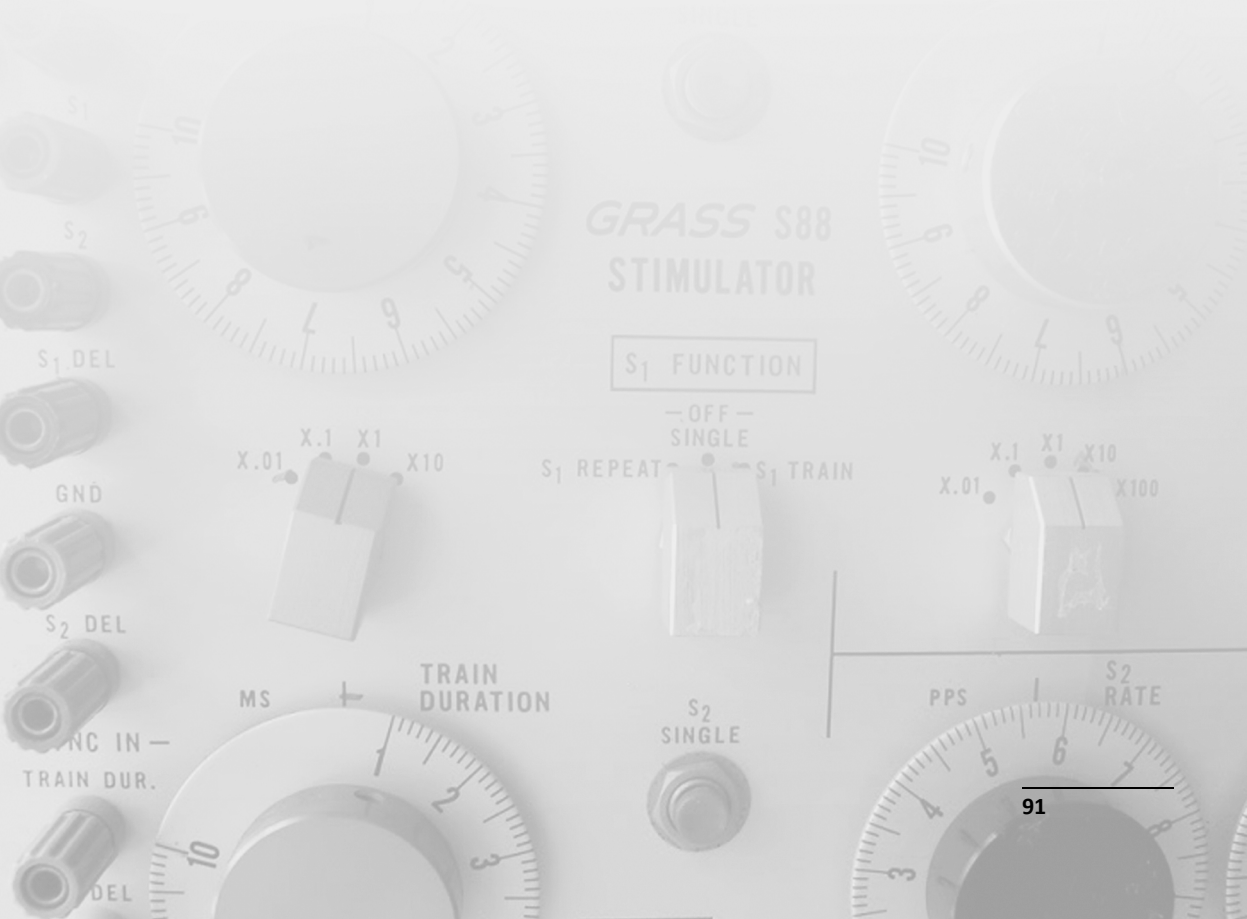
Spinal cord stimulation in neuropathic pain technical aspects and effectiveness

Chapter 7

Summary and general discussion



General aim of this thesis

This thesis includes both experimental and clinical work on SCS in chronic neuropathic pain (NNP). In the experimental part of this thesis the first three research questions were explored in an animal model of NPP and SCS. The latter and clinical part of this thesis focuses on the fourth research question.

The following research questions were addressed (see Chapter 1, Introduction page 20) and based on our research we are able to formulate the following answers:

RQ 1. What is the current status and effectiveness of SCS in the treatment of NPP as related to its technical and anatomic aspects?

SCS is a valuable therapy for neuropathic pain in CRPS-1 and FBSS that still has a 40 % failure rate. In order to reach a possible future enhancement of the effectiveness of SCS therapy a greater understanding of the mechanism(s) and site(s) of action of SCS combined with a science based and effective use of technical aspects of SCS is needed. In Chapter 2 we summarized all data on technical aspects related to SCS as well as the computer modelling related to the physical and mathematical calculations of conductivity and tissue characteristics. From this we concluded that in order to enhance the effectiveness of SCS a combined translational research effort should be taken that is aimed at

1. The search for clinical predictors of a successful outcome of SCS
2. The development of a computer model that integrates new findings on the neurophysiology, biochemistry and circuitry of SCS into a model that can be used to calculate optimal SCS settings.
3. Experimental research in order to further elucidate the mechanisms of SCS.

RQ 2 Are there signs or symptoms of neuropathic pain that may predict the outcome of SCS in terms of pain relief?

In Chapter 3 we report two important observations: Firstly the response to SCS differed with the severity of mechanical allodynia; mildly allodynic rats completely recovered to their baseline pre-injury sensory levels compared to moderate and severe allodynic animals which showed a partial and a non-response respectively. Secondly, mildly allodynic animals reached the optimal response twice as fast as moderately allodynic animals. These findings might be of clinical importance.

RQ 3 Does SCS of the dorsal columns act via a segmental spinal mechanism?

Our data in Chapters 4 and 5 demonstrate that SCS of the dorsal columns at the level where the injured fibres enter the spinal cord dorsal horn result in a much better pain relieving effect than SCS at more rostral levels. Furthermore, the increased amount of c-Fos IR cells in the dorsal horns of allodynic rats after successful SCS indicates cellular activation at the level of stimulation. From this we conclude

that SCS in treatment of chronic neuropathic pain acts through a segmental spinal site of action.

RQ 4 What is the long term (twelve year follow-up) effectiveness of SCS in CRPS-1 in terms of pain relief and what are the frequency and nature of long-term complications of this therapy.

SCS for intractable CRPS-1 pain proves to be a valuable therapy with long term efficacy (years) in about 40% of the patients (Chapter 6). Serious complications like infections and epidural haematomas did not occur in our study population. Surgical re-interventions are quite common and mostly comprise of battery changes and lead repositioning after dislocation.

In experimental pain research the selection of an animal model is crucial. The use of animal models in studies on chronic pain has been under debate as translation of the results to the clinical situation if often of limited success (169). The limited progress in translating preclinical findings may have been caused by failure to recognize the limitations of different assessment methods, over interpretation of behavioural responses and failure to acknowledge which neural circuits are involved in the expression of specific behaviours (170). Nevertheless, an experimental animal model can be an important tool to study underlying mechanisms of disease and create or improve therapies, provided the animal model has enough clinical relevancy. It should be taken into account that studies on experimental SCS in (chronic) neuropathic pain require a complex animal model which is basically consisting of two components; firstly, the induction of neuropathic pain and secondly the treatment with SCS. Whereas in our studies we focussed, clinically at the CRPS-1 patients (see Chapter 6) our animal model should meet the requirements needed. CRPS-1 is characterized by sensory abnormalities, vascular abnormalities, oedema and sweating abnormalities and motor and trophic changes (171) **(see also Chapter 1).** The sensory abnormalities consist of spontaneous (burning) pain that is disproportionate to any inciting event, touch evoked allodynia/hyperalgesia and cold allodynia (172). The development of CRPS-1 is likely to be caused by an aberrant inflammatory response that causes central sensitization which then might contribute to pain. Increased concentrations of the inflammatory mediators interleukine (IL) -6 and IL-1β were reported in spinal fluid of chronic CRPS-1 patients (172,173). In contrast to CRPS-2, CRPS-1 is thought not to be preceded by a nerve lesion. Hence, from a clinical point of view the animal models of sciatic nerve mononeuropathy as they are commonly used in research on SCS are more likely to mimic CRPS-2. Nevertheless experimental neuropathic pain models characterized by the absence of an axotomy of primary sensory neurons in the dorsal root have been described in literature, for instance; the Ventral Root Transection or VRT-model (174). In the VRT-model the ventral root fibres are lesioned which results in an inflammatory response and this

subsequently affects the uninjured dorsal root sensory afferents. A major limitation of this VRT-model is the bilateral presence of sensory abnormalities in contrast to the clinically observed unilateral symptoms in the CRPS-1 patients (172). Bilateral sensory abnormalities are noted only in very severe CRPS-1 patients (172). Other animal models that have been used to mimic CRPS-1 are the Chronic Post Ischemia Pain model (175), the tibia fracture (176) and the intra-arterial Substance-P injection model (177). Although these models do mimic CRPS-1 to some extend none of them have yet been tried in combination with SCS. Although some of these models may display symptoms that are similar to the symptoms seen in CRPS-1 it is important to realize that CRPS-1, as mentioned before, is a multifactorial disease that is probably caused by environmental as well as genetic factors. Mailis and Wade provided evidence for a genetic basis of CRPS-1 (178). In order to provide a possible future animal model of CRPS-1 based on its genetic profile, the use of mice models may be more useful as the mouse genome displays an easy mutagenesis and 95% of the mouse genome is similar to that in humans (179,180). A functional SCS neuropathic mouse model has already been introduced by Truin et al (103).

Important factors in the choice of an animal model of neuropathic pain (CRPS-1) are reproducibility, time of onset of the pain symptoms and stability and duration of the symptoms over time. With this in mind, the partial ligation of the sciatic nerve or Seltzer model of neuropathic pain has a very good profile as the onset of mechanical allodynia/hyperalgesia is almost immediate (hours), the duration of symptoms is reported to be months and this model is characterized by a response: non-response rate of about 70:30 (56).

In view of the response to experimental nerve injury and development of neuropathic symptoms genetic (181) as well as dietary factors (133,134) have been suggested to play an important role.

Genetic differences in sensitivity to mechanical allodynia in rats is reported (182). However, little is known about the identity of predisposing genes. Recently the gene CACNG2 is shown to significantly affect the susceptibility to chronic pain following nerve injury. CACNG2 encodes for stargazin, a protein intimately involved in the trafficking of glutamatergic AMPA receptors (183). which forms a critical step in the central sensitization process (23,184). With respect to dietary factors mediating the response to nerve injury a study by Shir and co-workers reported that the presence of dietary phyto-estrogens in soy containing food reduced NPP symptoms in rats (133,134). However in our own experiments (Chapters 3,4 and 5) the Seltzer (56) rat model of neuropathic pain resulted in high response rates of mechanical allodynia even in the presence of phyto-estrogens in the food. As explained and discussed in Chapter 3 nerve ligation performed exactly at the site that is described in the paper by Seltzer (56) resulted in a high reproducibility and response rate.

Then with respect to the second component of our animal model: the SCS, it is important to stress that the Seltzer-model used is known to allow the study of a pain relieving effect of the SCS treatment (see Chapter 1). For example neuropathic pain induced by the Gazelius (185) photochemical sciatic nerve lesion model animals do not respond to SCS therapy without additional administration of intrathecal drugs. A recent experimental neuropathic pain model that also seems to respond poorly to SCS is the spared nerve injury model (SNI) (132). Commonly used successful animal models of mononeuropathy and experimental SCS are the partial ligation of the sciatic nerve (56) but also the Chronic Constriction Injury (CCI) of the sciatic nerve by Bennett and Xie (90). Despite all possible limitations the Seltzer model of chronic neuropathic pain has been shown to be very translational with respect to study and effects of SCS as related to CRPS type 1 patients:

1. **Analogy between experimental and clinical findings in pain relieving effect**
   Both in clinical use of SCS in CRPS-1 patients as well as the experimental use of SCS in Seltzer injured animals resulted in similar proportions of responders (2/3) and non-responders (1/3). This is striking because we should take into account that different outcome measurements are used in experimental and clinical evaluation of the pain relieving effects. In the clinical setting pain reduction is measured by the VAS scores which relates to a reduction in spontaneous pain (49). The experimental results refer to a decrease in mechanical allodynia, as measured by an increase in withdrawal threshold to tactile stimuli with the von Frey test.
2. **Analogy between experimental and clinical findings in the mechanism underlying non-response to SCS**
   In various experimental neuropathic pain models, including the partial ligation of the sciatic nerve or Seltzer model, a loss of GABA and its synthesizing enzyme glutamate decarboxylase from the dorsal horn has been reported following nerve injury in rats (111,184,186,187). An important proposed mechanism underlying the effect of SCS in neuropathic pain is the increase of extracellular GABA in the dorsal horn through the facilitation of the GABA-release (38,58). Whereas the responders to SCS were characterized by enhanced GABA-release in the spinal dorsal horn the non-responders did not (38,73). However, when extracellular GABA concentrations in non-responders to SCS were pharmacologically increased through the intrathecal application of sub effective doses of GABA analogues like gabapentin or pregabalin or through the application of the $GABA_B$ receptor agonist baclofen, these animals showed a marked decrease in withdrawal thresholds. Furthermore, intrathecal administration of a sub effective dose of the $GABA_A$ receptor agonist muscimol did not result in efficient reversal of SCS non-responders into responders (58,82,128). These findings were translated to the clinic where also neuropathic pain patients initially non-

responding to SCS, did respond to SCS if co-treated with sub effective doses of intrathecally applied baclofen (83,188,189).

3. **Analogy between experimental and clinical findings and the prediction of the pain relieving effect SCS related to the severity of allodynia.**
   Our experimental results as presented in Chapter 3 on the severity of allodynia and effect of SCS on the withdrawal response to tactile stimuli with the von Frey test were translated to the clinic. In Chapter 3 we report an inverse relationship between the severity of mechanical allodynia and the pain relieving effect of SCS: severe allodynic rats do not respond to SCS (Chapter 3; Figure 3). In analogy to this a follow-up study by van Eijs et al. (68) reported that brush evoked allodynia may be a significant negative prognostic factor of SCS treatment outcome after 1 year in chronic CRPS-1 patients.

In this thesis indirect evidence is provided that SCS mainly acts via a segmental spinal mechanism (see Smits et al., 2009; 2011; Chapters 4 and 5). Based on the segmental localization of the electrode (Smits et al., 2011, Chapter 4) as well as the local activation of cells in the dorsal horn of the spinal cord (71) (Chapter 5) it is now clear that in order to obtain a maximal effective pain relief the localization of the electrodes as related to the segmental spinal level is of the utmost importance. However, it should be noted that our data do not completely rule out a possible contribution of supraspinal elements. The latter is based on the fact that also a more rostral localization of the electrodes (i.e T11) still results in some pain relief. There is literature demonstrating the contribution of supraspinal centres based on lesioning of the dorsal columns rostral to the electrode (65,190). It is known that selective lesioning experiments focused at the dorsal columns are very complicated, highly variable in both size and impact and very difficult to qualify in particular at the behavioural level. The additional evidence we provide with respect to a SCS segmental spinal mechanism is a so-called repositioning experiment, which is similar to the paresthesia-steering in the clinic: In the same animal the repositioning of the electrode from T13 to only one segment rostral (T12) already resulted in a significant reduction of the pain relieving effect in our experimental chronic neuropathic pain model.

In view of the positioning of the electrode not only the segmental localization is of the utmost importance but also the medio-lateral positioning. Whereas lateralization of the electrodes is indeed important to SCS-induced analgesia we always examined the medial-lateral position of the electrodes based on X-Ray. It is known that the clinical percutaneous circular leads allow for a lot of medial lateral movement. In our experimental setting we used 1 mm wide platina-iridium plate electrodes custom made by Medtronics (Bakken Research Centre, Maastricht, The Netherlands).Whereas the dimensions of our leads (width (1mm) and thickness 0.10 mm) were specifically based on rat spinal cord anatomy and related to the dimen-

sions of MRI images of the rat spinal cord, the electrodes exactly fit to the space above the dorsal columns without compression of the spinal cord. Macroscopic evaluation of the spinal cord tissue after SCS (as previously mentioned in a histological study (71) (see Chapter 5) allow the localization of the electrodes based on the presence of a sharply imprinted minimal brown coloured deposition of old blood and fibrin from the implantation operation on the dura mater. From this sharply edged print on the dura we concluded that the electrodes were fixed in one place at the midline where they initially are implanted. We suggest that the main reason for this fixation is related to the fact that the electrode is pushed to the arched bone at the dorsal side by the dura and that results in an evenly balanced pressure from the ventral side of the electrode by the underlying CSF underneath which will not allow easy lateral movement. Moreover, in our laboratory the wire of the SCS electrode is secured with histo-acryl tissue glue to the spine processes situated next to the area of burr hole which is exactly in the midline. This also minimizes the medial-lateral as well as the rostral-caudal movement. Although it might be suggested that a CT-scan is needed and results in a conclusive answer on the exact medio-lateral localization of the electrodes we like to indicate that the metal plates of the electrodes will probably produce a scatter in the image due to reflection of the metal, resulting in a deformed image of the electrode and it's direct surroundings. The anterior posterior X-ray we used does mimic the clinical situation in a best possible way. Clinically the medial lateral position of the electrode is adjusted by "paraesthesia steering" which is not possible in animals, although our repositioning experiment (Chapter 4) comes close.

The size of the experimental electrodes related to the dimensions of the spinal cord and spinal roots does not rule out a possible stimulation effect via the dorsal afferents. A electrophysiological study by Guan and colleagues (141) further substantiated this: they studied the effect of a bipolar electrical conditioning stimulation of the dorsal column and lumbar dorsal roots on the response properties of the spinal wide dynamic range (WDR) neurons in rats after L5 spinal nerve injury. Whereas the conditioning stimulation intensity was set at the lowest current that evoked a peak antidromic sciatic Aβ-compound action potential without inducing an Aδ- or C-compound action potential they noted that both the dorsal column and the dorsal root conditioning stimulation significantly attenuated WDR neuronal responses to mechanical stimuli in nerve injured rats. Moreover they noted that stimulation of both dorsal columns and dorsal roots inhibited short-term neuronal sensitization (141). These findings indicate that dorsal root stimulation, due to the relatively large size of the electrodes in our rat model, still might form a serious complication in the experimental setting. On the other hand these electrophysiological studies point to the fact that probably also in the clinical setting dorsal root stimulation in treatment of neuropathic pain might be effective as well. In view of the fact that, at least in the experimental setting it cannot be excluded that other

structures then the dorsal columns are involved and may account for the therapeutic effect of SCS the term dorsal column stimulation may be replaced by the more neutral phrase “spinal axis stimulation”, as already suggested earlier (191).

Whereas the WDR cells, located in the deeper dorsal horn layers are, based on the electrophysiological data (55,141) clearly involved in the mechanism underlying SCS induced pain relief, the question still remains how the activation of the large myelinated primary afferents in the dorsal columns finally results in modulating the incoming pain signal. The spinal nociceptive network and the relation with the myelinated primary afferents in the dorsal columns is presented in Chapter 2, Figure 1. In general SCS of the myelinated primary afferents is thought to induce changes at spinal levels as the balance of inhibitory and excitatory neurotransmitters in the dorsal horn is changed (58) (see Chapter 2). In addition several biochemical and pharmacological experimental studies on the mechanisms of action of SCS showed an alteration of the chemical transmission in the spinal dorsal horn (52,64,72,73)**.** 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 due to an increased release of the excitatory neurotransmitters glutamate and aspartate (74) and at the same time a loss of tonic GABA mediated inhibition. Basically a decreased extracellular concentration of glutamate and at the same time an increased extracellular GABA-concentration have been noted after SCS (58,72) and this results in the suppression of hyperexcitable WDR neurons (55).

The importance of central sensitization and the role of (phosphorylation of) the NMDA receptor during the pain relieving effect of SCS in chronic neuropathic rats was shown in a pharmacological study performed by Michiel Truin (66). It was already known that interference with the process of central sensitization through the antagonism of the NMDA receptor attenuates chronic neuropathic pain. The use of the non-competitive NMDA blocker ketamine has been shown to have analgesic effect on neuropathic pain in both experimental and clinical studies (110,192,193). A combined treatment of SCS and sub-effective dose of i.t. ketamine in non-responders resulted in a significant reduction of the withdrawal threshold in all previous non-responders to SCS (66).

As indicated in the Figure 1 (Chapter 2) the spinal dorsal horn has been reported to contain a ‘silent’ circuit between low-threshold afferent fibres and Nociceptive Specific (NS) projection neurons located in lamina I. Although the composition of this circuit has been only partly described 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 (77) especially because PKC-γ interneurons are known to be activated via A_β fibres signalling (79). In order to develop further insights into the cellular components involved in the SCS mediated modulation of the

spinal nociceptive network neuro-anatomical studies might add. In a first attempt we studied the number of c-Fos-immunoreactive cells in the dorsal horn immediately after SCS (Chapter 3). Immediate early genes, like c-Fos, have been used as indirect markers of neuronal activity (144) and increases in the number of c-Fos immunoreactive cells have been reported a few hours to a few days after peripheral nerve injury (147). In our study we noted an increase in the number of c-Fos immunoreactive cells in the dorsal horn after SCS at the level of stimulation (Chapter 5). Further characterization of these c-Fos immunoreactive cells is needed. Whereas GABA-ergic inhibitory interneurons are predominantly located in spinal laminae 1-3 (34) and their interference with nociceptive activation of pain signalling neurons has already been pointed out decennia ago (24) a double immunostaining of c-Fos with antibodies directed against the neurotransmitter GABA -is a logical first next step in analyzing the cellular components involved the mechanism underlying SCS mode of action (194).

Another approach might be the in vivo imaging of metabolic activity of cells in neuropathic animals after SCS. Metabolic activity of cells can be visualized using flavoproteins: Mitochondrial oxidized flavoproteins have the ability to absorb blue spectrum photons. This causes an immediate emission of green spectrum photons, whose intensity (detected by a CCD camera) is a direct measure of neuronal metabolic activity.

The autofluorescent flavoprotein imaging (AFI) technique is an optical technique suitable for monitoring metabolic activity in the superficial areas of nervous tissue thereby studying cellular processes in vivo in the cerebellum (195) and cerebral cortex (196). Moreover using the AFI-technique it was possible to demonstrate simultaneously the temporal and spatial propagation of spinal nociceptive activity in vivo in the spinal cord dorsal horn (197). In a pilot study we investigated the effect of spinal cord stimulation on spinal dorsal horn metabolic activity in neuropathic rats in vivo (198). Our preliminary data showed a short-lasting, but strong reduction in AFI intensity relative to baseline in SCS animals, which was not observed in animals that underwent sham stimulation. These observations directly visualize the temporal and spatial extension of spinal hyperexcitability following nerve injury. At present we are analyzing the same animals used for AFI intensity measurements but now, after perfusion fixation, for double immunohistochemical analysis of the immediate early gene c-Fos and the GABA synthesizing enzyme glutamate-decarboxylase (GAD) in the dorsal horn(198).

The latter and clinical part of this thesis focuses on the long term effectiveness of SCS in CRPS-1 patients based on a prospective (cohort) 12 year follow up study of SCS in CRPS-1 patients. Data on the long term outcome beyond five years of treatment of SCS in CRPS-1 patients are sparsely available. As stabilization or improvement of CRPS-1 only occurs early on in the disease, analysis of the efficacy of thera-

peutic interventions in chronic CRPS-1 patients is therefore of the utmost importance.

Future research

Both in clinic and in the experimental setting chronic neuropathic pain is characterized by a wide variety of different grades of allodynia. The significant differences in pain relief in groups with different grades of allodynia after SCS in the Seltzer animal model (Chapter 3) did initiate a translational clinical study performed by van Eijs et al. (68). This clinical study showed that the presence of brush-evoked allodynia was associated with a lower chance (31 %) of achieving long-term (up to 1 year) pain reduction with SCS treatment, versus an 81% chance of pain reduction in patients without brush evoked allodynia. Hence the mean and maximum value of brush-evoked allodynia proved to be statistically significant predictors of outcome (68). Despite this important translational finding future research should be aimed at the understanding of SCS and the process of central sensitization, as this is believed to be among the most important cellular changes present in chronic neuropathic pain. This then may lead to new clinical predictors on the effect of SCS in pain relief in neuropathic patients and finally result in an increased effectiveness of SCS.

The wide variety of allodynia noted in the experimental model (Chapter 3) also shares a lot of analogy to the clinic of CRPS-1 patients and raises the issue of the relatively vague 1994 International Association for the Study of Pain (IASP) definition of CRPS-1 (2). There is a lack of agreement between the different diagnostic sets for CRPS I and this results in different clinical profiles leading to different therapeutic and study populations. This will slow down scientific development and adequate treatment of CRPS-1(199). With respect to our findings on severity of allodynia and the effect of SCS it may be useful to define a gradation of spontaneous pain and positive sensory signs (gain) CRPS-1 and mild, moderate and severe allodynia. It may well be that the presence or absence of allodynia in CRPS-1 patients is based on differences in CRPS-1 pathophysiology, which finally result in a different pain-relief response to SCS. A study by Eberle et al (200) noted differences in clinical symptoms in patients with so-called warm and cold CRPS-1. This might indicate a difference in pathophysiology. Based on this study and the possible different pathophysiological mechanisms in sub-populations of CRPS-1 patients the presence of allodynia and pinprick hyperalgesia, as signs of secondary hyperalgesia, indicate the involvement of central sensitization. A recent study in 692 CRPS-1 patients by de Boer et al (17) demonstrated that the pain and sensory signs in CRPS-1 tend to increase in time thereby also pointing towards involvement of cellular modulation of the pain signal at different brain levels (central sensitization). From this the authors favour the development of a more mechanism based classification of CRPS-1 which ultimately should lead to a mechanism based (SCS)-treatment. We have shown that

the experimental Seltzer model is of use in the understanding of mechanisms underlying SCS and thus can be of great use for future translational research on effectiveness of SCS in neuropathic pain.