Neuromodulation in non-operated discogenic low back pain

APPENDIX

Impact Paragraph

Curriculum Vitae

List of Publications

Acknowledgements

Chronic discogenic low back pain (CD-LBP) is a debilitating condition known to significantly impact quality of life, work attendance, and psychological well-being. The efficacy of conventional therapies based on pharmacological and minimally invasive treatments for CD-LBP has proven challenging. For individuals unresponsive to conventional pain therapies, neuromodulation offers a valuable last-resort option. This thesis aims to enhance the understanding of neuromodulation in CD-LBP through a literature review, clinical investigations into the impact of neuromodulation on pain alleviation in CD-LBP patients, and a preclinical mechanistic study aimed at replicating a previously published animal model for CD-LBP to study the pain-relieving effects of neuromodulation.

In order to provide preliminary evidence for the use of neuromodulation in clinical CD-LBP populations, we first performed a literature review in Chapter 2, and subsequently a clinical study as described in Chapter 3. The results from these studies provide evidence that neuromodulation in the form of dorsal root ganglion Stimulation (DRGS) or spinal cord stimulation (SCS) of the dorsal columns using various stimulation paradigms can provide effective long-term pain relief in CD-LBP. These findings are significant since the success of long-term pharmaceutical or interventional treatment is limited, neuromodulation may act as a last-resort treatment option to expand the treatment arsenal available to physicians. Nevertheless, the use of tonic SCS is still characterized by serious drawbacks in treatment of chronic neuropathic pain. While data regarding effectivity of tonic SCS in CD-LBP is lacking, there is evidence related to use and effectivity in various chronic neuropathic pain conditions; In general the proportion of chronic neuropathic pain patients achieving more than 50% pain reduction through tonic SCS is frequently constrained to 40-60%, with overall pain relief typically capped at 60% (1–4). Consequently, approximately 40%, of SCS explants can be linked to a limited efficacy on pain relief (5,6), combined with a loss of efficacy over both short and long periods of time (7–9). Furthermore, a significant number of patients

experience the paresthesias with tonic SCS to be uncomfortable. The various neuromodulation paradigms and locations of stimulation described in this thesis could hold the potential to address these challenges. As data regarding loss of efficacy and dropout rates with these paradigms and locations has not been studied in detail, the impact of our findings might be significant for treatment of CD-LBP and chronic neuropathic pain patients by allowing them to vary waveforms in a rotating fashion in order to circumvent long-term decreases in efficacy. As both DRGS and SCS with use of waveforms such as high frequency (HF) and burst are paresthesia free, these can offer an alternative to patients that find paresthesias uncomfortable.

Chapter 4 presents a comparative analysis of the outcomes on pain relief, disability and quality of life scores obtained in Chapter 3 with a previously conducted prospective study that assessed the use of L2 DRGS. The L2 DRG is an interesting stimulation target for CD-LBP as innervation of the lumbar discs has been demonstrated to flow via the sympathetic nervous system, culminating at the L2 level. Within these restricted cohorts, L2 DRGS demonstrated superior long-term pain relief and enhanced quality of life in comparison to burst SCS. These results bear significance, particularly due to the susceptibility of SCS of the dorsal columns to variations in posture, leading to alterations in the distance between the electrode and spinal cord, subsequently resulting in uncomfortable over- or under-stimulation. In contrast, stimulation intensity of DRGS remains unaffected by postural changes. The findings of these clinical studies in Chapters 3 and 4 mark the initial strides toward identifying an optimal neuromodulation regimen for individuals with CD-LBP. Given the limited sample size of this preliminary analysis, future investigations should aim to corroborate and extend these observations.

The results described in Chapters 2, 3 and 4 are essential steps needed to obtain evidence for the effectiveness of neuromodulation for pain relief in CD-LBP. For clinicians who are exploring experimental or alternative neuromodulation options

for patients with CD-LBP, these results provide handholds in establishing a treatment plan. Although the outcome of the studies in Chapters 2,3 and 4 fall short of definitively pinpointing an optimal stimulation technique for CD-LBP patients, the results will definitely direct the way to go and function as stepping-stones for further explorations. Clearly our clinical observations on the effects of various neuromodulation strategies on pain relief in CD-LBP need to be followed by multicenter randomized trials which allow for more final conclusion on the effectivity and differences between neuromodulation strategies. Ultimately, the goal is to assess the viability of neuromodulation as an intervention for patients who have not responded to conventional treatment.

In the pursuit for novel SCS paradigms, a crucial factor to take into account is the waveform recharge mode. There are two strategies of recharge mode to counteract the buildup of positive charge within stimulated tissue in burst stimulation: active and passive recharge. It has been suggested that differences in pain relief exist between active and passive recharge paradigms, potentially due to their different underlying mechanisms of action, resulting in contrasting effects on pain mitigation. Active recharge has been shown to activate both the medial spinal pathway, while passive recharge has been suggested to act via modulation of thalamic neurons. These differences might not be limited in pain reduction but also to the impact of SCS on emotional, motivational and cognitive aspects of pain. In Chapter 3, the effectivity of passive burst SCS in CD-LBP is described. Differences in the clinical efficacy between actively recharged Burst and passively recharged Burst for chronic neuropathic pain remains presently unexplored. There is a pressing requirement for clinical data to elucidate which waveform is most suitable for specific indications. To that end, Chapter 5 describes a protocol which aims to compare the effect of active and passive recharge burst SCS in a population of persistent spinal pain syndrome type 2 (PSPS type 2). PSPS type 2 is an indication where SCS has become an integral component of long-term pain management, and the utilization of

neuromodulation therapy is presently covered by Dutch insurance. This makes PSPS type 2 an excellent candidate to test investigate burst differences. The results from this study, regardless the outcome, are likely to have an impact on the choice of stimulation on an individual patient basis in PSPS type 2 and other indications, relating to the effect in pain reduction and the impact of burst stimulation on emotional aspects of pain. Subsequently, this research may lead to investigations expanding on possible differences between these two types of recharged Burst waveforms in other chronic neuropathic pain conditions including effects on emotional and motivational aspects of pain.

In order to better understand how and where various neuromodulation treatments act in CD-LBP, mechanistic studies are needed. It is therefore that we attempted to develop an animal model for neuromodulation in CD-LBP. We evaluated the Anterior Annular Puncture (AAP) model in Chapter 6 of this thesis using both of reflex and operant-based behavioral tests for low back pain. In these experiments, we concluded that the AAP model resulted in reproducible levels of disc degeneration, which was not always reflected in pain behavior. Reflex-based testing of LBP performed using the low back pain sensitivity (LBPS) test could not be recommended due to high intra-animal variability. Operant-based testing using the conditioned place preference (CPP) test revealed AAP-animals to be subdivided into a painful and non-painful subgroup. While preclinical pain research has long depended on reflex-based pain tests such as the von Frey or LBPS test, the field is moving towards the use of operant-based tests of pain, such as the CPP test or the mechanical conflict-avoidance system (MCAS) (10). In this context, the findings described here are important to preclinical pain research, as they show that the CPP test can be an effective method for pain detection. Furthermore, it shows that use of the CPP is not limited to classic neuropathic pain models, and can work in instances where hands-on performance of reflex based tests such as the LBPS test is difficult. As previous research has highlighted discrepancies between reflex-based testing and

operant-based testing (11), studies combining operant-based and reflex-based pain testing, such as described in Chapter 6, will become essential in the experimental pain laboratory of the future. While not performed in these experiments, the CPP could be ideal to test the effect of neuromodulation versus sham stimulation in AAP-animals. Our research will form de fundament for such studies on the effectivity of therapeutic interventions including neuromodulation in a variety of chronic neuropathic pain models

The aim of this thesis was to study the mechanism and effect of SCS and DRGS in non-operated CD-LBP. Here we have described a series of investigations that have broadly addressed this aim based on specified research questions. The results hold the potential to significantly enhance pain relief for CD-LBP patients through neuromodulation and may act as a fundament for better treatment of other chronic neuropathic pain indications

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