG during neuropathic pain), thus amplifying the effect by temporal summation (*Le Bars, Dickenson et al. 1979*). LEPs may also be affected by chronic neuropathic spontaneous pain acting as a heterotopic-like pain stimulus. We hypothesize that spontaneous continuous chronic pain could actually function as an overload of neuronal input leading to painful evoked-response signal disruption. This concept was confirmed in humans with CO_2 laser stimuli, corroborating a counter-irritation mechanism following a painful stimulus, which decreased VAS ratings of laser-evoked painful stimuli in normal subjects (*Kakigi 1994*).

As a complement to DNIC, DRGS inhibition of PSN hyperexcitablity synergistically amplifies pain alleviation. Spontaneous or facilitated firing of lowered threshold DRG neurons in neuropathic pain conditions can substantially increase pain signals in the direction of the spinal cord. Electrical DRGS has been shown to modulate ion channels, restore the filtration of high-frequency APs and activate DRG somata (*Bradford 1970, Fuchs, Rigaud et al. 2007, Koopmeiners, Mueller et al. 2013*). We hypothesize that DRGS can function by decreasing the excessive

discharges caused by the DRG hyperexcitable neurons in neuropathic pain, thereby restoring the functional integrity of pain pathways. Ultimately, this could lead to the normalization of cortical processing, as suggested by our findings.

It is known that precise synchronous neuronal firing is essential for normal APs transmission. One of the roles of the DRG is to function as a low pass filter and to modulate electrical impulses from the nociceptors to the dorsal root entry zone (DREZ) (*Gemes, Koopmeiners et al. 2013*). Pain relief may be a consequence of the restoration of the high-frequency action potentials filtering in the DRG (*Liem 2015*). Here, chronic spontaneous pain inhibited acute laser-evoked pain, as reflected by LEPs. In fact, LEPs abnormalities may reflect a lesion on the thermo-algesic transmission and not the pain per se. Therefore, the restoration of pain pathways during DRGS may explain the LEP amplitude increase *(Garcia-Larrea 2012)*.

As suggested by previous work, the electrode's position is of critical importance to optimize pain relief. In a study testing SCS in rats, placing the lead contacts at the level where the damaged fibers reach the dorsal horn resulted in superior pain relief than placing them rostrally to the lesion (*Smits, van Kleef et al. 2012*).

Moreover, SCS of the dorsal column can regularly activate cutaneous afferents via the dorsal root (*Buonocore, Bonezzi et al. 2008*). Dorsal root stimulation has been associated with pain relief and has been shown to decrease WDR neuronal spontaneous activity in the dorsal horn to a similar degree as dorsal column stimulation (*Guan, Wacnik et al. 2010*). In line with this finding, we hypothesize that the DRG may play a role during dorsal root stimulation, explaining, at least partially, the pain relieving effect of decreasing the spontaneous activity of WDR neurons.

Magnetoencephalograpy (MEG) has also been used to record evoked potentials during SCS for chronic neuropathic pain. A small study reported restoration of SI organization after tactile-evoked responses in two patients receiving SCS for CRPS (*Pahapill and Zhang 2014*).

In summary, LEP serves as an objective measure of DRGS efficacy for chronic peripheral localized neuropathic pain. The restoration of N2/P2 peak-to-peak

LEPs amplitudes suggests a normalization of the pain signal transmission through the thermo-algesic pathways and a normalization of pain processing at the cortical level.

5.5 Pain intensity assessment

The visual analog scale (VAS), numerical rating scale (NRS) and verbal rating scales (VRS) are the most commonly used pain scales in the literature (*Haanpaa, Attal et al. 2011*). A systematic review concluded that NRS is superior to VAS and VRS and recommends standardization based on the NRS-11 (*Hjermstad, Fayers et al. 2011*). Also, recent neuropathic pain guidelines graded NRS as level A recommendation for pain intensity measurement (*Haanpaa, Attal et al. 2011*).

To measure pain intensity, the patient is asked to assign a number between 0 and 10 that best represents the pain intensity he or she is experiencing. '0' means no pain and '10' is the worst possible pain. As ongoing burning pain is the most typical type of pain associated with neuropathic pain (*Marchettini 2005*), the NRS is one of the primary outcome measures in this work.

5.5.1 Effects of dorsal root ganglion stimulation on pain intensity

In our group of seven patients there was a significant decrease in NRS pain scores in comparison to baseline after one and six months of DRGS. The mean values of spontaneous pain intensity in the affected area decreased from 7.6 at baseline to 2.1 at 1 month and 2.2 at 6 months after introduction of DRGS. This corresponds to an overall NRS pain score decrease of 73% at 1 month and 72% at 6 months and is in accordance with the published data in the literature (*Liem, Russo et al. 2013*).

Deer et al. reported 70% overall pain reduction in VAS scores after a pilot study to evaluate the short-term safety and effectiveness of DRGS (*Deer, Grigsby et al. 2013*). Similarly, Liem et al. reported 58% overall pain reduction in VAS scores at the 6-month follow-up in a group of 32 patients treated with DRGS for various chronic pain etiologies (*Liem, Russo et al. 2013*). At the one-year follow-up, published two years later, overall pain was still reduced by 56% (*Liem, Russo et al. 2015*).

Other studies evaluating single etiology neuropathic pain patients also showed positive pain relief outcomes using DRGS. Schu et al. reported an overall pain reduction of 71.4% in VAS scores in a study with 25 patients managed with DRGS for chronic groin pain after a mean follow-up of 42.5 months (*Schu, Gulve et al. 2014*). Similarly, Van Buyten et al. reported 62% overall pain reduction in a study with eight patients diagnosed with CRPS (*Van Buyten, Smet et al. 2014*). Eldabe et al. reported 50.8% in overall pain reduction in VAS scores in a study addressing phantom limb pain after a mean follow-up of 14.4 months (*Eldabe, Burger et al. 2015*). Single case reports, although using different electrode designs, also showed positive results (*Lynch, McJunkin et al. 2011, Garg and Danesh 2015*).

Another important measurement is the rate of patients who experience more than 50% pain relief after DRGS. In our group, five out of seven patients (71%) had at least 50% pain relief at both the 1 and 6 month follow-ups. This finding is also in line with the literature, which reports rates between 60 and 82% (*Deer, Grigsby et al. 2013, Liem, Russo et al. 2013, Schu, Gulve et al. 2014, Van Buyten, Smet et al. 2014, Liem, Russo et al. 2015*). Moreover, these rates of pain relief are better than results reported in studies with traditional SCS of the dorsal column, which are between 40-50% for radicular pain.

5.6 Neuropathic pain screening tools

The aim of the neuropathic pain screening tools is to identify neuropathic pain for clinical or research purposes (*Haanpaa, Attal et al. 2011*). These tools consist of standardized questionnaires designed to recognize pain characteristics associated with neuropathic pain. In comparison to one-dimensional pain scales such as the NRS-11, neuropathic pain screening tools assess neuropathic pain syndromes in greater detail. Identifying neuropathic pain is important to select the right therapy, including neuromodulation. Pain descriptors included in such questionnaires are considered to have a discriminant diagnostic value (*Bouhassira and Attal 2011*). The 5 validated screening tools recommended by recent guidelines include the Leeds Assessment of Neuropathic Pain Symptoms and Signs (LANNS), Douleur Neuropatique en 4 questions (DN4), Neuropathic Pain Questionnaire (NPQ), ID Pain and painDETECT (*Haanpaa, Attal et al. 2011*). Overall, these tools fail to indicate the correct diagnosis

in 10 to 20% of patients with clinically diagnosed neuropathic pain (*Bouhassira and Attal 2011*).

5.6.1 PainDETECT

PainDETECT is a neuropathic pain screening tool that was developed and validated in German (*Haanpaa, Attal et al. 2011*). PainDETECT is an easy-to-apply questionnaire that requires no physical examination (*Freynhagen, Baron et al. 2006*). It evaluates seven sensory descriptors and two items related to spatial and temporal aspects of pain. Scores range from 0 to 38, and scores 12 and below indicate a 15% or less likelihood of having a neuropathic pain component. Scores between 13 and 18 represent an uncertainty zone where there is a possible neuropathic pain component but no measurable likelihood ratio. Finally, scores of 19 and above indicate a greater than 90% chance of having neuropathic pain.

5.6.2 Effects of dorsal root ganglion stimulation on PainDETECT

PainDETECT was validated as a screening tool to predict the likelihood of a neuropathic pain component in chronic pain disorders (*Freynhagen, Baron et al. 2006*). A cutoff score of ≥ 19 is thought to indicate a likely neuropathic pain component (> 90%). PainDETECT has a sensitivity of 85% and specificity of 80%, which is slightly higher in comparison with other screening tool questionnaires and has been recommended as a reliable screening tool in neuropathic pain assessment guidelines (*Haanpaa, Attal et al. 2011*). To the best of our knowledge, this is the first time PainDETECT is used to assess pain disability associated with DRGS. In the present study, mean scores on this measure decreased from 19.7 at M0 to 15.7 at M1 and 14.5 at M6. This can be interpreted as a trend towards improvement in neuropathic pain components with the use of DRGS.

5.7 Quality of life assessment in neuropathic pain

QoL is broadly assessed as an indirect measure of the effectiveness of a treatment for chronic pain. There is a close association between neuropathic pain and reduced QoL, even though decreased pain scores may not necessarily lead to better QoL. Also, neuropathic pain was shown to have a greater negative impact on QoL

than non-neuropathic chronic pain (*Jensen, Chodroff et al. 2007, Smith and Torrance 2012*). Generic QoL measures are scales or questionnaires that assess common elements of health, well-being and functionality. The Medical Outcomes Survey Short Form (SF-36; *Brazier, Harper et al. 1992*) is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (*Dworkin, Turk et al. 2005*). Recent guidelines also recommended the SF-36 or EuroQol five dimensions questionnaire (EQ-5D) to assess QoL in clinical research (*Haanpaa, Attal et al. 2011*).

5.7.1 Effects of dorsal root ganglion stimulation on quality of life

We observed an increase in SF-36 mean scores for Vitality, Physical Functioning, Pain, Physical Role Functioning, Social Role Functioning and Mental Health at M1 and M6 relative to M0. Moreover, just on Pain, scores increased from 22.5 at M0 to 43.2 at M1 and 52.5 at M6. However, no trend towards improvement was detected on two items: General Health Perception and Emotional Role Function.

The results presented here show a trend towards improvement in six of the eight items on the SF-36. Kumar et al. showed a significant score increase on all items of the SF-36 questionnaire after 6 months of SCS of the dorsal column in 24 patients diagnosed with FBSS (*Kumar, Taylor et al. 2007*). Rutten et al. also reported significant improvement on all items of the SF-36 in a similar group of patients at the 12 and 24 month follow-ups (*Rutten, Komp et al. 2002*). To date, no study has assessed SF-36 together with DRGS. Liem at al. reported a significant increase in QoL as measured by EQ-5D, a similar test, at 6 months (*Liem, Russo et al. 2013*) and at 12 months (*Liem, Russo et al. 2015*) during the use of DRGS for diverse chronic neuropathic pain conditions. Van Buyten et al. also reported significant improvement in EQ-5D scores at the 12-month follow-up for CRPS patients treated with DRGS (*Van Buyten, Smet et al. 2014*). Finally, Eldabe et al. reported improvement on EQ-5D scores in two patients diagnosed with PLP (*Eldabe, Burger et al. 2015*).

In conclusion, the present results show a trend towards improvement in most of the SF-36 items. This shows that SF-36 is a valuable tool to assess QoL in patients treated with DRGS.

5.8 Pain-related disability assessment in neuropathic pain

Measures of disability are implemented as an indirect evidence of chronic pain therapy outcomes. It is well established that chronic neuropathic pain interferes with the physical and psychological functioning of patients. Disability is defined as a "physical or mental condition that limits a person's movements, senses or activities" (*Haanpaa, Attal et al. 2011*). Some tools for measuring disability have been specifically designed for neuropathic pain. The Brief Pain Inventory (BPI) and PDI are recommended for general neuropathic pain conditions (level A) (*Haanpaa, Attal et al. 2011*). PDI is a validated tool that measures an individual's ability to participate in essential life activities (*Tait, Pollard et al. 1987, Chibnall and Tait 1994*) on a scale of 0-70 (higher scores reflect greater disability). PDI assesses seven different life dimensions: Family/Home responsibilities, Recreation, Social Activity, Occupation, Sexual Behavior, Self Care and Life-Support Activities (*Tait, Pollard et al. 1987)*.

5.8.1 Effects of dorsal root ganglion stimulation on pain-related disability

The mean PDI score was 38.5 at M0 and decreased to 22.8 (41%) at M1 and 18 (54%) at M6, revealing DRGS improved disability over time. In a previous study of patients diagnosed with postherpetic neuralgia and acute herpes zoster pain treated with SCS, PDI scores decreased significantly after stimulation onset (*Harke, Gretenkort et al. 2002*). In another study of SCS of the dorsal column in FBSS patients, the median PDI score dropped from 43 at baseline to 26 (a 40% decrease) at the 12-month follow-up and to 28 (a 35% decrease) at the 24-month follow-up (*Rutten, Komp et al. 2002*). Similar findings were also found in a study testing SCS in the cervical region, where mean scores dropped from 49.6 at baseline to 28.4 (a 43% decrease) at the 12-month follow-up (*Deer, Skaribas et al. 2014*). No published study investigating DRGS has assessed PDI. However, BPI has been implemented as a disability measure in some publications showing significant BPI improvement after DRGS at 6 months (*Liem, Russo et al. 2013*) and 1 year (*Liem, Russo et al. 2015*). Finally, a study testing patients diagnosed with CRPS also showed significant improvement in BPI scores after 12 months of DRGS onset (*Van Buyten, Smet et al. 2014*).

In summary, PDI scores decreased, supporting a trend towards improvement in disability in our study group. These findings are in accordance with the literature and reinforce the use of PDI as a measure of disability in patients under DRGS.

6 CONCLUSION

6.1 Laser-evoked potentials

We found a significant increase in N2/P2 peak-to-peak amplitudes on the painful side at M1 and M6 in comparison to M0 ($p < .05$). On the control non-painful side, we detected no visible change in N2/P2 peak-to-peak amplitudes across the three time-points. Moreover, when comparing the ratio of the peak-to-peak amplitude between painful and non-painful sides at each time-point (M0, M1 and M6), we observed a significant decrease of the ratio at M0 only ($p < .05$). At M1 and M6, both ratios were around 1, suggesting LEPs amplitudes were restored to near normal levels.

6.2 Clinical assessment

The clinical assessment results showed a clear benefit of using DRGS. NRS pain intensity rating scores significantly decreased at M1 and M6 relative to M0 ($p < .05$). As secondary outcomes, PainDETECT, SF-36 and PDI scores also showed a trend towards positive outcomes at M1 and M6 relative to M0, except for two items in the SF-36 (GHP and ERF).

7 SUMMARY

The modern era in neuromodulation for the treatment of pain began after Melzack and Wall's seminal work describing the so-called gate control theory (*Melzack and Wall 1965*). The first application of neuromodulation in a chronic pain patient was performed by Shealy in 1967 (*Shealy, Mortimer et al. 1967*). Since then, SCS - traditionally involving the placement of an electrode placed on the dorsal column of the spinal cord - has become a valuable method to treat chronic neuropathic pain.

DRGS appeared in 2011 as an interesting new option in neuromodulation for chronic neuropathic pain. Even though clinical results addressing DRGS have already been published and show encouraging clinical results, limited data concerning mechanisms of action have been released to date. This observation highlights the need for further investigation into DRGS, e.g. by implementing standardized clinical assessment tools or neurophysiological techniques (*Forget, Boyer et al. 2015*).

The primary aim of this study was to assess LEPs and to evaluate pain intensity changes at 1 and 6 months after DRGS onset in comparison to baseline (no stimulation). A secondary aim was to evaluate how DRGS affects different clinical measures, as assessed with a neuropathic pain screening tool questionnaire (PainDETECT), a generic QoL questionnaire (SF-36), and a questionnaire of disability associated with chronic neuropathic pain (PDI).

Through an open-label study design, we evaluated seven patients (4 men and 3 women; mean age 50.7 years) diagnosed with unilateral chronic peripheral localized neuropathic pain of the groin, knee or leg who were implanted with DRGS electrodes. LEPs N2/P2 peak-to-peak amplitude values significantly increased after 1 and 6 months of DRGS in comparison to baseline ($p < .05$). The N2/P2 mean values increased from 3.7 µV at baseline to 11.3 µV and 10.7 µV at 1 and 6 months, respectively. At the end of the sixth month under stimulation, LEPs amplitudes were restored to normal values. On the other hand, pain intensity ratings measured through NRS scores significantly decreased after 1 and 6 months of DRGS in comparison to

baseline ($p < .05$). The scores dropped from a mean of 7.6 at baseline to 2.1 and 2.2 at 1 and 6 months, respectively. We also confirmed a trend for improvement in the PainDETECT, SF-36, and PDI measures.

These findings suggest that DRGS increases LEPs amplitude and decreases chronic neuropathic pain, resulting in treatment efficacy. We suggest that the observed LEPs restoration reflects normalization of pain pathway signal transmission.

Therefore, a better understanding of the role of the DRG in neuromodulation for chronic neuropathic pain will surely impact the field of neuromodulative techniques. The present work represents a contribution towards this goal.

8 ZUSAMMENFASSUNG

Die moderne Neuromodulations-Ära für die Behandlung von Schmerzen begann nach der bahnbrechenden Arbeit von Melzack und Wall, die die sogenannte Gate-Steuertheorie (Melzack und Wall 1965) beschrieben. Die erste Anwendung von Neuromodulation bei einem chronischen Schmerzpatienten wurde im Jahre 1967 von Shealy (Shealy, Mortimer et al. 1967) durchgeführt. Die Rückenmarkstimulation (SCS) – traditionell praktiziert durch das Platzieren einer Elektrode am Hinterstrang des Rückenmarks – hat sich seitdem als wertvolle Methode etabliert, um chronisch neuropathische Schmerzen zu behandeln.

Die Stimulation des Dorsalganglions (DRGS) wurde im Jahr 2011 als eine neue interessante Option der Neuromodulation zur Behandlung chronisch neuropathischer Schmerzen eingeführt. Obwohl klinische Ergebnisse der Dorsalganglienstimulation bereits veröffentlicht wurden und ermutigende Ergebnisse zeigen konnten, wurden bislang nur begrenzte Daten bezüglich ihrer Wirkungsmechanismen veröffentlicht. Diese Tatsache unterstreicht die Notwendigkeit, weitere Untersuchungen bzgl. DRGS durchzuführen, zum Beispiel mittels standardisierter klinischer Bewertungsinstrumente oder neurophysiologischer Techniken (Forget, Boyer et al. 2015).

Das primäre Ziel dieser Studie war die Untersuchung von Laser evozierten Potentialen (LEPs) und die Auswertung von Veränderungen der Schmerzintensität ein bzw. sechs Monate nach Beginn der DRGS Behandlung im Vergleich zu Ausgangsdaten ohne Stimulation. Ein sekundäres Ziel war die Beurteilung des Effekts der Stimulation des Dorsalganglions auf verschiedene klinische Messwerte mittels eines Screening-Fragebogens für neuropathische Schmerzen (PainDETECT), eines generischen Fragebogens zur Lebensqualität (SF-36) und eines Fragebogens bzgl. der Lebensbeeinträchtigungen durch chronische neuropathische Schmerzen (PDI).

Mittels eines Open-Label-Study-Designs werteten wir sieben Patienten mit der Diagnose einseitiger chronisch neuropathischer, peripher lokalisierter Schmerzen im Bereich der Leiste, des Knies oder Beines aus, bei denen DRG Elektroden implantiert

worden waren. Das mittlere Alter der Studiengruppe war 50.7 Jahre (4 Männer und 3 Frauen). Die LEPs N2/P2 peak-to-peak Amplitudenwerte waren ein und sechs Monate nach Stimulation des Dorsalganglions im Vergleich zum Ausgangswert ($p < .05$) signifikant erhöht. Die N2/P2 Mittelwerte erhöhten sich von 3.7 μV zu Beginn der Studie auf 11.3 μV nach einem Monat bzw. auf 10.7 μV nach sechs Monaten. Weiterhin hatten sich nach sechs Monaten unter Stimulation die LEPs Amplituden wieder auf Normalwerte erholt. Die durch NRS Scores gemessenen Bewertungen der Schmerzintensität sind nach einem und sechs Monaten nach Stimulation des DRG im Vergleich zu den Ausgangswerten ($p < .05$) deutlich zurückgegangen. Die Werte fielen von einem Mittelwert von 7.6 bei Studienbeginn auf 2.1 nach einem Monat bzw. auf 2.2 nach sechs Monaten. Ein Verbesserungstrend bei neuropathischen Schmerzkomponenten durch PainDETECT, SF-36 und PDI konnte ebenso aufgezeigt werden.

Diese Ergebnisse deuten darauf hin, dass die Stimulation des DRG die LEPs peak-to-peak Amplituden erhöht und chronische neuropathische Schmerzen verringert, wodurch eine wirksame Behandlung ermöglicht wird. Wir vermuten, dass die Wiederherstellung der LEPs Amplituden auf Normalwerte die Normalisierung der Schmerzbahnen-Signalübertragung widerspiegelt.

Daher wird das bessere Verständnis für die Rolle des DRG in der Neuromodulation bei chronischen neuropathischen Schmerzen mit Sicherheit eine Auswirkung auf das Gebiet der neuromodulativen Techniken haben. Die vorliegende Arbeit leistet einen Beitrag zu diesem Ziel.

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10 APPENDIX

10.1 Figures list

10.2 Tables list

10.3 Vote of the ethics committee – University of Tuebingen

EBERHARD KARLS
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TÜBINGEN

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nachrichtlich:
Herrn Prof. Dr. med. Marcos Tatagiba

096/2011BO2	18. Februar 2011	24. März 2011
unsere Projekt-Nummer	eingegangen am	Datum

Untersuchungen zur Veränderung der Schmerzwahrnehmung durch Rückenmarksstimulation. Prüfplan Version 1 vom 07.02.2011
Begleitschreiben vom 07.02.2011

Sehr geehrter Herr Kollege,

die Unterlagen zur o.g. Studie haben der Ethik-Kommission an der Medizinischen Fakultät und am Universitätsklinikum Tübingen zur Beratung vorgelegen.

Danach bestehen gegen die Durchführung dieser Studie seitens der Kommission keine Bedenken.

Dabei geht die Ethik-Kommission davon aus, dass sämtliche in der Studie verwendeten Medizinprodukte eine CE-Kennzeichnung tragen, in der zugelassenen Zweckbestimmung eingesetzt und nur von Personen betrieben, angewendet und instand gehalten werden, die dafür die erforderliche Ausbildung oder Kenntnis und Erfahrung besitzen (z. B. SSEP und LEP).

Die Ethik-Kommission empfiehlt Ergänzungen im Prüfplan sowie der Patienteninformation, die Sie im Folgenden aufgelistet finden.

Prüfplan:

1. Es ist unklar, was unter *Evidenzklasse A* (Seite 3, Absatz 2) zu verstehen sein soll. Falls es sich hier um eine Definition aus dem Bereich der Evidenz-basierten Medizin handeln sollte, sollten hier entsprechende Literaturhinweise (Metaanalysen aus prospektiven kontrollierten, randomisierten Studien) zitiert werden.
2. Es ist unklar, aufgrund welcher Überlegungen eine Fallzahl von 50 Patienten gewählt wurde.
3. Die Ethik-Kommission empfiehlt die Formulierung eines Hauptstudienziels und ggf. mehrerer sekundärer Studienziele.
4. Unklar ist, wie ein "psychosomatischer" Schmerz ausgeschlossen werden soll.
5. Die Ethik-Kommission empfiehlt, die Einwilligungsfähigkeit immer in den Einschlusskriterien zu nennen.
6. Der letzte Absatz auf Seite 5 (Abschnitt 6 a) ist unklar. Was bedeutet VAS 6?

7. Der Text muss daraufhin überprüft werden, dass es hier ausschließlich um mononeuropathische Schmerzsyndrome handelt.
8. Es muss darauf eingegangen werden, wie bei einer Zunahme von Schmerzen nach Abschalten des Stimulators (Teil B der Studie) eine Rescue-Medikation eingesetzt werden soll.
9. Es muss darauf eingegangen werden, dass eine fehlende Behandlung der Schmerzen über 2 Wochen toleriert werden kann.
10. Die Kommission weist darauf hin, dass bei einer *pseudonymisierten* Speicherung der Daten grundsätzlich eine Zuordnung der Daten zu den Studienteilnehmern möglich ist.
11. Nach einem Vorschlag der DFG sollten Daten, die in Studien gesammelt werden, 10 Jahre gespeichert werden. In diesem Abschnitt sollte Speicherort, Speicherdauer (korrigiert), Umfang der Datensammlung und Zugangsberechtigte genannt werden.
12. Da im Abschnitt 7 des Prüfplans darauf hingewiesen wird, Patienten mit Herzschrittmachern könnten nicht an den SSEP-Untersuchungen teilnehmen, müsste dies als Ausschlusskriterium im Abschnitt 5.2 aufgeführt werden.

Patientenaufklärung:

1. Informationen, die über wissenschaftliche Studien aufklären sollen, enthalten zunächst einen kurzen Abschnitt über den wissenschaftlichen Hintergrund der geplanten Untersuchungen und anschließend eine Fragestellung, die die Ziele der Studie beschreibt.
2. Das auf Seite 1 unten genannte Studienziel sollte korrigiert werden. Es ist gerade Ziel der Studie, Schmerzverarbeitung sowohl mit als auch ohne Rückenmarkstimulation zu untersuchen.
3. Angaben zur Zahl der Studienteilnehmer, mögliche Vor- und Nachteile durch die Teilnahme an der Studie, ggf. Hinweise auf Nebenwirkungen und Komplikationen durch die Teilnahme, Hinweise auf Freiwilligkeit und Rücktrittsrecht sowie eine ausführliche Darstellung des Umgangs mit den in der Studie erhobenen Daten sollte eingefügt werden.
4. Die in der Studie durchgeführten Untersuchungen sollten ausführlich dargestellt werden.
5. In der Information muss ausführlich auf die möglichen Folgen des Ausschaltens der SCS-Stimulation für 2 Wochen eingegangen werden. Die dann dem Patienten bei einer Zunahme der Beschwerden zur Verfügung stehenden Medikamente müssen genannt werden.
6. Es muss ausdrücklich darauf hingewiesen werden, dass durch die Studienteilnahme keinerlei Vorteile zu erwarten sind.
7. Es muss darauf hingewiesen werden, dass ein Patient jederzeit von der Teilnahme an der Studie zurücktreten kann, ohne dass ihm darauf Nachteile für die weitere medizinische Betreuung erwachsen.
8. Die Angaben zum Umgang mit den in der Studie erhobenen Daten müssen ausführlich dargestellt werden. Gemäß Prüfplan werden die Daten *pseudonymisiert*.
9. In einer Einverständniserklärung sollte ein Studienteilnehmer bestätigen können, dass er über Wesen, Bedeutung und Tragweite einer Studie, persönliche Vor- und Nachteile, Risiken und Komplikationen, Freiwilligkeit und Rücktrittsrecht sowie den Umgang mit den in der Studie erhobenen Daten informiert wurde, zusätzliche Fragen zu seiner Zufriedenheit beantwortet wurden und er der Teilnahme an der Studie und der Verwendung der in der Studie erhobenen Daten zustimmt. Die Einverständniserklärung muss sowohl vom Studienteilnehmer mit eigenhändig geschriebenem Datum als auch vom aufklärenden Arzt mit eigenhändig geschriebenem Datum unterschrieben sein.
10. Die Ethik-Kommission weist darauf hin, dass in der Information zum Datenschutz der letzte Satz der Einwilligungserklärung in dieser Form zwar vereinbart werden kann. Der Patient muss aber darauf hingewiesen werden, dass bei einem Rücktritt von der Studie er selber entscheiden kann, ob die bereits vorhandenen Daten weiterverwendet werden dürfen oder gelöscht werden müssen.

Für Rückfragen stehe ich Ihnen gerne zur Verfügung.

Mit freundlichen Grüßen

Prof. Dr. med. Dieter Luft
Vorsitzender der Ethik-Kommission
ALLGEMEINE HINWEISE ZUM VOTUM DER ETHIK-KOMMISSION SEITE 2

Mitglieder der Ethik-Kommission

Privatdozent Dr.med. Margitta Albinus	Pharmakologie, Toxikologie
Professor Dr.med. Thomas Gasser	Neurologie
Professor Dr.med. Henner Giedke	Psychiatrie
Professor Dr.med. Else Heidemann	Innere Medizin
Professor Dr.med. Jürgen Honegger	Neurochirurgie
Professor Dr.med. Dieter Luft	Innere Medizin
Professor Dr.med. Christian F. Poets	Kinderheilkunde
Professor Dr.iur. Dr.h.c. Georg Sandberger	Medizinorganisationsrecht, Hochschulrecht, deutsches und internationales Wirtschaftsrecht
Professor Dr. Dr. Dr.h.c. Norbert Schwenzer	Zahnheilkunde, Kieferchirurgie
Professor Dr.med. Dr.phil. Urban Wiesing	Medizinische Ethik und Theoretische Medizin

Die Ethik-Kommission an der Medizinischen Fakultät der Universität Tübingen verfährt entsprechend den GCP-/ICH- Richtlinien, der Deklaration von Helsinki in der jeweils gültigen Fassung sowie den gesetzlichen Bestimmungen.

Die Ethik-Kommission ist gemäß § 20 Abs. 7 MPG, Aktenzeichen: Z14-A1871-14924/97, gemäß § 92 Strahlenschutzverordnung, Aktenzeichen: Z 2.1.2-22471/2-EK-012-Ber und gemäß § 28g der Röntgenverordnung, Aktenzeichen: Z 2.1.2-22472/2.EK-013/R registriert.

Die berufsethische und berufsrechtliche Beratung gemäß §15 Abs.1 Berufsordnung für Ärzte in Baden-Württemberg ist für 3 Jahre ab Ausstellungsdatum gültig.

Änderungen im Prüfplan und in der Phase der Umsetzung bitten wir der Kommission mitzuteilen; dabei wären wir Ihnen dankbar, wenn Sie geänderte Passagen deutlich kennzeichnen würden.

Unabhängig vom Beratungsergebnis macht die Ethik-Kommission darauf aufmerksam, dass die medizinische, ethische und rechtliche Verantwortung für die Durchführung einer klinischen Prüfung beim Leiter der klinischen Prüfung und auch bei allen an der Prüfung teilnehmenden Ärzten liegt.

Nach Abschluss der Studie bittet die Kommission um einen abschließenden Bericht.

10.4 Informed consent for patients

Patienten-Information und -Einwilligung
zur Durchführung einer klinischen Studie

Prüfstelle: Neurochirurgische Klinik der Universität Tübingen, Hoppe-Seyler-Str. 3, 72076 Tübingen

Leiter der Studie: Prof. Dr. med. MH Morgalla

Titel der Studie
Untersuchungen zur Veränderung der Schmerzwahrnehmung durch Rückenmarksstimulation

Sehr geehrte Patientin, sehr geehrter Patient,

wir möchten Sie fragen, ob Sie bereit sind, an der nachfolgend beschriebenen klinischen Studie teilzunehmen.

Klinische Studien sind notwendig, um Erkenntnisse über die Sicherheit, Eignung und Leistungsfähigkeit von Medizinprodukten zu gewinnen oder zu erweitern. Die klinische Studie, die wir Ihnen hier vorstellen, wurde – wie es das Gesetz verlangt – von einer Ethikkommission zustimmend bewertet.

Ihre Teilnahme an dieser klinischen Prüfung ist freiwillig. Sie werden in diese Prüfung also nur dann einbezogen, wenn Sie dazu schriftlich Ihre Einwilligung erklären. Sofern Sie nicht an der klinischen Studie teilnehmen oder später aus ihr ausscheiden möchten, erwachsen Ihnen daraus keine Nachteile.

Sie wurden bereits auf die geplante Studie angesprochen. Der nachfolgende Text soll Ihnen die Ziele und den Ablauf erläutern. Anschließend wird ein Prüfarzt das Aufklärungsgespräch mit Ihnen führen.

1. Was ist das für eine Studie und warum wird sie durchgeführt.

Verletzung des peripheren zentralen Nervensystem bewirken einen Zustand welcher für die Ausbildung des chronischen neuropathischen Schmerzes verantwortlich ist. Die Ursache dieser Prozesse besteht in einer zentralen Überempfindlichkeit auf verschiedenen Funktionsebenen des Gehirnes. Die Behandlung dieses sehr schwerwiegenden klinischen Krankheitsbildes ist interdisziplinär. Diese umfasst Physiotherapie Psychotherapie und medikamentöse Behandlung mit Antidepressiva und Antiepileptika. Zusätzlich kann auch eine elektrische Stimulation des Nervensystems angewendet werden. Die Stimulationsverfahren können im Bereich der peripheren Nerven des Rückenmarkes oder auch der tiefen Hirnstrukturen angewandt werden. Meistens wird aufgrund der geringeren Invasivität und niedriger Komplikationsraten als erste Behandlungsoption die Stimulation der peripheren Nerven oder des Rückenmarkes gewählt. Diese Eingriffe können in Lokalanästhesie durchgeführt werden. Durch die Anwendung der Rückenmarksstimulation werden die Schmerzimpulse auf Rückenmarksebene unterdrückt so dass hier die Patienten eine Schmerzreduzierung feststellen. Ein derartiges System wurde bereits bei Ihnen implantiert. Es soll nun durch die zusätzliche Anwendung von Laser evozierten Potenzialen

untersucht werden, welche Mechanismen bei der Schmerzverarbeitung eine Rolle spielen. Laser evoziert bedeutet, dass durch einen feinen Laserstrahl auf der Haut des Patienten im Schmerzgebiet jeweils ein kurzer Schmerzreiz ausgelöst wird. Das dadurch hervorgerufenen Potenzial im Gehirn wird durch die Elektroden auf dem Kopf des Patienten abgeleitet. Es handelt sich dabei um eine wichtige Studie, weil dadurch die zentrale Verarbeitung des Schmerzes genauer untersucht werden kann.

2. Wie ist der Ablauf der Studie und was muss man bei Teilnahme beachten?

Die Studie läuft den folgenden Schritten ab.

Zunächst wird der Generator ausgeschaltet. Sie nehmen anschließend auf einem Untersuchungsstuhl bequem Platz. Nun wird ihnen eine EEG Haube aufgesetzt. Die Elektroden werden an einen Computer angeschlossen. Anschließend setzen sie eine Spezialbrille auf. Daraufhin werden ihnen Ohrhörer im Ohr platziert. Dadurch sollen Nebengeräusche ausgeschaltet werden. Sie hören über die Ohrhörer ein Rauschgeräusch. Anschließend wird mit einem Lasergerät im Abstand von 10 s im Bereich ihres Unterschenkels oder Fußes oder Oberschenkels jeweils ein kurzer Schmerzreiz gesetzt. Sie wissen nicht, zu welchem Zeitpunkt dieser Schmerzreiz gesetzt wird. Der Schmerzreiz kann von den Patienten gut vertragen werden. Durch diesen Schmerzreiz wird ein Potenzial im Gehirn ausgelöst. Dieses Potenzial wird von uns abgeleitet und später ausgewertet. Es werden 20 Messungen an verschiedenen Stellen hintereinander durchgeführt. Die Messung wird anschließend nochmals wiederholt.

Anschließend wird die Haube entfernt.

Der Generator wird nun wieder eingeschaltet.
Sie können nun nach Hause gehen. Die gleiche Untersuchung wird nach 1 Monat und 6 Monaten wiederholt. Sie kommen dazu ambulant zu uns.

3. Welchen persönlichen Nutzen habe ich von der Teilnahme an der Studie?

Durch die Teilnahme an dieser Studie habe ich selbst keinen persönlichen zusätzlichen Vorteil oder Nutzen.

4. Welche Risiken sind mit der Teilnahme an der Studie verbunden?

Die Laserimpulse können leichte Schmerzen verursachen.
Durch die Laserimpulse kann es zu einer Verletzung der Haut kommen. Es können hier möglicherweise dauernde kleine punktförmige Hautveränderungen eintreten.
Während des Anbringens der Haube am Kopf wird zusätzlich Kontaktgel auf die Kopfhaut aufgebracht. Dadurch kann es zu einem Verkleben der Haare kommen. Das Gel lässt sich jedoch mit Wasser problemlos auswaschen.

5. Entstehen für mich Kosten durch die Teilnahme an der klinischen Prüfung? Erhalte ich eine Aufwandsentschädigung?

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten

Für Ihre Teilnahme an dieser klinischen Prüfung erhalten Sie keine zusätzliche Aufwandsentschädigung.

6. Was geschieht mit meinen Daten?

Während der klinischen Prüfung werden medizinische Befunde und persönliche Informationen von Ihnen erhoben und in der Prüfstelle in Ihrer persönlichen Akte niedergeschrieben oder elektronisch gespeichert. Die für die klinische Prüfung wichtigen Daten werden zusätzlich in pseudonymisierter Form gespeichert, ausgewertet und gegebenenfalls weitergegeben.

Pseudonymisiert bedeutet, dass keine Angaben von Namen oder Initialen verwendet werden, sondern nur ein Nummern- und/oder Buchstabencode, evtl. mit Angabe des Geburtsjahres.

Die Daten sind gegen unbefugten Zugriff gesichert. Eine Entschlüsselung erfolgt nur unter den vom Gesetz vorgeschriebenen Voraussetzungen.

Die gesetzlichen Bestimmungen enthalten nähere Vorgaben für den erforderlichen Umfang der Einwilligung in die Datenerhebung und -verwendung. **Einzelheiten, insbesondere zur Möglichkeit eines Widerrufs, entnehmen Sie bitte der Einwilligungserklärung, die im Anschluss an diese Patienteninformation abgedruckt ist.**

Einwilligungserklärung

.....
Name des Patienten in Druckbuchstaben

geb. am ..... Teilnehmer-Nr. .....

Ich bin in einem persönlichen Gespräch durch den Prüfarzt

.....
Name der Ärztin / des Arztes

ausführlich und verständlich über die Studie sowie über Wesen, Bedeutung, Risiken und Tragweite dieser Studie aufgeklärt worden. Ich habe darüber hinaus den Text der Patienteninformation sowie die hier nachfolgend abgedruckte Datenschutzerklärung gelesen und verstanden. Ich hatte die Gelegenheit, mit dem Prüfarzt über die Durchführung der klinischen Studie zu sprechen. Alle meine Fragen wurden zufrieden stellend beantwortet.

Ich hatte ausreichend Zeit, mich zu entscheiden.

Mir ist bekannt, dass ich jederzeit und ohne Angabe von Gründen meine Einwilligung zur Teilnahme an der Prüfung zurückziehen kann (mündlich oder schriftlich), ohne dass mir daraus Nachteile für meine medizinische Behandlung entstehen.

Ich erkläre mich bereit, an der oben genannten klinischen Prüfung freiwillig teilzunehmen.

Ein Exemplar der Patienten-Information und -Einwilligung habe ich erhalten. Ein Exemplar verbleibt im Prüfzentrum.

....
Datum Unterschrift des **Patienten**

Ich habe das Aufklärungsgespräch geführt und die Einwilligung des Patienten eingeholt.

.....
Name des Prüfarztes/der Prüfärztin in Druckbuchstaben

....
Datum Unterschrift des aufklärenden **Prüfarztes/der Prüfärztin**

Datenschutz:

Mir ist bekannt, dass bei dieser klinischen Prüfung personenbezogene Daten, insbesondere medizinische Befunde über mich erhoben, gespeichert und ausgewertet werden sollen. Die Verwendung der Angaben über meine Gesundheit erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der klinischen Prüfung folgende freiwillig abgegebene Einwilligungserklärung voraus, das heißt ohne die nachfolgende Einwilligung kann ich nicht an der klinischen Prüfung teilnehmen.

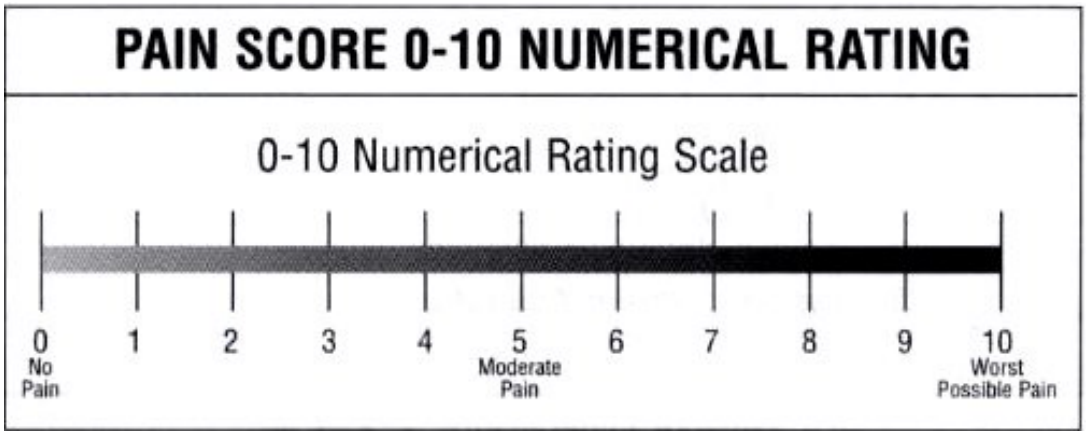
1. Ich erkläre mich damit einverstanden, dass im Rahmen dieser klinischen Prüfung personenbezogene Daten, insbesondere Angaben über meine Gesundheit, über mich erhoben und in Papierform sowie auf elektronischen Datenträgern bei/in Neurochirurgische Klinik Tübingen aufgezeichnet werden.

2. Außerdem erkläre ich mich damit einverstanden, dass autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des Auftraggebers sowie die zuständigen Überwachungsbehörden in meine beim Prüfarzt vorhandenen personenbezogenen Daten, insbesondere meine Gesundheitsdaten, Einsicht nehmen, soweit dies für die Überprüfung der ordnungsgemäßen Durchführung der Studie notwendig ist. Für diese Maßnahme entbinde ich den Prüfarzt von der ärztlichen Schweigepflicht.

3. Ich bin darüber aufgeklärt worden, dass ich jederzeit die Teilnahme an der klinischen Prüfung beenden kann. Beim Widerruf meiner Einwilligung, an der Studie teilzunehmen, habe ich das Recht, die Löschung aller meiner bis dahin gespeicherten personenbezogenen Daten zu verlangen.

4. Ich erkläre mich damit einverstanden, dass meine Daten nach Beendigung oder Abbruch der Prüfung mindestens zehn Jahre aufbewahrt werden. Danach werden meine personenbezogenen Daten gelöscht, soweit nicht gesetzliche, satzungsmäßige oder vertragliche Aufbewahrungsfristen entgegenstehen.

10.5 _NRS - English version



10.6 PainDETECT – English version

painDETECT

PAIN QUESTIONNAIRE

Date: _____ Patient: Last name: _____ First name: _____

How would you assess your pain now, at this moment?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the strongest pain during the past 4 weeks?

0 1 2 3 4 5 6 7 8 9 10

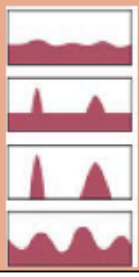
none max.

How strong was the pain during the past 4 weeks on average?

0 1 2 3 4 5 6 7 8 9 10

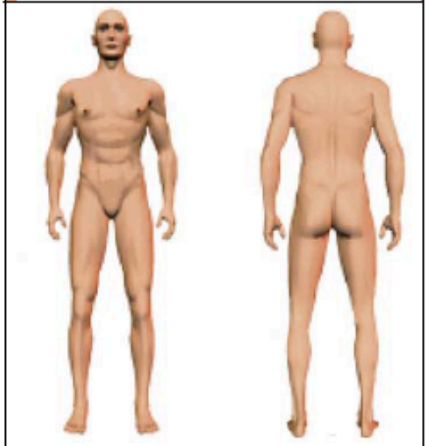
none max.

Mark the picture that best describes the course of your pain:



- Persistent pain with slight fluctuations ☐
- Persistent pain with pain attacks ☐
- Pain attacks without pain between them ☐
- Pain attacks with pain between them ☐

Please mark your main area of pain



Does your pain radiate to other regions of your body? yes ☐ no ☐

If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

never	hardly noticed	slightly	moderately	strongly	very strongly
x 0 = 0	x 1 =	x 2 =	x 3 =	x 4 =	x 5 =

Total score ____ out of 35

painDETECT

SCORING OF PAIN QUESTIONNAIRE

Date: _____ Patient: Last name: _____ First name: _____

Please transfer the total score from the pain questionnaire:

Total score | | |

Please add up the following numbers, depending on the marked pain behavior pattern and the pain radiation. Then total up the final score:

Persistent pain with slight fluctuations — 0

Persistent pain with pain attacks — - 1 if marked, or

Pain attacks without pain between them — + 1 if marked, or

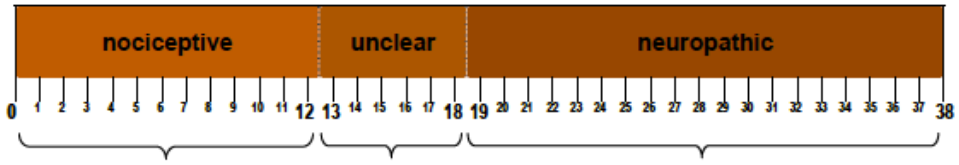
Pain attacks with pain between them — + 1 if marked

Radiating pains? — + 2 if yes

Final score | | |

Screening Result

Final score



A neuropathic pain component is unlikely (< 15%)

Result is ambiguous, however a neuropathic pain component can be present

A neuropathic pain component is likely (> 90%)

This sheet does not replace medical diagnostics.
It is used for screening the presence of a neuropathic pain component.

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006)

10.7 SF-36 – English version

SF-36 QUESTIONNAIRE
(1992 -- Medical Outcomes Trust)

Patient Name: _____ **Date:** _____

1. In general, would you say your health is: (circle one)

   Excellent Very good Good Fair Poor

2. Compared to one year ago, how would you rate your health in general now? (circle one)

   Much better now than one year ago.

   Somewhat better now than one year ago.

   About the same as one year ago.

   Somewhat worse than one year ago.

   Much worse than one year ago.

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Mark each answer with an X)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing several flights of stairs			
e. Climbing one flight of stairs			
f. Bending, kneeling or stooping			
g. Walking more than a mile			
h. Walking several blocks			
i. Walking one block			
j. Bathing or dressing yourself			

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Mark each answer with an X)

	YES	NO
a. Cut down on the **amount of time** you spent on work or other activites		
b. **Accomplished** less than you would like		
c. Were limited in the **kind** of work or other activities		
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Mark each answer with an X)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities		
b. **Accomplished** less than you would like		
c. Didn't do work or other activities as **carefully** as usual		

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors or groups? (circle one)

Not at all Slightly Moderately Quite a bit Extremely

7. How much bodily pain have you had during the past 4 weeks? (circle one)

None Very mild Mild Moderate Severe Very severe

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks – (Mark each answer with an X)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?						
b. Have you been a very nervous person?						
c. Have you felt so down in the dumps that nothing could cheer you up?						
d. Have you felt calm and peaceful?						
e. Did you have a lot of energy?						
f. Have you felt downhearted and blue?						
g. Did you feel worn out?						
h. Have you been a happy person?						
i. Did you feel tired?						

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? (circle one)

All of the time Most of the time Some of the time A little of the time None of the time

11. How TRUE or FALSE is each of the following statements for you?

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get sick a little easier than other people					
b. I am as healthy as anybody I know					
c. I expect my health to get worse					
d. My health is excellent					

10.8 PDI – English version

Pain Disability Index

Pain Disability Index: The rating scales below are designed to measure the degree to which aspects of your life are disrupted by chronic pain. In other words, we would like to know how much pain is preventing you from doing what you would normally do or from doing it as well as you normally would. Respond to each category indicating the overall impact of pain in your life, not just when pain is at its worst.

For each of the 7 categories of life activity listed, please circle the number on the scale that describes the level of disability you typically experience. A score of 0 means no disability at all, and a score of 10 signifies that all of the activities in which you would normally be involved have been totally disrupted or prevented by your pain.

Family/Home Responsibilities: This category refers to activities of the home or family. It includes chores or duties performed around the house (e.g. yard work) and errands or favors for other family members (e.g. driving the children to school).
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Recreation: This disability includes hobbies, sports, and other similar leisure time activities.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Social Activity: This category refers to activities, which involve participation with friends and acquaintances other than family members. It includes parties, theater, concerts, dining out, and other social functions.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Occupation: This category refers to activities that are part of or directly related to one's job. This includes non-paying jobs as well, such as that of a housewife or volunteer.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Sexual Behavior: This category refers to the frequency and quality of one's sex life.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Self Care: This category includes activities, which involve personal maintenance and independent daily living (e.g. taking a shower, driving, getting dressed, etc.)
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Life-Support Activities: This category refers to basic life supporting behaviors such as eating, sleeping and breathing.
No Disability 0__. 1__. 2__. 3__. 4__. 5__. 6__. 7 __. 8__. 9__. 10__. Worst Disability

Signature_____ **Please Print**_____

Date _____

11 DECLARATION OF OWN CONTRIBUTION

This work was performed in the University Hospital of Tuebingen - Neurosurgery Clinic under the supervision of PD Dr. med. Guilherme Lepski.

I designed the study in cooperation with Bankim S. Chander and Prof. Dr. med. Matthias Morgalla.

I performed all experiments with the support of Bankim S. Chander, and Prof. Dr. med. Matthias Morgalla. The experiments with laser were performed at MEG Center Tuebingen - laser laboratory room.

I performed statistical analysis after consultation in the Department of Biometry with Mrs. Aline Naumman.

I declare that I have written the manuscript independently and have not used other references than those indicated by me.

Tuebingen, June 21st 2016

Marcos Fortunato de Barros Filho

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13 CURRICULUM VITAE

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1989-1990	EEPG Prof. Mario Patarra Frattini - Brazil
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1992-1993	Colégio Cidade de Americana - Brazil
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