
REVIEW ARTICLE

Experimental Spinal Cord Stimulation and Neuropathic Pain: Mechanism of Action, Technical Aspects, and Effectiveness

Helwin Smits, MD*; Maarten van Kleef, MD, PhD*; Jan Holsheimer, PhD[†]; Elbert A. J. Joosten, PhD*

**Department of Anaesthesiology and Pain Management, Pain Management and Research Centre, Maastricht University Hospital, Maastricht, The Netherlands; [†]Institute for Biomedical Technology, University of Twente, Enschede, The Netherlands*

■ **Abstract:** Spinal cord stimulation (SCS) is a valuable treatment for chronic intractable neuropathic pain. Although SCS has gone through a technological revolution over the last four decades, the neurophysiologic and biochemical mechanisms of action have only been partly elucidated. Animal experimental work has provided some evidence for spinal as well as supraspinal mechanisms of neuropathic pain relief of SCS. A SCS computer model of the electrical properties of the human spinal cord revealed many basic neurophysiologic principles that were clinically validated later on. The main question in clinical SCS is how to further improve the effectiveness of SCS as there is still a significant failure rate of 30%. In this context, experimental studies are needed to elucidate which target pain neuron(s) are involved, as well as with what exact electrical stimulation this target neuron can be influenced to produce an optimal suppression of neuropathic pain. This article

reviews the basic clinical and experimental technical aspects in relation to the effectiveness of SCS in view of recent understanding of the dorsal horn pain circuit involved. These data may then result in experiments needed for an improved understanding of the mechanisms underlying SCS and consequently lead to improvement and increased effectiveness of SCS in neuropathic pain as a clinical therapy. ■

Key Words: neuropathic pain, spinal cord stimulation, spinal cord, dorsal column, computer modeling, spine, spinal pain gate, review

INTRODUCTION

Spinal Cord Stimulation (SCS)

Clinical use of electrical stimulation of the spinal cord was first reported by Shealy et al.¹ in 1967 and was a direct result of the new insight into pain and pain modulation provided by the Gate Control theory of Melzack and Wall² 2 years earlier. Today, spinal cord stimulation (SCS) is used in the treatment for intractable neuropathic pain in CRPS-1 as well as in a variety of other neuropathic pain conditions. Despite the existence of SCS as a pain therapy for over 40 years,

Address correspondence and reprint requests to: Elbert A. J. Joosten, PhD, Department of Anaesthesiology, Pain Management and Research Centre, Maastricht University Hospital, P. Debyelaan 25, PO Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: b.joosten@maastrichtuniversity.nl

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up till now, **only two randomized clinical trials** (RCTs) have been performed: one in patients with CRPS-1³ and the other in patients with failed back surgery syndrome FBSS,⁴ both of which provide limited (level 3) evidence that SCS relieves neuropathic pain.⁵ A RCT of SCS in patients with CRPS-1³ demonstrated that two-thirds of patients responded to this therapy with a 50% pain reduction after 6 months, as monitored by the Visual Analogue Scale (VAS). Unfortunately, the remaining one-third of patients with CRPS-1 receiving SCS treatment did not respond with a 50% pain reduction for unknown reasons. The purpose of this review is to present an up-to-date overview of the basic physical and technical aspects of experimental and clinical SCS. This may be of use in our further understanding of this therapy and can give direction to future research and development. We need to identify the target neurons of SCS and determine how they can best be electrically stimulated to give an optimal relief in neuropathic pain. In other words, increased insight into the underlying mechanisms of SCS along with further optimization of the technical aspects of SCS may improve the success rate and effectiveness of SCS.

Proposed Mechanisms of Action in SCS

In clinical SCS, a longitudinal array of contacts (electrode) is placed into the dorsal epidural space either by a percutaneous technique or by means of a small laminectomy. Large myelinated primary afferent dorsal column (DC) fibers are depolarized and excited somewhere along their trajectory in the spinal cord at a *node of Ranvier* (not at a peripheral receptor) near the electrode, leading to an action potential propagating in both directions⁶:

1. Orthodromically in rostral direction to supraspinal centers: A β -fibers directly projecting to the DC nuclei and then further connected to the periaqueductal gray and the thalamus.
2. Antidromically via A β -collaterals into the spinal cord target region where interneuronal connections exist with C-fibers and wide dynamic range (WDR) neurons in the dorsal horn.
3. Antidromically to the peripheral part of the A β -dorsal root (DR) fibers.

The **activation of the DC axons** is thought to be **responsible for the paresthesia** experienced by patients during SCS. A supraspinal pathway of pain relief in SCS was also shown experimentally by El-Khoury

et al.⁷ Here, DC stimulation, rostral to selective dorsal spinal lesions at upper cervical levels, resulted in significant pain relief.⁷ This shows that inhibitory effects of DC stimulation on neuropathic pain can be attributed to the activation of brainstem-modulating centers via rostral projections of the DC nuclei. However, it should be stressed that these findings cannot automatically be transferred to and form an explanation for the common approach in clinical as well as experimental studies where SCS is applied at lumbar spinal levels for the treatment for neuropathic pain. Here, experimental data strongly point to a **spinal segmental mode of action**.

A recent study on the localization of the electrodes on the DC and the effect on pain relief in an experimental neuropathic pain model demonstrated that SCS of the DCs at the level where the injured sciatic nerve fibers enter the spinal cord dorsal horn results in a much better pain-relieving effect than SCS at more rostral levels. From this, it was concluded that SCS in the treatment for neuropathic pain acts almost exclusively through a segmental spinal site of action.⁸ In line with these findings are anatomical and biochemical observations in the lumbar dorsal horn: the antidromically propagated impulses are thought to induce changes at spinal levels as the balance of inhibitory and excitatory neurotransmitters in the dorsal horn is changed.⁹ Indeed, a segmental mode of action is supported by the fact that an increased neuronal activation in the spinal cord dorsal horn after SCS has been noted using c-Fos immunostaining.¹⁰

In addition, several experimental studies on the mechanisms of action of SCS showed an alteration of the chemical transmission in the spinal dorsal horn^{11–14} (Figure 1). There is evidence that the **neuropathic pain syndrome**, described as **peripheral hypersensitivity** with allodynia and hyperalgesia, is a **result of central sensitization**. Central sensitization is a result of neurochemical changes in the pain transmission in the dorsal horn mainly because of an increased release of the excitatory neurotransmitters glutamate and aspartate¹⁵ and at the same time a loss of tonic gamma-amino-butyric acid (GABA)-mediated inhibition. Basically, a decreased extracellular concentration of glutamate and at the same time an increased extracellular GABA concentration have been noted^{9,16} and this results in the **suppression of hyperexcitable WDR neurons**¹⁷ (Figure 1).

The WDR neurons are located in the dorsal horn laminae I, II, IV, V, VI, and X and their main physiological function is to encode for the stimulus intensity

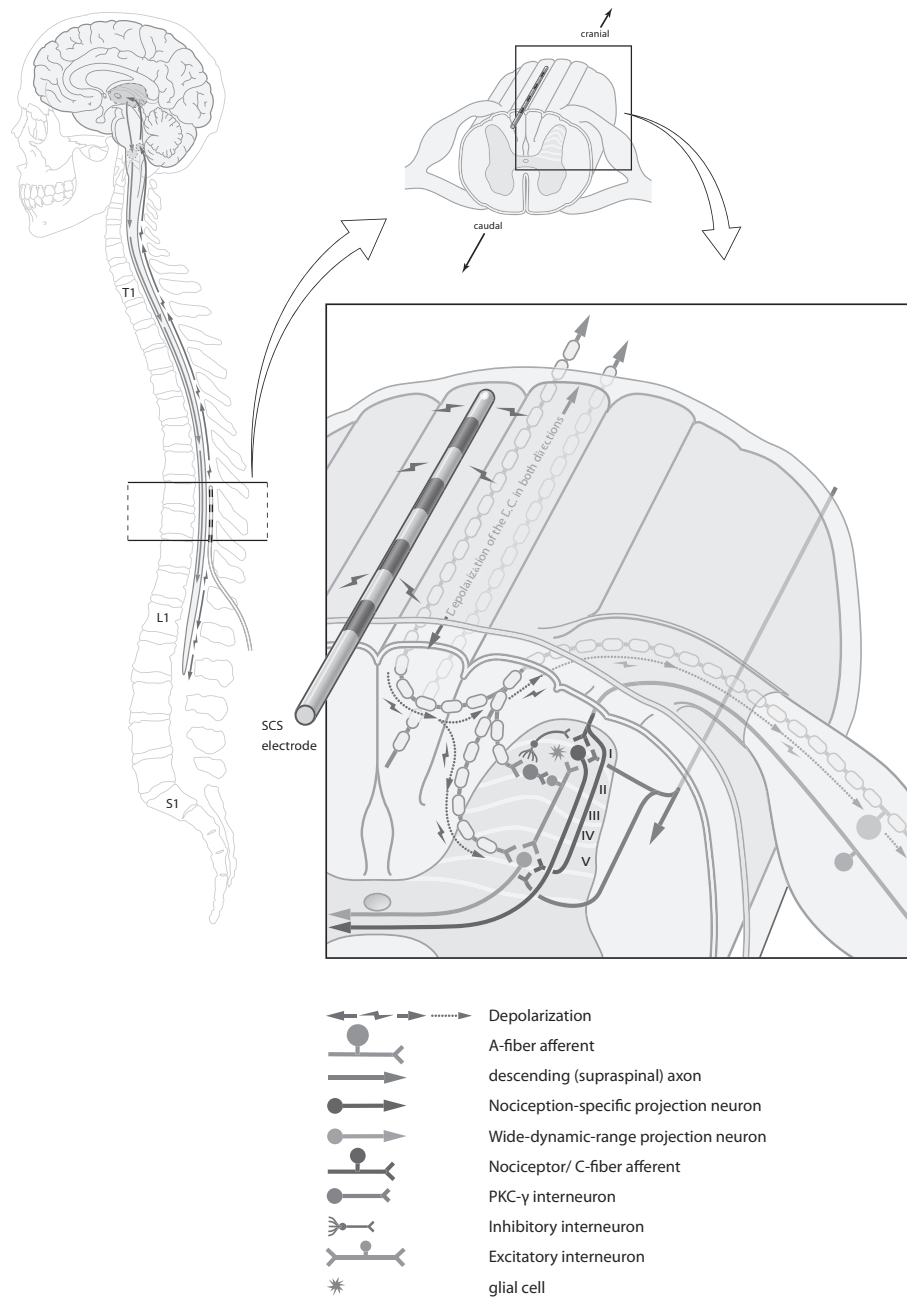


Figure 1. The spinal nociceptive network and mechanism of Spinal Cord Stimulation (SCS). The spinal dorsal horn contains two major types of projection neurons: the NS located in the superficial laminae I and the WDR neurons located in the deeper dorsal laminae IV, V and VI. These projection neurons receive input from primary afferents, descending (aminergic) pathways, and spinal interneurons. Among the primary afferents are low-thresholds such as highly myelinated A β fibers originating from large-sized DRG neurons and further projecting into the dorsal columns (DCs) to the DC nuclei. Furthermore the projection neurons receive input from low threshold unmyelinated mechanoreceptive C-fibers. The spinal nociceptive network also contains numerous interneurons, both of excitatory and inhibitory (gamma-amino-butyric acid [GABA]-ergic) nature, which modulate the processing of pain signals at the “gate” to the brain (“Gate-Control theory”). The spinal nociceptive network also contains a silent circuit between low threshold primary afferents and NS projection neurons. This circuit, which contains interneurons expressing γ -isoform of protein kinase C (PKC- γ) is normally inactive, but is thought to be activated under neuropathic conditions and, as such, turns “touch into pain”. Electrical stimulation of the DCs results in an action potential propagating in both directions: orthodromically in rostral directions to supraspinal centers and antidromically via A β collaterals into the spinal cord nociceptive network. The antidromic stimulation of the A β fibers has been shown to result in changed (decreased) release of glutamate of the primary (and presumably high-threshold C-afferents and at the same time an increased release of the inhibitory neurotransmitter GABA (“Gate Control Theory”). If and how the antidromic stimulation of large A β collaterals results in modulation and or sensitization of the silent circuit containing PKC- γ interneurons is not yet known.

of the received afferent input.¹⁸ WDR neurons play a key role as a modulator unit in the Gate Control theory for the relief of pain. In a recent paper,¹⁹ the effect of bipolar electrical SCS on the response properties of WDR neurons in the rat after L5 spinal nerve injury were examined. It was concluded that bipolar stimulation at the DC, but also after stimulation of the lumbar DR, attenuated the WDR hyperexcitability in nerve-injured rats and inhibited short-term neuronal sensitization.¹⁹ Other neurotransmitters, which might be related to either supraspinal or to spinal segmental mechanisms, have been suggested to be involved in the pain-relieving effect of SCS are serotonin, substance P, adenosine, and the muscarine receptor (M4 in particular).^{12,13,20–22} In view of the mechanism involved in the development of neuropathic pain (as reviewed by Berger et al.²³) and/or in the mode of action of SCS recent developments from the experimental field cannot be neglected.

The spinal dorsal horn has been reported to contain a “silent” circuit between low-threshold afferent fibers and **nociceptive-specific (NS)** projection neurons located in lamina I. Up to now, the composition of this circuit has been only partly described.²⁴ Within this circuit, excitatory interneurons in the innermost part of lamina II, which express the γ -isoform of protein kinase C (PKC- γ), are suggested to be important (Figure 1). Whereas these excitatory interneurons receive A β -fiber innervations, this implies that innocuous stimuli are thus able to activate PKC- γ interneurons via A β -fiber signaling.²⁵ This information is not gated to NS projection neurons in the more superficial dorsal horn because PKC- γ interneurons are under inhibition of glycinergic and GABA-ergic neurons.²⁶ Activation of this silent circuit would result in the gating of innocuous stimuli to the NS projection neurons and thus turn “touch into pain.” Hence, “touch can be turned into pain” by means of activation and/or sensitization of a silent dorsal horn circuit containing PKC- γ interneurons, thereby gating A β -fiber input to NS projection neurons. Clearly, future research should be focused at understanding when and how SCS interacts and modulates the pain circuit in the dorsal horn of the spinal cord (Figure 1).

Nonresponders to SCS

Nonresponsiveness to SCS has been documented in patients with CRPS type-1 as well as in an animal model for CRPS in about 1/3 of individuals. It should

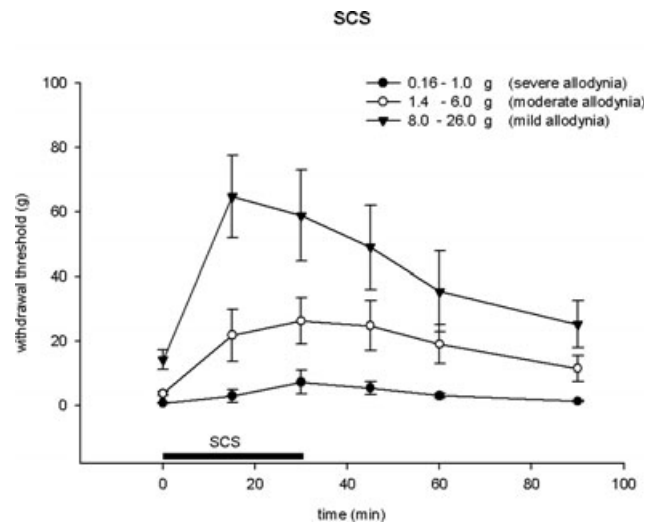


Figure 2. Effect of spinal cord stimulation (SCS) in an animal model of neuropathic pain relates to degree of tactile “allodynia”. SCS leads to a better and faster pain relief in mildly allodynic rats as compared with more severely allodynic rats. Reproduced from Smits et al.²⁷ Figure 3, page 544, with permission. Copyright Elsevier Ltd. (2006).

be noted that **nonresponsiveness** in a clinical setting is based on a reduction in the pain as assessed with the **VAS score**, whereas in an experimental settings, this is almost exclusively measured with **von Frey filaments** and thus is based on a reduction in the tactile hypersensitivity. Nonresponsiveness to SCS may have several origins. A predictor for the absence of a significant response to SCS has recently been documented and shown to be related to the severity of allodynia experimentally²⁷ (Figure 2) as well as clinically.²⁸ Nonresponders to SCS in severely allodynic rats may be related to a severe type of central neuropathic derangement and may imply an inability to produce appropriate amounts of the inhibitory neurotransmitter GABA, either alone or accompanied by an increased loss of inhibitory interneurons.²⁹ In this scenario, modulation of dorsal horn neurons could have either little or no effect. In an experimental study, nonresponders to SCS could be turned into responders after an intrathecal application of low concentrations of the GABAB receptor agonist baclofen³⁰ or other drugs (gabapentin, pregabalin, clonidine, and adenosine) modulating GABA-ergic neurotransmission in the dorsal horn.^{11,21,31,32}

Another explanation for nonresponsiveness to mechanical (tactile) allodynia in the experimental setting or to pain in the clinical setting may be of anatomical origin. Mechanical allodynia is reported to be primarily relayed by large myelinated fast A β -fibers,

which pass through the DRs and gather in the ipsilateral DCs and then terminate in the supraspinal nuclei^{33,34} after which the signal proceeds to higher centers. Holsheimer et al. demonstrated that during SCS, only a small fraction (1%) of the DC fibers is depolarized (see section The Development of a Computer Model for SCS).

Furthermore, a lack of response to SCS maybe related to a nonoptimal application of SCS from a physical point of view. First, if the thickness of the dorsal CSF layer (dCSF) between the epidural electrode and the spinal cord is too large, this will cause a predominant stimulation of DR fibers leading to paresthesias in one or in two adjacent segments only.³⁵ Other technical aspects of SCS, such as stimulation parameters, stimulation regime, electrode geometry, configuration, and localization, are currently under investigation and may need to be optimized. In this respect, it is important to consider and fine-tune technical parameters in the context of the mechanism of SCS. In other words, we need to explore exactly how SCS relieves pain to select the best electrophysiological stimuli for an optimal pain relief. Stimulation parameters currently used clinically and experimentally are only partly based on empirical studies as a thorough theoretical basis does often not exist. In this respect, it is interesting that many basic neuro-electrophysiological principles of SCS were explored in a computer model by Holsheimer et al.³⁶ These principles are often translatable to the clinic and have already led to improvements in the design of electrodes for clinical use.

In conclusion, the nonresponsiveness to SCS is still poorly understood. Differences in the stage or primary mechanism of the treated neuropathic pain could differ, possibly leading either to success or failure of SCS. Also, differences of anatomy or physiology of the patient could lead to failure and it may well be that the response to SCS can still be improved with more effective stimulation parameters and hardware that can only be developed with a solid understanding of anatomy physiology and biochemistry of neuropathic pain and SCS.

ANATOMICAL AND NEUROPHYSIOLOGICAL ASPECTS OF SCS

Functional Anatomy of the DCs

The **fasciculus gracilis** and **fasciculus cuneatus** form a large bundle of axons located on the dorsal side of the

spinal cord: the **DC**. These axons carry information about fine touch, vibration, and conscious proprioception from the body to the brainstem. The fasciculi consist of axons within a wide range of diameters including **A β** -fibers, all having their cell bodies in the ipsilateral DR ganglia. Twenty-five percent of the A β -fibers run through the medial division of the posterior nerve roots and ascend as far as the medulla oblongata where they end and make synapses on the second-order neurons in the cuneatus and gracilis nuclei.^{37,38} From the cuneate and gracilis nuclei, the second-order neurons are recognized as the lemniscus medialis which decussates to the contralateral side of the brainstem and projects to the ventromedial nuclei of the thalamus and to the sensorimotor cortex.

The fasciculus cuneatus consists of fibers from T6 up to C1 and is situated laterally in the DCs. The fasciculus gracilis containing fibers from spinal segment T7 down to S5 runs medially in the DCs. The DC fibers stay ipsilateral in the spinal cord are distributed somatotopically and end in the brainstem nuclei, decussate at brainstem levels too. Fibers from higher spinal levels are positioned more lateral and lower spinal levels more medial in the DCs in a pallet formed fashion. Furthermore, it is known that the rat DC is characterized by a very organized somatotopic arrangement: the primary afferents which enter the spinal cord and bundle into the DC are initially located at the surface but rearrange to more ventromedial areas at rostral spinal levels.³⁹ This implies that in most neuropathic pain models which are based on rat sciatic nerve lesions,^{40–42} the DC afferents involved are located at the dorsolateral surface of the DC at vertebral level T13, whereas these afferents are located much deeper or ventromedially into the DC only a few spinal segments rostral.

Apart from the primary afferent fibers, the DCs also contain a major sensory pathway of thousands of second-order postsynaptic projection neurons from the dorsal horn. These neurons originate from the nucleus proprius and from lamina III, IV, V, and VI. The (SCS) stimulus-evoked action potentials in the DCs are also propagated to the dorsal horn, where interneuronal modulation can take place. The dendrites of some of those neurons located into deeper dorsal layers extend even into lamina I and II and the axons often have local collaterals.⁴³ The **DCs are separated from the SCS electrode by the dura mater and a layer of cerebrospinal fluid** with a thickness varying between approximately 2.4 and 5.6 mm.⁴⁴

Neurophysiology of SCS

In SCS, a relatively large electrode injects current into the extracellular space at a multicellular level. This ionic current passes neuronal membranes and causes either polarization or depolarization of the neuronal membrane. The myelinated nerve fiber consists of a cylindrical axon covered by an insulating myelin sheet that is interrupted by Ranvier nodes at regular intervals where ionic currents can pass the nerve fiber membrane. The myelinated axons have the electrical characteristics of a cable network including resistors and capacitors. This network can be used to calculate the influence of the stimulation-induced electrical field on the nodal transmembrane voltages.⁴⁵

The driving force of the change of the nodal transmembrane voltages leading to de- or hyperpolarization of the axon is called the **activation function (AF)**. This AF is primarily **determined by the second-order difference in the nodal field potentials**.⁴⁶ A positive value of AF results in membrane depolarization, whereas a negative value of AF results in membrane hyperpolarization. In SCS, axons are depolarized by cathodic (electrode with negative charge) stimulation. When a nerve fiber approaches a cathode, the AF value will rise and the threshold stimulus needed for excitation will be reduced.⁴⁷ The Ranvier node closest to the cathode will be excited first. The recruitment of nerve fibers by the SCS electrode is determined by the distance of the electrode from the nerve fiber as well as the nerve fiber diameter. In the conductive medium around the SCS electrode, the current density is inversely proportional to the 2nd–3rd power of the distance, rapidly increasing the stimulation threshold as we move away from the electrode.⁴⁸ The nerve fiber diameter has an effect on the value of AF of the nerve fiber as the potential differences between adjacent Ranvier nodes in large fibers are bigger, resulting in a greater peak value of AF, thus lowering the stimulation threshold. Hence, in SCS, the first fibers to be recruited are large fibers located close to the electrode (at a few mm). Increasing the stimulation amplitude leads to recruitment of larger fibers at some distance and smaller fibers close to the electrode. However, in SCS, the stimulation amplitude is limited to approximately 40–70% of the **paresthesia perception threshold (PT)**, thus limiting further recruitment of additional larger and smaller fibers. In bipolar SCS, DC fibers with a diameter < 9 μm are not being recruited at all. With the largest DC fibers having only 12 μm diameter, the

total estimated amount of DC fibers recruited in SCS is only about 1% of the total population.⁴⁹

In conclusion, **SCS leads to bidirectional propagation of stimulus-evoked APs of myelinated A β -fibers** that are located in the highly organized structure of the DC. This presumably leads to the activation of the spinal dorsal horn pain network and consequently to pain relief. The electrical driving force of SCS rapidly declines as the distance of the SCS electrode to the nerve fiber increases and also depends on the size of the nerve fiber, causing a strong limitation in the actual number of DC fibers that can be depolarized.

TECHNICAL ASPECTS OF SCS

Types of SCS Stimulation Electrodes

Spinal cord stimulation electrodes used in the clinic are either minimally invasive cylindrical electrodes to be implanted percutaneously or surgical (paddle or plate) electrodes to be implanted by open surgery. Percutaneous electrodes can be threaded many segments above the point of insertion and allow displacement in a medial or lateral direction within the epidural space, but also permit electrode placement near the target area of the DCs.⁵⁰ Percutaneous electrodes were originally used for short stimulation trials only, but over time they have evolved to devices that can be anchored for permanent implantation. Today, SCS electrodes, whether percutaneous or laminectomy plate electrodes, have multiple longitudinal contact arrays and can be programmed to connect the proper contacts as anodes and cathodes, which allows adjustment of the focus of the electric field of stimulation.

Anodic vs. Cathodic Stimulation

Cathodic stimulation is the most efficient way of stimulation as the **cathodic (negatively charged) threshold for nerve fiber excitation is 3–7 times lower than the anodic threshold current**.⁵⁰ The much lower threshold for cathodic stimulation implies that the exact location of stimulation of the axons is determined by the position of the cathode.

Preferred Anode–Cathode Configurations

In SCS, the most common anode–cathode configurations are **monopolar** (cathode), **bipolar** (cathode + anode), and **tripolar stimulation** (+ – +; named guarded cathode

or split anode). In monopolar stimulation, only the cathode is close to the axons that are to be stimulated. The anode is located at a large distance and often the metal container of the stimulator is used for this purpose in such a way that the anodal field has no influence on the stimulation.⁵⁰ Monopolar stimulation is characterized by a current injection from the cathode. If the anode is placed close to the cathode, thus creating a bipolar field, the largest current density is in the direction of the bipole axis. Consequently, the threshold current to stimulate nerve fibers parallel to the cathode–anode axis is selectively decreased. In a tripolar or guarded cathode configuration, a central cathode is flanked by two anodes (Figure 3). If the two anodes and the cathode are close enough, this will lead to the superposition of the cathodic and anodic AFs. Consequently, the resultant increased positive cathodic AF results in an increased depolarization and a decreased stimulation threshold.

Therapeutic Range of Stimulation

For optimal therapeutic effect of SCS on neuropathic pain, the painful area has to be covered largely by the paresthesias elicited.⁵¹ In SCS, the electrode is placed in the epidural fat on the dorsal side of the dura. The distance between the electrode and the spinal cord is similar to the **dorsal CSF thickness (dCSF)**. This thickness varies among subjects. When dCSF is small, the threshold current of DR fibers exceeds the threshold current of DC fibers. The PT is low and the discomfort threshold is high, thus resulting in a high therapeutic range and a large paresthesia area. When dCSF is larger, the PT rises more steeply than the discomfort threshold,⁵² resulting in a reduced therapeutic range and a smaller paresthesia area. At mid and low thoracic spinal cord levels, the relatively thick CSF layer results in an elevation in PT while the discomfort threshold remains low. This leads to a decrease in the therapeutic range and increases patient side effects of discomfort or motor threshold at this level.^{53,54} This phenomenon also limits the management of widespread pain patterns as seen in CRPS-1, as only a limited portion of DC fibers can be stimulated. Moreover, if the distance between electrode and spinal cord is decreased, the paresthesia coverage increases with a reduction in energy consumption. The mean voltage within this therapeutic range is approximately 1.4 times PT.

The use of laminectomy electrodes instead of percutaneous electrodes in the low thoracic region of

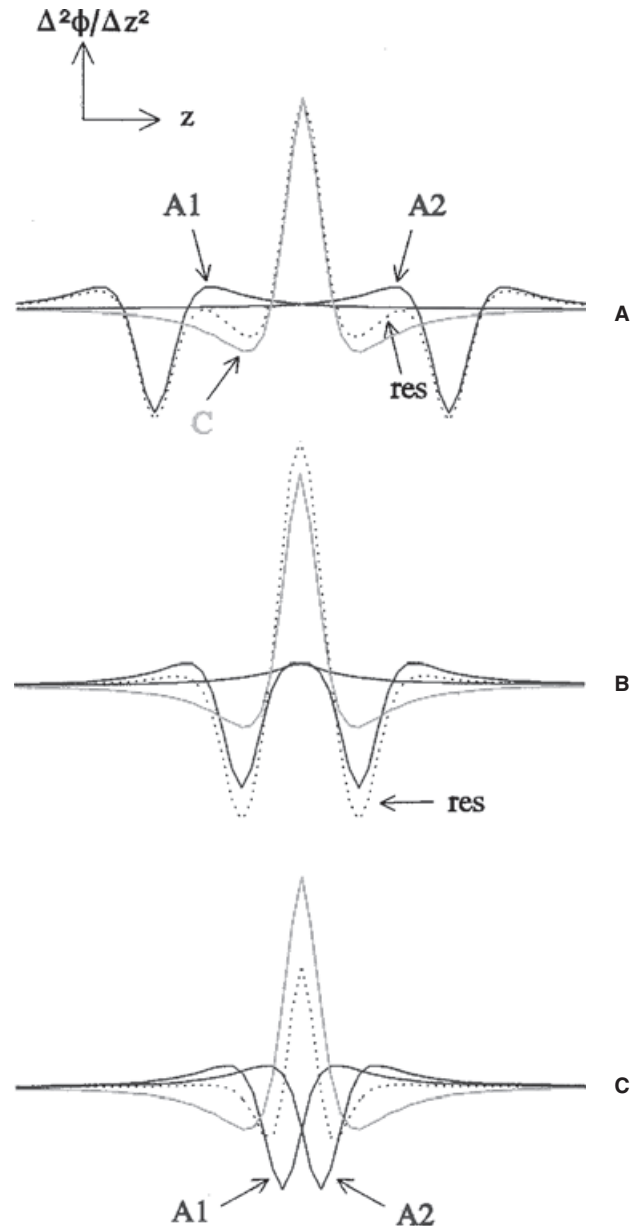


Figure 3. Superposition of the activation functions (AFs) corresponding to the cathode (C) and the two anodes (A1, A2) of a tripole ("guarded cathode"), dotted line (sum) is the superimposed AF; (A) large anodecathode distance, cathodic peak value is not affected by the anodic AFs; (B) smaller electrode distance, summed cathodic peak value is larger (C) small electrode distance cathodic peak value is smaller. Reproduced with permission from Simpson BA (ed) *Pain Research and Clinical Management*, isbn 0-444-51258-6 Electrical Stimulation and the Relief of Pain, Volume 15, Figure 5, page 24. Copyright Elsevier Ltd (2003).

patients with failed back surgery syndrome leads to an improved pain relief: 90% vs. 21% pain relief at 34 months, respectively.⁵⁵ The **superiority of laminectomy electrodes** can be explained by their **larger mass**

as well as their **better fixation** to the surrounding tissue. A larger mass causes a displacement of CSF, decreasing dCSF, lowering DC stimulation threshold, and increasing therapeutic range and paresthesia coverage. A better fixation of the electrodes reduces the chances for electrode dislocation. In addition, the use of a laminectomy electrode (as compared to percutaneous electrodes) results in less injected current needed to activate DC fibers, because current is now injected on the anterior side of the electrode. In addition to the effect of dCSF on paresthesia coverage, other favorable conditions are a bipole or guarded cathode and a small center distance between the contacts of the SCS (4 mm instead of 7–10 mm).

Electrodes Applied in Animal Experiments

Experimental SCS studies are either fundamental neurophysiologic studies focusing on the neuronal pathways of SCS or clinically oriented translational studies on the mechanisms and the effects of SCS on neuropathic pain (Table 1). Almost every translational experimental SCS study has been performed with a monopolar plate (platinum–iridium or solid silver) electrode with a rich variety in shapes and dimensions. In particular, the handmade silver electrodes used in the early experimental SCS studies were irregular in size and shape with a large thickness and often sharp edges. Thickness of the electrode may considerably affect the outcome: Meada et al.⁵⁶ using an electrode with a thickness of 0.35 and 2 mm wide reported spinal cord compression as a significant complication. Even when there is no sign of motor disturbance, spinal cord compression is very likely to interfere in the sensory system and cause a bias in study results. It is far from unlikely that a considerable risk in dural damage exists using large or irregularly shaped electrodes causing CSF leakage and alteration of SCS electrophysiology, thereby decreasing the accuracy of the SCS rat model. To decrease the probability of spinal cord compression, DR/column stimulation, or dural damage, a 0.10-mm-thin platinum–iridium rectangular plate electrode with a width of 1 mm and very smooth edges was developed and tested in a rat experimental SCS model.²⁷ Also, the insulation of the wire connected to the electrode is crucial, as even small damage to this wire can cause current leakage and ultimately result in nonresponse. Recently, an even smaller version of this platinum–iridium electrode with a length and a width of 2.25 and 0.76 mm, respectively,

was introduced for SCS in a mouse model.⁵⁷ In addition to the use of monopolar electrodes, the first bipolar and quadripolar electrodes have been developed for experimental work.

Stimulation Parameters

Spinal cord stimulation results in stimulation at a multicellular level because of the injection of current into the extracellular space around the neurons. Generally, a nerve fiber generates an action potential if its membrane is depolarized by more than 15 mV. Until some years ago, all pulse generators for SCS were voltage-controlled devices that produce a potential difference between cathode (-) and anode (+). The resulting current depends on the applied voltage and the impedance between the two poles according to Ohm's law: I (current) = V (voltage)/ R (impedance). The relation between stimulation voltage and current is nonlinear, which is caused by the complex impedance of the electrode–tissue interface.⁵³ Therefore, a voltage pulse does not have a rectangular shape. During the last few years, **constant current devices** have been introduced, which produce constant current between the cathode and the anode(s), which is **not influenced by the impedance**. The current injected creates a 3-dimensional electric field that can be represented graphically by isopotential and isocurrent density lines. The electrical stimulation applied to the target neurons is controlled by 3 parameters: first, the amplitude (magnitude) of the pulse in volts or amperes; second, the pulse width (the duration of the pulse) in microseconds; and third, the rate of the applied pulses in pulses per second (pps). Together, the amplitude, the pulse width, and the pulse rate determine the charge per second. The frequency used in most experimental and clinical studies is around 50–100 pps. Two clinical studies reported that the majority of patients preferred stimulation frequencies around 120 Hz while some preferred frequencies as high as 250 Hz.^{58,59}

It has to be taken into account that after every action potential, the sodium channels of a neuron are temporarily inactivated. This so-called refractory period is inversely related to the fiber diameter. Therefore, **large diameter fibers will be able to follow higher stimulation rates**, whereas the **activation of smaller fibers will be desynchronized**. Stimulation at very high pulse rates 300–500 pps may cause a depolarization block or neurotransmitter depletion. In this respect, it is interesting to note that in an experimental SCS study

Table 1 Spinal Cord Stimulation (SCS) in Experimental Neuropathic Pain Models: Electrode and Stimulation Characteristics

Experimental SCS studies			Electrode			Stimulation				
Study	Material	Implant. Level	Location	Anode Dimens. (mm)	Cathode Dimens. (mm)	Freq. (Hz)	Pw	Intensity	Stim. (mA)	Duration
Cui et al. (1999) ⁷¹	Silver	T11	Epid	nsp	2 × 3 × 0.2	50 Hz	0.2 ms	66% MT	nsp	30 minutes
Cui et al. (1998) ³¹	Silver	T11	Epid	nsp	2 × 3 × 0.2	50 Hz	0.2 ms	66% MT	nsp	30 minutes
Cui et al. (1997) ¹¹	Silver	T11	Epid	Circle/diam 5 mm	2 × 3 × 0.2	50 Hz	0.2 ms	66% MT	nsp	30 minutes
Cui et al. (1997) ¹¹	Silver	T11	Epid	circle/diam. 4 mm	2 × 3 × 0.2	50 Hz	0.2 ms	66% MT	nsp	40 minutes
Cui et al. (1996) ⁹	Silver	T11	Epid	Circle/diam 4 mm	2 × 3 × 0.2	50 Hz	0.2 ms	66% MT	nsp	40 minutes
Smits et al. (2006) ²⁷	Plat-ir	T13	Epid	Circle/diam 6 mm	3 × 1 × 0.10	50 Hz	0.2 ms	66% MT	0.4–1.5 mA	40 minutes
Smits et al. (2009) ⁷²	Plat-ir	T13	Epid	Circle/diam 6 mm	3 × 1 × 0.10	50 Hz	0.2 ms	66% MT	0.2–0.4 mA	30 minutes
Wallin et al. (2002) ⁷³	Silver	T12	Epid	Circle/diam 6 mm	3 × 1.5 × 0.25	50 Hz	0.2 ms	90% MT	0.2–0.4 mA	30 minutes
Wallin et al. (2003) ⁷⁴	Silver	T12	Epid	Circle/diam 6 mm	3 × 1.5 × 0.25	50 Hz	0.2 ms	90% MT	nsp	30 minutes
Schechtmann et al. (2004) ³²	Silver	T12	Epid	Circle/diam 6 mm	3 × 1.5 × 0.25	50 Hz	0.2 ms	90% MT	nsp	30 minutes
Schechtmann et al. (2008) ¹³	Silver	T12	Epid	Circle/diam 6 mm	3 × 1.5 × 0.25	50 Hz	0.2 ms	66% MT	nsp	30 minutes
Linderroth et al. (1992) ¹²	Silver	T11	Epid	Circle/diam 6 mm	3 × 1.5 × 0.25	50 Hz	0.2 ms	66% MT	nsp	30 minutes
Linderroth et al. (1994) ⁷⁵	Silver	Thoraco-lumbar T12-T13	Spin	Bipolar/nsp	Bipolar/nsp	100 Hz	0.2 ms	66% MT	nsp	nsp
Meyerson (1994) ⁷⁶	Silver	T12	Spin	Needle/nsp	Spheric/1 mm wide 2 × 3 × 0.2	100 Hz	0.2 ms	66% MT	nsp	30 minutes
Gao et al. (1996) ⁷⁷	Silver	T12	Epid	Circle/diam 4 mm	Disk/diam 2 mm × Spheric/1 mm wide × 0.25	50 Hz	0.2 ms	66% MT	nsp	20 minutes
Yakhnitsa et al. (1999) ¹⁷	Silver	T13	Spin	Circle/diam 4 mm	1 mm wide × 0.25	50 Hz	0.2 ms	66% MT	Mean 1.9 mA	30 minutes repetitive
Li et al. (2006) ⁷⁸	Silver	T10-T11	Epid	Circle/diam 4 mm	Disk/diam 2 mm	50 Hz	0.2 ms	66% MT	Mean 0.62 mA	5–10 minutes
Stiller et al. (1995) ⁷⁹	Silver	T12-T13	Epid	Circle/diam 4 mm	Circular/diam 2 mm	50 Hz	0.2 ms	90% MT	nsp	30 minutes
Stiller et al. (1996) ¹⁴	Silver	T11	Epid	Circle/diam 4 mm	Circular/diam 2 mm × 0.25	100 Hz	0.2 ms	66% MT	0.25–0.29 mA	30 minutes repetitive
El-Khoury ⁷ (2002)	Copper	Obex (occipital)	Spin	Needle/25 G	Disk/diam 2 mm × 0.25	50 Hz	0.2 ms	66% MT	Mean 1.25 mA	30 minutes
Maeda et al. (2008) ⁵⁶	nsp	T10-T12	Epid	Multipolar/nsp	Wire/diam nsp	75–100 Hz	0.2 ms	20–60% MT	0.25–0.7 mA	10–30 minutes daily
Wu et al. (2008) ⁸⁰	Silver	Cervical T11	Epid	nsp	7.6 × 1.6 × 0.35	4–60–100–250 Hz	0.2 ms	90% MT	nsp	30 minutes daily
Song et al. (2009) ²²	Silver	T11	Epid	Circle/diam 6 mm	Ball/1 mm	1–10–20 & 50 Hz	0.2 ms	90% MT	0.32 ± 0.72 ma	nsp
Truin et al. (2009) ⁵⁷	Plat-ir	T13 (mice)	Epid	Circle diam 6 mm	3 × 1.5 × 0.25	50 Hz	0.2 ms	80% MT	nsp	30 minutes
Truin et al. (2011) ⁶³	Plat-ir	T13 (rat)	Epid	Circle diam 6 mm	2.25 × 0.76 × 0.10	50 Hz	0.2 ms	66% MT	nsp	30 minutes
Guan et al. (2010) ¹⁹	Tungsten	T13-L1	Spin	Bipolar	3 × 1.0 × 0.10	50 Hz	0.2 ms	66% MT	nsp	30 minutes
					nsp	50 Hz	0.2 ms	No MT	0.01–3 mA	5 minutes

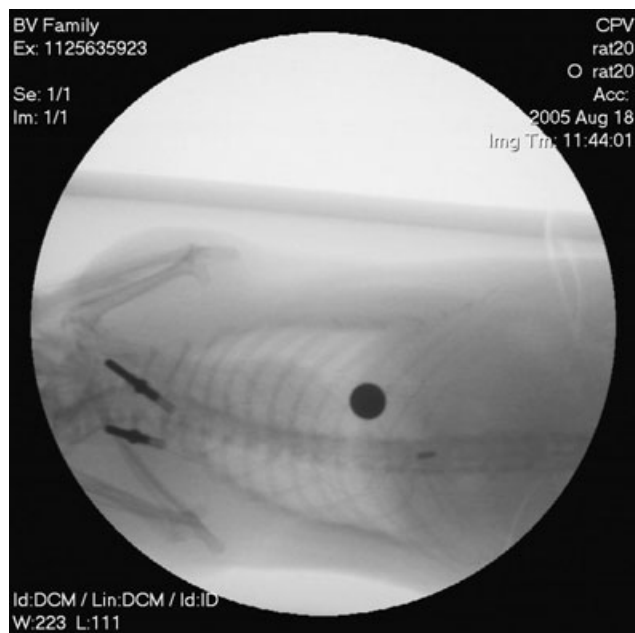


Figure 4. X-ray verification of electrode position at T13. Localization of the electrode was based on the position of the 13th floating rib which is attached to the corpus of the 13th vertebrae. Reproduced from Smits et al.²⁷ Figure 1, page 543, with permission. Copyright Elsevier (2006).

on rats with neuropathic pain, lower pulse rates (4–60 pps) were reported to result into a better pain relief than using higher pulse rates (100–250 pps).⁵ In experimental SCS, a variety of stimulation parameters have been used (Table 1). So far in all experimental studies, a pulse width of 0.2 ms was used. A constant current stimulator and stimulation amplitudes varying from 66% motor threshold (MT) (71% of studies) to 90% MT (in 24% of the studies) were used in nearly all studies, whereas only one study reported the use of an amplitude of 20–60% MT. From the few experimental SCS studies where motor thresholds were measured, it seemed that the current amplitude necessary to elicit a motor response is larger with an electrode implanted at T11 (implantation level verified by X-ray; Figure 4) compared to T13. This may be due to differences in CSF space (dCSF) (see Therapeutic Range of Stimulation).

Stimulation Regimes: Tonic Stimulation and Burst Stimulation

To date, clinical SCS, as well as SCS in experimental studies (Table 1), has mainly been performed using tonic stimulation. Tonic stimulation consists of electrical pulses, each one having the same pulse width, pulse

rate, and amplitude. Recent studies show that many central synapses are hardly or not at all signaling in response to any single action potential that arrives presynaptically. In fact, most neurons require multiple synaptic inputs to respond and single action potentials are regarded by the central nervous system as noise. However, in central neurons, depolarization by a short cluster (burst) of spikes results in an increase in presynaptic intracellular Ca^{2+} concentration. Ca^{2+} binding has not returned to baseline on arrival of the second stimulus and this so-called facilitation will reliably lead to synaptic signaling.⁶⁰ Bursts in the CNS are now regarded as intrinsic functional units of information and single bursts can produce long-term potentiation (LTP) or long-term depression (LTD). In a recent study, tonic SCS (40 pps) was interspersed by short bursts of 5 spikes at 500 pps. This protocol was used in a small group of 12 patients and resulted in a paresthesia-free pain suppression.⁶¹ These findings may substantially add to the efficacy of SCS in neuropathic pain, but the efficacy of this paresthesia-free SCS remains to be proven in a controlled study.

OTHER ASPECTS

Development of Neuropathic Pain and Timing of SCS

Timing of SCS may considerably affect the outcome: SCS performed at an early stage of neuropathic pain may be clinically beneficial. Complete relief of CRPS-1 with SCS at 4 months after its onset was described in a recent case report.⁶² In an experiment on a rat model of neuropathic pain by Truin et al.⁶³ (article accepted for publication), early SCS 24 hours after Seltzer partial sciatic nerve ligation resulted in an increased number of responders to SCS (positive response defined as > 50% reduction in pain behavior) of 77% as compared to 38% responders in late SCS 16 days after nerve injury. Moreover, in early SCS, the duration of the effect of early SCS was also increased. On the other hand, a study from our laboratory by van Eijs et al. (Neuromodulation 2012, accepted for publication) indicated that test stimulation in patients with CRPS-1 at a mean disease duration of 7.5 months did not increase the response percentage to SCS: in 50% of patients, test stimulation resulted in 50% pain relief, which is comparable to earlier data of SCS in chronic patients with CRPS-1.³

The experimental data on early timing of SCS in a rat model of neuropathic pain could not yet be

confirmed by clinical studies. The timeframe for the development of neuropathic pain and successful early treatment with SCS in the rat model is days or hours. It is highly likely that, even if there is an increased response to early SCS in man, the stimulation probably has to be started much earlier than 7 months after the onset of neuropathic pain as reported. A study by Schwartzman et al. demonstrated that 1 year after the onset of the disease, the signs and symptoms of CRPS-1 are well developed and after this point, progression is only moderate.⁶⁴ The process of central sensitization in neuropathic pain may well have different phases that generate distinct therapeutic windows for different therapeutic options as related to their mechanism of action. Cui et al.²¹ demonstrated that an important mechanism in the relief of neuropathic pain by SCS is a partial resolution of decreased GABA-ergic inhibition and increased excitation by glutamate (NMDA receptor) induced in the process of central sensitization. Eaton et al.⁶⁵ demonstrated that the supplementation of GABA shortly after a CCI nerve injury significantly reversed mechanical hyperalgesia while late application failed to do so. In the experimental setting, timing of SCS earlier in the process of a still developing neuropathic pain possibly increases the chances of interfering into a more intact GABA-ergic system, leading to an increased number of responders. As central sensitization progresses more permanent changes in the GABA-ergic system may reduce the chance of SCS-induced GABA-ergic inhibition. Over the years, clinical SCS has evolved into more of an end-stage therapy that is used in well-selected patients with intractable neuropathic pain, primarily because of the invasive nature and the high costs of SCS. It is however far from unlikely that SCS applied earlier on in the process of neuropathic disease might result in an increased number of responders.

Repetitive Stimulation

Experimental studies are often based on one single SCS treatment applied either early or late after the development of neuropathic pain. In this context, it is important to note that a recent experimental study has shown that repetition of the stimulation itself results in a better pain-reducing effect.⁵⁶ In that study, a repetitive 30 minutes per day SCS was applied for 4 days. A critical note concerning the latter publication is that the pain-relieving effect of repetitive SCS was expressed as area-under-the-curve, which makes the

absolute effect uncertain or at least less comparable to other experimental work.

THE DEVELOPMENT OF A COMPUTER MODEL FOR SCS

Holsheimer and colleagues developed a computer model to simulate the SCS-induced electric field and the response of myelinated nerve fibers.^{36,45} From this model, it was calculated that the stimulus amplitude ratio for DC and DR fibers is strongly influenced by the anode-cathode configuration (mono-, bi-, or tripolar) and the geometry of the electrode (size and longitudinal separation of the contacts). The computer model represents both the geometry and the electrical conductivities of the constituting anatomical structures at 3 different spine levels. The intravertebral geometries were based on earlier human MRI studies. From these computer models, it was calculated that the thickness of the dCSF, which varied between 2.4 and 5.6 mm, was the main factor determining the PT and paresthesia coverage in SCS.³⁵ Increasing the CSF thickness raised the threshold and reduced the paresthesia coverage. Furthermore, it was documented that a lateral asymmetry of < 1 mm with respect to the spinal cord midline gives a significant reduction in PT because the cathode is close to a right or left side DR and may result in unilateral (segmental) paraesthesiae.

1. The computer model by Holsheimer⁵⁴ and colleagues allows the design of an optimal electrode geometry, contact separation, contact size, and configuration (mono-, bi-, or multipolar) for SCS under various stimulation conditions with a longitudinal and/or transverse contact array, both surgical and percutaneous. The development of a computer model has led to the following recommendations and clinical validation for human longitudinal contact array electrodes. Tripolar (guarded cathode or split anode) stimulation with one central cathode placed at the physiological midline provides the most efficient stimulation of the DCs.
2. The contact center separation is the most critical parameter and should be between 4 and 4.5 mm.
3. Minimal electrode contact surface should be 6 mm², according to FDA regulations regarding maximum current density and maximum charge per pulse.⁶⁶

4. The contact length should be between 1.5 and 3.0 mm.
5. Using a laminectomy electrode, the contact should be approximately 4 mm wide.

The calculated optimal electrode geometry from the model was later confirmed by clinical data.^{51,67} Many currently available electrodes have larger contact surfaces (approximately 12 mm²) and contact center separation (7 mm).⁶⁸ Electrodes with a reduced contact separation (5 mm) appeared to have a 3-fold increase in therapeutic range when compared to conventional electrodes contact separation (9–10 mm).³⁶ In patients, a statistically significant preference for the guarded tri-pole electrode was reported.⁶⁷

HOW TO INCREASE THE SUCCESS RATE OF SCS AT THE EXPENSE OF NONRESPONSE

One aspect in the nonresponse to SCS therapy may be the **timing of SCS**. New experimental data point out that SCS should possibly be performed earlier, which then might interfere with the process of central sensitization of glutamatergic synapses in the spinal dorsal horn. Current SCS treatment in patients with CRPS and/or FBSS occurs at late stages in the disease when central sensitization is much more matured: long lasting and even irreversible (see section Development of Neuropathic Pain and Timing of SCS).

Another aspect of nonresponse in SCS is the presence of **mechanical allodynia**, which has some predictive value for the outcome of SCS (see section Nonresponders to SCS). In the future, the identification of possible signs, symptoms, or markers that predict the outcome of SCS in advance may be crucial, as this may decrease nonresponse to SCS by improved selection criteria. The increased nonresponse in the presence of mechanical allodynia could also be explained in terms of basic mechanisms and highlights the need for more experimental work on this subject, as understanding of the nonresponse to SCS might be key to the development of innovations to improve the response to SCS.

From this review, it is suggested that another major improvement in the nonresponse to SCS in the treatment for neuropathic pain can almost certainly be expected from optimization of the technical aspects of SCS. The SCS electrode is the interface between the electrical signal of the stimulator and the neuronal tissue of the DCs/roots, and many electrode-specific

basic technical aspects have already been calculated from the computer model of Holsheimer and colleagues and were often validated clinically afterward. For the success and reproducibility of experimental SCS, certain basic recommendations can be made. As in the clinical setting, the material, size, shape, thickness, and uniformity of the experimental SCS electrode are crucial to the effectiveness of SCS as well as the reproducibility of results and the comparability of the different studies. Thus, far in experimental studies, a variety of different electrodes (Table 1) have been, often irregular in shape and with a considerable variation in size. Other electrodes had a thickness of more than 0.3 mm resulting in spinal cord compression. Using thin 0.10 mm platinum–iridium electrodes, we obtained highly reproducible results in a rat model of SCS.²⁷ As to the stimulation parameters, in particular when we take into account that the traditional clinical tonic stimulation parameters ($f = 50\text{Hz}$, pulsewidth 0.2 ms) were copied to the experimental setting and remained unchanged for almost two decades, much research still lies ahead (Table 1). We can conclude that it is now time to start exploring the effects of other SCS parameters and SCS stimulation regimes that may enhance the understanding and efficacy of SCS.⁶⁶

From a basic scientific point of view, it is important to detect the main target neuron(s) in SCS and how and which fibers are actually stimulated. From Figure 1, it can be deduced that, besides the well-known GABA-ergic⁶⁹ and glutamatergic cells involved in the mechanism underlying SCS in treatment for neuropathic pain,^{20,23} other cells, like the PKC γ cells, the excitatory interneurons, as well as various types of glial cells located in the dorsal horn of the spinal cord, probably will play an important role in the modulation of the SCS-evoked signal. A broad range of tonic and burst stimulation regimes should be tested in the future. However, the concept of a SCS target pain neuron that needs to be stimulated in an optimal way may call for the approach of “listening” more to the nervous system instead of offering “noise” to it to find out physiological parameters of the electrical communication in neuronal cells and come up with a more goal-directed approach to SCS parameters.

CONCLUSION

Spinal cord stimulation undoubtedly is a valuable therapy for intractable neuropathic pain in CRPS-1 and FBSS. However, the fact that still 30% of the patients

do not respond to SCS remains unexplained. Based on our review, we conclude that the following steps, in a combined translational research effort, need to be taken:

1. Predictors: A search for the predictors of a successful outcome following SCS. Recent experimental and clinical data on the relation between the severity (or presence) of mechanical allodynia and success of SCS are hopeful.
2. Computer modeling: As SCS of CNS fibers is a very complex system, future computer modeling will be needed in our effort to increase the effect or the number of responders in SCS. New findings on the basic neurophysiology, biochemistry, and plasticity of SCS may be inserted into a computer model to calculate optimal SCS settings.⁷⁰
3. Experimental research: SCS rodent models have proven to be clinically relevant, and therefore, more experimental research should be performed to elucidate the mechanisms behind response and nonresponse. From our limited understanding of the mechanisms involved, important progress has already been made as it became clear both experimentally and clinically that the therapeutic effect of SCS can be potentiated by a simultaneous pharmacological intervention.

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