# Neuromodulation in non-operated discogenic low back pain

# CHAPTER 8

## Summary

In the Western world, the primary source of years lived with disability is attributed to low back pain (LBP) (1). The etiological factors contributing to pain in a majority of LBP cases present a serious challenge for diagnosis. Nonetheless, among the cohort of patients undergoing LBP treatment, a significant subgroup, comprising 21-42%, may experience pain stemming from discogenic origins (2–4). This chronic discogenic low back pain (CD-LBP) is caused by a degenerating intervertebral disc. Effectivity of long-term pharmaceutical treatments for pain relief of CD-LBP is very limited. Neuromodulation is an interesting last resort treatment option for CD-LBP patients who do not respond to conventional pharmacological treatment. The anatomy, development and possible treatment options for pain relief in CD-LBP are described in Chapter 1. Degenerated discs are marked by nerve ingrowth and altered chemistry. Nociceptive signaling originating from within the degenerated discs moves through the sinuvertebral nerve (SVN) to the ventral root of the spinal nerve (VR) and a sympathetic branch from the ramus communicants (RC) to move into the spinal cord. The origin of pain in CD-LBP is due to a combination of an inflammatory response in the degenerated disc combined with nerve ingrowth or sprouting, as well as a mechanical aspect due to reduced disc height and hypermobility. Various techniques such as centralization of painful symptoms, disc visualization and positive discography have been used to diagnose CD-LBP however; the diagnosis of CD-LBP remains controversial. Both spinal cord stimulation (SCS) and dorsal root ganglion stimulation (DRGS) have been used for pain reduction in CD-LBP. There is a variety of SCS waveforms used for neuromodulation, these range from conventional stimulation to active or passive recharge burst or high frequency (HF) stimulation. This thesis aimed to investigate the mechanisms and impacts of SCS and DRGS within clinical populations, as well as in a preclinical animal model for CD-LBP. In pursuit of this objective, the following research questions were formulated:

Research question 1: What is the status of neuromodulation on pain relief in patients with non-operated chronic discogenic low back pain? In Chapter 2, a systematic review on the use of neuromodulation in CD-LBP is presented. This review revealed that a variety of neuromodulation techniques and stimulation paradigms are used for pain reduction in CD-LBP. Both conventional SCS, high frequency SCS, burst SCS, high-density (HD) SCS and DRGS at the level of L2. Across the examined studies, neuromodulation consistently led to significant pain score reductions for up to 12 months. Although not all studies indicated statistically significant decreases in disability scores, there was a general trend of reduction throughout the treatment period. Moreover, a notable increase in quality of life scores was observed. This indicates that neuromodulation can successfully be used for pain reduction and quality of life increase in CD-LBP.

Research question 2: Does passive recharge burst SCS result in effective pain relief in non-operated CD-LBP patients? Burst stimulation involves administering brief burst trains of dorsal column stimulation, repeating at a predetermined frequency. Various approaches are employed in burst stimulation to mitigate the accumulation of positive charge in the stimulated tissue following a burst, commonly known as the recharge phase. These strategies encompass burst with a passive recharge phase or BurstDR, as well as burst involving an active recharge phase (refer to Figure 6, chapter 1). In Chapter 3, we provided further evidence for the successful use of passive recharge burst SCS for pain relief in CD-LBP. Patients reported significant reductions of LBP and associated neuropathic components over a period of 12 months. Disability scores followed a similar trend of reduction. Patient quality of life scores remained constant, as well as impression of change scores. Combined, these data show that burst SCS can be an effective tool to treat pain in CD-LBP patients over a long-term period.

Research question 3: Do passive recharge burst SCS and L2 DRGS differ in effectivity of pain relief in non-operated CD-LBP patients? Chapter 4 describes an analysis of two clinical datasets. The data from passive recharge burst stimulation from chapter 3 was compared against a clinical dataset using L2 DRGS for CD-LBP. Both studies used identical inclusion criteria. In this comparison, L2 DRGS provided better long-term pain relief and increases in quality of life compared to burst SCS.

Research question 4: Do active recharge and passive recharge burst SCS differ in effectivity, with emphasis on emotional aspects of pain, in patients with non-operated CD-LBP? Chapter 5 describes a protocol for the BURST-RAP study, which formed the basis for a now ongoing multicenter clinical trial in persistent spinal pain syndrome (PSPS) type 2 that aims to compare the differences in both pain relief and psychological aspects of pain after treatment with active and passive recharge Burst SCS. PSPS type 2 is a chronic condition characterized by long-lasting and recurring pain leg pain sometimes combined with back pain originating from the spinal area, which persists following spinal operation aimed at providing pain relief. PSPS type 2 is an indication for which SCS has become an essential part of the long-term pain treatment. Drawing from clinical observations and findings in preclinical studies documented in the literature, distinctions in pain relief may exist between active and passive recharge paradigms, influencing their underlying mechanisms of action and potentially resulting in divergent effects on pain relief. It is possible that active recharge has the ability to stimulate both the medial spinal pathway, engaging cortical sensorimotor regions responsible for pain location and intensity, and the lateral pathway, affecting brain areas involved in the cognitive and emotional dimensions of pain. On the other hand, passive recharge is suggested to act via thalamic neurons, which exhibit a similar electrical pattern, leading to the modulation of activity in various cortical areas related to the motivational and emotional aspects of pain. This Randomized Clinical Trial aims to evaluate and

compare the impact of active and passive recharge Burst SCS on a various aspects of pain experienced by PSPS Type 2 patients. This clinical trial is currently ongoing.

Research question 5: Is it possible to develop a reproducible animal model of non-operated CD-LBP? Chapter 6 describes and evaluates the anterior annular puncture (AAP) model of the L4-L5 and L5-L6 IVD for mirroring CD-LBP in the rat using both reflex-based an operant based pain tests. Animals subjected to the AAP procedure developed histologically confirmed degenerated vertebral discs, which is a hallmark of this indication. The reflex- based low back pain sensitivity (LBPS) test, where pressure is applied to the level of the painful disc at a steady increasing rate until a pain response is detected, was used to test for CD-LBP in animals with degenerated discs. Our observations indicated significant variability in the LBPS test, potentially influenced by the tester's subjective interpretation of the animals' discomfort. Consequently, we cannot recommend the use of the LBPS test for assessing low back pain in the AAP model. In order to further characterize pain behavior in the AAP model, we employed the operant based conditioned place preference (CPP) test. In the CPP test, animals were conditioned to gabapentin, an analgesic previously shown to induce preference only in animals with chronic pain in order to detect the presence of CD-LBP. Use of CPP test resulted in a subdivision in AAP responders versus AAP non-responders to pain. It is recommended that further experiments be conducted to thoroughly analyze and investigate the mechanisms distinguishing responders from non-responders in the context of AAP-induced pain.

The aim of this thesis was to study the mechanism and effect of SCS and DRGS in non-operated chronic discogenic low back pain (CD-LBP). The findings presented indicate the viability of various SCS waveforms and L2 DRGS for alleviating pain in CD-LBP. While both passive recharge SCS and L2 DRGS demonstrated effectiveness, L2 DRGS might exhibit superior long-term pain relief. Nonetheless,

comprehensive investigations are necessary to assess the impact of stimulation sites and waveforms in CD-LBP. In this context, we introduced the BURST-RAP clinical trial protocol, designed to explore distinctions in pain catastrophizing and pain perception between active and passive burst stimulation in persistent spinal pain syndrome Type 2. The clinical and preclinical studies presented here could ultimately improve the treatment for pain reduction of CD-LBP and PSPS type 2, and aid physicians in formulating an optimal stimulation strategy.

## 8.1 References


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