From the Institute of Environmental Medicine
Karolinska Institutet, Stockholm, Sweden

THE EFFECT OF SPINAL MANIPULATIVE THERAPY ON HEART RATE VARIABILITY AND PAIN IN PATIENTS WITH PERSISTENT OR RECURRENT NECK PAIN

Anders Galaasen Bakken

Karolinska Institutet

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The effect of spinal manipulative therapy on heart rate variability and pain in patients with persistent or recurrent neck pain

THESIS FOR DOCTORAL DEGREE

By

Anders Galaasen Bakken

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Principal Supervisor:
Iben Axén, DC,
Assoc. Professor, PhD
Karolinska Institutet
Department of Environmental Medicine
Unit of Intervention and Implementation
Research for Worker Health

Co-supervisor(s):
Andreas Eklund, DC, MSc,
Asst. Professor, PhD
Karolinska Institutet
Department of Environmental Medicine
Unit of Intervention and Implementation
Research for Worker Health

Søren O'Neill, Chiropractor,
Assoc. Clinical Professor, PhD
Spine Centre Southern Denmark,
University Hospital of Southern Denmark
Institute of Regional Health Research,
University of Southern Denmark

Opponent:
Mette Korshøj, BSc, MS,
Senior Researcher, Ph.D.
Department of Occupational and Social Medicine,
Holbæk Hospital, Denmark

Examination Board:
Björn Äng, Professor, PhD
Region Dalarna, Department of Research and Higher Education, Falun, Sweden;
School of Health and Welfare, Dalarna University, Falun, Sweden, and
Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden

Margreth Grotle, Professor, PhD
Department of Physiotherapy, Faculty of Health Science, Oslo Metropolitan University, Norway

Henrik Wulff Christensen, DC, MD, PhD
Forskningsleder, Kiropraktorernes Videnscenter, Denmark
Chiropractic Knowledge Hub

POPULAR SCIENCE SUMMARY OF THE THESIS

This thesis is based on a clinical trial investigating the effects of adding manual treatment of the spine to home stretching exercises for patients with recurrent or persistent neck pain. The effects on pain and heart rate variability (HRV) (a measure of the balance of the nervous system) are investigated over a two-week treatment period. The study also investigates the link between changes in pain and HRV during this treatment period, and the temporal stability of conditioned pain modulation (CPM) measurements in this patient group.

The study found no additional effects from manual treatment of the spine for pain and HRV. Considering what we already know about manual treatment, pain and HRV, this is surprising. As manual treatment combined with other therapies has been shown to positively affect neck pain and is recommended in current guidelines, we expected to see a difference in changes in pain between the groups. People with persistent or recurrent neck pain also have a lower (worse) HRV than people without pain, so a reduction in pain was thought to be associated with a change in HRV.

In this thesis, the new findings are discussed in the context of previous research. There could be several possible reasons for the observed differences. The following are the most plausible explanations:

Manual therapy might not have a substantial effect on HRV beyond the immediate effect. Also, two weeks of treatment might not have been long enough to detect a difference in pain between the two interventions considering the chronicity of the patient group. Possibly, the addition of SMT was superfluous, and the observed results are due to stretching exercises only. The observed results could also be driven by contextual effects. Many patients were also experiencing pain in other regions of the body, which could have influenced the results. Finally, the lack of association between changes in pain and changes in HRV could also be due to the limitation of a two-week intervention period, as HRV would possibly need a longer time to adapt to changes in pain levels.

CPM is a measure of the “pain inhibits pain” mechanism. As a reduced response is commonly observed in patients with chronic pain, we investigated whether subjects with a clinical improvement in pain over two weeks experienced a change in the CPM response. We found that the CPM test had moderate temporal stability for both clinically improved and non-clinically improved subjects, and that the response was similar, regardless of pain changes.

This thesis has assembled some of the missing pieces of the complex jigsaw puzzle concerning the knowledge of persistent or recurrent neck pain, and the mechanisms and the response of manual treatment. Nevertheless, more pieces of the puzzle need to be identified and placed correctly in order to understand the association between changes in pain and HRV among patients with persistent or recurrent neck pain undergoing manual therapy and home stretching exercises.

1 ABSTRACT

1.1 OBJECTIVE

Persistent or recurrent neck pain is a common reason to seek healthcare. Manual therapy in combination with exercises is recommended by clinical guidelines for this patient group.

Autonomic dysregulation with reduced parasympathetic activity, increased sympathetic activity, and impaired conditioned pain modulation is seen in a range of chronic pain conditions such as persistent or recurrent neck pain.

An immediate response to spinal manipulative therapy of the autonomic nervous system has been observed, but the evidence is of very low to moderate quality and the underlying mechanisms are unknown.

Examining the long-term effect of spinal manipulative therapy on the autonomic nervous system, pain, and disability is thus relevant, and measures of heart rate variability can provide an objective measure of this relationship.

The aim of this project was to examine the effects on pain, disability, and heart rate variability of adding spinal manipulative therapy to home stretching exercises over a period of two weeks. Further, an explorative investigation into the relationship between changes in pain and changes in heart rate variability was undertaken. In addition the temporal stability and responsiveness of the conditioned pain modulation measurements was also investigated.

1.2 METHOD

A randomized controlled clinical trial was carried out in multidisciplinary primary care clinics. One group received home stretching exercises and spinal manipulative therapy, and the other group received home stretching exercises only.

The subjective pain experience was investigated by assessing pain intensity (NRS-11) and the affective quality of pain (McGill questionnaire). Neck disability (NDI) and health status (EQ-5D) were also measured.

Heart rate variability at rest was measured using a portable heart monitor.

CPM was measured using a universal “clamp” from Clas Ohlson (https://www.clasohlson.com/se/Universalklämma-Cocraft/p/40-7211) and a cold-water bath (0-2 ℃).

The subjects received four treatments over two weeks.

Linear mixed models were used to investigate the group by time interaction.

Multivariate analysis of variance (MANOVA) was used to investigate the temporal stability of the CPM test.

The study was approved by the Regional Ethical Review Board (Stockholm) (ref: 2018/2137-31).

1.3 RESULTS

No statistically significant group effect was found for pain, disability, or any of the heart rate variability indices.

No statistically significant association was found between changes in pain (NRS-11) and changes in HRV.

The CPM test appears to be moderately stable over time for both subjects who experienced a clinically important difference and those who did not over a two-week treatment period.

1.4 CONCLUSION

Adding spinal manipulative therapy to a two-week stretching protocol did not significantly improve heart rate variability, pain or disability in this well-controlled RCT. Further investigations found no significant association between treatment response from spinal manipulative therapy and home stretching exercises and HRV over two weeks. Further research on pain, disability and HRV should focus on subjects with higher pain intensity and a longer intervention period. Also, further investigation of the relationship between pain and HRV is warranted.

The CPM utilized showed moderate temporal stability for this patient group. Changes in persistent or recurrent neck pain over two weeks were not associated with changes in the CPM test response.

2 LIST OF SCIENTIFIC PAPERS

I. The effect of two weeks of spinal manipulative therapy and home stretching exercises on pain and disability in patients with persistent or recurrent neck pain; a randomized controlled trial

II. The effect of spinal manipulative therapy and home stretching exercises on heart rate variability in patients with persistent or recurrent neck pain; a randomized controlled trial

III. Are changes in pain associated with changes in heart rate variability in patients treated for recurrent or persistent neck pain?

IV. Temporal stability and responsiveness of a conditioned pain modulation test. A study of conservative treatment of neck pain patients

Scientific papers not included in this thesis

V. The effect of spinal manipulative therapy on heart rate variability and pain in patients with chronic neck pain: a randomized controlled trial - protocol

VI. Recruiting in intervention studies: challenges and solutions

CONTENTS

LIST OF ABBREVIATIONS

ANS	Autonomic Nervous system
CPM	Conditioned Pain Modulation
CS	Central Sensitization
HRV	Heart Rate Variability
HVLA	High Velocity Low Amplitude
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
MCID	Minimal Clinical Important Difference
NDI	Neck Disability Index
NP	Neck Pain
NRS	Numerical Rating Scale
PTSD	Post-Traumatic Stress Disorder
Q-Q plot	Quantile-Quantile plot
SEK	Swedish Krona
SMT	Spinal Manipulative Therapy
USA	United States of America
WAD	Whiplash Associated Disorders
YLD	Years Lived with Disability
DNIC	Diffuse Noxious Inhibitory Control
VAS	Visual Analogue Scale
PPI	Pressure Pain Intensity

3 INTRODUCTION

Previous research has examined the effect of spinal manipulative therapy (SMT) and exercise on neck pain (NP), including research on the effect of a single treatment with SMT on heart rate variability (HRV). There are, however, no well-controlled trials on the long-term effect of a combination of SMT and home stretching exercises on pain and HRV. Therefore, a randomized controlled clinical trial investigating subjects with persistent or recurrent NP was designed, with the primary focus being the relationship between changes in pain and changes in HRV. The protocol was published in Trials, October 2019.

3.1 DEFINITION OF NECK PAIN

There are two common definitions of NP, referring to slightly different anatomical regions.

The Bone and Joint Decade 2000-2010 Task Force on NP and Its Associated Disorders defines the neck as the posterior neck region from the superior nuchal line to the spine of the scapula and the side region down to the superior border of the clavicle and the suprasternal notch. Thus, NP is pain located between the scapula and base of the skull, with or without radiation to the head, trunk, and upper limbs (1).

The International Association for the Study of Pain (IASP) defines NP as occurring in the area of the posterior part of the cervical spine, from the superior nuchal line to the first thoracic spinous process (2).

In addition to this, 'neck or shoulder' pain is often used synonymously with NP (3).

3.2 PERSISTENT OR RECURRENT NECK PAIN

Different definitions of chronic pain exist, as they have changed over the years. However, all pertain to the duration of symptoms. Chronic pain was initially defined as pain persisting after the expected healing time (4). Then, pain for a minimum of 6 months was used. Today, the consensus is that chronic NP is located in the area of the neck, is persistent or recurrent, with a minimum duration of 3 months (5-7).

Chronic NP falls under the category of chronic primary pain (4), defined by IASP (8). The definition given in the ICD-11 states that "Chronic primary pain is pain in one or more anatomic region(s) that persists or recurs for longer than three months and is associated with significant emotional distress or significant functional disability (interference with activities of daily life and participation in social roles) and that cannot be better explained by another chronic pain condition" (4). Chronic pain cannot be assumed to be an extension of acute pain, as the initial cause of nociception has presumably healed. Rather, it is maintained by distinct factors pathogenetically and physically, such as altered pain modulation, central sensitization, neuroimmune signalling, and glial activation. Several psychological and social factors also influence the development of chronic pain, such as catastrophizing, depression, avoidance behaviours, somatization, attention from significant others, and cultural adaptations (9).

There are different interpretations of the term chronic pain. It has been shown that a vast majority of patients who experience NP regularly do not experience pain all the time but can have pain-free episodes and varying pain levels (10). Hence, using "chronic neck pain" as a term in clinical encounters may lead to misunderstandings. It does not describe the true experience of pain and fails to account for the multifactorial complexity of the condition (9). This becomes evident when considering that both migraine and fibromyalgia are classified as chronic pain, though they have different pain mechanisms and courses. Therefore, in this Ph.D. thesis, chronic NP has been termed recurrent or persistent NP. All other chronic pain conditions will be included under the generic term “chronic pain”, as specific definitions for each condition will be too difficult to obtain.

3.3 AUTONOMIC NERVOUS SYSTEM AND PERSISTENT OR RECURRENT NECK PAIN

Reduced heart rate variability (HRV) has been observed in subjects with persistent or recurrent NP, but also with other chronic pain conditions (11, 12). Subjects with persistent or recurrent NP have been investigated when using breathing exercises to improve the autonomic nervous system (ANS) balance. In addition to decreased sympathetic activation, improvement of the NP was also observed (13). This indicates that the ANS-pain-connection is influenced by treatment aimed at the ANS, and that there is a link between pain and central processes.

4 LITERATURE REVIEW (BACKGROUND)

4.1 HISTORY OF EXPLANATORY MODELS IN CHIROPRACTIC

The chiropractic profession was founded by DD Palmer in 1895. The early chiropractic concepts proposed that a misalignment of a vertebrae, also known as a subluxation, would interfere with the function of the sympathetic or parasympathetic nervous system (14, 15) due to pinching or irritation of a nerve (14). This could arguably lead to a range of symptoms and diseases based on the location of the subluxation. Chiropractic treatment was thought to remove these interferences by correcting the subluxations. The Meric system is an overview of the spinal segmental anatomy with areas and body parts linked to each spinal level and the possible symptoms a subluxation at a certain spinal level could lead to (15-17).

Even though this practice is not supported by research (18), some chiropractors still choose to follow the old principles of chiropractic (19). This is, however, not common practice as chiropractic today is mainly concerned with the treatment of biomechanical disorders (20). Chiropractic is, however, not the only manual profession developed with the intention to treat diseases. Professions such as osteopathy and naprapathy have similar histories as chiropractic, with improved visceral function as the initial goal (21, 22).

4.2 EPIDEMIOLOGY OF CHRONIC PAIN

Chronic pain is a frequent condition, affecting an estimated 20% of the population globally (4). The prevalence is expected to increase in low-income and middle-income countries in the coming years (23) due to an increased life expectancy leading to more age-related musculoskeletal pain (24). Also, an increase in obesity is expected in these countries, another known risk factor for musculoskeletal pain. The prevalence of NP was 3551 per 100 000 globally in 2015 (25), illustrating the already large worldwide impact of NP suffering. The prevalence has not changed significantly since 1990 (25).

4.3 CONSEQUENCES OF MUSCULOSKELETAL PAIN

Musculoskeletal pain is now the third largest cause of disability worldwide (26), with NP as a significant contributor. In 2015, NP was globally ranked top 5 in terms of disability as measured by years lived with disability (YLD) (27), with an age standardized rate per 100 000 population of 352 in 2017 (25). Also, NP sufferers develop persistent or recurrent NP in 19-37% of cases (27, 28).

Musculoskeletal pain is associated with major costs. In the USA, the annual average cost of such pain was estimated to be close to $US 1000 billion in 2004-2006, reflecting the direct cost of ambulatory visits, surgery, rehabilitative interventions and drugs, and indirect cost due to absence from work or reduced work productivity (24). In Sweden, musculoskeletal pain is responsible for 24% of the total cost of disease, roughly SEK 165 billion /$US 20 billion annually (2017) (29).

NP sufferers are at a high risk of sick leave (30) and have reduced ability to manage everyday life (31). People with persistent or recurrent NP have reduced health-related quality of life, both mental and physical (32). The consequences seem to increase with the increase in the NP severity (32).

A complete resolution of NP does not seem to be the norm for the individual NP sufferer. It has been shown that most of those who experience NP at a given time report either persistent (37%), recurrent (23%) or worsening (10%) symptoms up to one year later (33). NP is more common among women than men and tends to increase up to middle age before reaching a plateau and possibly even decreasing in prevalence in older age (34, 35).

4.3.1 Neck pain trajectories

Previous studies on low back pain and NP have revealed common trajectory groups, generally described as ongoing, fluctuating, episodic or recovering (36, 37), with severity classified as minor, mild, moderate or severe (38). For NP, the majority of patients are found in the episodic and persistent fluctuating groups (37). It has been found that patients with the persistent fluctuating pattern are most bothered by their pain (37).

4.4 RISK FACTORS OF PERSISTENT OR RECURRENT NECK PAIN

There is a range of well-known factors that seem to contribute to the development of persistent or recurrent NP.

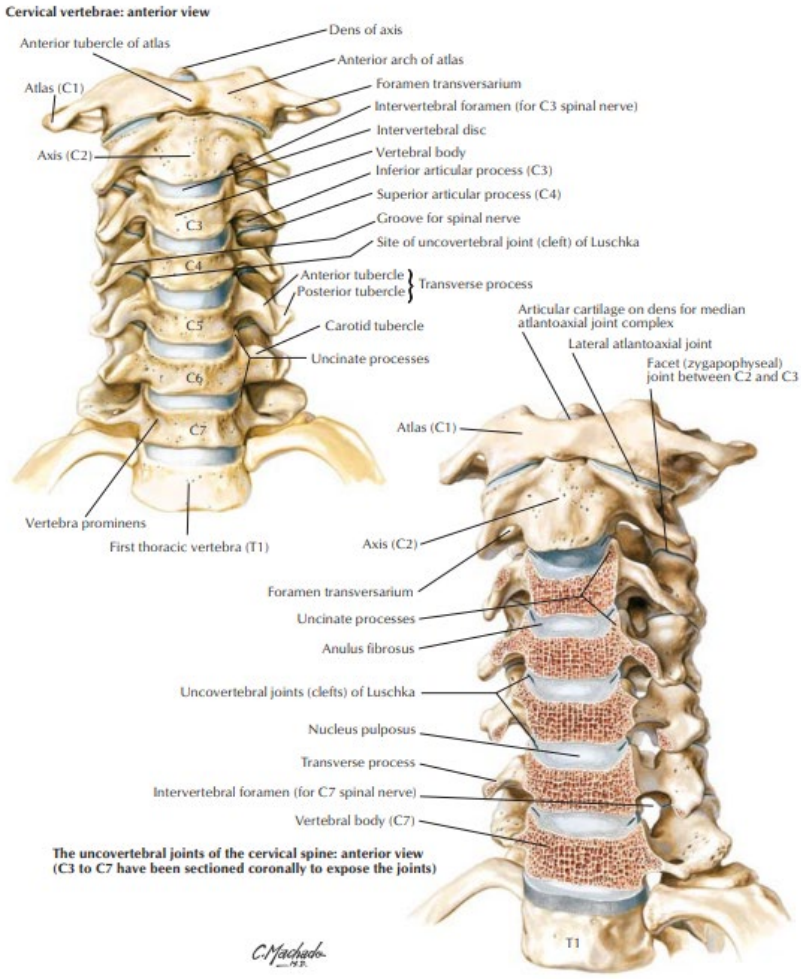
4.4.1 Physical

NP is commonly labelled mechanical or nonspecific when no direct underlying cause is found, such as myelopathy or malignancy (39). The pain is commonly thought to arise from pain-producing structures such as myofascia, cervical facet joints, or the disc. However, one can assume that all structures in the neck that have nerve innervation are capable of producing a nociceptive input (39).

Initial tissue damage can be the first cause of persistent or recurrent NP, commonly seen with whiplash injury *or cervical spondylosis* (40). The significance of such injury in contribution to the development of chronicity is, however, not known. (40).

Some of the above-mentioned sources of pain have been studied. Degenerative changes or trauma may cause the zygapophyseal joints to produce persistent or recurrent NP in subsets of patients (39, 41). The role of the intervertebral disc has recently been investigated. It is thought to be a pain generator in 16-41% of people with persistent or recurrent NP (37). However, the diagnosis is controversial, mainly due to the large number of pain-free subjects with cervical disc degeneration (39, 42).

Figure 1. Anatomy of the cervical spine



Muscle pain such as trigger points and myofascial pain syndrome has been found to be present in people with repetitive work-related tasks with long static loads and persistent or recurrent NP (43, 44). Increased tension in the neck musculature has also been found together with stress and anxiety (45).

4.4.2 Psychosocial

Emotional trauma such as posttraumatic stress syndrome (PTSD) is a potent pain modulator, commonly seen with all types of chronic pain, particularly whiplash associated disorders (WAD) (46). Chronic pain patients with PTSD have greater pain severity and more pain complaints than chronic pain patients without PTSD (47). It has, however, also been shown

that PTSD is associated with hyposensitivity to noxious stimulus, which demonstrates the complexity of pain perception (48). The prevalence of PTSD among the general population is 6% - 12%. For people with chronic pain, the prevalence has been reported to be 10-50%.

High pain sensitivity prior to the first pain experience, low expectation of recovery and high sensory sensitivity at the acute stage of pain are all predictors of chronic musculoskeletal pain (49).

There is a range of other psychosocial factors that strongly contribute to the transition of acute to chronic pain. Emotional distress such as maladaptive cognition, depression, and anxiety as well as fear-avoidance, poor self-expectation, and pain catastrophizing are recognized as important factors (50, 51). The link between pain and depression have been rigorously studied, and there seem to be a correlation between the severity of the two (52). Persistent pain more commonly lead to depression than vice versa (53). Strategies on how to deal with this have been investigated, and it has been found that this patient group, when undergoing treatment for depression such as medical treatment or seeing a mental health specialist, also experience reduced pain and improved daily function (54, 55). The combined effect of pain and depression relief has an impact on daily functioning and quality of life, and it is recommended that patients suffering from both conditions should be treated simultaneously for both symptoms (55).

Stressors related to occupational status such as high job demands, job dissatisfaction, financial uncertainty, and loss (of a job or a loved one) are all factors of psychosocial stressors well known to increase the risk of chronic pain (50). In particular, highly monotonous work and low social support are recognized as high risks for the development of chronic musculoskeletal pain (50, 56).

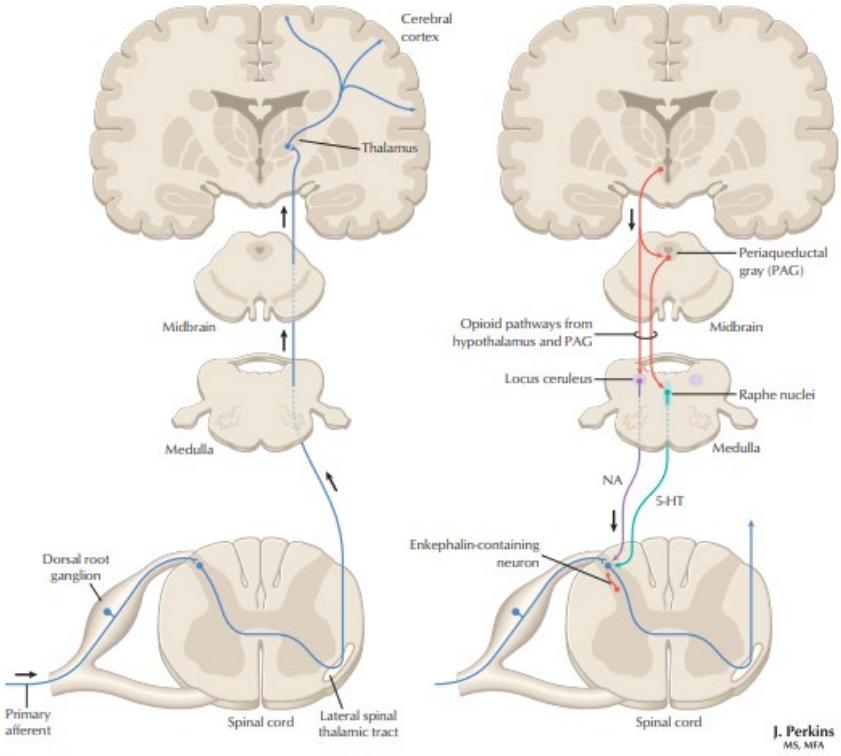
Even though certain psychosocial risk factors have been recognized, research on psychosocial factors in NP is complicated due to three reasons; i) As pain and psychosocial aspects seem to impact each other, knowing what came first can be challenging. ii) Psychosocial factors are an umbrella term including a range of variables potentially increasing the risk of persistent or recurrent NP. Thus, a range of theoretical notions exists regarding how these factors influence persistent or recurrent NP development. iii) The development of pain from acute to persistent or recurrent will lead to different effects from psychosocial factors at different time points. This, together with reason i), creates innumerable combinations of a given risk (57).

4.4.3 Neurophysiological

Central sensitization (CS) is a term commonly used in the development of chronic musculoskeletal pain. It is defined as a change in the responsiveness of central neurons to afferent input (58). The central sensitization stems from increased responsiveness of dorsal horn neurons, leading to secondary hyperalgesia away from the initial pain site. The brain is usually able to control this pain by descending inhibitory mechanisms (58). In chronic pain, the descending inhibition is often impaired. Also, the pain faciliatory pathways become overactivated, leading to an increase instead of inhibition of nociceptive transmission (59). This response seems to be individually adapted and influenced by different areas of the brain.

Katz and Melzack (1990) (60) described a widely distributed neural network in the cortical and subcortical brain regions, termed the neuromatrix. This is now widely recognized and describes a network of interacting factors contributing to a personalized pain experience. The neuromatrix determines the persistent or recurrent pain experience, shaped by previous experiences and emotional status (60).

Figure 2. Pain pathway and pain inhibition.



Altered central pain modulation is an interesting phenomenon in chronic musculoskeletal pain. It is recognized as not being synonymous with nociceptive or neuropathic pain mechanisms but rather explained as hyper-excitability due to dysregulation of the central nervous system, leading to a generalized hypersensitivity to stimuli. (49). This is seen clinically as a "disproportionate, nonmechanical, unpredictable pattern of pain provocation in response to multiple/nonspecific aggravating/easing factors" (61). IASP has suggested a new term to cover this pain experience, termed nociplastic pain, described as a third category of pain that is mechanistically distinct from nociceptive pain, which is caused by ongoing inflammation and damage of tissues, and neuropathic pain, which is caused by nerve damage (62) .

For persistent or recurrent NP where the cause of the pain is a traumatic event such as WAD, CS is of clinical importance (63). For idiopathic persistent or recurrent NP, this relationship seems to be present for a subgroup of the pain population (64). There are, however, very few studies available on the role of CS in idiopathic pain, and further investigations are needed.

Even though the evidence for CS in non-specific chronic NP is sparse, altered endogenous pain modulation is a known factor in idiopathic pain syndromes (65, 66). Endogenous pain modulation is a term used for all the actions the central nervous system can use to reduce pain (65).

4.4.4 Conditioned Pain Modulation

Conditioned pain modulation (CPM), is a test paradigm which can be used to assess diffuse noxious inhibitory control (DNIC) mechanisms, lower brainstem-mediated inhibitory mechanisms capable of influencing the processing of the incoming pain signals from the entire body (endogenous pain modulation) (67), likely influenced by higher cortical structures (68-70). A normal CPM response would lead to a reduction in perceived pain after a painful stimulus by inhibition of the transmission of noxious information, known as “pain inhibits pain”. CPM is one of many quantitative sensory testing protocols, which involves a controlled painful stimulus and a measure of the pain experience.

The dysregulation of nociceptive signalling may contribute to a reduced conditioned pain modulation (67). A meta-analysis concluded that in a population of patients with chronic pain, diffuse noxious inhibition might not occur, leading to a reduced or absent "pain inhibits pain" reaction (71). A recent prospective study showed a reduced CPM response in subjects developing persistent NP, indicating that dysfunction of the endogenous pain inhibitory pathway is a risk factor for persistent or recurrent NP (72). There is not consensus on the role of CPM among NP patients as Heredia-Rizo et al. (73) found that an increased CPM response in NP patients improved with exercise and Coppieters et al. (74) found a reduced CPM response only among subjects with whiplash-associated NP.

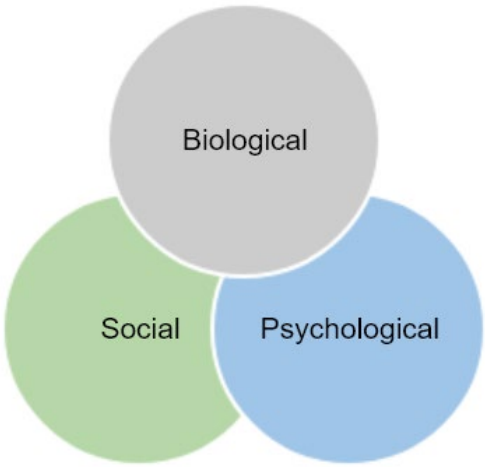
4.5 THE BIOPSYCHOSOCIAL MODEL

The biopsychosocial model describes the dynamic interaction of the biological, psychological, and social contributors to pain, unique to each individual (75). It also acknowledges the time component of this model, as the dynamics can change over time (75). Due to the observed risk factors and complexity of NP, the biopsychosocial model should be used as a foundation of pain management of patients with persistent or recurrent NP. Treatment based on the biopsychosocial model addresses the biological basis of symptoms and incorporates social and psychological factors known to affect pain (76). To achieve this, alteration of physical factors can help the patients gain a sense of control over the pain's effect on daily life (75).

A recent study by Weigl et al. (77) investigated prognostic factors for improvement in pain and disability among subjects with persistent or recurrent NP undergoing treatment based on

the current guidelines. They recommend active cervical range of motion (ROM) and mental health status to be implemented in prognostic models. This demonstrates the importance of a biopsychosocial approach for this patient group.

Figure 3. Biopsychosocial model



4.6 AUTONOMIC NERVOUS SYSTEM

The ANS is responsible for the homeostasis of the body's organs, cells, and tissues when the body is experiencing internal or external perturbations. The ANS was first described by John Newport Langley in 1916, with the word "autonomy", meaning local independence of the central nervous system (78). It comprises three main divisions, the sympathetic, the parasympathetic, and the enteric nervous system (79). The enteric division is mainly responsible for digestion and is affected by both the sympathetic and the parasympathetic systems (79). This part of the ANS will not be further discussed as it is not relevant to this project.

The ANS is also referred to as the involuntary nervous system, as the conscious mind does not control its actions, as seen from the overview from Wehrwein et al. (79)

Feature	Autonomic Nervous System
Effector organs	Smooth muscle, cardiac muscle, cardiac conducting fibres, glands
The action of neurotransmitter on effector organ	Contraction or relaxation of smooth muscle; increased or decreased rate and force of contraction of cardiac muscle; increased or decreased secretions from glands
Functions	Controls all visceral organs; regulates airway resistance, blood flow, blood pressure, body temperature, digestion, energy balance, waste excretion, fluid volume, glandular secretions, heart rate, immune system, inflammatory processes, salt and water balance, sexual function, urination
Control system	Primarily unconscious, involuntary control; related to hormonal control

Regulations of the ANS are necessary for tasks such as the cardiorespiratory responses to strenuous activity, dangerous situations, illness, or simply getting out of bed in the morning (79). In such cases, the ANS changes cardiac output, regional blood flow, and respiratory factors to prepare and allow for the activity in question (79). A dangerous situation, for instance, would cause the ANS to increase the cardiorespiratory activity to allow for potential high physical demand. The ANS is sensitive to feedback from organs and can change its output using a reflex circuit to quickly adapt to the body's physiological state (80).

The parasympathetic and sympathetic nervous systems work together to control these changes. Different mechanisms exist, as they can work antagonistically or synergistically but also independently. A typical example of the interplay of the two branches is the heart, as it is innervated by both sympathetic and parasympathetic branches that function as physiological antagonists, upregulated by sympathetic and downregulated by parasympathetic branches respectively (79).

The sympathetic nervous system is also known as the "fight or flight" part of the ANS. However, this is an oversimplification, as the sympathetic nervous system also actively maintains homeostasis at rest, such as relaxation of the urinary bladder as it distends with urine (79).

The parasympathetic nervous system promotes digestion, conserves energy, and gets rid of the body's waste products. Due to this, the parasympathetic nervous system is often referred to as the "rest and digest" part of the ANS. This is also not wholly accurate, as parts of the parasympathetic nervous system control functions that do not fit under the "rest and digest" term, such as penile erection (79).

In people with chronic neck and shoulder pain, increased sympathetic activation and reduced parasympathetic modulation of the heart have been shown (81, 82). Increased sympathetic activity is associated with increased muscle tension and possibly altered pain sensitivity/perception (83), and restriction of the muscles' local circulation (84). Investigation into the effect of different pain levels on HRV has not shown a clear relationship (85-88). Other factors related to the pain experience, such as disability and psychological distress have been shown to be associated with reduced HRV levels (85, 89).

There are several ways to measure fluctuations in the ANS, such as skin conductance, blood pressure, skin temperature, and pupil diameter (90). One of the most commonly used measurements for detecting changes in the ANS is using Heart Rate Variability (HRV), an acceptable biomarker of autonomic regulation (91). In a study on people with persistent or recurrent NP, breathing exercises were used to improve the ANS balance by stimulating parasympathetic activity. Decreased sympathetic activation was observed, as well as improvement of the NP (13). This indicates that there is a strong link between pain and central processes and that the ANS-pain-connection changes with treatment aimed at the ANS. It is possible that this change will also occur with treatment aimed at the pain itself.

4.7 MEASUREMENTS USED IN THIS THESIS

4.7.1 Pain

When measuring pain, it is essential to consider different aspects of pain, such as how much it hurts (intensity), what it feels like (sensory quality), how it makes us feel (affective quality), and what it prevents us from doing (function). The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends 6 outcome domains to be considered when designing clinical trials involving subjects with chronic pain. These are: i) pain experience, ii) physical functioning, iii) emotional functioning, iv) participant ratings of improvement and satisfaction with treatment, v) adverse symptoms and events, and vi) participant disposition (information regarding the recruitment of participants and their progression through the trial) (92).

The International Classification of Functioning, Disability and Health (ICF) is a framework that provides a conceptual basis for the definition and measurement of health and disability in accordance with the biopsychosocial model. In relation to research, the aims are to:

i) “provide a scientific basis for understanding and studying health and health-related states, outcomes, determinants, and changes in health status and functioning “

ii) “permit comparison of data across countries, health care disciplines, services and time” (93)

There are no known core sets for ICF of NP (94). Studies have investigated which components within the ICF represent commonly reported functions and activities among subjects with persistent or recurrent NP and have been found to be covered mainly by the Neck Disability Index (NDI). However, components such as maintaining a body position, mobility of joint functions, doing housework, and using communication devices and techniques should complement the NDI questionnaire. Also, interpersonal interactions and relationship are not included in the NDI (94). In this project, different outcome tools were used to cover the ICF components related to persistent or recurrent NP.

Subjectively reported pain intensity using the NRS-11, or the Visual Analogue pain scale are the most common ways to quantify pain in research. These variables are often measured by quantifying change in pain intensity between two or more time points (95, 96). Furthermore, the secondary psychological effects of pain, such as distress, catastrophic thoughts, and behaviours such as fear avoidance may be assessed using specific questionnaires (97). The neuromatrix adapts to interactions from factors like emotions, somatosensory input (nociception), and previous pain experiences, and the effect of these on pain and daily life (98). This can contribute to different ways pain is experienced and characterized, such as stabbing, burning, and aching (sensory domains) and threatening, punishing (affective domains). These parameters are important when it comes to explaining the patients' pain experience (99). The affective quality of pain can be measured using the validated short-form McGill Pain Questionnaire-2 (100, 101) which has been found to serve as a valuable index of the overall affective status of pain patients (102). A recent systematic review, however, found all existing patient reported outcome measures of affective quality of pain (including McGill questionnaire) to have inadequate psychometric measurement properties and to lack content

validity, and concluded that there is a need for the development of new assessment tools (103).

4.7.2 Disability

Disability is an important measure in persistent or recurrent pain as it reflects how the pain affects daily life. It is related to pain intensity (104, 105) and can be predicted by anxiety and catastrophizing (106) as this commonly interferes with daily activity (107). It has been stated that for a symptomatic episode of low back pain, the functional status is similar to those who suffer from metastatic cancer or congestive heart failure (108). Using the NDI (109), the perceived level of disability during persistent or recurrent NP can be quantified. This is the most widely used scale for self-rating disability in patients with NP (110).

4.7.3 Health-related quality of life

When assessing pain management outcomes, health-related quality of life (HRQoL) is recommended as an outcome measure (41, 42). It reflects the individual's overall sense of the effect of an intervention. It is used as a proxy to assess secondary effects of pain, such as emotions, previous pain experiences, and the effect on daily life (99, 111, 112).

4.7.4 Heart Rate variability

HRV is the physiological phenomenon of variation in inter-beat intervals (IBIs), providing indirect insight into the balance between parasympathetic and sympathetic activity. More specifically, it is a marker of the sympathetic and parasympathetic (vagal) components on the heart's sinus node that can be measured using non-invasive equipment (91, 113). A well-functioning ANS and a healthy heart will manifest as a constantly changing HRV, dependent on complex adaptations of internal and external stimulus (114).

The IBIs provide a range of indices suitable for analysis of HRV. These are divided into i) time, ii) frequency, and iii) non-linear domains.

Time domains quantify the amount of HRV observed in a given time period. Values may be expressed as the natural logarithm (Ln) of original units to achieve normal distribution.

Frequency domain measurements calculate the relative or absolute amount of signal energy within component bands. There are four possible frequency bands:

Ultra-Low Frequency (ULF): $\leq$0.003 Hz

Very Low Frequency (VLF): 0.003 - 0.04 Hz

Low Frequency (LF): 0.04 - 0.15 Hz

High Frequency (HF): 0.15 - 0.4 Hz

The measurements obtained are the signal energy within each energy band, defined as power. Total power is the sum of the energy in the VLF, LF, and HF bands for short-term recordings.

Non-linear measurements quantify the unpredictability and complexity of a series of IBIs and are not used in this project.

Table 1. provides a description of the HRV indices used in this study.

Table 1. HRV indices

HRV indices	**Indicator of**	**Domain measure**	**Change that improves HRV**
R-R interval	Global HRV activity	Time	Increase
Root mean squared successive differences between IBIs (RMSSD)	Parasympathetic (vagal) activity	Time	Increase
The standard deviation of IBIs (SDNN)	Global HRV	Time	Increase
Low frequency power (LF, 0.04–0.15 Hz)	Baroreceptor-sympathetic and parasympathetic cardiac activity	Frequency	Increase
High frequency power (HF, 0.15–0.4 Hz)	Parasympathetic (vagal) activity	Frequency	Increase
LF/HF ratio	Sympathetic-to-parasympathetic balance	Frequency	Decrease
Total power	Global HRV activity	Frequency	Increase

4.7.5 Conditioned Pain Modulation

Conditioned Pain Modulation (CPM) can be assessed in different ways. It is a quantified pain response to a controlled test stimulus, followed by an intensely painful conditioning stimulus, followed by a re-test of the initial test stimulus (115). The change in the experienced pain response to the test stimulus before/after the conditioning stimulus reflects the conditioned pain modulation.

The validated test setup utilized in this project was a standardized mechanical clamp from Clas Ohlson as the test stimulus, pressing on the thumb nail for 10 seconds with the force of 7.3 kg at a 2.6 cm opening. The subject then reported the perceived pain intensity (NRS-11). For the conditioning stimulus, the opposite hand was subsequently submerged in cold, circulating water (0–2 °C) for up to 2 minutes, for as long as the subject was able to withstand the pain. The perceived pain intensity of the cold water was reported using a visual analogue scale (VAS). Directly after this, the second test stimulus was applied to the same thumb nail again (115). The change in reported pain intensity pre and post conditioning stimulus was

recorded as the CPM score, indicating the level of endogenous pain modulation the subject is experiencing.

This CPM measurement protocol have previously been used at Rygcenter Syddanmark, University of Southern Denmark. No serious complications have been reported (116).

4.8 TREATMENT GUIDELINES

Recent systematic reviews of the current guidelines for the treatment of NP recommended a multimodal approach with exercise, manual therapy, reassurance, and education for the treatment of general NP (117, 118). There is, however, not an absolute consensus on the use of manual therapy in the treatment of NP (119). Half of all guidelines recommended the use of medication alone or in combination with other treatments (118), and adequate medication might be appropriate in combination with the multimodal approach for chronic musculoskeletal pain and fibromyalgia (120). Blanpied et al. (121) summarized the guidelines for specific NP conditions, including persistent or recurrent NP, as presented in Table 2.

Table 2. Specific neck pain conditions and recommended interventions.

For patients with persistent or recurrent NP with mobility deficits	Thoracic manipulation and cervical manipulation or mobilization. Mixed exercise for cervical/scapulothoracic regions: neuromuscular exercise (e.g., coordination, proprioception, and postural training), stretching, strengthening, endurance training, aerobic conditioning, and cognitive affective elements. Dry needling, laser, or intermittent mechanical/manual traction. Patient education and counselling strategies that promote an active lifestyle and address cognitive and affective factors.
For patients with persistent or recurrent NP with movement coordination impairments (including WAD)	Patient education and advice with a focus on assurance, encouragement, prognosis, and pain management. Mobilization combined with an individualized, progressive submaximal exercise programme including cervicothoracic strengthening, endurance, flexibility, and coordination, using principles of cognitive behavioural therapy. Transcutaneous electrical nerve stimulation (TENS).
For patients with persistent or recurrent NP with headache	Cervical or cervicothoracic manipulation or mobilizations combined with shoulder girdle and neck stretching, strengthening, and endurance exercise.
For patients with persistent or recurrent NP with radiating pain	Mechanical intermittent cervical traction, combined with interventions such as stretching and strengthening exercise plus cervical and thoracic mobilization/ manipulation. Clinicians should provide education and counselling to encourage participation in occupational and exercise activities.

Patients will usually experience a combination of manual treatments, advice, and exercise in a clinical setting (122), based on the evidence-based medicine model. This model consists of three main components: i) Best available research, ii) The clinicians' expertise, experience and resources, and iii) The patient's values and preferences (123).

The most common treatment alternatives from current guidelines and their mechanisms are listed below.

4.8.1 Home exercises

Activity and exercise can reduce pain for patients with chronic pain (124, 125). The association between general activity and NP is not clear (126), while therapeutic and strengthening exercises are effective in the management of persistent or recurrent NP (127, 128). Home exercises are an essential part of NP management (129). The exercises are usually adapted to the patient's diagnosis and capability. Home exercises can also improve the patient's mood, commonly affected in persistent or recurrent pain conditions (130). Stretching has been shown to have a pain reducing effect together with strengthening exercises and is, alone or in combination with other treatments, known to reduce pain and analgesic intake (117, 131, 132). The evidence on the effect of stretching exercises alone is conflicting (127, 132). Neck stretching exercises have been found to have similar effect-sizes as manual therapy in women with nonspecific NP (131). Different exercise strategies aim to affect the functional status of the muscular and skeletal systems. The three main elements are extensibility for muscles and fascia, mobility for neuro-meningeal tissues, and strengthening/endurance of muscles (127). It has been shown that stretching can induce immediate changes in the tension-length relationship in muscle tissue, giving greater muscle flexibility (133). This can be due to changes in the viscoelastic properties of muscle tissue (133), but the changes in the tension-length relationship are more clearly affected by stretch tolerance (134-138). The pain-reducing effects are thought to be explained by reduced neuronal discharge by inhibition of Golgi tendon organs, assumed to lead to pain reduction as tension in the muscle reduces and pain tolerance increases (139). Stretching is also considered to have pain-relieving mechanisms through i) the gate control theory, where activation of afferent nerve fibres reduces the capability of the nociceptive signals or leads to descending inhibition, or ii) conditioned pain modulation (pain inhibits pain) by activating the descending analgesic system and releasing endogenous opioids, leading to global pain inhibition (140).

Stretching is thought to have a short-term effect on ANS, based on a few available studies (141-145).

4.8.2 Spinal Manipulative Therapy

It is also evident that some passive treatments effectively reduce pain and have a place in the management of patients with chronic pain (146). Among these, spinal manipulative therapy (SMT) is a commonly used treatment modality. This includes mobilization, various techniques where the joint is not taken beyond its passive limits, and High-Velocity, Low-Amplitude (HVLA) thrust to the spinal joints. HVLA is described as a treatment where the joint is taken beyond its passive limit, which usually elicits a cracking sound caused by tribonucleation in the manipulated joints' synovial fluid (147-150). Tribonucleation is, however, not necessary for the beneficial effects of HVLA manipulation (151-154), and clinicians always adapt the application of SMT to the patient's tolerance and preference (155-157). The proposed mechanical difference between HVLA and mobilization is the joint capsule's fast stretch, leading to a protective muscular contraction (158). However, it has been

found that the magnitude of the applied force does not affect the reflex activation of the musculature (147, 158). It has been suggested that a protective muscular contraction is followed by relaxation of hypertonic muscle (158), but the relaxation has been suggested as being due to reductions in paraspinal spontaneous electromyographic signals and hypoalgesia from alterations in central sanitization of the dorsal horn in the area of HVLA manipulation (158, 159), rather than direct "motor" effects. Substance P, produced in the dorsal root ganglion, has been found to increase in plasma levels only when the applied forces are sufficient to cause cavitation (160). The clinical relevance of this finding is unknown.

Mobilization and HVLA have similar effect sizes when treating persistent or recurrent NP in studies using a pragmatic design (161). They are both favourable compared to other interventions (162), particularly in combination with multimodal approaches (162, 163). SMT in combination with exercise has also been shown to be more beneficial in the short term for persistent or recurrent NP, compared to exercise alone (164).

SMT in this thesis is therefore used as a term describing both mobilization and HVLA.

The desired effects of SMT are improved range of motion, decreased pain, and decreased muscle spasm (165). Mechanisms behind the pain reducing effect of SMT have been proposed, but it has been difficult to confirm a definitive explanatory model (165). Based on a comprehensive model of manual therapy by Bialosky et al. (165), the following summary describes the known mechanisms of the analgesic effect of SMT, including effects on movement, inflammation, the spinal cord, and neurophysiology (locally or centrally):

Increased motion in the treated spinal area has been seen in response to *Mechanical Stimulus* (166-168). The clinical implications are, however, questionable due to the lack of lasting changes and improvement in pain distant from the treatment site (165).

A reduction in blood and serum inflammatory cytokines after SMT indicates a decrease in *inflammatory responses* (169).

The firing of muscle proprioceptors is seen with SMT (170). Afferent discharge (171-173), change in muscle activity (174, 175), motoneuron pool activity (176, 177), and hypoalgesia (172, 173, 178) all indicate a *central mechanism* mediated through the spinal cord.

Placebo, distraction, and expectations are important factors in any treatment affecting the *supraspinal structures,* possibly affecting sympathetic activity (179). This can also be seen with SMT (179). The direct association of SMT and supraspinal structures are not identified (179).

A reduction in temporal summation in the dorsal horn could be part of the analgesic effect seen after SMT (178). Involvement of the periaqueductal grey is suggested due to the relationship between hypoalgesia and sympathetic activity (180). This is, however, proposed as an implication since direct *neurophysiological responses* are not possible to observe (165). A systematic review from 2008 (181) proposed an alternative neurophysiological model, in which passive joint mobilization stimulates areas within the central nervous system. This is based on responses in the ANS from passive joint mobilizations (181).

It is known that therapeutic alliance, patient and provider expectation, and context of the intervention strongly influence the clinical outcomes of MT (182). Also, patients experiencing reduced NP are likely to experience improvement in other outcome measures, and the improvement is affected by individual characteristics (183).

4.8.2.1 The effect on the ANS

An effect on the ANS has been proposed as part of the pain reducing neurophysiological mechanism of SMT. Recent investigations into the immediate effect of SMT on the ANS have been conducted, and several systematic reviews have been published (184-194) and summarized in a recently published overview (90). An additional systematic review was published in 2020 (195), likely after the overview was submitted for publication.

A number of different ANS outcome measures were included in the studies: skin conductance, blood pressure, skin temperature, respiratory rate, heart rate, salivary alpha amylase activity, plasma catecholamine, skin blood flow, pupillometry, heart rate variability, and oxy-haemoglobin concentration

Summarizing the conclusions from these reviews: Based on these studies, manual therapy, including SMT, is suggested to produce an immediate ANS response, but due to the low quality of the evidence, a definitive conclusion of such effects is uncertain. More specifically, a parasympathetic excitation seems to occur in cardiovascular autonomic activity (HRV), and sympathetic excitation when assessing skin autonomic activity. Skin autonomic activity was mainly affected by mobilisation, and HRV affected by manipulations. High quality reviews could not find a specific effect based on treatment location. The clinical relevance of the acute changes in ANS is unclear. A gold standard for ANS measurements is yet to be decided upon, but Roura et al. suggest a combination of measures for further research (90)

4.8.3 Stress management

Stress management has also been shown to be of value for reducing persistent or recurrent NP (196). Several methods are available, some are widely used such as mindfulness and meditation techniques (197, 198). Heart Rate Variability Biofeedback (HRV BF) (13) has been shown to have a positive effect on persistent or recurrent NP and HRV (13). HRV BF is a breathing exercise where HRV is used to give continuous feedback during slow breathing exercises to maximize the Respiratory Sinus Arrhythmia. This normal heart response occurs with breathing (199). Typically, the heart rate increases with inhalation and decreases with exhalation. This type of exercise has also been shown to positively affect a range of conditions, such as depression, anxiety, asthma, and muscle pain (200).

4.8.4 Pharmacological treatment

The guidelines on pharmacological treatment of persistent or recurrent pain vary in their quality and conclusions, underlining the complexity of the area. Only one guideline specifically mentions persistent or recurrent NP (201), recommending non-steroidal anti-

inflammatory drugs. There is a lack of studies investigating pharmacological treatment for persistent or recurrent NP, leading to the administration of drugs being based on the results of studies performed for other chronic pain conditions such as chronic low back pain and expert opinions (202).

When taking medication for chronic pain considered to be due to central sensitization, the overall aim is to reduce the increased pain sensitivity (120). Tricyclic antidepressants and anti-seizure medications Pregabalin and Gabapentin seem to be effective in achieving this. The only effective analgesic for this pain process recommended by Goldenberg (120) is the synthetic opioid Tramadol. The use of opioids to treat chronic pain is controversial due to the risk of abuse and addiction, and the concerns about efficacy and safety (203). Lately, focus on the misuse of opioids has led to critical reports on chronic pain treatment and the failure to implement medication guidelines in primary care (204). Therefore, other analgesics are recommended for chronic pain in general (205). When there are signs of other underlying types of pain mechanisms involved, such as inflammation or neuropathic pain, specific medications may be indicated (204).

4.8.5 Contextual effects

Non-specific, contextual factors play an important role in enhancing or reducing treatment effect (206). Contextual factors are specific to the context where the therapist and the patient meet and are difficult to measure. Testa and Rossettini (206) have summarized the therapist and patient features for the influence on treatment effect to be:

- Treatment: clear diagnosis, overt therapy (mirror feedback), observational learning, patient-centred approach, global process of care (same therapist, on time, not too expensive appropriate duration etc.), and therapeutic touch.
- Therapist: professional reputation, appearance, beliefs, and behaviour.
- Patient: expectation, preferences, previous experience, musculoskeletal conditions, gender, and age.
- Patient-therapist relationship: verbal communication and non-verbal communication.
- Healthcare setting: environment, architecture, and interior design.

The factors mentioned will vary greatly from patient to patient and from therapist to therapist. Thus, these factors are probably capable of determining the outcome of a treatment in a few seconds. One could imagine that if a therapist were to dress unprofessionally and behave in a rude manner, the outcome of an intervention would be worse than if the opposite were the case. In a well conducted RCT, it is assumed that the contextual effects are equally distributed between the groups.

4.8.6 Summary

Considering the worldwide suffering and costs of musculoskeletal pain, investigating and developing effective approaches for this patient group is essential. As multimodal treatment strategies are recommended for persistent or recurrent NP patients, investigating commonly used treatment modalities and a combination of these can play an essential role in the management of this global epidemic. Contextual effects of manual therapy play an important role in modulating the treatment effect, but the exact amplitude is difficult to measure.

The specific combination of home stretching exercises and manual spinal therapy has not previously been investigated in detail, and the effects of manual therapy on HRV have not been rigorously investigated beyond the immediate effect of the intervention.

5 RESEARCH AIMS

The overall aim of the project was to examine changes in pain, disability, and HRV after receiving home stretching exercises, alone or in combination with SMT, in patients with recurrent or persistent NP in a clinical setting.

This project included two interventions: 1) SMT, including manipulation and mobilization techniques aimed at spinal joints, and 2) home stretching exercises of the neck musculature.

We hypothesized that the combination of SMT and stretching exercises, both evidence-based interventions, would give a greater reduction in pain and disability and improvement in HRV than stretching alone in a clinical setting.

In addition, we investigated the temporal stability of a conditioned pain modulation test, and whether this stability was affected by changes in pain over a two-week period.

5.1 AIM

More specifically, we aimed to investigate the:

- Effects of a two-week treatment series consisting of i) home stretching exercises and SMT versus ii) home stretching exercises alone, on pain and disability in a population of patients with recurrent or persistent NP.
- Effects of a two-week treatment series consisting of i) home stretching exercises and SMT versus ii) home stretching exercises alone, on HRV in a population of patients with recurrent or persistent NP.
- Relationship between changes in pain and changes in HRV among patients receiving a treatment series consisting of i) home stretching exercises and SMT or ii) home stretching exercises alone, in a population of patients with persistent or recurrent NP.
- Temporal stability of a conditioned pain modulation test among chiropractic patients with persistent or recurrent NP, and the association between changes in pain and changes in CPM response.

6 MATERIALS AND METHODS

The only way to investigate the effect of SMT on HRV and pain was to conduct a randomized controlled trial. As earlier research on manual therapy and HRV have investigated the short-term effect (90) a study designed to investigate the long-term effect over two weeks was chosen. Four treatment sessions were chosen based on previous research on persistent low back pain, which found that improvement after four treatments predicts improvement at three and twelve months (207), indicating that four treatments in two weeks is sufficient to detect responders with a definite improvement on NRS-11 while also being considered long-term in relation to previous research on HRV (208, 209). The CPM response has been investigated directly after intervention (210, 211) and for patients with persistent NP following 5 weeks of rehab, showing an enhanced CPM response. Hence, when comparing improved vs non-improved individuals, two weeks was also considered a good period for investigating this relationship. The treatment response for low back and NP sufferers has been found to be equal (212) and psychological impact and disability levels are similar or less in NP patients (213). Low back pain patients often have longer pain duration than NP sufferers (213). A course of four treatments was also considered of sufficiently limited duration if no improvement was seen. Also, as the study included subjects seeking care for their pain, a pure placebo group was not indicated (214).

In this thesis, the results in changes in pain and HRV after two weeks are presented. As seen from the protocol, data on pain was obtained two months after the intervention period. The results from the two months follow-up period and the effect of individualized intervention will be presented in an article following the completion of these Ph.D. studies.

6.1 SETTING

The data collection was possible with the help of 5 clinics in the Stockholm area. We decided to include multidisciplinary primary care clinics to reduce bias from patient preference. These clinics were part of the regional health service, where chiropractors, dietitians, occupational therapists, and physiotherapists were employed. A total of 18 chiropractors contributed their time and skills to the study, all licensed by the Swedish National Board of Health and Welfare.

6.2 SUBJECTS (RECRUITMENT, INCLUSION/EXCLUSION)

Subjects were recruited if they had suffered persistent or recurrent NP for more than six months. This was based on the older definition of chronic NP (4-7) and was chosen to reduce the risk of including patients with transient pain. Also, only respondents who had not received chiropractic treatment during the previous three months were included. This condition was chosen based on previous research showing that the effects of chiropractic treatment are limited to three months (215). We wanted to be sure that any changes observed would be related to the intervention provided in the study. A range of exclusion criteria were also defined in order to be able to acquire accurate HRV measurements as HRV is sensitive to certain conditions and medications. As many as possible of these were controlled, by

following the exclusion criteria used in previous research (13). A list describing the exclusion and inclusion criteria of the trial is found in Table 3.

Table 3. Inclusion/Exclusion criteria

Inclusion criteria	Presence of recurrent (at least one previous episode) or persistent (duration more than six months) NP No chiropractic treatment for the previous three months Minimum 18 years of age Able to read and write Swedish
Exclusion criteria	Conditions or medications that could affect the HRV measurements, such as diagnosed with cardiovascular disease diagnosed with hypertension diagnosed with diabetes type I or II pregnancy obesity (BMI > 30) on steroid medication on β-blocker medication on antidepressant medication
	Also, subjects were excluded if they had serious, competing diagnoses, e.g., cancer, infection, or recent severe trauma contra-indications to spinal manipulation, e.g., the recent development of headache or dizziness previous drop-attacks, or acute cervical radiculopathy

Three-hundred-and-ninety-three subjects showed an interest in taking part in the study, but 80 could not be reached for eligibility screening. Thus, 313 subjects were screened for eligibility, and 156 were consequently excluded due to various exclusion criteria. A total of 157 subjects were included, 26 out of these could not participate in the end when the data collection commenced. In total 131 subjects completed the baseline data collection.

A detailed overview of the recruitment process is found below.

Figure 4. Timeline of measurements (Flow chart)

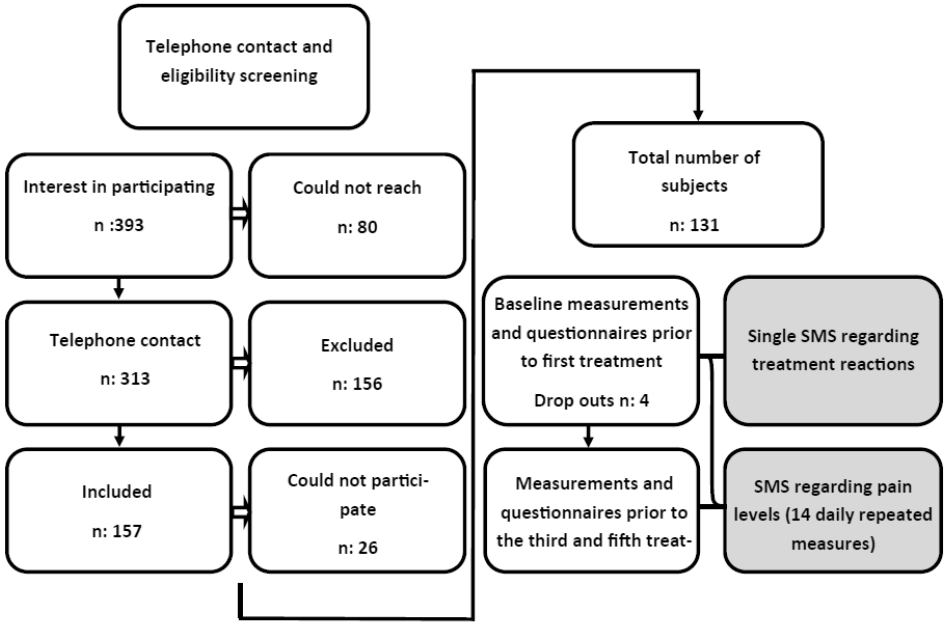


Table 4. Reasons for not being included, but not due to the inclusion/exclusion criteria

Clinic	Time constraint	Could not reach (E-mailed)	E-mailed after all slots were taken
Clinic 1	1	2	Phoned all subjects interested in participating
Clinic 2	4	0	Phoned all subjects interested in participating
Clinic 3 (1)	7	8	11
Clinic 4 (1)	3	3	4
Clinic 5 (1)	6	7	13
Clinic 3 (2)	6	21	8
Clinic 4 (2)	5	0	Phoned all subjects interested in participating
Clinic 5 (2)	6	3	Phoned all subjects interested in participating
Sum	38	44	36

Table 5. Causes of exclusion

Clinic	Excluded	Heart disease	BMI over 30	Medication	"Wrong pain"	Pregnant	Treatment <3 months	Did not want to pay	No Swedish
Clinic 1	12	1	1	2	1	0	2	0	0
Clinic 2	5	0	0	1	0	0	0	0	0
Clinic 3 (1)	49	4	6	13	2	1	3	0	0
Clinic 4 (1)	22	1	3	3	0	0	0	4	0
Clinic 5 (1)	14	0	2	1	1	0	2	2	0
Clinic 3 (2)	19	2	3	4	1	0	1	1	0
Clinic 4 (2)	14	1	1	2	0	0	1	0	0
Clinic 5 (2)	22	0	0	3	4	0	2	1	1
Sum	118	9	16	29	9	1	11	8	1
Percentage		8%	14%	25%	8%	1%	9%	7%	1%

Clinic	Diabetes	Unknown	Inflammatory disease	High blood pressure	Do not use E-mail	Poor health	Not interested
Clinic 1	0	0	1	0	0	3	0
Clinic 2	0	0	0	0	0	0	0
Clinic 3 (1)	2	1	4	5	1	0	0
Clinic 4 (1)	1	1	0	0	0	1	1
Clinic 5 (1)	0	0	0	0	0	0	0
Clinic 3 (2)	0	1	0	0	0	0	0
Clinic 4 (2)	1	0	1	0	1	1	0
Clinic 5 (2)	1	1	0	0	0	0	0
Sum	5	4	6	5	2	5	1
Percentage	4%	3%	5%	4%	2%	4%	1%

Table 6. Target for recruitment and reasons for participants not able to attend after inclusion

Clinic	Target for n subjects	Included	Could not participate	Time issue	Health-related issues	Personal reasons
Clinic 1	20	7	1	0	0	0
Clinic 2	20	3	0	0	0	0
Clinic 3 (1)	20	21	1	0	0	1
Clinic 4 (1)	20	21	1	0	0	0
Clinic 5 (1)	20	22	5	1	1	1
Clinic 3 (2)	20	29	8	3	1	2
Clinic 4 (2)	20	21	6	0	2	3
Clinic 5 (2)	30	33	4	0	2	0
Sum		157	26	4	6	7

Clinic	Did not show/cancelled without a reason	Worried about Covid-19	Started treatment elsewhere	Total subjects recruited
Clinic 1	1	0	0	6
Clinic 2	0	0	0	3
Clinic 3 (1)	0	0	0	20
Clinic 4 (1)	1	0	0	20
Clinic 5 (1)	2	0	0	16
Clinic 3 (2)	1	0	1	19
Clinic 4 (2)	1	0	0	14
Clinic 5 (2)	0	1	1	27
Sum	6	1	2	131

We only had four dropouts during the study period.

Table 7. Reasons for dropouts

Clinic	Drop out	Time issue	Did not show/cancelled without a reason	Not happy with stretching only
Clinic 1		0	0	0
Clinic 2		0	0	0
Clinic 3 (1)		0	0	0
Clinic 4 (1)		0	0	0
Clinic 5 (1)		0	0	0
Clinic 3 (2)	2	0	0	2
Clinic 4 (2)	1	0	1	0
Clinic 5 (2)	1	1	0	0

6.3 RANDOMIZATION

A research assistant created a randomization sequence using a 1:1 allocation ratio in randomly permuted blocks of different sizes according to a randomization schedule. Envelopes with group allocation were created off-site by the same research assistant. The envelopes were opened by the treating chiropractor after the baseline measurements were done.

6.4 BLINDING

Subjects were unaware of what treatment the other group was receiving. The Ph.D. student and research assistant who undertook the measurements were blinded to the treatment allocation, but this was impossible for the treating chiropractor. The leading statistician was blinded to group allocation.

6.5 INTERVENTION

The interventions were carefully chosen. They had to be controlled while also allowing the treating clinician to adapt the appropriate technique for each patient within the limitations of the interventions. Therefore, SMT was defined as "mobilization or manipulation of the spinal joints", or "manual treatment aimed at spinal joints without the use of stretching or manual treatment to muscle and fascia". This is in line with previous studies examining the immediate effect of these interventions on HRV and the effect on pain and disability (185, 187, 189, 192, 216). The pragmatic design was also thought to improve the recruitment process. Some subjects might have been reluctant to participate if they had to receive one specific treatment to the neck, such as HVLA manipulation. This is commonly seen in practice, where patients with NP find the neck to be a sensitive area and may be apprehensive about HVLA manipulation in that area. Also, for the treatment of NP using SMT, the treatment does not need to be applied to the neck itself. It has been reported that SMT to the thoracic joints is equally effective in reducing NP as treatment to the neck itself (209, 217, 218). Also, there is no clear consensus on the difference in effect between mobilization and HVLA for HRV, or for the area of treatment (90, 185, 187, 192, 216, 219).

It was considered important that the control group receive equal amounts of attention from the clinician as the intervention group. Not treating this group was thus not an option and home rehab exercises without follow-up in the clinic would affect contextual factors. Treatment as usual is commonly used as a control group. The SMT and stretching procedures used in this study are often part of normal treatments offered by chiropractors, considered a part of usual care and are recommended in recent guidelines (118). The use of sham treatment was discussed, as this form of procedure which mimics SMT has recently been developed (220, 221). The existing sham treatments have, however, not been investigated with regards to changes in HRV. Also, training clinicians to use the sham technique would be necessary. Thus, home stretching exercises with an equal number of follow-up appointments at the clinic as the intervention group were chosen and considered the most appropriate control intervention.

Home stretching exercises were also included in the intervention group to investigate the added effect of SMT on pain and disability compared to home stretching exercises alone.

We wanted to collect three HRV measurements within the treatment series of four chiropractic treatments. We were careful to avoid any acute effects from SMT, such as measuring HRV immediately after the intervention. HRV was measured prior to the consultations, and a fifth consultation was added in order to have the subjects come back for their final measurement. Thus, measurements of HRV were taken prior to the first, third, and fifth visits.

After the final measurement (prior to the fifth treatment), subjects would see their chiropractor in a normal visit where the treatment would be individually tailored to the patients' needs and preferences, as the study had then finished. Further follow up was planned if deemed necessary.

6.5.1 Adherence to home stretching exercises

Lack of adherence, specifically to home exercises, might reduce the effectiveness of an intervention and has been reported as a severe problem regarding improvement for chronic pain patients (222). Roughly 50% or more of the subjects included in trials did not perform their exercises as recommended by the clinician. This seems to be based on the patient's own beliefs and perceptions (222). For this project, measuring the adherence to home stretching exercises was essential in order to draw conclusions about the comparative effectiveness between groups.

6.6 BASELINE

6.6.1 Procedures

In order to reach a desirable recruitment rate, advertisements were posted through the clinic, in the local newspaper, in digital newsletters, and on social media. Information to local general medical practices was also sent out to allow for the direct referral of suitable patients. These strategies were individually adapted to each clinic. Patients seeking care at the clinic for any reason could also be recruited if they fulfilled the inclusion criteria.

Initially, the screening procedure and booking of patients relied on clinic receptionists identifying subjects and screening them for eligibility. This screening process was found to be too involved for the receptionists and hindered their usual work in the clinics. Also, with regards to our study population, a large total number of possible subjects would have to go through the receptionist, leading to an even bigger disruption of the workday. Thus, the Ph.D. student undertook the entire screening and booking process.

In order to minimize the number of ineligible subjects to screen, potential subjects were directed to a web page with information about inclusion/exclusion criteria, after which they could register their interest. After this, all subjects were contacted by phone where information on the study was given. They would receive the consent form if needed, but all information on the study was provided orally.

Discussions concerning their ability to participate were held, and if interested, appointments for the entire study period at the clinic were scheduled.

Before commencing data collection, a description of the clinicians' role was produced and distributed to all clinicians involved in each of the participating clinics in order to ensure that subjects would receive the same instructions from all clinicians. This description is located in Appendix 1. Pre-trial meetings were held with participating clinicians to maximize protocol adherence.

The subjects met with the Ph.D. student or the research assistant in a private room before their first visit with their chiropractor. After reading the study description and having the opportunity to ask questions, the subjects signed the consent form. They then answered the baseline questionnaire, included as Appendix 2. The first HRV measurement was then obtained.

All subjects were given a diary with all the stretching exercises explained and asked to fill in the dates of when they performed the stretching protocol. These diaries were returned at the last measurement visit. The diary is included as Appendix 3.

6.7 MEASUREMENTS

6.7.1 Demographics

The baseline demographics questionnaire included questions concerning the subject's age, sex, civil status, and type of work. The questions are located in Appendix 2.

6.7.2 Pain

Data concerning the subject's experience of pain, including whether they were experiencing pain anywhere else, length of the NP experience and sick leave due to NP were collected. NP related activity limitation, the affective pain experience and quality of life were also measured (described in detail below).

6.7.3 Previous experience and expectations

Data on whether or not the subject had seen a chiropractor before, what the experience of that encounter was, and the expectations regarding effectiveness of the intervention they received in the study was collected. The questions are included in Appendix 2.

6.7.4 Psychological measures

Secondary psychological effects of pain, such as distress, catastrophic thoughts, and fear-avoidance behaviours (31) were measured at baseline using the Start Back tool (32). The questionnaire is included in Appendix 2.

6.8 OUTCOME MEASURES

The measurements were performed by the Ph.D. student and a research assistant (a chiropractor with 30 years of clinical experience). Measurements and test procedures were practised before starting the study. The two researchers observed each other in the pilot study to calibrate the instructions given and the measurements performed.

6.8.1 NRS-11

NRS-11 is a measurement of subjective pain intensity. It ranges from 0 to 10, where 0 signifies no pain, and 10 the worst pain imaginable, reported on paper (95, 96). It is considered a validated measure of pain (95, 96). An MCID of 2/10 was chosen based on a study investigating chronic pain (223). The NRS-11 scale is found in Appendix 2.

6.8.2 McGill Questionnaire

The short-form McGill Pain Questionnaire is a validated tool that assesses the qualitative characteristics of pain (100, 101). It consists of 15 descriptors of pain, where four of these are affective categories, and eleven are sensory categories.

The McGill Questionnaire was found to be challenging for several subjects to complete. This seemed to be due to the numerous alternatives for pain quality. Subjects would typically ask questions such as “How do I know if it is cramp or pain?” or “How can I answer this if I do not know what a stabbing pain feels like?”. As the subjects were scheduled to see the chiropractor following the baseline measurement, there was a time constraint on completing the questionnaire, so subjects were instructed to skip all questions that did not relate to their particular pain. Therefore, in the analysis, it was assumed that if parts of a question were not answered, the subject did not experience that particular pain sensation.

A MCID of 5/45 was chosen based on a study investigating patients with a range of musculoskeletal conditions reporting improvements in pain after rehabilitation (224). The short-form McGill Questionnaire is included in Appendix 2.

6.8.3 Neck Disability Index (NDI)

The NDI is a validated questionnaire that uses a scale ranging from 0 to 5, measuring the impact of NP on the individual's life. 0 indicates no pain/activity limitation, while 5 indicates that the activity is impossible to perform due to NP (109). The questionnaire includes ten items, each relating to specific activities, personal care, lifting, reading, headaches, concentration, work, driving, sleeping, and recreation, with a maximum score of 50 (109). The patient is asked to reflect on the degree of limitation of activities the previous week. A higher score indicates a higher degree of perceived disability. The NDI is the most commonly used validated test of neck disability (109). A MCID of 10/50 was used based on a study investigating patients with mechanical neck pain (225). The neck disability index is included in Appendix 2.

6.8.4 EQ-5D

Secondary effects of pain on health-related quality of life (42), such as emotions, previous pain experiences, and the effect on daily life, were assessed using the validated EQ-5D questionnaire (99, 111, 112). The questionnaire gives the individual's health status by a single summary index ranging from 0 to 1, where 0 corresponds to death, and 1 corresponds to total health (112, 226). The EQ-5D questionnaire has been validated in patients living with persistent pain (227). Any improvement on the EQ-5D can be categorized as clinically important, based on a study on patients with nonspecific CLBP (228). This questionnaire can be found in Appendix 2.

6.8.5 Heart Rate Variability

There are many different instruments used to measure HRV (229, 230), such as plethysmography (IPG) now being used in modern smartwatches such as IWatch (https://support.apple.com/en-us/HT204666) which can provide data over a long period of time. A commonly used device in research is the Bodyguard2 (Firstbeat Technologies Oy, Jyväskylä, Finland). This is a small portable instrument attached to the chest with (Kendal Arbo H92SG) electrodes, measuring ECG (231) using a standard 2-lead ECG configuration. The device measures R-R intervals with a sampling rate of 1000 Hz. In this way, measurement of time series of R-R intervals after five minutes of relaxation and a following 24-hour measurement can be obtained and stored directly on the device before being downloaded to a PC for off-line analysis. HRV measurements are used for various purposes such as medical and sports research, and clinically to improve athletes' recovery time (229).

The HRV measurement was obtained by attaching the FirstBeat device to the chest before placing the subject in the corner of the room, facing the wall, wearing hearing protection to prevent any disruption. The initial five minutes were used as relaxation time and measurements discarded; the measurements from the final five minutes were extracted as the resting HRV measurement after the Firstbeat device was handed in. The FirstBeat was left in place until the following morning, allowing for night time measurement as well.

HRV is considered an acceptable biomarker of autonomic regulation (91). It is, however, recognized that about 40% of a single HRV measurement variance can be explained by the situational effects and person-situation interaction (232). Based on this, several measurements are recommended to achieve more reliable data (233).

It is also important to acknowledge the difference of the indices of an HRV measurement. They should all be considered an individual outcome measure with different levels of validity and reliability. In this project, RMSSD was used as the primary outcome, on which power was based. RMSSD has been reported to be minimally effected by respiration (114), and is a measure of parasympathetic activity, found to have good reliability (232). Significant results for any of the other indices would have to be interpreted cautiously. At the same time, having a battery of indices could lead to an interesting discussion if the results suggested a significant difference between groups. The least usable indices based on reliability and validity in this project were LF and LF/HF, the use of which has been discouraged in several articles (234-237).

6.8.6 CPM

We used a validated test setup with a standardized mechanical clamp as the test stimulus, pressing the thumbnail for 10 seconds. For the conditioning stimulus, the opposite hand was then submerged in cold, circulating water (0–2 °C) for 2 minutes before the second test stimulus was applied to the same thumbnail again (115). Pain associated with both stimuli was assessed with a Numeric Rating Scale (NRS)-11. The change in reported pain in the pre- and post-conditioning stimulus was recorded as the CPM score. This was an indicator of the level of endogenous pain modulation the subject is experiencing.

6.8.7 Adverse reactions

Adverse reactions were measured using text messages (SMS) (238) sent out one day following the baseline measurements and first visit with the chiropractor. Subjects were asked whether they experienced a reaction to the first treatment, e.g., increased tenderness or fatigue in the neck, and answered with an NRS-11 scale anchored by the descriptors 'No reaction' (0) and 'Worst reaction imaginable' (10). No additional SMSs were sent out during the treatment period as adverse reactions are most common after the first treatment (239) and to keep the subjects' total project work load low, to assure a higher response rate for NRS-11 SMSs and email questionnaires.

6.9 FOLLOW UP

The following day, a single text message was sent out asking about pain and soreness (on a scale from 0 to 10) after the first visit with the chiropractor. Daily SMSs over a period of fourteen days collected data on pain intensity (using NRS-11) the previous 24 hours, starting from the first day following the first treatment.

The following week, before the subjects' third visit, the second HRV measurement was performed similarly to the first visit. An email was sent out asking follow-up questions, included here as Appendix 4. The same procedure was repeated before the fifth visit, i.e., after the subjects had completed the four treatments in the study.

The digital follow-up questionnaires including NRS-11, McGill questionnaire, NDI, and EQ5D were sent out every other week during the two months after the final measurement.

Specific treatment content for each treatment and subject were gathered after the study was completed.

6.10 STATISTICAL ANALYSIS

For all articles,

An intention to treat protocol was applied in the primary analysis. Per protocol analyses were performed as sensitivity analyses to investigate the robustness of the results.

In all tables, categorical variables are reported as counts and percentages, continuous variables are reported with means and standard deviations.

Significance level was set to 0.05.

Analyses were performed using SPSS 27 (240), Stata version 15 (StataCorp. 2017), and R.

Table 8. Overview of articles and statistical analysis

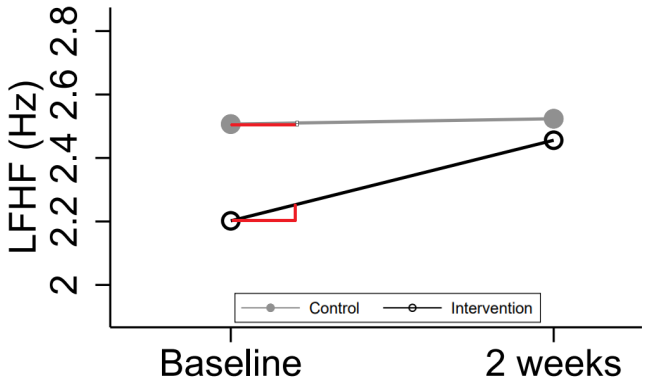
	Article 1	**Article 2**	**Article 3**	**Article 4**
Aim	To investigate the effect on pain and disability in i) a combination of home stretching exercises and spinal manipulative therapy, versus ii) home stretching exercises alone.	To investigate the effect on Heart Rate Variability in i) a combination of home stretching exercises and spinal manipulative therapy, versus ii) home stretching exercises alone.	To investigate the relationship between changes in pain and changes in HRV over a two-week treatment period. A secondary aim is to investigate different pain trajectories and the relationship with changes in HRV.	To investigate the temporal stability and responsiveness of a conditioned pain modulation test over a two-week period among patients undergoing treatment.
Design	RCT	RCT	Cohort study	Cohort study
Analysis	Linear mixed effects model with person specific random intercept was used to investigate the time x group interaction. A quadratic model was also investigated to control for fit. The quadratic model did not have a better fit than the linear model. The difference between groups in the probability of attaining Minimal Clinical Important	Linear mixed effects model with person specific random intercept was used to investigate the time x group interaction. Linear mixed-effects model without adding group allocation was undertaken to investigate the overall change in the population. The impact of outliers on the results were investigated with a sensitivity analysis, excluding all outliers	Linear mixed effects model with person specific random intercept was used to investigate the time x group interaction. Latent class analysis was performed to investigate groups with distinct response patterns by a group-based trajectory modelling using Stata package traj. Group one was estimated using a quadratic model.	The CPM data were analysed with a multivariate linear regression (repeated measures MANOVA type III), with five CPM variables (first pressure pain intensity, time in cold pressor test, max. pain in the cold pressor test, cold pressor test area under the curve, and CPM response) as dependent variables. Clinical responder status, RCT group

	Difference (MCID) was estimated using logistic regression due to the data being dichotomous. All analysis adjusted for baseline values, age, and gender. A per-protocol analysis was also performed. This was done to investigate whether drop-outs influenced the results significantly.	visually disproportionally distant to the mean. All analysis adjusted for baseline values, age, and gender. A per-protocol analysis was also performed. This was done to investigate whether drop-outs influenced the results significantly.	Group two was estimated using a fourth order model, and groups three and four were estimated using a linear model. All models were chosen based on AIC.	allocation and test day were included as independent variables. It was found that residuals were normally distributed and homoscedastic for all measurements except for time with hand under water. No better fit for statistical analysis was found. We did not hypothesize on the normality of the variables, but the mean distribution which is assumed normal based on the central limit theorem.

6.10.1 Clarification of interpretation of the linear mixed effects model

Linear mixed regression with person specific intercept was used to investigate the difference between groups. The interaction between group allocation and time was the parameter of interest. This gave us a beta value indicating the difference in the groups' regression slopes for each time-point (one and two weeks), with a control as reference in Articles 1 and 2. For Article 3, the trajectory group with the lowest levels of pain and the “No change” was selected as reference.

Figure 5. Illustration of the difference in slopes between groups.



In this example, the **β**-value (regression coefficient) of the difference between intervention groups is 0.24 with the control group as reference, indicating that the intervention group increased the LFHF-value by 0.24 more on average then the control group for every time unit change. In other words, if the control group increased .01 on average in a week, the intervention group increased .01 + .24 = .25 units per week on average.

6.10.2 Clarification of interpretation of the MANOVA model

The MANOVA utilized in the third article does not provide any estimation of the scale of difference between groups. The output only shows whether or not the group difference at any time points with adjusting for different dependent variables are significant or not. In other words, whether any of the interactions lead to a significant difference between the groups.

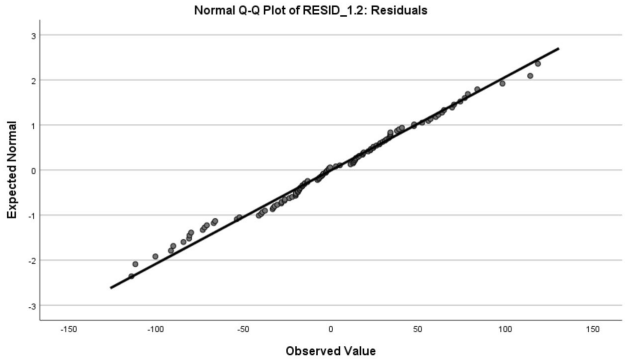
6.10.3 Mathematical assumptions

For all analyses performed in this thesis, linearity was assumed. Quadratic modelling was also performed, and the best fit was decided by the AIC (Akaike Information Criteria) and BIC (Bayesian Information Criteria) values.

It was concluded in the mixed linear model that all person specific random intercepts were normally distributed around the mean.

It was also found that residuals were normally distributed and homoscedastic.
A check for normality was performed for the RMSSD measure, as shown in Figure 6.

Figure 6. Q-Q plot of residuals of a RMSSD measurement.



6.10.4 Cleaning of the HRV measurements

R-R intervals at rest was used to measure HRV. To ensure sufficient quality, the data had to be cleaned for artifacts and ectopic beats (common changes in a heartbeat involving an extra or skipped heartbeat). Kubios software (241) was used to manually and visually inspect the R-R intervals from the ECG recordings, following a protocol from a previous study (242). Threshold-based beat correction algorithm testing with different sensitivity filters of R-R intervals was used, and there are five of these filters in the Kubios software, ranging from 0.45 to 0.05 seconds difference from the local sample average. These were used to exclude ectopic beats and artifacts to a point where the R-R intervals were visually acceptable. If the proportion of excluded artifacts exceeded 5%, the sample was excluded (242). This was based on finding a trade-off between reducing bias due to artifacts and removing too much data as 100% clean data is difficult to obtain. An alternative to this would be to adjust the time the 5-minute samples were extracted from, but this would also introduce bias. Five percent has also been used in a previous study (242). The process was carried out according to the Task Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology (243), under the supervision of David Hallman, an experienced researcher in this field.

6.10.5 Imputation

The McGill questionnaire also contained an NRS-11 score. This data overlapped with four incomplete SMS data and was obtained through the questionnaire. In total, the NRS-11 obtained through SMS was incomplete, with seven non-responses, and the final 3 missing observations were imputed using the Last Observation Carried Forward (LOCF). For NDI and EQ-5D, multiple imputations with fully conditional specification and twenty imputation rounds were used (244). This was only done for article one as the subjects included in articles two and three had a low number of dropouts. No imputation was deemed necessary for CPM and HRV data as only a small proportion was missing, including measurement errors, dropouts, and missed appointments.

6.11 ETHICS

6.11.1 Interventions

While it is estimated that about 50% of patients experience minor to moderate side effects after manual treatment (245) including SMT (239), particularly after the first visit (246), the risk of major adverse events is low (245). Severe complications from SMT are extremely rare (239, 247). There have been no studies of adverse reactions to home stretching exercises. Static stretching in sports, however, has been associated with reduced performance (248).

SMT and home stretching exercises are used regularly by clinicians; hence the interventions included in this study did not differ from what would typically be included in a treatment plan for this patient group. Both interventions are also recommended in current treatment guidelines (118).

All subjects were insured in case of adverse events in the same manner as any patient at the clinics. The treating chiropractors had liability insurance (Nordic Insurances) through their professional federation (https://www.lkr.se/) and were licensed by the Swedish National Board of Health and Welfare (hence the national Patient Safety Act applies).

6.11.2 Consent

Written and verbal information concerning the practical aspects of the study (number of treatments, measurements, and SMS/email procedures) was provided when the subjects were screened for eligibility. At baseline, a consent form with information concerning the number of treatments, measurements, SMS/Email, protected identity, data storage, and legal rights was given to and signed by all subjects before commencing the study. The consent form is attached as Appendix 5. Subjects also had the opportunity to ask the Ph.D. student or research assistant questions concerning the study. A telephone number was also provided where the PI of the research group, who was not involved in the data collection, could answer questions concerning the intervention.

6.11.3 Data handling

Each subject in the study received an identification number (ID) when recruited. All self-reported and objectively measured data were linked with the individual's ID, with a key matching the subject's personal identity number, name, and phone number. This key was securely stored in a locked fireproof cabinet at Karolinska Institutet in accordance with the National Board of Health and Welfare's requirements for storage of journal documents.

Only researchers involved in the study had access to the data. Following the local rules and European GDPR, the data were stored electronically at Karolinska Institutet.

All reporting was done at a group level without the possibility of identifying any individual study subjects.

The Regional Ethical Review Board in Stockholm approved this study (reference approval no. 2018/2137-31).

7 RESULTS

7.1.1 Participating subjects

It is important to keep in mind that all subjects participating in this study had experienced pain for an extended period of time. It was expected and confirmed in the conversation with the subjects in the recruitment phase that many had previously explored several different treatments and seen clinicians and specialists earlier in the course of their pain. A common reason to participate seemed to be the hope that the study interventions would be able to solve their persistent or recurrent NP, despite insufficient effects of previous treatments.

Clinic newsletters and local newspapers were found to generate the most subjects compared to letting clinic receptionists identify possible subjects.

7.1.2 Adverse reactions

In this study, no unexpected severe reactions to the treatment were reported. Four subjects (3 in the intervention group, 1 in the control group) reported intense side effects after the first visit ≥ 8 (NRS-11) (246), with no drop out observed due to adverse reactions. One subject fainted during the first CPM testing procedure. The subject did not undergo more CPM tests but stayed on for the other parts of the study after consulting with a medical practitioner who diagnosed the subject with a stress response.

Results

The following is a short summary of the main results and a collection of results that are not included in the published/submitted peer-reviewed articles. As these did not provide any additional information or change the conclusion, they are only described briefly in the articles.

7.1.3 Article 1

7.1.3.1 Main findings

Both groups showed improvements in NRS-11, McGill questionnaire, NDI and EQ-5D, with no statistically significant differences between the two groups in change scores of MCID for any of the outcome measures.

7.1.3.2 Covariates

Age and gender were evenly distributed between the intervention and control groups. As stated in the protocol, they were still adjusted for, as reported in Table 9.

Table 9. Mixed Linear model of all outcome measures adjusted for age, gender, and baseline values, with the control group as reference

	B	**CI**		**P-value**
NRS-11	-0.01	-0.03	0.13	0.39
McGill questionnaire	0.52	-0.59	1.63	0.36
EQ5D	0.0001	-0.016	0.013	0.99
Neck Disability Index	-0.05	-0.24	0.15	0.63

7.1.3.3 Quadratic model

A quadratic model was also generated for the NRS-11-outcome (as it has 14 repeated measurements) but was not reported in the article as AIC and BIC showed that the mixed linear model was a better fit for the data. Also, a quadratic model would be harder to interpret as it represents the difference in curvature of the modelled lines and not the difference in linear improvement seen in the linear regression.

Results from the quadratic model of NRS-11 are found in Table 10.

Table 10. Output from an unadjusted quadratic model of NRS-11 with the control group as reference

	Coefficient	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Group						
Group 3	0.564	0.310	1.82	0.068	0.042	1.169
Time	-0.111	0.007	-16.87	0.000	-0.124	-0.098
Group#Time						
Group 3	-0.057	0.009	-6.29	0.000	-0.075	-0.039
Daysq	0.004	0.001	9.53	0.000	0.003	0.005
Group#Timesq						
Group 3	0.003	0.001	5.18	0.000	0.002	0.004
_cons	3.851	0.224	17.16	0.000	3.411	4.291

7.1.3.4 Per protocol

A per protocol analysis was also performed as a sensitivity analysis to investigate the robustness of the results to protocol deviations. In this analysis, all participants who violated

the protocol were excluded. This did not change the significance of the results, as shown in Table 11.

Table 11. Unadjusted per protocol mixed linear model analysis with the control group as reference

	B	CI		P-value
NRS-11	-0.01	-0.03	0.02	0.42
McGill questionnaire	0.51	-0.63	1.65	0.38
EQ5D	-0.003	-0.015	0.010	0.68
Neck Disability Index	-0.032	-0.24	0.18	0.76

Table 12. Proportion of numbers of questions answered in each questionnaire in the intervention period

	BL	3. treatment	5. treatment	Total
McGill	1481/1965	1663/1905	1629/1905	4723/5715
%	75%	87%	86%	83%
NDI	1288/1310	1238/1270	1235/1270	3722/3810
%	98%	97%	97%	98%
EQ-5D	651/655	624/635	615/635	1870/1905
%	99%	98%	97%	98%
Total	3420/3930	3525/3810	3479/3810	10424/11550
%	87%	93%	91%	90%

Table 13. Response rate of daily NRS- measurements

SMS	Baseline	Dag 1	Dag 2	Dag 3	Dag 4	Dag 5	Dag 6	Dag 7
NRS-11	126/128	127/128	126/128	127/128	128/128	128/128	128/128	128/128
%	98%	99%	98%	99%	100%	100%	100%	100%

Dag 8	Dag 9	Dag 10	Dag 11	Dag 12	Dag 13	Dag 14	Total
126/128	128/128	126/128	128/128	127/128	128/128	121/127	1902/1919
98%	100%	98%	100%	99%	100%	95%	99%

Following the data collection, questionnaires were sent out every other week for two months. The response rate is found below. The results of these data will be presented in a separate article following the completion of the Ph.D. studies.

Table 14. Proportion of numbers of questions answered in each questionnaire at each time point after the intervention period

	2 weeks	4 weeks	6 weeks	8 weeks	Total
NRS-11	119/127	120/127	118/127	122/127	479/508
%	94%	94%	93%	96%	94%
McGill	1522/1905	1574/1905	1599/1905	1668/1905	6363/7620
%	80%	83%	84%	88%	84%
NDI	1176/1270	1220/1270	1180/1270	1230/1270	4806/5080
%	93%	96%	93%	97%	95%
EQ-5D	587/635	613/635	583/635	612/635	2395/2540
%	92%	97%	92%	96%	94%
Total	3404/3973	3527/3973	3480/3973	3632/3973	14043/15748
%	86%	89%	88%	91%	89%

The McGill questionnaire had a lower response rate than the other questionnaires. This was most likely related to the fact that the patients were instructed to skip the questions not related to their pain experience when the baseline questionnaire was undertaken. This was done to utilize the time window as efficiently as possible. In the analysis performed in article 1, the skipped questions were therefore assumed to be irrelevant to the respondent and coded as 0.

7.1.4 Article 2

7.1.4.1 Main results

No statistically significant group effect was found for any of the HRV indices. For the study population as a whole, a slight decrease in HRV for all indices were seen. Only SDNN showed a statistically significant change (B = 1.58, p = 0.018), indicating reduced global HRV.

7.1.4.2 Quadratic model

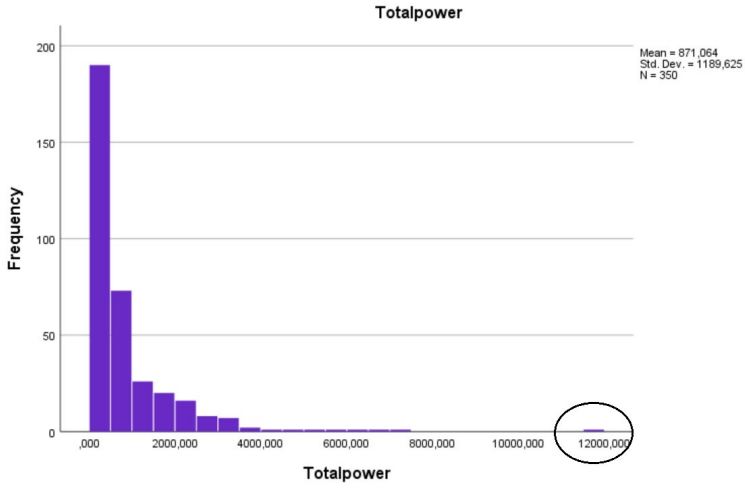
A quadratic model was not suitable for the data as only three repeated measurements were obtained for the HRV outcome variables.

7.1.4.3 Outliers

Outliers were investigated as a sensitivity analysis to assess whether they affected the results.

Outliers of the HRV indices were excluded by visually investigating the histogram of each index of HRV and setting a cut-off point to exclude the measurements obviously detached from the rest of the sample, as demonstrated in Figure 7.

Figure 7. Demonstration of an outlier from the total power index.



Removing outliers did not affect the precision of the results.

Table 15. Results of the unadjusted mixed linear regression model of all HRV indices with outliers removed

	Treatment effect				
Group x Time	B	P-value	95% CI		Outliers
R-R (ms)	1.5	0.87	-15.8	18.8	1
RMSSD (ms)	0.6	0.70	-2.3	3.5	6
SDNN (ms)	1.4	0.27	-1.2	4.0	2
LF (ms^2)	74.7	0.11	-16.5	165.8	4
HF (ms^2)	12.5	0.69	-50.0	14.9	6
LF/HF	0.3	0.21	-0.2	0.8	4
Total Power (ms^2)	86.6	0.26	-63.7	237.0	1

7.1.4.4 Per protocol

A per protocol analysis was also performed as a sensitivity analysis to investigate the robustness of the results to protocol deviations, similar to Article 1. This did not change the precision of the results, as shown in Table 16.

Table 16. Results of an unadjusted per protocol mixed linear regression model of all HRV indices

	Treatment effect			
Group x Time	B	P-value	95% CI	
R-R (ms)	1.8	0.84	-16.6	20.3
RMSSD (ms)	0.2	0.90	-3.6	4.0
SDNN (ms)	1.3	0.36	-1.5	4.1
LF (ms^2)	78.8	0.25	-55.9	213.5
HF (ms^2)	-14.8	0.72	-96.2	66.6
LF/HF	0.6	0.10	-0.1	1.2
Total Power (ms^2)	60.9	0.52	-123.8	245.6

Table 17. Rate of obtained HRV measurements

	Baseline	One week	Two weeks	Total
HRV	129/131	123/127	123/127	375/385
%	98%	97%	97%	97%
Lost due to artifacts	9/129	9/123	7/123	25/375
%	7%	7%	6%	7%
Total for analysis	120/131	114/127	116/127	350/385
%	92%	90%	91%	91%

7.1.5 Article 3

7.1.5.1 Main results

For the treatment response strategy, no significant changes between "improved" and "not improved" groups were found for any of the HRV measurements, but all HRV indices except for LF are in favour of the "improved" group with small effect sizes.

For the pain trajectories strategy, no significant difference between groups were observed. A non-significant trend towards a stronger reduction in HRV with higher NRS-11 pain trajectories was seen.

Care should be taken when discussing trends in non-significant results. In theory, the observed trend could be in the opposite direction, as the risk of it happening by chance is too high. As this is an exploratory analysis, I would still like to briefly discuss the observed results.

Table 18. Association between pain trajectories (data-driven analysis) and changes in HRV over two weeks including LF and LF/HF (n=127).

	Trajectory	β	P-value	Confidence intervals	
RR GroupxTime	2	14.9	0.19	-7.5	37.6
	3	10.3	0.38	-12.8	33.3
	4	-21.3	0.22	-55.1	12.5
RMSSD GroupxTime	2	3.0	0.42	-1.9	7.9
	3	-0.1	0.97	-4.9	5.1
	4	-3.8	0.26	-10.4	4.3
SDNN GroupxTime	2	1.4	0.44	-2.2	5.0
	3	-0.06	0.98	-3.7	3.6
	4	-3.0	0.28	-8.3	2.4
LFms GroupxTime	2	130.0	0.12	-35.2	302.9
	3	113.3	0.19	-56.3	289.7
	4	-13.3	0.91	-262.9	295.2
HFms GroupxTime	2	28.1	0.63	-86.6	142.8
	3	-43.7	0.47	-161.5	74.0
	4	-108.4	0.22	-281.1	64.1
LF/HF GroupxTime	2	-0.3	0.48	-1.2	1.5
	3	-0.1	0.92	-1.0	0.9
	4	0.2	0.82	-1.2	0.6
Total Power GroupxTime	2	146.1	0.24	-97.3	389.4
	3	47.9	0.71	-202.0	297.7
	4	-130.0	0.49	-496.3	232.4

The table shows the β coefficient with trajectory 1 as reference.

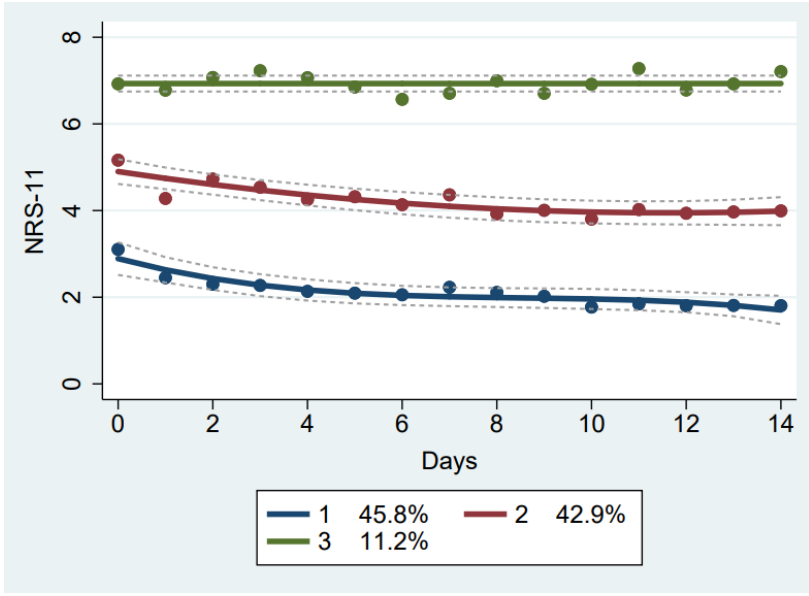
It can be observed that trajectory 2 always increase compared to group 1, except for LF/HF where a reduction indicates improved HRV. Trajectory 3 always does worse than trajectory 2, but can increase or decrease compared to group 1, and trajectory 4 always decreases

compared to group 1 (except for LF/HF). This can be termed a non-significant trend, but as discussed earlier, we cannot rule out the fact that this all happened by chance. Other researchers of HRV might view this as an interesting observation and conduct further research on the area.

7.1.5.2 Latent class analysis

An alternative graph with three pain trajectory groups is presented in Figure 8.

Figure 8. Three pain trajectories were produced using group-based trajectory models (249).



7.1.6 Article 4

7.1.6.1 Main results

The conditioned pain modulation test had stable measurements, not influenced by any of the independent variables, including changes in clinical pain. The mean change in individual CPM responses was 0.22 from baseline to one (SD:1.35), and -0.15 from the first to the second week with (SD:1.24).

An Interclass Correlation Coefficient (ICC3 – single, fixed rater) for CPM across the three time points yielded a coefficient of 0.54 (P<0.001), which is considered moderate stability.

7.1.6.2 Explanation of all dependent variables

NRS-11 clamp measurements (pressure pain intensity (PPI)) before the cold pressor test: This is a measure of overall pain intensity (NRS-11) during 10 seconds of the clamp pressing on the thumbnail before the hand is submerged in cold water (conditioning stimulus). A similar test performed after the cold pressor test is used to calculate the CPM response.

Time with hand under water (cold pressor test): The total time in which the subject keeps his or her hand under cold water (conditioning stimulus).

Max. pain when hand under water (cold pressor test): Maximum pain reported in the VAS scale during the time the hand was under water.

Area under the curve: The sum of all registered VAS measurements during the total time the hand was submerged in water.

CPM response: The second clamp measurement subtracted by the first measurement.

7.1.6.3 Box plots for independent variables not included in the manuscript

Figure 9. Distribution of NRS-11 clamp measurements (PPI) before cold pressor test

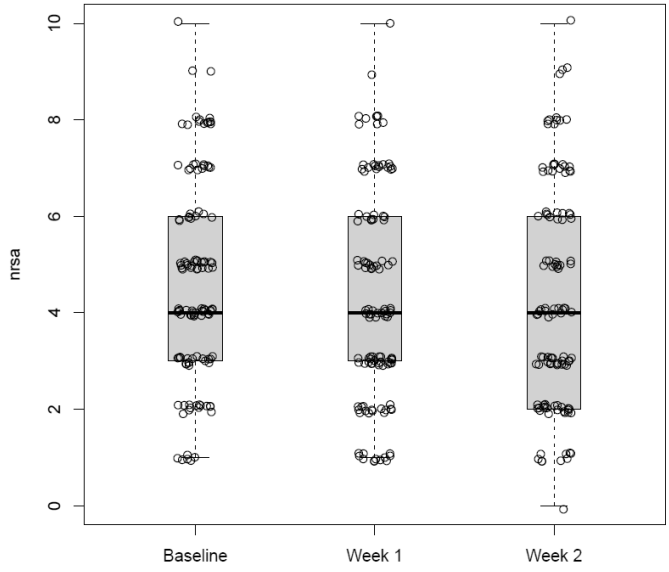


Figure 10. Distribution of max. pain when hand under water (cold pressor test)

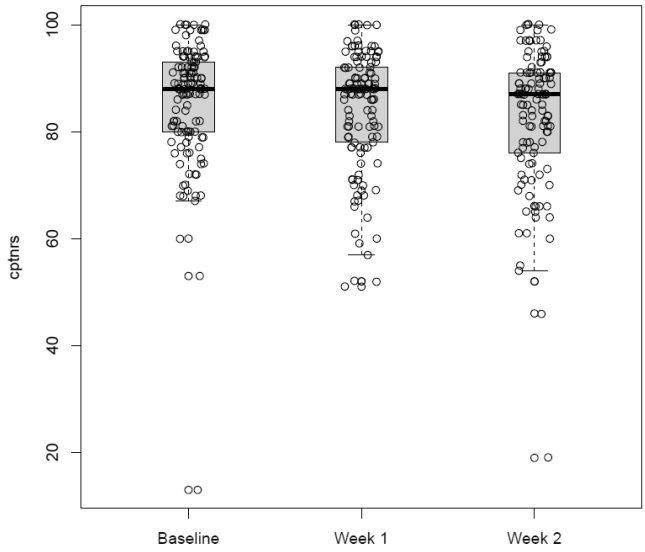


Figure 11. Distribution of time with hand under water (cold pressor test)

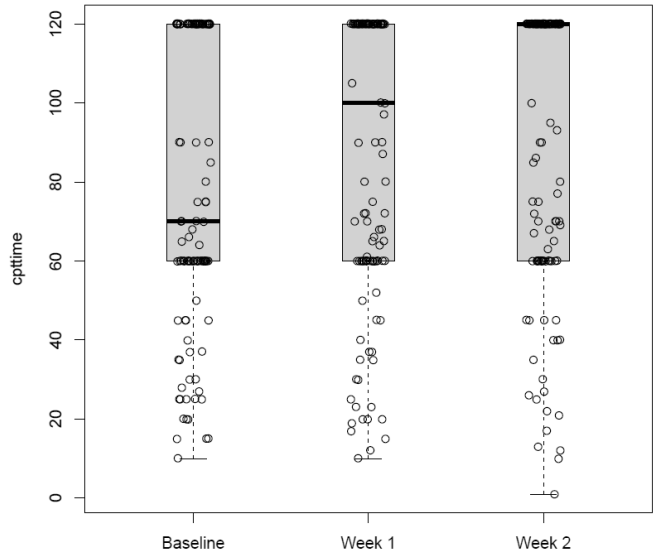
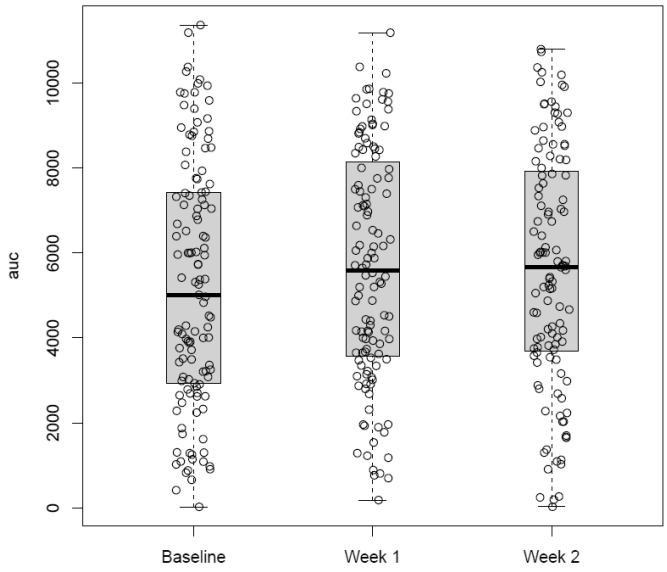


Figure 12. Distribution of time for area under the curve (cold pressor test)



This analysis investigated the temporal stability of the CPM test in the cohort before adjusting for variables in the analysis investigating if this significantly changed the observed temporal stability.

7.1.6.4 Distribution of residuals - normality

The following is the presentation of distribution of residuals for all independent variables

Figure 13. Residuals of NRS-11 clamp measurements (PPI) before cold pressor test

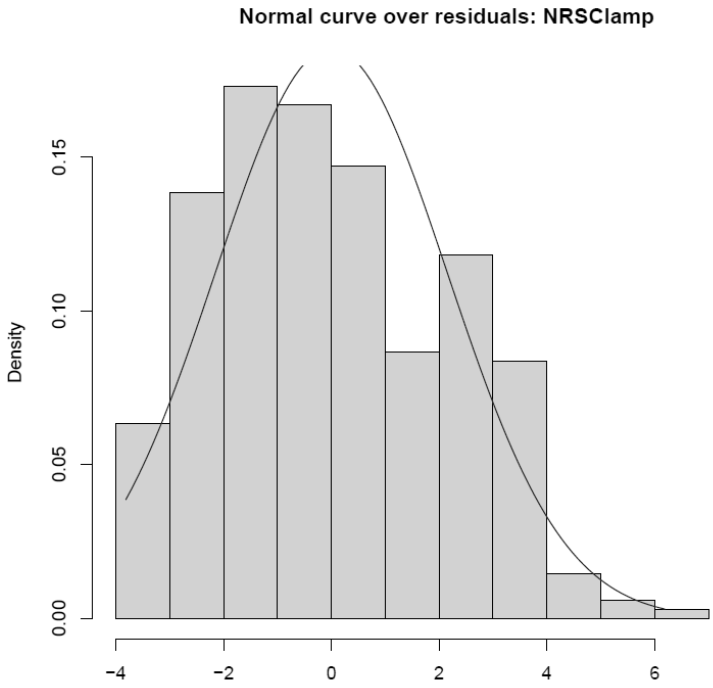


Figure 14. Residuals of time with hand under water (cold pressor test)

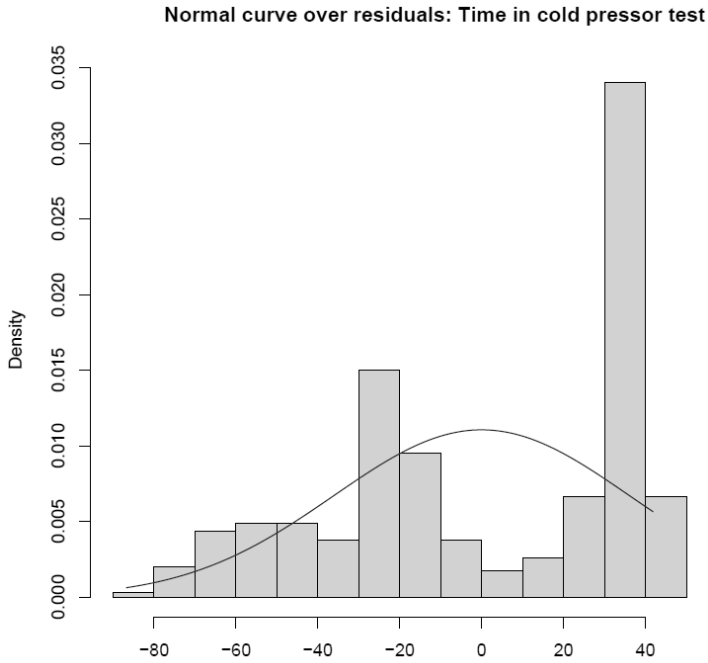


Figure 15. Residuals for max. pain when hand under water (cold pressor test)

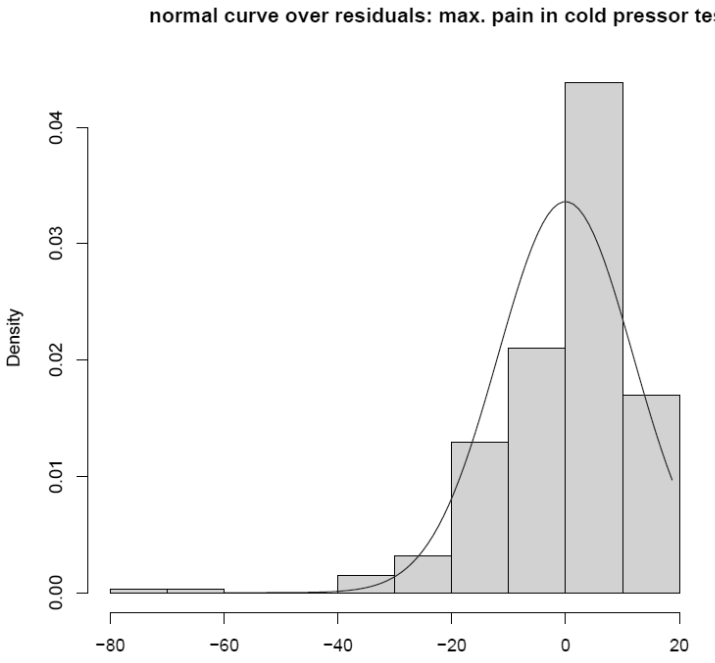


Figure 16. Residuals for area under the curve

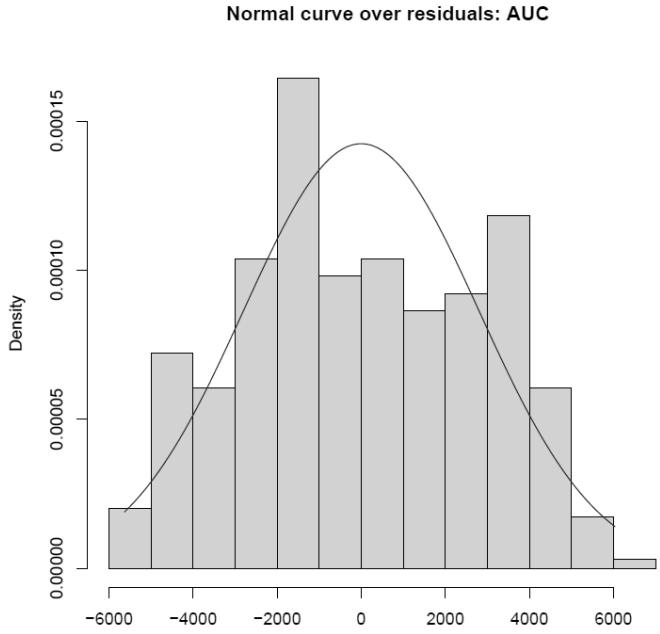
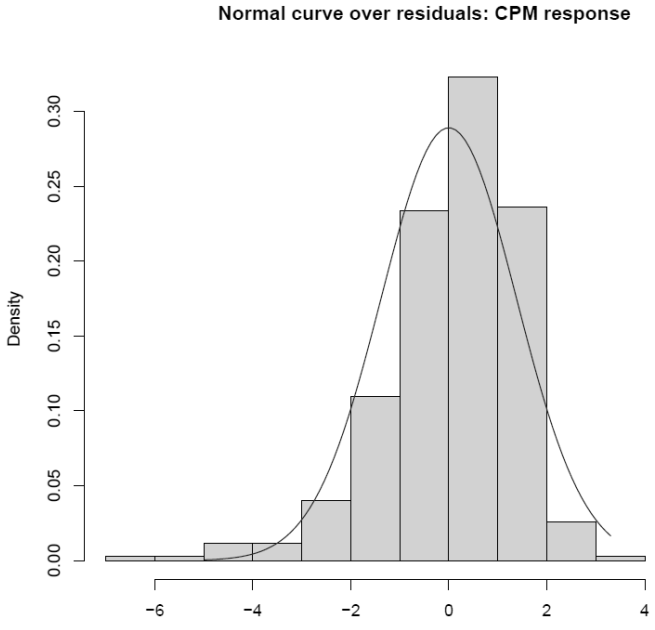


Figure 17. Residuals for changes in CPM response



7.1.6.5 Outliers

As all the depended variables were measured using a bound scale (VAS or time, with a maximum of 100 points and 2 minutes respectively), no major outliers were expected. After investigating the box plots, no actions were needed to assess this.

Table 19. Rate of obtained CPM measurements

	Baseline	**One week**	**Two weeks**	**Total**
CPM response	122/131	119/127	118/127	359/385
%	0.93	0.94	0.93	0.93

8 DISCUSSION

We conducted a randomized clinical trial on subjects with persistent or recurrent neck pain, investigating the effect of home stretching exercises and SMT on pain, disability and HRV. The data also allowed us to investigate the relationship between changes in pain and changes in HRV and conduct a CPM experiment examining the temporal stability of the utilized test, and whether or not the changes in CPM response were related to changes in pain.

No significant differences between the control and intervention groups were found for any of the outcome measures. For the whole cohort, irrespective of treatment group, we observed a trend towards reduction in HRV for the "improved" group with a trajectory of increasing pain severity.

Previous research in this area has focused on the acute effects of SMT on HRV and the relationship between chronic pain and HRV. This project contributes to this area of research by investigating the long-term effect of SMT and home stretching exercises on HRV, and also the relationship between changes in pain and changes in HRV over a two-week period for this patient group.

Further, we found that the CPM measurements were stable over time regardless of clinical improvement.

Below, each of the articles and findings are discussed separately or together, with relation to previous research and possible explanations for the outcome. Finally, there is an overview discussion of internal and external validity of the study.

8.1.1 Strengths and limitations of the study

The RCT methodology was chosen due to its robust and highly controlled design, necessary to investigate effect.

The clinics involved in the study employed therapists from different professions, and the most common way to recruit subjects for the trial was by means of clinic newsletters. Thus, subjects in the study were probably familiar with the clinics and some of the therapists working there. This could have led to selection bias as many of the subjects already had a positive experience of the clinic where the data collection took place. This effect was expected to be stronger if the subject had seen the participating chiropractor before and if the intervention utilized was similar to previously received treatments. However, it could also be argued that subjects with a previous successful treatment experience and help in managing their neck pain would not need to participate in the study.

All subjects reported having performed their home stretching exercises at least 10 out of 14 days, and most subjects (77%) performed their home stretching exercises 13 or 14 out of 14 days. This high compliance is a strength of this study and yields stronger confidence in the

observed results. All study subjects received the same amount of time with the chiropractor and underwent the same physical examination to ensure the same attention and contextual factors. Pain explanations, advice, and reassurance were given in both intervention groups. Workshops with the clinicians were held before the study commenced, in order to emphasise this and answer any potential questions from the participating clinicians. It was not possible to blind the participating chiropractors to the intervention. As no significant difference was observed between the intervention groups, this protocol appeared successful.

The researchers performing the measurements had practised the routines together and observed each other to assure congruency in measurements and patient communication.

It is important to consider the contextual factors when interpreting the results. It is possible that the observed improvements in pain were due to contextual factors, hence any intervention applied in the treatment groups would produce similar results. If we were to consider this as an option, then the main aspects of choosing the right intervention would be i) associated risks, ii) patient preferences and iii) cost effectiveness. This is beyond the scope of this thesis, but still important to bear in mind.

One of the study's strength is that we investigated a majority of the ICF components (body functions (b), body structures (s), activities and participation (d), and contextual factors: environmental factors (e) and personal factors (94).) Certain aspects are, however, not included as we decided to include validated questionnaires, and were reluctant to add too many questions as this would increase the workload on the participants, possibly leading to a lower response rate. These included body position, mobility of joint functions, doing housework, using communication devices and techniques, and interpersonal interactions (94).

All articles in this thesis investigate patients receiving treatment aimed at reducing their NP. However, we observed that our population also experienced other painful regions in their body. This may not be an issue when investigating neck pain as the outcome, but when investigating CPM and HRV, we have to acknowledge that the other painful regions reported at baseline could have affected these outcomes. This is based on the fact that these outcomes are known to be associated with other pain conditions (12, 250, 251), hence improving one out of several pain conditions might not have been enough to affect CPM and HRV. In other words, this would potentially limit any observed effect from reduced NP on these outcomes.

Considering the nature of the NP experienced by this population (>6 months), a significant improvement due to the intervention and its associations with HRV and CPM might have been difficult to achieve.

The exclusion criteria applied to subjects in this project were necessary for good quality HRV data. Without these, the internal validity of the measurements would have been challenged. The exclusion criteria affected the external validity, as the study group might have been healthier than other persistent or recurrent NP populations. Some known comorbidities to persistent spinal pain were among the chronic diseases and mental disorders used to exclude subjects in this study (252). Depression in subjects with spinal pain is considered to reduce

the treatment effect in primary care (253). However, by excluding subjects on antidepressants, a reverse relationship could have occurred. Subjects treated with antidepressants have been found to experience pain reduction and improved function (54, 55), indicating that subjects taking antidepressants are similar to the intended study population. We may, on the other hand, have included subjects with untreated depression in the study, subjects who may therefore report poor outcomes, underestimating the observed effects. In summary, the risk of excluding subjects taking antidepressants from the study population was not expected to reduce the external validity to any great extent.

The study used logRMSSD as the primary outcome, and power was calculated based on this outcome. As a consequence, it is important to note that the analyses of secondary outcomes were not considered to have sufficient power.

8.1.2 Difference between SMT and home stretching exercises and home stretching exercises alone on pain and disability (Article 1.)

No significant differences between groups were observed for any of the outcome measures. Also, no statistically significant difference between the number of subjects reaching MCID in each group was observed. Overall, both groups improved during the intervention period.

These results are not in line with previous research showing a better effect of combining interventions, such as home exercises and SMT, compared to SMT alone (163, 254). Also, current guidelines recommend multi-modal care for this patient group, where both home stretching exercises and SMT are included (117, 118). Our results imply that the exact combination of home stretching exercises and SMT may not be as good at reducing pain and disability in this patient group as other combinations of treatment modalities investigated previously (163, 254). Daily home stretching exercises provide the same benefit as a combination of home stretching exercises and SMT on pain and disability over a two-week period for this patient group.

The interventions used in this trial are commonly used by clinicians working with this patient group, where around 90% use manipulation and prescription of home exercises for most patients (122). Chiropractors of the Swedish Chiropractic Association are generally in favour of following evidence based guidelines (255).

Considering that previous research has shown a definite improvement in persistent low back pain after four treatment sessions of SMT (207), this might not translate to populations with persistent or recurrent NP. Also, as the subjects have had pain for a long period of time, they have tried a range of different treatments plans and might be non-responsive to these types of interventions. Finally, a floor effect may have influenced the results as a large number of subjects had low levels of pain at baseline, leaving limited room for improvement. It is possible that the inclusion of all subjects with persistent or recurrent NP might have reduced the likelihood of showing a difference between groups, and a minimum level of pain intensity

might have been a better choice. The study design had a pragmatic approach as the study population represented the target population.

Subjects were recruited up to five weeks before the baseline measurements. It is therefore possible that subjects may have experienced a spontaneous improvement or a flare up, resulting in low levels of pain at the start of the study compared to when they announced their interest in participating in the study.

To utilize different pain measurements is recognized as an essential procedure when measuring chronic pain conditions. This study used NRS-11, EQ-5D, and McGill to cover important aspects of the subjective experience of persistent or recurrent NP.

Just below 40% of the total study population reached MCID for NRS-11, in contrast to 20% for the McGill Questionnaire. We did not expect a large number of subjects to reach MCID during a two-week treatment period due to the chronic nature of the condition. The NRS-11 and McGill Questionnaire measures different psychometric aspects of the pain experience, though it could be argued that they should be closely related to each other. They have shown correlation in dental pain assessment (256). This does not seem to be the case for this study population, as pain intensity decreased more than the affective and sensory qualities of pain.

It is also important to remember that patient-reported outcome measures such as the McGill questionnaire, have been reported to have inadequate psychometric measurement properties and to lack content validity (103). There does not seem to be a clear consensus in this, and there are no validated alternatives to date (103). This did not change the interpretation of our results.

Among the subjects, decrease, increase, or no change in NP was observed during the study period, as expected considering the periodic pain experience seen in patients with persistent or recurrent NP (10). A part of the explanation of these varying outcomes could be increased discomfort from the interventions. About half of all patients receiving manual therapy experience some additional discomfort following treatment (246). The adverse events were, however, most commonly related to the first treatment (246). The recorded adverse events in this study mirrored previous research (246).

A difference in pain levels (NRS-11) between treatment groups at baseline was observed. This can only have happened by chance in the randomization process. When adjusted for, this did not change the effect estimates or the precision of either of the outcomes.

8.1.3 Difference between SMT and home stretching exercises and home stretching exercises alone on Heart Rate Variability (Article 2.)

No significant effect on HRV after two weeks of SMT and home stretching exercises vs. home stretching exercises alone was found.

Rather, a slight worsening of HRV could be seen for the study population as a whole, with a significant worsening of SDNN, indicating a decrease in global HRV (257).

These results indicate that neither two weeks of home stretching exercises or home stretching exercises and SMT affected HRV in a sample of patients with recurrent or persistent NP.

This is in line with previous research investigating the association between pain and HRV (12). This study did not observe a significant effect on pain and disability between groups (257), and therefore, an effect on HRV was not expected. It was noted that a difference in pain levels (NRS-11) between treatment groups at baseline was also observed here. This happened by chance and did not significantly affect the results.

However, previous research has suggested an acute effect of SMT on HRV, both for symptomatic and non-symptomatic subjects (90). An effect of SMT over two weeks was not seen in this study.

No overall improvement in HRV for the study population was seen. This is not in line with previous research suggesting an acute effect of both SMT and stretching (90, 141-145, 185, 187, 189, 192, 216). Also, an overall improvement in pain was seen for the whole study population (258), indicating no association between improvement in pain and reduction in HRV. The amount of change in pain over two weeks was possibly not sufficient to detect changes in HRV considering the chronic nature of the study population's condition. The slight worsening of HRV, one out of seven HRV indices, contradicts previous research. An explanation of this trend could be the possible effect of the measurement procedure. The CPM test mentioned in this thesis consisted of a painful test stimulus, where the hand was submerged in cold water (0-2°C). The test procedure was designed so that the acute effect of this test procedure would not affect the HRV measurement. The subjects' expectations of the painful experience, on the other hand, could have affected the HRV. This would be less evident at the baseline visit when the subjects had no experience of the testing procedure.

A two-week intervention period could have been suboptimal to detect an improvement in HRV. The period used was expected to be sufficient to improve HRV as acute effects of HRV have been reported in previous studies, but a response to SMT over time, not measured directly after the treatment, could depend on other mechanisms such as its relation to pain. Thus, two weeks might not have been sufficient time to observe this improvement.

HRV is known to fluctuate during the day. As this was a multicentre randomized controlled trial, the subjects were fitted into the regular schedule at the clinic, where available appointments and patient preference had to be the basis of scheduling a treatment series for each subject. Therefore, the subjects were not necessarily booked at the same time of the day for each measurement. All measurements were, however, performed within a typical working day (between the hours 0700 and 1600).

Certain variables were not possible to control for. These include internal factors such as psychological distress, disease and external factors such as stress or physical sensations in

close relation to the measurements. These factors should, however, have been balanced out between treatment groups in the randomized study design.

It was seen that the intervention group had an overall higher HRV at baseline. Adjusting for baseline values did not significantly change the results.

HRV is a validated and reliable non-invasive measure of the ANS. Even so, situational effects and person-situation interaction explain about 40% of the variance in HRV measurements (232). To minimize this, a protocol of the procedures was implemented for each clinic before commencing data collection. Two researchers were responsible for the measurements. Similar conditions for all measurements were maintained by assuring the same temperature and light conditions for each measurement and controlling for alcohol, exercise, caffeine, and medication on the same day of the measurement. We could not control all factors affecting HRV, however, as it is influenced by things that are difficult to measure, such as emotions or unknown underlying diseases.

Based on the variance of the HRV measures, performing several measurements during the two-week period would have increased the reliability of the HRV data (233, 259).

A difference in pain levels (NRS-11) between treatment groups at baseline was observed. This can only have happened by chance in the randomization process. When adjusted for, this did not change the effect estimates or the precision of either of the outcomes.

8.1.4 Changes in pain and changes in Heart Rate Variability in a population of patients with recurrent or persistent neck pain (Article 3.)

Two groups based on improvement in pain intensity were formed, but no significant association with changes in HRV were observed. All HRV indices were, however, in favour of the “improved” group with small effect sizes. Then, four pain trajectories were found in an exploratory analysis, but no significant association with changes in HRV was observed.

The results were not significant, thus no relationship between changes in pain and changes in HRV for patients with persistent and recurrent NP, over two weeks of home stretching exercises with or without SMT, was found.

The results are not in line with previous research, showing a relation between pain and HRV (12). It has also been reported that treatment over ten weeks aimed at improving HRV reduced NP (13). A significant relationship in the opposite direction (reduced NP improved HRV) was not observed in this study.

It is also possible that the changes in pain observed were normal fluctuations common in persistent or recurrent NP and not a genuine improvement due to the interventions. This would potentially have had a smaller impact on HRV. Also, several measurements during the

two-week period would have increased reliability of the data due to the normal day to day variation in HRV (233, 259).

In this study, the entire study sample was viewed as a cohort and divided into groups based on treatment response or pain trajectories. The study design, however, was a randomized controlled trial. Due to this, the results should be interpreted with caution. The participants did not receive the same treatments during the intervention period. This was not assumed to affect the outcome as no differences between home stretching with or without SMT was observed for pain or HRV.

8.1.5 Temporal stability and responsiveness of a conditioned pain modulation test (Article 4.)

In this article, the study sample was viewed as a cohort and divided into two groups based on treatment response. The aim was to investigate the temporal stability and responsiveness of the conditioned pain modulation (CPM) test. Moderate temporal stability for the cohort was observed, and no significant difference in the stability of the CPM test was observed when adjusted for clinical improvement, indicating that an improvement in persistent or recurrent NP from conservative treatment over two weeks was not associated with changes in the utilized CPM test.

No directly relatable studies have been found, but a previous study showed that individuals who reported exercise-induced hypoalgesia also experienced a reduced CPM directly after exercise (210). An opposite relationship was found when patients with chronic osteoarthritis of the knee was treated with pain reducing joint mobilization, as CPM improved directly after the treatment (211). No such effects of pain reducing treatment over two weeks was observed in this study.

As we investigated the stability of CPM for responders and non-responders over two weeks, the mechanisms might differ from the mentioned acute changes in pain.

The participants did not receive the same intervention in the two-week treatment period. Previous research did not find a difference in pain reduction between home stretching exercises with or without SMT, hence this is assumed not to have affected CPM response.

A MCID of 2/10 (mean change -3.3) could have been too little to influence the CPM response. With a study population consisting of patients suffering from persistent or recurrent NP (>6 months), at least some degree of CPM attenuation was expected. Without a control group, however, CPM attenuation can only be expected.

Arguably, this result does not preclude greater changes over time for individuals if those changes are roughly equal in either direction. The analysis of variance, however, demonstrated that this was not the case, and the mean change in CPM response for individuals between tests was found to be relatively small.

As no control group of subjects without pain was included, we could only investigate CPM in relation to changes in pain and not the magnitude of CPM response itself.

Based on this, the CPM test is considered to have moderate temporal stability, and to be in line with previous research on the reliability of CPM testing (260). As changes in pain did not significantly affect the stability, the test is also considered reliable for patients with persistent or recurrent NP undergoing treatment aimed at improving their NP. Also, as the test is not affected by changes in pain over two weeks, the clinical value as an objective marker of changes in pain over a two-week period is considered low.

8.2 INTERNAL AND EXTERNAL VALIDITY

The project was designed as a high-quality randomized controlled clinical trial with good internal and external validity (167). Internal validity measures the degree to which a change in the outcome measure can be attributed to the intervention. In other words, internal validity is the difference between actual observed effect and observed correlation between variables (168). External validity is the generalizability of the findings in the study, in other words, how it relates to the full population and clinical practice (168).

There follows an overview of vital areas for internal validity of the project design based on the Scottish Intercollegiate Guidelines Network (SIGN) (261).

8.2.1.1 Internal validity

Positive aspects

- The project addresses focused research questions.
- There is a clear definition of persistent or recurrent NP.
- The assignment of subjects to treatment groups was randomized.
- An adequate concealment method was used.
- Subjects were blinded to treatment allocation.
- The results of this study are clinically applicable to the management of persistent or recurrent NP.
- Investigators were blinded to treatment allocation.
- The control intervention (stretching protocol) is described in detail.
- The outcome measures are measured in a reliable and valid way.
- There were few dropouts from the study. All dropouts occurred in the control group (6.2%). However, this did not affect the overall power.
- All subjects were analysed in the groups to which they were randomly allocated using intention-to-treat analysis.
- As a protocol was developed, the results from all clinics were comparable.
- An appropriate analysis was performed in alignment with the research questions.

Conflicting aspects

- The treatment groups were similar at the start of the trial with regards to demographics. Slight differences in NRS-11 and HRV were seen at baseline. This is a

result of random error and could not be controlled for. It is unlikely that the difference was large enough to affect the results.
- The SMT intervention is described in sufficient detail but still allowed for flexibility regarding choice of technique. This could have been more rigorously controlled but would have resulted in a reduction in the external validity, as clinicians normally adapt the SMT technique to suit the patient.
- The methodology in this project is of high quality. Power was calculated using the main index of HRV, hence the observed effect between groups is assumed to be due to the interventions. It is, however, difficult to control for all potential variables influencing HRV and pain, as these are complex measures. The RCT design reduces the risk of unknown variables causing an effect on the reported outcome.

8.2.1.2 External validity,

Based on Steven and Asmundson 2008 (168).

Interaction of selection and experimental condition:
- Due to the variation in demographics among the study population and the broad definition of persistent or recurrent NP, the results are applicable for people who fit this study's inclusion/exclusion criteria.
- The exclusion criteria set for the HRV measurement could have led to a healthier study population, thus reducing the external validity for NP sufferers.

Interaction of setting or context and experimental condition:
- The study setting can be generalized to other clinical settings where clinicians are working with this patient group. The interventions were adapted to patients within the study's limitations.

Interaction of history and experimental condition:
- The burden of NP has not changed substantially the past 30 years (262), but unknown variables may affect this development in the future. If performed in the past or the future, it is likely that this study would yield the same results as today.

Summary
- The project minimized bias as much as possible.
- If the project was affected by biases such as external influences on HRV and pain, the results would likely be skewed towards "no effect" as it would increase randomness in the data.
- The outcome measures are valid and reliable.
- Good external validity was obtained due to the pragmatic design of the interventions. The design has been used with success in previous research.
- A possible weakness would be the exclusion criteria utilized in the RCT, as this excluded certain medical conditions, possibly leading to a healthier population, more likely to respond to the intervention.

9 CONCLUSIONS

This thesis has demonstrated that adding SMT to a two-week home stretching protocol did not result in improvement in NP, disability or HRV. The previously suggested short-term effect of SMT on HRV does not seem to relate to changes over two weeks. Also, changes in NP among subjects with persistent or recurrent NP over two weeks is not significantly related to changes in HRV. Further research is warranted to investigate this relationship over a longer time-period. Future research should focus on different pain populations and longer intervention periods. Also, investigating different HRV profiles is warranted to gain further knowledge on the relationship between changes in pain and changes in HRV.

The conditioned pain modulation test has moderate temporal stability in patients with persistent or recurrent NP. No association between minimally important changes in NP and changes in CPM response were observed.

10 POINTS OF PERSPECTIVE

We set out to investigate the effect of SMT on HRV, pain and disability, and the relationship between changes in pain and changes in HRV among subjects with persistent or recurrent NP. In addition, the temporal stability of a CPM test was investigated.

Regarding pain, there is robust evidence showing a positive effect of SMT together with exercise on persistent or recurrent NP (164, 254). This study does not support the current best evidence on the effect of pain. However, SMT and home stretching exercises have not previously been investigated in detail. It can be assumed that this combination applied for a two-week period does not provide any additional treatment effect compared to stretching alone. Individually adapted manual therapy combined with rehab exercises, education, and reassurance are still considered the first-line treatment for this patient group; our study alone does not change this (118, 254). Further research into the combination of home stretching exercises and SMT over an extended treatment period with patients with higher pain levels is warranted.

Previous research has suggested some acute effects of manual therapy, including SMT, on HRV (90). Considering the responsiveness of the ANS, possible acute changes in HRV with manual therapy is not surprising. The question is whether changes in HRV from manual therapy is long-lasting and can be measured over time. Our study indicates that this is not the case. No additional effect on HRV was observed by adding SMT to home stretching exercises over two weeks. It is possible that administering four treatments in the intervention period was not sufficient to detect changes in HRV. Even so, based on this study there are no clinical implications of the acute effect of SMT on HRV.

We know from previous research that several chronic pain disorders are related to autonomic dysregulation with reduced HRV (12, 251). We found no difference in pain between groups which can explain why no effect on HRV was observed. Changes in HRV due to changes in pain would be different from the acute effect mentioned previously, which has been suggested for both symptomatic and asymptomatic subjects (90). We investigated this further by comparing subjects who improved with subjects who did not and observed a non-significant relationship with changes in HRV. It is possible that the observed correlation with HRV in chronic pain cannot be significantly affected in two weeks. As chronic pain builds up slowly (defined by pain for a minimum of 3 months, and 6 months in this study), it is possible that it also reverses slowly, hence the adaption to chronic pain in the ANS takes a long time. This relationship between improvement in HRV and improvement in persistent or recurrent NP was observed when investigated over ten weeks administering treatment intended to affect HRV (13). It is also important to remember that this is the first study of its kind, and it cannot be expected to capture the whole picture of the long-term effects of SMT on HRV and the relationship between changes in pain and changes in HRV among this patient group. The findings included in this thesis need to be challenged by further research, but based on this study, the clinical implications of changes in HRV over two weeks are questionable, as HRV did not differ between groups and was not significantly related to changes in pain.

The CPM test utilized is a moderately reliable measurement over time for this patient group. No significant difference in the stability of the CPM test was seen between groups with or

without MCID in persistent or recurrent NP over two weeks. The results suggest that the CPM test is not clinically useful as an objective measure of pain improvement.

In summary:

Previous research suggests that SMT has a possible acute effect on HRV. An effect from SMT could be expected, considering the responsiveness of the ANS. No effect of SMT on HRV was observed over two weeks in subjects with persistent or recurrent NP. Also, no significant relationship between changes in pain and changes in HRV after two weeks of SMT and home stretching exercises or home stretching exercises alone was observed. This indicates that the acute effect of manual therapy found in previous studies on HRV is short-lasting. Two weeks might be a short time to observe a significant relationship between changes in pain and HRV. Further research on the long-lasting effect of SMT on HRV is warranted. Moderate temporal stability of the CPM test was observed.

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APPENDICES

Appendix 1.

Hej alla!

Tack för att ni vill bidra till i studien.

Det hade inte gått utan er hjälp!

Jag har sammanställt en kort lista med viktiga punkter inför studien.

- Alla patienterna får en vanlig undersökning och bedömning vid första besöket. Du förklarar besvären som du vanligtvis gör.
- Berätta för patienten vad de kan förvänta sig av besöken utifrån den behandlingsgrupp de lottats till, men berätta **inte** vad den andra gruppen kommer få för insats.
- Förklara även att det är viktigt att de genomför minst 4 besök med den insats de lottats till, men att det därefter är fritt att utforma behandlingen helt efter patientens behov. Boka därför gärna tidigt under studieförloppet en uppföljning efter studien avslutats.
- Kom ihåg att studien är avklarad efter mätningen innan det 5e besöket. Det betyder att patienten kan få den behandling/övning du tycker är mest lämplig, utifrån individuella behov, redan vid 5e besöket.
- De som lottats till stretching-gruppen ska bli palperad enligt den procedur som utförs i behandlingsgruppen (dock försiktigt så att ingen mobilisering utförs) under återbesöken. Syftet med detta är att besöken i så många delar som är möjligt skall likna varandra. Båda grupper bör uppleva återbesöken som meningsfulla t.ex. diskutera deras smärta, mät ROM eller liknande uppföljning av symptom och/eller funktion.
- Om någon inte är nöjd, absolut vill veta vad den andra gruppen får för insats eller har liknande frågor ska de ta kontakt med Iben Axén. Tlf.: 0852483228. Denna information finns i det samtyckesformulär de läst och signerat.
- De flesta av er kommer träffa samma patient genom hela studien. Ni identifierar vilken grupp patienten tillhör genom att läsa vilken insats som utförts vid tidigare besök. Vill ni förenkla proceduren ytterligare kan ni skriva in vilken grupp patienten lottats till i patientjournalen.
- Behandlingsgruppen kan behandlas på olika sätt. All form av ledbehandling är godkänd, såsom traktion, mobilisering, manipulation eller liknande. Du får behandla alla leder i kroppen ut ifrån din kliniska bedömning. Dock får du inte utföra någon form av mjukdelsbehandling. I behandlingsgruppen, precis som bland våra patienter i övrigt, kommer det finnas individer som inte vill ha manipulationsbehandling i nacken, detta måste givetvis respekteras.

Om det finns några frågor så hör av er!

Appendix 2. KOD:……..

1: När är du född? År…….. Månad…….. Dag……..

2: Kön:

Kvinna ☐

Man ☐

Vill inte definiera ☐

3: Civil status:

Singel ☐

Gift/sammanboende ☐

Särbo ☐

4: Vilken typ av **jobb/sysselsättning** har du?

Jag jobbar inte just nu ☐

För det mesta tungt fysiskt jobb ☐

För det mesta varierande mellan tungt och lättare arbete ☐

För det mesta stående och gående ☐

För det mesta sittande ☐

5: I allmänhet, skulle du säga att **din hälsa** är?

Utmärkt ☐

Mycket god ☐

God ☐

Någorlunda ☐

Dålig ☐

6: Om du har varit hos kiropraktor tidigare, hur var effekten för din dåvarande smärta?

Inte varit hos kiropraktor någon gång ☐

Utmärkt ☐

God ☐

Ingen skillnad ☐

Blev sämre ☐

Rörande din smärta:

6.1: Hur **länge** har du haft besvär med smärta **i nacken**:

Mindre än 6 månader ☐

6-12 månader ☐

Flera år: ☐ Skriv ungefär hur många år:_____

6.2: Har du haft liknande besvär **tidigare** i livet?

Nej ☐

Ja, en gång ☐

Ja, flera gånger ☐

6.3: Har du ont även i **armarna**?

Nej ☐

Ja, endast i överarmen/-arna ☐

Ja, i hela armen/ -arna ☐

Ja, i endast handen/ -händerna ☐

6.4: Nacksmärtans **intensitet** (i genomsnitt)det senaste dygnet

Inte alls ont Outhärdligt ont

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

6.5: **Beskriv** smärtan i nacken som du känner just nu: (sätt kryss)	Ingen	Lindrig	Måttlig	Uttalad
Pulserande				
Blixtrande				
Stickande				
Skärande				
Krampaktig				
Gnagande				
Brännande				
Molande				
Tung				
Ömmande				
Sprängande				
Utmattande				
Kväljande				
Fasansfull				
Straffande-grym				

6.6: Har du även ont i **bröstryggen** (mellan skulderbladen)? Ja ☐ Nej ☐

6.7: Har du även ont i **ländryggen** (svanken)? Ja ☐ Nej ☐

6.8: Har du varit **sjukskriven pga. din nacksmärta** det senaste året?

Jag jobbar inte ☐

Nej ☐

Ja, totalt mellan 1 och 7 dagar ☐

Ja, totalt mellan 8-14 dagar ☐

Ja, totalt mer än 15 dagar ☐

6.9: På en skala från 0 till 10, där 0 är helt osannolikt, och 10 är mycket sannolikt, tror du att **du kommer att bli bättre** inom loppet av de två veckorna som studien pågår?

Gradera din åsikt (ringa in ditt svar):

0 1 2 3 4 5 6 7 8 9 10

Helt osannolikt Mycket sannolikt

6.10: Nuvarande smärtintensitet (ringa in ditt svar):

0 – Ingen smärta

1 – Lindrig

2 – Obehaglig

3 – Besvärlig

4 – Fruktansvärd

5 - Outhärdlig

Markera, genom att kryssa i en ruta i varje nedanstående grupp, vilket påstående som bäst beskriver Ditt hälsotillstånd **i dag**.

11.1: RÖRELSE

☐ Jag går utan svårigheter

☐ Jag kan gå men med viss svårighet

☐ Jag är sängliggande

11.2: PERSONLIG OMVÅRDNAD

☐ Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning

☐ Jag har vissa problem att tvätta eller klä mig själv

☐ Jag kan inte tvätta eller klä mig själv

11.3: DAGLIGA AKTIVITETER *(ex arbete, studier, hushållssysslor, familj eller fritid)*

☐ Jag klarar av min huvudsakliga sysselsättning

☐ Jag har vissa problem med att klara av min huvudsakliga sysselsättning

☐ Jag klarar inte av min huvudsakliga sysselsättning

11.4: SMÄRTA / BESVÄR

☐ Jag har varken smärtor eller besvär

☐ Jag har måttliga smärtor eller besvär

☐ Jag har svåra smärtor eller besvär

11.5: ÅNGEST / DEPRESSION

☐ Jag är inte orolig eller nedstämd

☐ Jag är orolig eller nedstämd i viss utsträckning

☐ Jag är i högsta grad orolig eller nedstämd

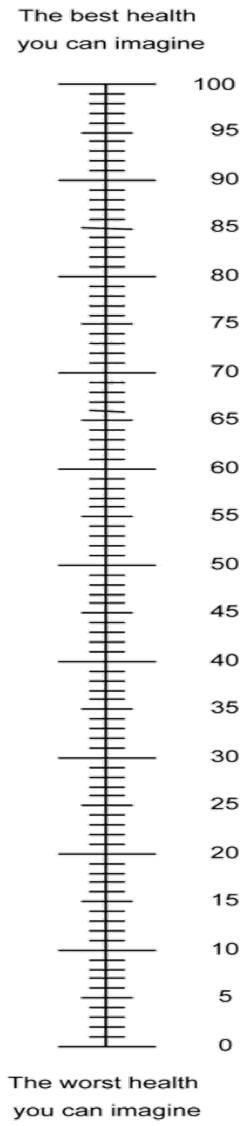
11.6: Hur tycker du att fin hälsa är I DAG.

Skalan till höger går från 0 till 100.

- 100 är den bästa hälsa du kan tänka dig.
- 0 är den sämsta hälsa du kan tänka dig.
- Markera med X på skalan för att indikera hur din hälsa är I DAG.

Var god att också skriv motsvarande siffra här:

DIN HÄLSA I DAG= _____



NACKFUNKTIONSSKALA

Följande frågor är utformade för att ge oss information om hur din nacksmärta påverkar ditt dagliga liv. Besvara varje avsnitt och markera bara den enda ruta som passar dig. Vi är medvetna om att det kan vara svårt att välja mellan två närstående påståenden, men var vänlig kryssa bara i den rutan som mest motsvarar er situation.

12.1: SMÄRTINTENSITET

☐ Jag har ingen smärta för närvarande

☐ Smärtan är mycket lätt

☐ Smärtan är måttlig

☐ Smärtan är svår

☐ Smärtan är mycket svår

☐ Smärtan är värsta tänkbara

12.2: PERSONLIG OMVÅRDNAD (Hygien, påklädning etc)

☐ Jag kan sköta mig själv som vanligt utan att få ökad smärta

☐ Jag kan sköta mig själv som vanligt, men det orsakar ökad smärta

☐ Det innebär smärta att sköta mig själv och jag är försiktig och långsam

☐Jag behöver en del hjälp, men klarar det mesta av min personliga omvårdnad

☐ Jag behöver hjälp varje dag med det mesta i min personliga omvårdnad

☐ Jag klär inte på mig, tvättar mig med svårigheter och ligger till sängs

12.3: LYFTA

☐ Jag kan lyfta tunga saker utan ökad smärta

☐ Jag kan lyfta tunga saker, men det ger ökad smärta

☐ Smärtan hindrar mig från att lyfta tunga föremål från golvet, men jag klarar det om det är lämpligt placerat, ex på ett bord

☐ Smärtan hindrar mig från att lyfta tunga föremål, men jag klarar medeltunga föremål, om

de är lämpligt placerade

☐ Jag kan lyfta mycket lätta föremål

☐ Jag kan inte lyfta eller bära något överhuvudtaget

12.4: LÄSNING

☐ Jag kan läsa så mycket som jag vill utan smärta från nacken

☐ Jag kan läsa så mycket jag vill med lätt smärta i nacken

☐ Jag kan läsa så mycket jag vill, men med måttlig smärta i nacken

☐ Jag kan inte läsa så mycket jag vill p g a måttlig smärta från nacken

☐ Jag kan knappast läsa alls p g a svår smärta från nacken

☐ Jag kan inte läsa alls p g a smärtan

12.5: HUVUDVÄRK

☐ Jag har ingen huvudvärk överhuvudtaget

☐ Jag har lätt huvudvärk då och då

☐ Jag har måttlig huvudvärk då och då

☐ Jag har måttlig huvudvärk ofta

☐ Jag har svår huvudvärk ofta

☐ Jag har svår huvudvärk praktiskt taget hela tiden

12.6: KONCENTRATION

☐ Jag kan koncentrera mig helt och hållet när jag behöver, utan problem

☐ Jag kan koncentrera mig helt och hållet när jag behöver, men får lindriga besvär

☐ Jag har måttliga svårigheter att koncentrera mig när jag behöver

☐ Jag har stora svårigheter att koncentrera mig när jag behöver

☐ Jag har avsevärda problem att koncentrera mig när jag behöver

☐ Jag kan inte koncentrera mig alls

12.7: ARBETE

☐ Jag kan utföra så mycket arbete som jag vill

☐ Jag kan bara göra mitt vanliga arbete, men inte mer

☐ Jag kan göra det mesta av mitt vanliga arbete, men inte mer

☐ Jag kan inte utföra mitt vanliga arbete

☐ Jag kan knappast utföra något arbete alls

☐ Jag kan inte utföra något arbete alls

12.8: BILKÖRNING

☐ Jag kan köra bil utan någon nacksmärta

☐ Jag kan köra bil så länge jag vill, med lätt smärta i nacken

☐ Jag kan köra bil så länge jag vill, med måttlig smärta i nacken

☐ Jag kan inte köra bil så länge jag vill p g a måttlig smärta från nacken

☐ Jag kan knappast köra bil alls p g a svår smärta från nacken

☐ Jag kan inte köra bil alls p g a nacksmärtan

12.9: SÖMN

☐ Jag har inga problem med sömnen

☐ Min sömn är lätt störd (mindre än 1 timme sömnlöshet pga. smärtan)

☐ Min sömn är måttligt störd (1-2 timmer sömnlöshet pga. smärtan)

☐ Min sömn är tämligen störd (2-3 timmer sömnlöshet pga. smärtan)

☐ Min sömn är kraftigt störd (3-5 timmer sömnlöshet pga. smärtan)

☐ Min sömn är helt och hållet störd (5-7 timmer sömnlöshet pga. smärtan)

12.10: FRITIDSAKTIVITETER

☐Jag klarar att utföra alla mina fritidsaktiviteter utan någon nacksmärta

☐ Jag klarar att utföra alla mina fritidsaktiviteter, men med lätt smärta i nacken

☐ Jag klarar att utföra de flesta, dock inte alla mina vanliga fritidsaktiviteter pga. smärta i nacken

☐ Jag klarar bara att utföra ett fåtal av mina vanliga fritidsaktiviteter pga. smärta i nacken

☐ Jag kan knappast utföra några fritidsaktiviteter pga. smärta i nacken

☐ Jag kan inte utföra några fritidsaktiviteter alls

Tänk på de 2 senaste veckorna när du svarar på följande frågor:

		Instämmer inte	**Instämmer**
		0	1
13.1:	Min nacksmärta har **strålat ut i min arm/mina armar** vid något tillfälle de senaste 2 veckorna.	□	□
13.2:	Jag har haft smärta i **ländryggen** vid något tillfälle de senaste 2 veckorna	□	□
13.3:	Jag har bara **gått korta sträckor** på grund av min nacksmärta.	□	□
13.4:	Under de senaste 2 veckorna har det tagit **längre tid än vanligt att klä mig** på grund av nacksmärtan.	□	□
13.5:	Det kan vara skadligt för en person med mina besvär att vara fysiskt aktiv	□	□
13.6:	Jag har haft oroande tankar en stor del av tiden.	□	□
13.7:	Jag upplever att **min nacksmärta är fruktansvärd** och att den **aldrig kommer att bli bättre.**	□	□
13.8:	I allmänhet har jag inte **glatt mig över** de saker som jag brukar glädja mig åt.	□	□

13.9: På det stora hela, hur **besvärlig** har din nacksmärta varit **de senaste 2 veckorna**?

Inte alls	Lätt	Måttligt	Väldigt mycket	Extremt
□	□	□	□	□

Appendix 3.

STRETCH-ÖVNINGAT ATT UTFÖRA DAGLIGEN UNDER 14 DAGAR

Övningarna ska göras varje dag i 14 dagar. De tar cirka 10 minuter att göra.

Det är väldigt viktigt att det görs så som beskrivet.

Använd träningsdagboken (sista sidan) för att komma ihåg att göra dina övningar.

Varje övning görs i 30 sekunder och upprepas 3 gånger.

1. Böj huvudet till vänster. Lägg vänster arm över huvudet och känn att det stretchar.
2. Böj huvudet till höger. Lägg höger arm över huvudet och känn att det stretchar.

3. Böj och rotera huvudet till vänster. Lägg vänster arm över huvudet och känn att det stretchar.

4. Böj och rotera huvudet till höger. Lägg höger arm över huvudet och känn att det stretchar.

5: Böj huvudet framåt. Lägg en arm over huvudet och känn att det stretchar.

6: Avsluta genom att sitta rakt med överkroppen eller ligg platt på ryggen. Gör en dubbelhaka genom att dra hakan mot dig och håll i 3-5 sekunder. Gör detta 5 gånger.

Lycka till!

DATUM FÖR KONSULTATION HOS KIROPRAKTOR:_____

KOD: _____

Ringa in ditt svar varje dag:

Dag 1: Stretching utfört enligt instruktion	Ja	Nej
Dag 2: Stretching utfört enligt instruktion	Ja	Nej
Dag 3: Stretching utfört enligt instruktion	Ja	Nej
Dag 4: Stretching utfört enligt instruktion	Ja	Nej
Dag 5: Stretching utfört enligt instruktion	Ja	Nej
Dag 6: Stretching utfört enligt instruktion	Ja	Nej
Dag 7: Stretching utfört enligt instruktion	Ja	Nej
Dag 8: Stretching utfört enligt instruktion	Ja	Nej
Dag 9: Stretching utfört enligt instruktion	Ja	Nej
Dag 10: Stretching utfört enligt instruktion	Ja	Nej
Dag 11: Stretching utfört enligt instruktion	Ja	Nej
Dag 12: Stretching utfört enligt instruktion	Ja	Nej
Dag 13: Stretching utfört enligt instruktion	Ja	Nej
Dag 14: Stretching utfört enligt instruktion	Ja	Nej

Eventuella kommentarer:

_____

Appendix 4.

Nacksmärtans **intensitet** (i genomsnitt)det senaste dygnet

Inte alls ont Outhärdligt ont

0 1 2 3 4 5 6 7 8 9 10

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Beskriv smärtan i nacken som du känner just nu: (sätt kryss)	Ingen	Lindrig	Måttlig	Uttalad
Pulserande				
Blixtrande				
Stickande				
Skärande				
Krampaktig				
Gnagande				
Brännande				
Molande				
Tung				
Ömmande				
Sprängande				
Utmattande				
Kväljande				
Fasansfull				
Straffande-grym				

Nuvarande smärtintensitet (ringa in ditt svar):

0 – Ingen smärta

1 – Lindrig

2 – Obehaglig

3 – Besvärlig

4 – Fruktansvärd

5 - Outhärdlig

Markera, genom att kryssa i en ruta i varje nedanstående grupp, vilket påstående som bäst beskriver Ditt hälsotillstånd **i dag**.

11.1: RÖRELSE

☐ Jag går utan svårigheter

☐ Jag kan gå men med viss svårighet

☐ Jag är sängliggande

11.2: PERSONLIG OMVÅRDNAD

☐ Jag behöver ingen hjälp med min dagliga hygien, mat eller påklädning

☐ Jag har vissa problem att tvätta eller klä mig själv

☐ Jag kan inte tvätta eller klä mig själv

11.3: DAGLIGA AKTIVITETER *(ex arbete, studier, hushållssysslor, familj eller fritid)*

☐ Jag klarar av min huvudsakliga sysselsättning

☐ Jag har vissa problem med att klara av min huvudsakliga sysselsättning

☐ Jag klarar inte av min huvudsakliga sysselsättning

11.4: SMÄRTA / BESVÄR

☐ Jag har varken smärtor eller besvär

☐ Jag har måttliga smärtor eller besvär

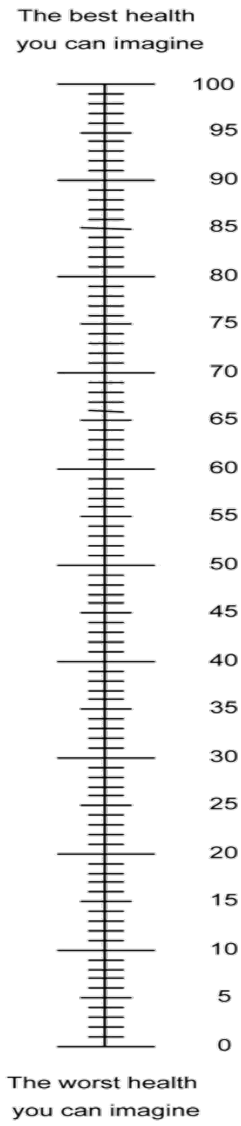
☐ Jag har svåra smärtor eller besvär

11.5: ÅNGEST / DEPRESSION

☐ Jag är inte orolig eller nedstämd

☐ Jag är orolig eller nedstämd i viss utsträckning

☐ Jag är i högsta grad orolig eller nedstämd



11.6: Hur tycker du att Din hälsa är I DAG?

Skalan till höger går från 0 till 100.

- 100 är den bästa hälsa du kan tänka dig.
- 0 är den sämsta hälsa du kan tänka dig.
- Markera med X på skalan för att indikera hur din hälsa är I DAG.

Var god att också skriv motsvarande siffra här:

DIN HÄLSA I DAG= _____

NACKFUNKTIONSSKALA

Följande frågor är utformade för att ge oss information om hur din nacksmärta påverkar ditt dagliga liv. Besvara varje avsnitt och markera bara den enda ruta som passar dig. Vi är medvetna om att det kan vara svårt att välja mellan två närstående påståenden, men var vänlig kryssa bara i den rutan som mest motsvarar er situation.

12.1: SMÄRTINTENSITET

☐ Jag har ingen smärta för närvarande

☐ Smärtan är mycket lätt

☐ Smärtan är måttlig

☐ Smärtan är svår

☐ Smärtan är mycket svår

☐ Smärtan är värsta tänkbara

12.2: PERSONLIG OMVÅRDNAD (Hygien, påklädning etc)

☐ Jag kan sköta mig själv som vanligt utan att få ökad smärta

☐ Jag kan sköta mig själv som vanligt, men det orsakar ökad smärta

☐ Det innebär smärta att sköta mig själv och jag är försiktig och långsam

☐Jag behöver en del hjälp, men klarar det mesta av min personliga omvårdnad

☐ Jag behöver hjälp varje dag med det mesta i min personliga omvårdnad

☐ Jag klär inte på mig, tvättar mig med svårigheter och ligger till sängs

12.3: LYFTA

☐ Jag kan lyfta tunga saker utan ökad smärta

☐ Jag kan lyfta tunga saker, men det ger ökad smärta

☐ Smärtan hindrar mig från att lyfta tunga föremål från golvet, men jag klarar det om det är lämpligt placerat, ex på ett bord

☐ Smärtan hindrar mig från att lyfta tunga föremål, men jag klarar medeltunga föremål, om

de är lämpligt placerade

☐ Jag kan lyfta mycket lätta föremål

☐ Jag kan inte lyfta eller bära något överhuvudtaget

12.4: LÄSNING

☐ Jag kan läsa så mycket som jag vill utan smärta från nacken

☐ Jag kan läsa så mycket jag vill med lätt smärta i nacken

☐ Jag kan läsa så mycket jag vill, men med måttlig smärta i nacken

☐ Jag kan inte läsa så mycket jag vill p g a måttlig smärta från nacken

☐ Jag kan knappast läsa alls p g a svår smärta från nacken

☐ Jag kan inte läsa alls p g a smärtan

12.5: HUVUDVÄRK

☐ Jag har ingen huvudvärk överhuvudtaget

☐ Jag har lätt huvudvärk då och då

☐ Jag har måttlig huvudvärk då och då

☐ Jag har måttlig huvudvärk ofta

☐ Jag har svår huvudvärk ofta

☐ Jag har svår huvudvärk praktiskt taget hela tiden

12.6: KONCENTRATION

☐ Jag kan koncentrera mig helt och hållet när jag behöver, utan problem

☐ Jag kan koncentrera mig helt och hållet när jag behöver, men får lindriga besvär

☐ Jag har måttliga svårigheter att koncentrera mig när jag behöver

☐ Jag har stora svårigheter att koncentrera mig när jag behöver

☐ Jag har avsevärda problem att koncentrera mig när jag behöver

☐ Jag kan inte koncentrera mig alls

12.7: ARBETE

☐ Jag kan utföra så mycket arbete som jag vill

☐ Jag kan bara göra mitt vanliga arbete, men inte mer

☐ Jag kan göra det mesta av mitt vanliga arbete, men inte mer

☐ Jag kan inte utföra mitt vanliga arbete

☐ Jag kan knappast utföra något arbete alls

☐ Jag kan inte utföra något arbete alls

12.8: BILKÖRNING

☐ Jag kan köra bil utan någon nacksmärta

☐ Jag kan köra bil så länge jag vill, med lätt smärta i nacken

☐ Jag kan köra bil så länge jag vill, med måttlig smärta i nacken

☐ Jag kan inte köra bil så länge jag vill p g a måttlig smärta från nacken

☐ Jag kan knappast köra bil alls p g a svår smärta från nacken

☐ Jag kan inte köra bil alls p g a nacksmärtan

12.9: SÖMN

☐ Jag har inga problem med sömnen

☐ Min sömn är lätt störd (mindre än 1 timme sömnlöshet pga. smärtan)

☐ Min sömn är måttligt störd (1-2 timmer sömnlöshet pga. smärtan)

☐ Min sömn är tämligen störd (2-3 timmer sömnlöshet pga. smärtan)

☐ Min sömn är kraftigt störd (3-5 timmer sömnlöshet pga. smärtan)

☐ Min sömn är helt och hållet störd (5-7 timmer sömnlöshet pga. smärtan)

12.10: FRITIDSAKTIVITETER

☐Jag klarar att utföra alla mina fritidsaktiviteter utan någon nacksmärta

☐ Jag klarar att utföra alla mina fritidsaktiviteter, men med lätt smärta i nacken

☐ Jag klarar att utföra de flesta, dock inte alla mina vanliga fritidsaktiviteter pga. smärta i nacken

☐ Jag klarar bara att utföra ett fåtal av mina vanliga fritidsaktiviteter pga. smärta i nacken

☐ Jag kan knappast utföra några fritidsaktiviteter pga. smärta i nacken

☐ Jag kan inte utföra några fritidsaktiviteter alls

Tänk på de 2 senaste veckorna när du svarar på följande frågor:

		Instämmer inte	**Instämmer**
		0	1
13.1:	Min nacksmärta har **strålat ut i min arm/mina armar** vid något tillfälle de senaste 2 veckorna.	□	□
13.2:	Jag har haft smärta i **ländryggen** vid något tillfälle de senaste 2 veckorna	□	□
13.3:	Jag har bara **gått korta sträckor** på grund av min nacksmärta.	□	□
13.4:	Under de senaste 2 veckorna har det tagit **längre tid än vanligt att klä mig** på grund av nacksmärtan.	□	□
13.5:	Det kan vara skadligt för en person med mina besvär att vara fysiskt aktiv	□	□
13.6:	Jag har haft oroande tankar en stor del av tiden.	□	□
13.7:	Jag upplever att **min nacksmärta är fruktansvärd** och att den **aldrig kommer att bli bättre.**	□	□
13.8:	I allmänhet har jag inte **glatt mig över** de saker som jag brukar glädja mig åt.	□	□

13.9: På det stora hela, hur **besvärlig** har din nacksmärta varit **de senaste 2 veckorna**?

Inte alls	Lätt	Måttligt	Väldigt mycket	Extremt
□	□	□	□	□

Appendix 5.

Fråga om medverkan i forskningsprojektet

EFFEKTEN AV MANUELL BEHANDLING PÅ HJÄRTRYTMVARIABILITET OCH SMÄRTA

Nacksmärta är ett vanligt problem i alla åldrar, och olika behandlingar finns för att förebygga och lindra besvären. Denna studie på Karolinska Institutet har som **syfte** att undersöka effekterna av kiropraktisk behandling hos individer med återkommande och långvarig nacksmärta, genom att undersöka fysiologiska parametrar som hjärtrytmvariabilitet och smärtkänslighet.

Om Du vill delta kommer du att lottas till en av två gängse behandlingsstrategier som innebär 4 behandlingar under 2 veckor. En forskare kommer att mäta din hjärtrytm (med ett EKG) och undersöka din smärtkänslighet (genom tryck-känslighet och kallt vattenbad) före behandlingsstart, samt efter 1 och 2 veckor. Detta sker i samband med behandlingarna, och tar ca 30 minuter. Du får också fylla i enkäter med frågor om Dig och Din hälsa, samt om de besvär Du söker för. Den första enkäten fylls i vid första behandlingen, den andra efter 1 vecka, sedan efter 2, 6 och 10 veckor (uppföljningsenkäterna kommer via email). Utöver detta vill vi följa smärtutvecklingen, vilket innebär att Du får svara på två frågor om Din smärta varje dag i två veckor genom att svara på SMS. Din kiropraktor kommer inte ta del av Dina svar. Din medverkan i studien medför inte några risker och heller inte fördelar för Dig utöver de som förväntas för sedvanlig behandling. Din kiropraktors patientskadeförsäkring gäller som vanligt. Nyttan kommer för patienter i framtiden, då vi kommer kunna förklara hur behandlingen påverkar fysiologiska parametrar.

Dina uppgifter sammanställs i ett dataregister på Karolinska Institutet, som är ansvarig för behandlingen av dina personuppgifter och de uppgifter som samlas in inom studien. Uppgifterna kommer inte att samköras med andra register och ingen obehörig får ta del av uppgifterna som skyddas av bestämmelser om sekretess enligt offentlighets- och sekretesslagen. Resultatet kommer att rapporteras på gruppnivå utan möjlighet att direkt identifiera enskilda individer då en kod ersätter alla direkt identifierande uppgifter. En s.k. kodnyckel, som vid behov kan användas av forskarna för att identifiera Dig, förvaras på en CD, åtskild från de kodade uppgifterna och inlåst i förvaringsskåp. Data lagras i 10 år. Resultaten publiceras i vetenskapliga tidskrifter med ”open access”, där alla som önskar kan ta del av dem. Det är frivilligt att delta i studien och du kan när som helst avbryta Din medverkan utan vidare motivering. Du har rätt att, efter skriftlig undertecknad begäran, kostnadsfritt få ett registerutdrag från Karolinska Institutet visande vilka uppgifter som finns registrerade om Dig inom studien och hur de behandlas. Du har också rätt att få eventuellt felaktiga uppgifter rättade, begränsade eller raderade.

Har du **frågor**, kontakta ansvarig projektledare, docent Iben Axén,

Telefon: 08 524 83 228 eller per mail: iben.axen@ki.se

Forskningshuvudman är Karolinska Institutet.

KOD __ ___

SAMTYCKESHANDLING

Var god TEXTA tydligt:

Namn:……..

Adress: ……

Postnummer och ort:……

Email: ……..

Mobilnr:……...

Jag har tagit del av vidstående information, fått möjlighet att ställa frågor om studien och fått dessa besvarade. Jag samtycker till att delta i studien och till att mina personuppgifter behandlas på det sätt jag fått information om.

20__-____-____ _____ _____

datum ort sign.