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Chronic Pain and Exercise

**Studies on pain intensity, biochemistry, adherence
and attitudes**

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Kinesiskt ordspråk

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ABSTRACT

Chronic pain is common in western countries and entails considerable consequences for the afflicted individuals as well as for the society. Furthermore, chronic pain is complex including an advanced interplay between biological-, psychological- and social aspects. Treatment of chronic pain attempts to decrease pain intensity and increase physical-, psychological- and social functioning. However, the treatment of chronic pain is still not optimized. Different types of physical activity and exercise (PA&E) are commonly applied as non-pharmacological treatment strategies for chronic pain, but the most efficient type and dose of PA&E are unclear. In addition, adherence to prescribed PA&E is often troublesome, which further complicates the application of PA&E as treatment for chronic pain.

The aim of this thesis is to increase the knowledge about PA&E as treatment for chronic pain regarding pain intensity, biochemical substances, adherence and attitudes.

The findings of this thesis were that a long-term, home-based PA&E intervention comprising strength exercises as well as stretch exercises decreased pain intensity and increased function in women with chronic neck- and shoulder pain. Using microdialysis technique, differences in pain modulatory biochemical substances were found, before the intervention, in painful trapezius muscle compared to pain-free trapezius muscle. In addition, alterations in pain modulatory substances in painful trapezius muscle after the intervention were found, which possibly could imply peripheral physiological effects of PA&E. Furthermore, psychological factors could be associated to the effects of and adherence to the PA&E intervention. An intention to be physically active were expressed by patients with chronic pain, but a discordance between the intention and PA&E-behaviour were evident, even though the PA&E were experienced as valuable.

In conclusion, this thesis strengthens the importance of PA&E as treatment for chronic pain. Especially, this thesis increases the knowledge about; possible peripheral pain inhibitory effects after long-term exercise; how psychological factors might affect the results of PA&E; and also about important behavioural aspects that might affect adherence to prescribed PA&E. This thesis highlights the need of more research on physiological pain inhibitory effects of long-term PA&E in chronic pain. Furthermore, improved methods for ensured adherence to prescribed PA&E are necessary in order to optimize the effect of PA&E as treatment for chronic pain.

Keywords: Adherence, biochemical substances, chronic pain, physical activity and exercise, treatment

SVENSK SAMMANFATTNING

Långvarig smärta är vanligt förekommande i västvärlden och medför stora konsekvenser för de drabbade individerna såväl som för samhället. Dessutom är långvarig smärta komplex och innefattar ett avancerat samspel mellan biologiska-, psykologiska och sociala aspekter. Behandling av långvarig smärta avser att minska smärtintensitet samt öka fysisk, psykisk och social funktion. Behandling av långvarig smärta är emellertid fortfarande inte optimal. Olika typer av fysisk aktivitet och träning (FA&T) används vanligen som icke-farmakologiska behandlingsstrategier, men den mest effektiva typen och dosen av FA&T är oklara. Dessutom är följsamheten till förskriften FA&T ofta låg, vilket ytterligare komplicerar användande av FA&T som behandling av långvarig smärta.

Syftet med avhandlingen är att öka kunskapen om FA&T som behandling vid långvarig smärta avseende smärtintensitet, biokemiska substanser, följsamhet och attityder till FA&T.

Fynden i avhandlingen var att en hemträningsintervention utförd under lång tid innehållande styrketräning såväl som stretching minskade smärtintensitet och förbättrade funktionen hos kvinnor med långvarig nack- skuldersmärta. Genom att använda mikrodialysteknik upptäcktes skillnader i smärtmodulerande biokemiska substanser innan interventionen mellan smärtande trapeziusmuskel och icke-smärtande trapeziusmuskel. Därtill upptäcktes förändringar i smärtmodulerande substanser i smärtande trapeziusmuskel efter interventionen, vilket möjligen skulle kunna innebära perifera fysiologiska effekter av FA&T. Dessutom kunde psykologiska faktorer associeras till effekterna av och följsamheten till FA&T interventionen. En intention att vara fysiskt aktiv uttrycktes av patienter med långvarig smärta, men en brist på samstämmighet mellan intentionen och genomförandet av FA&T var uppenbar, även då FA&T upplevdes som värdefullt.

Sammanfattningsvis så stärker den här av handlingen betydelsen av FA&T som behandling av långvarig smärta. Framförallt så bidrar avhandlingen till ökad kunskap om; möjliga perifera smärthämmande effekter av långvarig träning; hur psykologiska faktorer kan påverka resultaten av FA&T; och även om viktiga beteendemässiga aspekter som kan påverka följsamheten till förskriften FA&T. Avhandlingen belyser behovet av mer forskning om fysiologiska smärthämmande effekter av långvarig smärta. Dessutom så är förbättrade metoder för att säkerställa följsamheten till förskriften FA&T nödvändig för att optimera effekten av FA&T som behandling för långvarig smärta.

Nyckelord: Följsamhet, biokemiska substanser, långvarig smärta, fysisk aktivitet och träning, behandling

LIST OF PAPERS

The present thesis is based on the following studies, which will be referred to in the text by their numerals.

- Paper 1:** Karlsson L, Takala E-P, Gerdle B, Larsson B. Evaluation of pain and function after two home exercise programs in a clinical trial on women with chronic neck pain - With special emphasises on completers and responders. BMC Musculoskeletal Disorders, 2014. 15(1).
- Paper 2:** Karlsson L, Gerdle B, Ghafouri B, Bäckryd E, Olausson P, Ghafouri N, Larsson B. Intramuscular pain modulatory substances before and after exercise in women with chronic neck pain. Eur J Pain, 2015. 19(8): p. 1075-85.
- Paper 3:** Karlsson L, Gerdle B, Takala E-P, Andersson G, Larsson B. Associations between psychological factors and the effect of home-based physical exercise in women with chronic neck and shoulder pain. SAGE Open Med, 2016. 4: p. 2050312116668933.
- Paper 4:** Karlsson L, Gerdle B, Takala E-P, Andersson G, Larsson B Experiences and attitudes about physical activity and exercise in patients with chronic pain: A qualitative interview study. Submitted to Disability and Rehabilitation.

The papers **1 – 4** are appended to the thesis.

LIST OF ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
AUC	Area Under Curve
CBT	Cognitive Behavioural Therapy
HAPA	Health Action Process Approach
IASP	International Association for the Study of Pain
MeSH	Medical Sub Heading
NDI	Neck Disability Index
NRS	Numeric Rating Scale
PA&E	Physical Activity and Exercise
PCA	Principal Components Analysis
PLSR	Partial Least Squares Regression
PPT	Pressure Pain Threshold
ROM	Range of Motion
SDT	Self Determination Theory
VIP	Variable Importance in Projection
VO₂max	Maximal Oxygen uptake

BACKGROUND

DEFINITIONS

PAIN AND CHRONIC PAIN

Pain is, according to the Medical Subject Heading (MeSH) database in PubMed, described as “An unpleasant sensation induced by noxious stimuli which are detected by nerve endings of nociceptive neurons”. A more extended definition of pain is proposed by the International Association for the Study of Pain (IASP). The IASP definition of pain reads: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. The IASP definition of pain is widely recognized and has been the predominant definition in pain research for decades.

The definition of chronic pain is not as well established as the definition of pain above. The MeSH database in PubMed introduced in 2012 a description of chronic pain as: “Aching sensation that persists for more than a few months. It may or may not be associated with trauma or disease, and may persist after the initial injury has healed. Its localization, character, and timing are more vague than with acute pain.” The time-aspect is central in definitions of chronic pain. Chronic pain is often defined as pain lasting for more than three to six months [1, 2]. But chronic pain can also be described as pain that remains after the normal healing time, in general three months [2, 3].

PHYSICAL ACTIVITY AND PHYSICAL EXERCISE

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Physical exercise is a subset of physical activity characterized by planned, structured, and repetitive physical activities with an objective to maintain or improve physical fitness [4]. In the literature the terms physical activity and physical exercise are often used interchangeably or combined, thus not entirely consequent to the definitions. Because of the inconsistency in terminology in the literature, the term physical activity and exercise (PA&E) will be used in the following thesis.

ADHERENCE

The extent to which an individual adopts and follows a professional prescription or advice about treatment is in the literature described in terms of compliance, adherence or concordance [5, 6]. Most research in this field has focused on medication prescription [7, 8], even though the principle of properly conducting a treatment plan probably is important for optimizing improvement for other interventions as well, for example PA&E [7].

The terms compliance, adherence and concordance are sometimes used interchangeable, however differences between the concepts have been proposed [5, 6]. Compliance refers to the extent which the patients' behaviour is in line with the prescribed recommendations, that is the professional dictates the conditions. Adherence on the other hand, include the patients' perspective. Thus, adherence describe the conduction of a treatment which has been discussed, agreed on and where the patients' standpoints has been taken into consideration. The term concordance highlight the negotiation and consensus between the professional and patient even more [5, 6]. Adherence is suggested to be more preferable than compliance as adherence put more emphasises on the consent between the professional care-giver and the patient [6, 9], and thus is more judgeless. In this doctoral thesis, the term adherence will be used to describe the participants' adoption and conduction of agreed recommendations of PA&E.

CHRONIC PAIN AND THE BIOPSYCHOSOCIAL MODEL

The IASP definition of pain including "... a sensory and emotional experience..."[1], establish both biological and psychological aspects in the pain perception. This definition of pain can easily be connected to the concept of the biopsychosocial model [10-12], which argues against a dualistic approach in medicine and health sciences that separates biological aspects from psychological and social aspects. Instead, the biopsychosocial model attempts to include the interaction between biological as well as psychological and social factors in the understanding, treatment and evaluation of chronic pain, illustrated in figure 1. That is, the perception of pain is not equivalent to nociception (activation of nociceptors in the nervous system), but is rather an experience generated through both biological and psychosocial factors, for example previous pain experiences, mood, expectations, beliefs, reinforcement, predicted consequences and sociocultural aspects [13-15]. Thus, principles of the biopsychosocial model should be included in the clinical management of chronic pain and the model is an important basis in scientific studies of chronic pain. This present doctoral thesis has its foundation in parts of the biopsychosocial model and in the IASP definition of pain. Hence, the content include chronic pain in relation to biological factors as well as psychological factors. However, social factors are not covered in this thesis.

Figure 1: According to the biopsychosocial model there is a reciprocal interaction between biological-, psychological- and social factors affecting pain perception.

EPIDEMIOLOGY OF CHRONIC PAIN

Chronic pain is a significant health problem. In industrialized countries, the prevalence of chronic pain is approximately 20% [16-20], and in the general population, neck pain has a one-year prevalence of approximately 25% [21, 22]. Chronic pain entails major consequences for the individuals and the society [16-18, 20, 21]. Physical disability has been reported, for example in terms of difficulties to perform every day activities, from sleeping and basic household activities to engaging in social activities, working and maintaining an independent living [16, 23]. In addition, negative emotional experiences associated to chronic pain, for example a negatively affected mood state, catastrophizing thoughts and fear of the pain have frequently been reported by individuals suffering chronic pain [24], and the quality of life can be severely decreased [25-27]. Moreover, chronic pain entails as a huge socioeconomic burden for the society. The socioeconomic consequences include for example work absenteeism, health care utilization and allowance from the social insurance system [23, 28]. The consequences and characteristics (see below) for chronic pain are not linked to specific diagnoses or pain sites. Instead, most chronic pain conditions share several similar overall features, even if different sub-categories of patients suffering chronic pain there can be identified.

There is still a lack of highly effective methods for the management of chronic pain [29]. Currently, there are most often no curative options for the treatment of chronic pain [14, 15]. Management of chronic pain is instead aiming at increase bodily and vocational functioning, increase psychological well-being, and limit pain intensity [15]. The effects of the best available chronic pain treatment, such as pharmacological treatment [20, 30], multimodal rehabilitation [31, 32], PA&E [3, 33-39] and psychological treatment [40-42] have in general been weak to moderate. Thus, it is important to improve the treatment for chronic pain.

PAIN PHYSIOLOGY

Pain is a perception vital for survival as pain in the acute state is a sign of potential danger and risk for injury [43]. The physiological mechanisms underlying pain include nociception, which is activation of free nerve endings of nociceptors in peripheral tissue, sensitive to chemical, mechanical and thermal stimuli [43-45]. Two types of nerve fibers are involved in the transmission of nociceptive activity; myelinated A δ -fibers, and unmyelinated C-fibers. The A δ -fibers are fast leading fibers resulting in a sharp and well localized pain sensation. The C-fibers are transmitting the nociceptive activity with a slower speed, leading to a diffuse and dull pain sensation. The neural activity in peripheral neurons terminate at neurons in the dorsal horn of the spinal cord, from which the nociceptive information ascends further in the central nervous system [43, 44]. Via synapses in the brainstem and thalamus, the nociceptive pathways activate areas of the brain such as somatosensory cortex and pre-frontal cortex processing sensory – discriminative components of the pain perception, as well as insula and anterior cingulate cortex processing affective and motivational components [44, 46, 47]. Physiological mechanisms of pain also include descending, pain modulatory functions initiated in midbrain and medullary areas [47]. Activation of periaqueductal gray from higher brain centers can inhibit pain. The rostroventromedial medulla can likewise modulate nociceptive activity in the central nervous system [44, 47]. There are also endogenous pain inhibitory substances in the central and peripheral nervous system which have a pain modulatory effect for example endocannabinoids [48], and endorphins [49].

When pain persists longer than three months, or beyond the normal healing time, and becomes chronic [2], the pain implies more than just prolonged acute pain. One primary feature associated with chronic pain is central sensitization [50], which entails a long-lasting hyperexcitability [51], manifested as hypersensitivity for sensory input [52].

According to IASP, central sensitization is an increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input [51]. The increased responsiveness of the nociceptive activity in the central nervous system includes for example enhanced temporal summation, and long term potentiation [53, 54]. Also, changes in descending, pain inhibiting pathways are part of the central sensitization [51]. Implications of central sensitization are amplification of the ascending actions, and attenuation of the descending actions in the central nervous system [55, 56], which lead to increased sensitivity for all kinds of sensory input. These changes contribute to the pathophysiology of chronic pain. Remodulation of structures and function in the brain has been showed in chronic pain, for example decreased gray matter volume in specific areas of the brain, decreased connectivity in the descending pain-modulating pathways, and increased activity in the regions of the brain associated to pain processing [57]. However, changes in the central nervous system are not the only physiological explanation for chronic pain conditions. For example, the central hyperexcitability might be underpinned by input from activity in the peripheral nervous system [53, 58]. In addition, several underlying pain mechanisms has been proposed for example for chronic whiplash-associated disorder and non-specific neck pain, with central mechanisms proposed to be more prominent for the first diagnosis [59]. Thus, the physiological mechanisms in chronic pain also include peripheral neurobiological mechanisms [60].

In peripheral tissue, several neurobiological substances have been linked to either pain inducing, or pain inhibitory actions [60, 61]. Earlier research has targeted for example glutamate, lactate, pyruvate, serotonin, pro-inflammatory cytokines, bradykinin, and endocannabinoids [61, 62].

Glutamate is an excitatory neurotransmitter present in the central and peripheral nervous system [63-66]. In the peripheral nervous system, glutamate is stored in vesicles at peripheral and spinal terminals in afferent neurons. Glutamate is released from the nociceptive free nerve endings by noxious stimuli such as chemical activation and mechanical tissue damage. Extracellular glutamate is described to activate the same or adjacent nerve terminal through activation of excitatory amino acid receptors (for example N-methyl-D-Aspartate (NMDA) receptors) [64, 67, 68]. The algescic action of glutamate involves excitation of nociceptive neurons and sensitization of the neuron [64, 69-71]. Glutamate injections in pain-free human muscle have resulted in pain responses [71-76]. In addition, the experimental glutamate evoked pain can be reduced by a coinjection of an NMDA-antagonist [76-78] which indicates an association between glutamate concentrations in the muscle, activity in NMDA-receptors and pain response. Further, research about glutamate as a pain enhancing substance has reported higher concentrations of glutamate in the trapezius muscle in women with trapezius myalgia [61, 79-81], in the masseter muscle in patients with myofascial temporomandibular disorder [82] and in sore calf muscles [83].

Lactate and pyruvate, products of cell glycolysis has, with divergent results, been examined in muscle interstitium in painful and pain free muscles [79-81, 84-88]. Lactate has a complex physiological function as it can be produced during anaerobic and aerobic conditions and can be metabolized in the same cell or transported to other cells for metabolic use [89, 90]. Furthermore, lactate and pyruvate can be converted into each other [90, 91], by the enzyme lactate dehydrogenase which has been found for example in skeletal muscles, heart, liver, kidney, spleen and fat [92].

Substance P has an excitatory effect in the nervous system [93-95], and is also included in neurogenic inflammation [94, 96], thus acting as an algescic substance. Increased levels of substance P has been found in painful trapezius muscles [97, 98]. The presence of **beta-endorphin** and **cortisol** in painful muscles are less studied. Beta-endorphin has strong analgesic impact when present in peripheral tissue [99-102] and this effect is associated with attenuation of the excitability of nociceptive neurons and inhibiting the release of nociceptive and inflammatory substances (for example substance P) [101, 103]. The physiological effects of cortisol are complex with the main function to retain homeostasis in presence of changing demands and stress [104, 105].

To investigate peripheral pain modulatory substances in tissue, the microdialysis method can be used. The microdialysis method [61, 106] is a reliable and frequently used method for measuring the concentrations of unbound biochemical substances in bodily tissue. The equipment consists of a thin catheter with a semipermeable membrane which is inserted into the tissue of interest. The catheter mimics a blood vessel and molecules in the tissue diffuse into the catheter via the membrane. During microdialysis, a liquid similar to the muscle interstitium is pumped through the catheter and biochemical substances diffuse out through the membrane to vials which enables chemical analyse and quantification of the biochemical substances.

PSYCHOLOGICAL FACTORS

Several psychological factors have been linked to the perception of pain and to pain related function [107, 108]. Moreover, psychological interventions, for example variants of Cognitive Behavioural Therapy (CBT) for the treatment of chronic pain have been studied extensively [41, 42, 109, 110].

Psychological factors can have different effect on chronic pain conditions. Depression symptoms, anxiety, catastrophizing and fear-avoidance beliefs have for example been reported to entail poorer pain related functioning and increased pain perception, but self-efficacy and acceptance have on the other hand been suggested to lead to better function and decreased pain perception [108].

Anxiety and **depression** are negative emotions which may interfere with pain symptoms and increase the severity and complexity of the pain condition [108, 111-113]. Several associations between emotions and chronic pain have been described earlier such as poor outcome of chronic pain treatment, high pain intensity and as predictor of chronification [111]. Furthermore, in chronic pain conditions, high comorbidity with mood disorders have been reported [111, 112, 114]. Neurobiological [115, 116], as well as emotional aspects in terms of suffering [111], has been reported earlier to explain the link between pain and anxiety and depression. Hitherto, the associations are however not fully understood yet.

Anxiety and depression are emotions underpinning **catastrophizing**, which is a cognitive processes characterized by negative and irrational expectations about future events. Catastrophizing is a psychological factor which has been recognized as important for pain related disability. Catastrophizing related to pain is described as a mental set during a present or anticipated pain experience that magnifies the severity and impact of pain. Catastrophizing is related to pain and disability [108, 117, 118] and is also a prognostic factor for symptom severity in chronic pain [119]. The conceptualization of catastrophizing include three domains; magnification, rumination and helplessness [117, 118, 120].

In addition, catastrophizing is a suggested part of the **fear-avoidance** model [121-123], which is developed with an attempt to theoretically explain the wide variation in individual responses to pain [124]. The two factors fear and avoidance are at the core of the model, possibly preceded by catastrophizing as a result of a pain experience. Fear can be evoked as an emotional response to actual or anticipated pain, because of the potential danger the pain implies. Avoidance is a behaviour aiming to avoid, hinder or postpone the negative experience of pain [124].

The avoidance behaviour is problematic in chronic pain conditions, because the physical and psychological consequences of avoidance are for example deconditioning, depression and disability which in turn can lead to even more pain and suffering. In addition, avoidance is a reinforcing behaviour in the short term as it lead to a positive experience of not perceiving the expected pain. The disabling loop in the fear-avoidance is simplified and illustrated in figure 2.

Figure 2: A simplified illustration of the disabling loop in the fear avoidance model. Pain can lead to catastrophizing and pain related fear. Avoidance becomes a strategy to escape the aversive experience, or the anticipated aversive experience related to pain. Pain-related fear and avoidance lead to deconditioning, depression and disability, with in turn enhance and worsening the pain experience.

The fear-avoidance model also include a way to recovery and full function, characterized by no fear and confrontation. The fear-avoidance model has been studied extensively related to pain intensity and disability [125, 126].

Self-efficacy is in Social Cognitive Theory put forward as an essential factor preceding and predicting behaviour [127, 128]. Self-efficacy is defined as an individuals' own beliefs about the ability to perform tasks and activities, even if there are difficulties and adversities [127, 128]. General self-efficacy refers to an overall perception of a personal ability to effectively handle a broad range of stressful situations [129], whereas pain self-efficacy is a domain specific self-efficacy related to performing activities and tasks despite of pain [130]. Self-efficacy has received attention in research about chronic pain [130, 131] and has been defined as an important aspect for the performance of activities in spite of pain.

The ability to perform desired activities in presence of pain has also been associated to the concept of **acceptance**, a core component in the method Acceptance and Commitment Therapy (ACT), with roots in Cognitive Behavioural Therapy (CBT) [132, 133]. Acceptance implies to handle with situations as they are, not to seek options that is not available or trying to escape from the situation [132]. Related to chronic pain, acceptance is about not struggling with eliminating the pain, but performing activities that is in line with the own goals of daily life. The purpose of acceptance according to ACT, is not to decrease the pain. Rather, the intention and actions should be oriented towards performing important and valuable activities [134, 135].

PHYSICAL ACTIVITY AND EXERCISE AS TREATMENT FOR CHRONIC PAIN

Physical activity and exercise can be used as a single treatments, or as a part of multimodal rehabilitation for chronic pain [3, 31-33, 38]. One outcome of interest if often changes in physical functioning. In addition, psychological function, pain intensity, and quality of life are among the outcome measurements often studied in clinical research based on PA&E as treatment for chronic pain [3]. The types of PA&E most often studied include, separately or in combinations; aerobic PA&E, strength PA&E, flexibility PA&E and coordination PA&E [3]. Moreover, supervised PA&E is commonly studied, but also home-based PA&E for example for the treatment of neck pain as in **paper 1, 2 and 3** in this thesis , is also evaluated as beneficial in a recent review [136].

PHYSICAL ACTIVITY AND EXERCISE PHYSIOLOGY

The recommended dose of PA&E for healthy adults, in order to prevent illness and diseases, is at least 150 minutes of moderate intensive, or 75 minutes of intensive PA&E per week in combination with muscle strengthening PA&E two times per week [137]. Physical activity and exercise entails major physiological adaptations. Normally, regular PA&E lead to reactions including morphological-, hormonal-, metabolic-, and regenerative responses in healthy individuals.

Aerobic activity and exercise involves mainly the cardiovascular- and respiratory systems and also skeletal muscles. In addition, oxygen supply for the metabolism is required [138, 139]. The effects of aerobic PA&E are increased stroke volume of the heart, increased uptake of oxygen in the red blood cells, and increased blood volume in combination with extended capillary net and increased numbers of mitochondria, in order to receive and consume the oxygen for energy expenditure [139, 140]. Intensity of aerobic PA&E is described as percentages of maximal oxygen-uptake ($VO_2\text{max}$) [34], where light intensity refers to less than 60 % of $VO_2\text{max}$, medium intensity to 60 – 75 % of $VO_2\text{max}$ and high intensity to more than 75 % of $VO_2\text{max}$.

Muscular activity and exercise can target different qualities of muscular function, for example strength and endurance. Skeletal muscles are adaptable to PA&E as well as to sedentary activities. Four main types of muscle fibers exist; type I, type II a, type II x/d, and type II b [141, 142]. The difference between the fiber types can be explained by variants of their contractile- (slow-twitch and fast-twitch), and metabolic function (oxidative or glycolytic). The contractile function of the muscle fiber is depending on the molecular composition and Ca^{2+} release and uptake [142]. The type II fibers are mainly fast-contractile and as such the main target in strengthening PA&E.

The increase in muscular strength following strength PA&E involves stem cells in the muscles; satellite cells [143, 144], which activates as a response to PA&E and ensures restoration and growth of muscle tissue. Activation of the satellite cells is related to the intensity and length of the PA&E performed, as well as the physical fitness of the individual. In addition, strength PA&E leads to hormonal alterations and protein synthesis in the muscle which also stimulates increased strength [145]. Furthermore, neural adaptations have been proposed as one additional reason to increased strength [146]. The neural adaptations include for example increased single motor unit activity, improved correlated motor unit activity, increased spinal reflex activity, and improved efferent activity from motor cortex. However, the findings about neural adaptations to strength training are inconsistent [146].

To gain increased strength and muscle growth, the principle of overload is crucial [137, 145]. That is, an improvement of muscular functioning requires that the dose (intensity x time) of PA&E exceeds the current level of capacity. The response of such overload that is improved muscular function, is partly depending on what type of stimuli applied [137, 145, 147].

Flexibility activity and exercise can be performed as for example stretching. Flexibility of a muscle is related to its tension, which can be divided in active tension (innervation of motor neuron and reflexive activation), and passive tension (viscoelasticity and fascia) [148-150]. Consequently, the acute effects of stretch can be described in terms of viscoelastic and neural effects [150, 151]. Viscoelastic effects are shown as a decrease in resistance to passive tension of the muscle. The neural effects is related to an inhibition of contractile activity in the muscles, which leads to an acute stretch-induced strength loss [148, 150, 151].

Coordination activity and exercise is a broad concept which may for example include; symmetry, activation, timing, pattern, balance and force of movements. Moreover, coordination PA&E can include a combination of aerobic-, strengthening- and flexibility components and thus, the physiological effects of coordination PA&E is complicated to discern.

Physical activity and exercise focusing on local effects in the muscles is to a large extent specific [137, 145]. That is, if strength exercises targets the neck- and shoulder muscles the main effects are to be expected in those specific muscles, not in for example the lower extremities. Additionally, if the exercises mainly target muscular endurance, the main result is to be expected in endurance, not in for example maximal strength. However, it is difficult to definitely separate the different muscular qualities as functional overlap exists.

The cardiovascular- and muscular systems are adaptable and modifies as a response to the physiological loads they are exposed to [137, 139]. The physiological responses to PA&E are to some extent individual, but the amount of loading performed seems to be essential. An PA&E frequency of three times per week are recommended to improve physical fitness in an ordinary, non-athletic population [145]. When the physical fitness improves, more intensive PA&E are needed in line with the principles of overload [137, 145], to reach further improvements. Likewise, the physical effects of PA&E are reversible [139, 152]. That is, if dose and frequency of the PA&E decreases, the physical fitness decreases as well.

PHYSICAL ACTIVITY AND EXERCISE, AND PAIN INHIBITORY EFFECT MECHANISMS

Given that normal physiological responses to PA&E in terms of physiological adaptations leading to improved physiological fitness also are valid for individuals with chronic pain, principles of exercise physiology should be considered when designing a PA&E based intervention for chronic pain. There is a lack of studies specifically targeting the physiological effect mechanisms of PA&E interventions in chronic pain. Thus, detailed knowledge about alterations in physiological responses to PA&E in chronic pain are still unclear. In addition, PA&E interventions evaluated in clinical trials are often a blend between different types of PA&E, and thus the associations between the effect of the PA&E intervention and the probable physiological response is difficult to detect in such trials.

PHYSICAL ACTIVITY AND EXERCISE – SHORT TERM PAIN INHIBITORY MECHANISMS

Acute effects of decreased pain perception after PA&E, termed exercise-induced hypoalgesia, has been shown in healthy individual as well as in individuals suffering chronic pain [153, 154]. The pain inhibitory effects has been proposed to derive from descending pain modulating pathways in the central nervous system, as well as from the release of endogenous endorphins [153-155]. In addition, associations between blood pressure and pain inhibition has been noted, although the interactions between blood pressure and pain inhibition not is entirely understood [156-159].

Both aerobic PA&E and strength PA&E (isometric and dynamic) has been shown to decrease the perception of experimentally induced pain stimuli in healthy individuals. PA&E at relatively high intensity (70 % of $\text{VO}_{2\text{max}}$) have been reported to decrease pain sensitivity for up to 30 minutes post PA&E, whereas muscle strengthening PA&Es can decrease pain during a few minutes [154, 160]. In addition, there are data supporting a dose-response relationship between intensity or length of the PA&E and the hypoalgesic effect. Thus, an intensity of 75 % $\text{VO}_{2\text{max}}$ during >10 minutes, or an intensity of 50 % $\text{VO}_{2\text{max}}$ during 30 minutes seems to be required to get a moderate to high hypoalgesic effect in healthy individuals [153].

In individuals with chronic pain the effects of PA&E-related pain inhibition are however diverging. For individuals with chronic pain, the acute hypoalgesic effect on experimental induced pain are ranging from increased to decreased pain response after PA&E [153]. Recent research reports similar brain responses related to descending pain inhibition after PA&E in patients with fibromyalgia syndrome as in pain-free controls [161]. In addition, increased pain pressure thresholds after two weeks of high intensity aerobic PA&E (30 min, five days per week) has been shown for patients with chronic pain [162]. However, an immediately pain inhibitory effect after muscle contractions has not been shown in patients suffering from the chronic pain condition fibromyalgia syndrome [154, 163], which may indicate that a probable component of central hyperexcitability may diminish the pain inhibitory effect of muscle activity. In addition, patients with regional pain report pain inhibition after muscle contraction in non-painful muscles contrary to the painful muscles [154]. And furthermore, pain inhibition after isometric PA&E in non-painful muscles, but not after aerobic PA&E for individuals with whiplash associated disorders has been reported recently [164].

PHYSICAL ACTIVITY AND EXERCISE – LONG TERM PAIN INHIBITORY MECHANISMS

The long-term effect of PA&E on processes in the central nervous system, as well as peripheral pain modulatory substances are largely unknown. However, in healthy individuals, there are signs of decreased pain sensitivity following regular aerobic PA&E [165, 166]. Recent research has shown a normalization of glutamate and pyruvate in vastus lateralis muscle after a PA&E intervention [167], and alterations in parts of the endocannabinoid system in trapezius muscle after long term PA&E [168]. In addition, alterations in inflammatory substances and genes involved in neurotransmission after long term PA&E are reported [62]. But there is still a lack of research on the effect of different types of long term PA&E on mechanisms in the central nervous system, as well as on peripheral, pain modulatory substances.

PHYSICAL ACTIVITY AND EXERCISE – PSYCHOLOGICAL EFFECTS

PA&E applied as treatment for chronic pain do not only improve pain intensity and physical function, also the psychological function might be improved [3]. PA&E has a beneficial impact on psychological symptoms often found in combination with chronic pain such as depression [169], and anxiety [170]. In addition, psychological function is often an outcome of interest in research on PA&E as treatment for chronic pain, and positive changes in psychological function after PA&E. However, results are inconclusive as a no difference in psychological function after PA&E also are reported [3].

APPLICATION OF PHYSICAL ACTIVITY AND EXERCISE AS TREATMENT FOR CHRONIC PAIN

PA&E are per definition physiological actions, and they are also behaviours [171]. Thus, behavioural factors are crucial for research about PA&E as treatment for chronic pain. Behaviour is described in terms of overt behaviour (actions that is observable by others), and covert behaviour (actions that takes place within an individual, such as thoughts and emotions) [171]. Related to PA&E as treatment, covert behavioral factors could be psychological factors that might affect the PA&E, for example fear-avoidance, anxiety and pain acceptance. Overt behavioural factors could for example include the performance of prescribed PA&E in a proper way, and also adherence to the PA&E regimen.

Adherence to treatment plans can be troublesome, and poor adherence to prescribed PA&E is likely to diminish the effect of the PA&E treatment [7, 172]. Supervised PA&E, individually tailored treatment plans and self-management and behaviour change strategies can improve adherence to PA&E as treatment [7, 173], but there is still a lack of studies focusing on improving adherence to PA&E as treatment for chronic pain [174]. Behaviour change strategies might be especially useful in order to improve adherence, because the application of PA&E-based treatment most often entails a change of behaviour. There are a range of theories and models which have been used to explain health behaviour change, for example Social Cognitive Theory [127, 128], the Transtheoretical Model [175, 176], the Health Action Process Approach [177, 178], and motivational theories such as the Self-Determination Theory [179-181]. Knowledge on different aspects of behaviour such as behaviour change and action control are probable to be beneficial for a successful application of PA&E as treatment for chronic pain. However, such aspects are seldom included in clinical trials on PA&E as treatment for chronic pain.

AIM OF THE THESIS

This doctoral thesis aims to investigate the topic PA&E as treatment for chronic pain viewed from both biological- and psychosocial standpoints. The thesis is designed to provide deeper knowledge about the impact of PA&E on chronic pain in the neck and shoulders with respect to pain intensity and disability, as well as intramuscular biochemical factors. Furthermore, the thesis intends to generate more knowledge on psychological factors, attitudes and adherence in relation to PA&E as treatment in chronic pain conditions. To fulfill the aim, four papers with separate contents are included in the thesis, summarized in figure 3.

Figure 3: The central topic chronic pain and exercise, and the content of the four papers included.

AIMS

1. To evaluate the effect on pain and function of a one year home-based PA&E intervention and to evaluate adherence to the intervention.

Research questions:

Do strength exercises decrease pain intensity and increase function more than stretching exercises?

Do the participants manage to adhere to the PA&E intervention?

2. To compare concentrations of glutamate, lactate, pyruvate, substance P, beta-endorphin and cortisol, and pain pressure sensitivity in trapezius muscle between women with chronic neck and shoulder pain and pain-free women, and to examine concentrations in these substances and pain pressure sensitivity in trapezius muscle after a PA&E intervention for women with chronic neck and shoulder pain.

Research questions:

Are there any differences in pain modulatory substances of painful trapezius muscle compared to pain-free trapezius muscle?

Does PA&E induce alterations of pain modulatory substances in painful trapezius muscle?

3. To analyse associations between psychological factors and effects of a PA&E intervention on pain intensity and disability in women with chronic neck and shoulder pain, and to analyse if differences in psychological factors had an impact on adherence to a PA&E intervention.

Research questions:

Can psychological factors be associated to the effects of the PA&E intervention?

Are there differences in psychological factors between participants who adhere to a PA&E intervention and those who do not?

4. To describe experiences and attitudes about PA&E in participants with chronic pain using qualitative content analysis.

METHODS AND MATERIALS

METHODS AND MATERIALS (PAPER 1, 2 AND 3)

DESIGN AND PROCEDURES

Data included in paper 1, 2 and 3 were collected within a randomized controlled trial evaluating a one year, home-based PA&E intervention for chronic neck- and shoulder pain, performed at Linköping University Hospital (Linköping, Sweden) between September 2009 and February 2011. Participants with neck-and shoulder pain (included in paper 1, 2 and 3), and a healthy control group (included in paper 2) were recruited from the general population through advertisements in local newspapers.

Respondents to the advertisements were informed about the study and interviewed by phone to preliminary determine the eligibility for inclusion. The respondents were mailed a package including a detailed letter about the trial, the Nordic Style Questionnaire (NSQ) [182, 183], and in addition a Swedish version of the Neck Disability Index (NDI) [184] for participants with pain in the neck –and shoulders. The NSQ provided specific information on pain location and intensity for the previous 12 months and the NDI provided information about function related to neck pain.

Before final decision on inclusion in the trial, each respondent with pain in the neck and shoulders underwent a standardized clinical examination of the neck and upper extremities. This clinical examination included questions on pain, tiredness and stiffness in the neck- and shoulder muscles, in addition to physical tests such as range of motion, flexibility of the muscles, pain sensitivity, muscle strength, and palpation [185, 186]. The clinical examination in this trial was performed by a physiotherapist trained for this task. See appended **paper 1** for more details about the trial procedures. The trial was approved by the Regional Ethical Committee in Linköping, diary number M10-80, and performed with respect to the ethical principles of the declaration of Helsinki [187]. All participants signed an informed consent before entering the study.

PARTICIPANTS

WOMEN WITH NECK- AND SHOULDER PAIN (PAPER 1, 2 AND 3)

Fifty-seven women with neck- and shoulder pain were included in the trial. Inclusion criteria were female, 20 – 60 years old, and constantly or frequently occurring pain in the neck/shoulder area for more than six months. In addition, symptoms consistent with the clinical diagnosis of tension neck syndrome (i.e. neck pain; sense of fatigue or stiffness in the neck; pain radiating from the neck to the back of the head; tightness of muscles; tender spots in the muscles) [188] were required in addition to pain intensity of at least 3 on the Numeric Rating Scale (NRS) [189] and/or a reduction in function scored as at least 10 measured by the Swedish version of the NDI [184]. The participants also had to validate that they were motivated to follow the PA&E protocol. Exclusion criteria were widespread pain, major trauma in medical history, pregnancy, inflammatory and hormonal disorders, neurological causes of the pain, tendonitis in upper extremities, and severe psychiatric illness.

PAIN-FREE WOMEN (PAPER 2)

Twenty-four healthy women without neck- and shoulder pain were included in the control group. Inclusion criteria for participant in the pain-free control group were no ongoing pain in any region of the body, or any other health-issues or diseases. Participants in the control group were not offered any intervention, but were expected to continue with their ordinary lives. Exclusion criteria for the pain-free controls were ongoing pain in the neck-and shoulders, widespread pain, pain for more than one week in any region of the body during the previous 12 months, major trauma in medical history, pregnancy, inflammatory-, neurological-, or hormonal disorders, and severe psychiatric illness.

RANDOMIZATION AND BLINDING (PAPER 1)

The participants with neck- and shoulder pain were randomly assigned to either a strength-training group (STRENGTH) or a stretching group (STRETCH). In addition, participants from both groups were randomized to participation in the microdialysis experiments. The inclusion process continued for six months and participants entered the trial in groups, which of logistical reasons started every second week. The randomization was performed by randomly selecting the start-up sequence for the group affiliations, and participation in microdialysis, using the computer program Minitab v. 15. (Minitab Inc., www.minitab.com). Participants were assigned to groups and microdialysis in a consecutive manner until it was time for the groups to start exercising. The physiotherapist conducting the standardized clinical examination of the neck and upper extremities during the inclusion process was blinded with respect to group affiliation. There were no other blinding in the trial due to limited resources.

A flowchart of the recruitment of participants with neck-and shoulder pain and assignment to the PA&E groups (STRENGTH AND STRETCH) is presented in detail in **paper 1**. Figure 4 shows assignment to the PA&E groups and to microdialysis, and distribution of participants in **papers 1, 2 and 3**.

Figure 4: Flowcharts of: *a)* Assignment to the PA&E groups included in paper 1 evaluating the effects of two home-based PA&E interventions. *b)* Assignment to microdialysis and participants analysed as one group included in paper 2, addressing biochemical alterations in painful trapezius muscle after exercise. And *c)* participants analysed as one group included in paper 3, addressing associations between psychological factors and the effects of a PA&E intervention.

COMPLETERS AND RESPONDERS (PAPER 1 AND 3)

Adherence to prescribed PA&E was of interest in this trial. Hence, completers and responders of the 57 women with neck and shoulder pain were defined as subgroups for analyses. Discontinuers were participants who dropped out from the trial.

COMPLETER AND NON-COMPLETER

In our definition, a completer reported at least eight unbroken weeks of PA&E with a frequency of at least 1.5 times per week preceding the follow-up measurements (that is, after 4-6 months and 12 months of the PA&E intervention). A non-completer was a participant who remained as a participant in the trial (that is, still was exercising), but failed to reach the defined frequency of PA&E per week valid for a completer. Data from the exercise diaries were used for the completer analysis.

RESPONDER AND NON-RESPONDER

The responder definition for pain and function was based on criteria for clinically important changes in the two outcome areas. Thus, for neck pain and shoulder pain, a decrease of at least two points on the NRS was required [190, 191]; for function, a decrease of the total NDI score of at least four points was required [192]. A non-responder was a participant who remained as a participant in the trial (that is, still was exercising), but did not reach the defined level of improvement valid for a responder.

SAMPLE SIZE

When estimating the sample size for analysing changes in pain intensity (one of the primary outcomes) *within the groups*, we assumed that the mean difference should have a standard deviation of 3. Expectation of a mean improvement of two points on the NRS, which also represents a clinically relevant improvement [190, 191], required a sample size of 20 pairs of participants to reject the null hypothesis with a power of 0.80 and a probability of <0.05 (two tailed). When estimating the sample size for analysing changes in pain intensity (one of the primary outcomes) *between the groups*, we assumed that the mean difference should have a standard deviation of 3. Expectation of a mean improvement of two points on the NRS, which also represents a clinically relevant improvement [190, 191], required a sample size of 36 participants in each group to reject the null hypothesis with a power of 0.80 and a probability of <0.05 (two tailed). Sample size calculations were made using the computer program Power and Sample Size Calculations (v. 3.0.43, <http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>).

Based on the sample size estimations, also considering a probable presence of non-completers, and our available resources for running this trial, we aimed to include 50 participants in each group.

THE PHYSICAL ACTIVITY AND EXERCISE INTERVENTION

The PA&E intervention is described in detail in **paper 1**, and illustrations of the exercises are found the appendix of this thesis. Length of the PA&E intervention was one year for both groups. The exercises for the STRENGTH group were specific strength training for the neck and shoulder muscles. The strength exercises included arm abduction, upright row, biceps curls, flys, reverse flys, and pullovers. Dumbbells were used in all these exercises. Additionally, lifting the head up (without resistance) from a supine position was also performed as a strength exercise. Three series of dynamic exercises performed 20 times each for the trunk and legs followed the strength training. The strength training for the neck- and shoulder muscles was progressive and periodized throughout the one year training period. The initial eight weeks of the training period were characterized by learning to perform the exercises correctly. During the remaining training period of one year, the strength training periodized by three weeks of exercises with the heaviest weight possible (three sets of ten repetitions) and one week of exercises with 2-kg dumbbells (three sets of 20 repetitions).

Stretching exercises for the neck, shoulders, and upper limb muscles ended the exercise session for the STRENGTH group and constituted the only specific exercise session for the STRETCH group. The stretching exercises were the same as used in a previous study [193], which comprised retraction of the neck and stretching the following muscles: m. trapezius upper and middle portion, m. sternocleidomastoideus, m. rhomboids, m. pectoralis major, and the flexors and extensors of the wrist.

Both STRENGTH and STRETCH were expected to exercise three times a week and they were also encouraged to perform an optional aerobic exercise for 30 minutes with the same frequency. The STRENGTH group was instructed to give priority to the specific strength exercises if they could not manage to perform the complete session. The participants were encouraged to organize their home exercise so that it would fit into their everyday life. All participants were provided an exercise diary to record exercise frequency and content. The exercise diary included marking long-term and short-term goals, the latter also functioning as a detailed exercise plan. Furthermore, the exercise diary contained a weekly evaluation of the implementation of the training. The diary had the same structure for both the STRENGTH and the STRETCH group and the diary had two aims; 1) to support adherence, and 2) to register performed exercises. Furthermore, support for adherence to the home PA&E programme was provided by phone or e-mail every four to eight weeks. The support included questions about how the PA&E proceeded and enabled a dialogue about any difficulties about the PA&E that might have occurred. The support was more frequent at the beginning of the one-year training period and it was conducted in the same way for both intervention groups.

MICRODIALYSIS (PAPER 2)

In order to study alterations in peripheral pain modulatory substances (glutamate, lactate, pyruvate, substance P, beta-endorphin, and cortisol), microdialysis were performed in trapezius muscle at baseline and after 4-6 months on 41 participants with neck- and shoulder pain and on 24 pain-free participants.

PROCEDURE

In the microdialysis experiments, the data were not analysed according to affiliation to the two PA&E groups, but to affiliation to *a*) participants with neck- and shoulder pain, and *b*) pain-free controls. The microdialysis method, described in detail elsewhere [106], is a reliable and frequently used method for measuring the biochemical milieu in bodily tissue. Microdialysis in this experiment followed the same principal procedure as previously described [194]. Equipment from CMA Microdialysis AB (Solna, Sweden) was used. Two thin catheters with semipermeable membranes with cut-off points 20 kDa (CMA 60) and 100 kDa (CMA 71) were inserted parallel to the muscle fibres into the pars descendens of the trapezius muscle on the most painful side for participants with pain in the neck- and shoulders, or dominant side for the healthy controls. The exact insertion point in the muscle was in the thickest part of the muscle, midway between the 6th processus spinosus and the acromion. After insertion, a physiological solution; Ringer acetate solution containing 3mM glucose, 0.5mM lactate, 0.3 $\mu\text{L}/\text{mL}$ [^{14}C]-lactate (specific activity: 5.81 GBq/mmol; GE Healthcare, Buckinghamshire, UK) and 0.3 $\mu\text{L}/\text{mL}$ $^3\text{H}_2\text{O}$ (specific activity: 37 MBq/gram) was perfused with a high-precision syringe pump (CMA 107) through the catheter with a speed of 5 $\mu\text{L}/\text{min}$. In the tissue, the catheters mimic a blood vessel and extracellular molecules diffuse through the membrane into the catheter (figure 5).

Figure 5: Illustration of the microdialysis catheter in peripheral tissue, where biochemical substances are diffusing into the catheter. (Courtesy of CMA Microdialysis)

Samples were collected in vials in 20 minute intervals. The vials were weighted at once and after that, the samples were stored as aliquots at -70 °C until the analysis. Current pain in the neck, both on the side of the catheters and the contralateral side, was measured with NRS [189] before insertion, just after insertion, and every 20 minutes (the time at which vials were changed).

After insertion of the catheters, the participants rested comfortably for 120 minutes (the trauma phase) to enable muscle recovery from possible changes in the extracellular fluid due to the insertion of the catheters. The participants then rested for an additional 20 minutes (dialysate collected at time point 140). After 140 minutes, the participants performed a standardized low force work activity for the arm and shoulder on a pegboard, as described earlier [80] for 20 minutes (dialysate collected at time point 160). The experiment ended with a recovery period where the participants again rested comfortably for 60 minutes (dialysate collected at time points 180, 200, and 220).

In this trial, two microdialysis experiments were performed. Microdialysis experiment number one served as a baseline measurement. After that, the participants with neck- and shoulder pain underwent the PA&E intervention for the neck and shoulder muscles, and the pain-free controls continued their daily living without any intervention. Four to six months after the first experiment, microdialysis experiment number two, was performed. All microdialysis procedures were the same for both groups at both experiments. An overview of the microdialysis procedure is shown in figure 6.

Figure 6: Procedure for the microdialysis experiment, and for which time points the biochemical substances where analysed. Numbers represent time points in minutes.

CHEMICAL ANALYSES

During the chemical analyses, the chemist performing the analyses was blinded for the samples regarding group affiliation (participants with neck- and shoulder pain and healthy controls).

The chemical analysis of glutamate, lactate and pyruvate started by pipetting and then vortexing 5- μ L dialysate or perfusate into a counting vial containing 3-mL scintillation fluid (High-flash Point, Universal LSC-Cocktail, ULTIMA GOLD™, PerkinElmer, Inc.). β -counting was done in a liquid scintillation counter (Beckman LS 6000TA; Beckman Instruments, Inc., Fullerton, CA, USA). The relative recovery (RR) for lactate was calculated for each sample: $(\text{cpm}_p - \text{cpm}_d)/\text{cpm}_p$, where cpm_p was counts per min of perfusate and cpm_d was counts per min of dialysate. The interstitial levels of the substances were calculated as follows: $(C_d - C_p)/RR + C_p$, where C_d was the concentration of substance in the dialysate, and C_p was the concentration of substance in the perfusate.

For the quantification of substance P, beta-endorphin, and cortisol, microdialysis samples (50 μ L) were incubated with a mixture of beads dyed with different fluorescence and coated with specific antibodies directed against the different analytes. The different beads bind to their specific analytes. After a washing step to remove the unbound substances, the analytes of interest were detected by specific antibodies conjugated with R-phycoerythrin (RPE) present in the buffer solution. This approach allows for several analytes to be quantified in the same sample using a small sample volume. The concentrations were calculated by reference to a seven-point five-parameter logistic standard curve for each substance using MasterPlex QT 2010 (MiraiBio Inc., San Diego, CA, USA).

OUTCOME MEASUREMENTS

PAIN PERCEPTION AND SUBJECTIVE PAIN RELATED FUNCTION

(PAPER 1, 2 AND 3)

Pain intensity (*paper 1, 2 and 3*)

Pain intensity in the neck and shoulders respectively, during the previous week (paper 1 and 3) were measured by marking on an 11-grade (0 – 10) Numeric Rating Scale (NRS). Zero indicated no pain at all and 10 indicated worst pain possible [189]. In **paper 2**, pain intensity in the neck just before insertion of the catheters, and every 20 minute during the microdialysis experiment, was measured using a NRS.

Pressure pain threshold (*paper 2*)

Pressure pain threshold (PPT), were measured with a hand-held electronic algometer (Somedic, Hörby, Sweden) using the same procedure as previously described [195]. PPTs were performed on the m. trapezius, bilaterally over the medial, middle, and lateral part of the muscle, and a mean value was calculated. PPTs were also measured on the tibialis anterior muscle as a reference point. Values from the most painful trapezius muscle for the participants with neck- and shoulder pain, and dominant side for the pain-free controls are presented in **paper 2** together with the m. tibialis anterior results.

Subjective function/disability (*paper 1 and 3*)

The term function was used in **paper 1**, and the term disability was used in **paper 3** for the same outcome. Self-reported disability due to neck pain was measured using the Swedish version of the NDI [184]. The NDI includes ten items about pain intensity and activities that might be affected by neck pain: Pain intensity, personal care, lifting, sleeping, driving, recreation, headache, concentration, reading, and work. The items are scored from 0 (no limitations) to 5 (major limitations) and summed to create a total score reflecting degree of disability [184, 196]: 0-4 = none; 5-14 = mild; 15-24 = moderate; 25-34 = severe; and over 34 = complete [196].

PHYSICAL FUNCTION (PAPER 1)

Strength

Maximal isometric neck strength was measured in neck flexion and neck extension by a handheld dynamometer (MicroFet 2, Hoggan). The flexion strength was measured with the participant in a supine position with legs straight and arms alongside the body. The upper cervical spine was flexed with the chin kept as close as possible to the chest. The extension strength was measured with the participant lying in a prone position and the head lifted and bent back as much as possible. The test leader gradually increased pressure on the forehead and the back of the head until

the force was broken. During the test, the test leader did not give any encouragement. Each test was repeated three times and a mean value was calculated.

Shoulder strength was assessed by counting the number of two dynamic movements – arm abduction and upright row – with a pair of 4-kg dumbbells. The participant was told to do as many repetitions as possible, up to 50. During the test, the test leader did not give any encouragement.

Range of motion

Range of motion (ROM) of the neck was measured in two-degree increments with a cervical measurement system [197]. The measurement system consists of a plastic helmet with two gravity goniometers and a compass to measure flexion, extension, lateral flexion, and rotation. During the test, the test leader did not give any encouragement.

BIOCHEMICAL SUBSTANCES (PAPER 2)

Concentrations of **glutamate, lactate, and pyruvate** in microdialysate were analysed with an ISCUS^{flex} Clinical Microdialysis Analyser (Dipylon Medical AB, Solna, Sweden) according to previously described methods [194].

Concentrations of **substance P, beta-endorphin, and cortisol** in microdialysate were quantified using the MILLIPLEX® MAP Human Neuropeptide Magnetic Panel Kit (HNPMAG-35K, EMD Millipore Corporation, Billerica, MA, USA) and using a Luminex 200 instrument (Life Technologies, Invitrogen; Stockholm, Sweden).

PSYCHOLOGICAL FACTORS (PAPER 3)

Anxiety and depression

Anxiety and depression symptoms were measured using the Hospital Anxiety and Depression Scale (HADS) [198, 199]. This scale consists of 14 items covering two subscales, one for anxiety and one for depression. The HADS detects anxiety and depressive symptoms in a general medical setting. A higher score represents a higher symptom severity. The HADS makes use of two cut-off scores for each subscale; eight or more indicates the possible existence of a disorder and 11 or more indicates the probable existence of a disorder [200]. The range for each subscale is 0 – 21.

Pain catastrophizing

Pain catastrophizing was measured using the Pain Catastrophizing Scale (PCS) [201, 202]. This scale assesses catastrophizing in clinical and nonclinical settings. The scale consists of 13 items, including three aspects of catastrophizing; rumination, magnification, and helplessness. Each item is scored from 0 (not at all) to 4 (all the time). The possible range is 0 – 52 points, with lower scores indicating less catastrophizing.

Self-efficacy

General self-efficacy was measured using the General Self Efficacy Scale (GSES) [129, 203]. The GSES assesses individuals' beliefs in their own ability to handle novel or difficult situations in general and to cope with adversities. The scale consists of ten items, each item is scored from 1 (not at all true) to 4 (exactly true). The possible range is 10 – 40, with higher scores showing more self-efficacy.

Pain self-efficacy was measured using the Pain Self Efficacy Questionnaire (PSEQ) [130]. The PSEQ assesses individuals' confidence in performing a particular behaviour irrespective of their pain. The questionnaire consists of ten items that reflect a wide variety of tasks that can be affected by pain. Each item is scored from 0 (not at all confident) to 6 (completely confident) and the total score ranges between 0 – 60, with higher score showing more pain self-efficacy.

Fear-avoidance beliefs

Fear-avoidance beliefs was measured using the Fear Avoidance Beliefs Questionnaire (FABQ) [204]. The FABQ assesses fear-avoidance beliefs about the pain related to two subscales – physical activity and work. The questionnaire consists of in total 16 items about physical activity and work that may cause pain. Each item is scored from 0 (not agree at all) to 6 (completely agree). Total score ranges between 0 – 66, with lower scores representing lower levels of fear-avoidance.

Pain acceptance

Pain acceptance was measured using the Chronic Pain Acceptance Questionnaire (CPAQ) [205-207]. The CPAQ assesses acceptance of chronic pain focusing on behavioural aspects of acceptance. The questionnaire consists of two subscales – pain willingness and engagement in activities. The CPAQ includes 20 items, each scored from 0 (never true) to 6 (always true). Possible range is 0 – 120, with higher scores indicating more pain acceptance.

THE TRIAL SETUP AND OUTCOME MEASUREMENT TIME-POINTS

The conduction of the trial was organized to start new PA&E intervention groups every two weeks during six months. For each group, the start-up period consisted of two weeks during which base-line measurements took part and three PA&E introductions were offered. After the two start-up weeks, the participants started the PA&E intervention according to their assigned PA&E group (STRENGTH or STRETCH). The STRENGTH group increased the exercise intensity after 2 months of exercise. Follow-up measurements of the outcome variables were conducted after four to six months and after one year of training. Microdialysis was performed at follow-up after 4-6 months, not after one year. A summary of the trial setup and outcome measurement time-points for each group start is shown in figure 7.

Figure 7: Time-line over the trial setup (numbers represent months), including the start-up period, increase in exercise intensity for the STRENGTH group, the follow-up period after 4-6 months and the end of the trial after 12 months. During the whole trial, the participants marked their planned and performed PA&E in an exercise diary and were offered support from a physiotherapist by phone and e-mail.

STATISTICS

TRADITIONAL STATISTICS

Data from the trial are presented as descriptive data, differences between different time points and between groups, correlations, and linear regressions. The analyses are made using the statistical package IBM SPSS Statistics (versions 19.0 – 22.0; IBM Corporation, Route 100 Somers, New York, USA). When the data were ordinal and not normally distributed, non-parametric analyses were chosen and descriptive data are presented with median values and interquartile ranges (25th – 75th percentile). For group comparisons, Mann Whitney U-test, Wilcoxon signed-rank test, and χ^2 tests were used. Differences between different time-points were analysed using Wilcoxon Signed Rank Test. Spearman's rho correlation analysis was used to examine the correlation between the psychological variables and pain intensity and function. Linear regression analyses were used to examine psychological influences on function. For all statistical analyses, a probability of <0.05 (two-tailed) was set as criteria for statistical significance. Missing data in the questionnaires were not replaced with any value, so participants with missing data are not included in the statistical analyses.

MULTIVARIATE DATA ANALYSIS

Multiple Linear Regression assumes that the regressor (X) variables are independent (that is, multi-collinearity is not present). In **paper 2** and **paper 3**, interactions and multi-collinearity between factors measured were probable to be present. To handle this aspect, *partial least squares regression* (PLSR) was employed using SIMCA-P+ for the multivariate regression analyses [208]. The importance of the variables is measured as a Variable Influence in Projection (VIP) value. This value indicates the relevance of each X-variable pooled over all dimensions and Y-variables – the group of variables that best explains Y. VIP 1.0 was considered significant. Coefficients (partial least squared scaled and centred regression coefficients) were used to note the direction of the relationship (positive or negative). If necessary, the variables were transformed. R^2 describes the *goodness of fit* – the fraction of sum of squares of all the variables explained by a principal component [209]. Q^2 describes the *goodness of prediction* – the fraction of the total variation of the variables that can be predicted by a principal component using cross validation methods.

Prior to PLSR, *Principal Components Analysis* (PCA) was applied. PCA extracts and displays systematic variation in a data matrix. Variables loading on the same component are correlated and variables with high loadings but with different signs are negatively correlated. Significant variables with high loadings (positive or negative) are more important for the component under consideration than variables with lower absolute loadings [209]. The obtained components are per definition not correlated and are arranged in decreasing order with respect to explained variation. The purpose of applying PCA was to identify multivariate outliers using the two

powerful methods available in SIMCA-P+: 1) score plots in combination with Hotelling's T^2 (identifies strong outliers) and 2) distance to model in X-space (identifies moderate outliers). No multivariate outliers were identified.

METHODS AND MATERIALS (PAPER 4)

PROCEDURES

This qualitative interview study was performed at The Pain and Rehabilitation Centre, University Hospital, Linköping, Sweden; specialized in complex acute and chronic pain conditions. Patients with chronic pain who were scheduled to a six-week multidisciplinary pain rehabilitation program, but had not yet started any rehabilitation, were asked to participate. Written information about the study was sent by mail to all eligible patients. After one week, the presumptive participants were contacted via telephone and the prospective participants received more information about the study. The recruitment procedure consecutively followed the Pain and Rehabilitation Centre's ordinary flow of patients between January 2016 and June 2016.

The regional Ethical Review Board in Linköping approved the study (DN: 2014/279-31). The Code of Ethics of the World Medical Associations, Declaration of Helsinki [187], was applied. All participants signed informed consent before entering the study.

PARTICIPANTS

Written information about the study was given to 49 patients. Of these, 16 women and two men agreed to participate. Inclusion criteria were chronic pain with no further pharmacological or invasive treatment options scheduled, age 18 – 65, speaking and understanding Swedish language, and assessed by a specialized physician to be suitable for participation in a multidisciplinary pain rehabilitation program. Severe psychiatric illness was the only exclusion criteria.

In order to get a deeper understanding of the included participants in this study, information about current PA level, as well as several psychological factors were measured. Data about PA level were collected using the short form of the International PA Questionnaire (IPAQ) [210]. Symptoms of depression and anxiety were measured using the Hospital Anxiety and Depression Scale (HADS) [198, 199]. Pain self-efficacy was measured using the Pain Self-efficacy Questionnaire (PSEQ) [130]. Pain related fear-avoidance beliefs were measured using the Fear Avoidance Beliefs Questionnaire (FABQ) [204]. Pain-related psychological inflexibility was measured using the Psychological Inflexibility in Pain Scale (PIPS) [205].

INTERVIEWS

All interviews were conducted individually at the Pain and Rehabilitation Centre. The participants were all interviewed by LK using a semi-structured interview guide based on principles outlined by Kvale [211]. The semi-structured interview guide consisted of three main questions:

- I) Tell me about your experiences of PA.
- II) Tell me about your motivation to perform PA.
- III) Tell me about your experiences of PA&E as treatment for your pain.

The main questions were followed by sub-questions when more elaborations were needed. The interviews were audio recorded and transcribed verbatim.

QUALITATIVE CONTENT ANALYSIS

To understand the meaning of the content of the interviews and to get a deeper understanding about the research topic, the text was analysed using qualitative content analysis with an inductive approach [212, 213]. The analysis explores the manifest and the latent content in order to address the meaning of the interviews [214, 215]. Each interview was considered a unit of analysis. During the analysis, two of the authors (LK and BL) thoroughly discussed every step to enhance the trustworthiness of the findings. The analysis started with reading the interview text several times to get an understanding and a shared sense of the whole. The next step included identification of meaning units as related to the aim of the study. The software NVivo 10 (QSR International Pty Ltd. Version 10, 2012) was used during the practical procedures in the analysis. The meaning units were labelled with codes, and codes with similar content were grouped in categories. The categories were interpreted and abstracted into themes and a main theme. The analysis process included a continuous work forth and backwards between the meaning units, codes, categories, themes and the main theme. Thus, the result of this study developed through LK's and BL's continuous discussions, reflections, and agreements, which were based on consensus and directed by the aim of the study.

RESULTS

An extract of the results from the four papers are presented below. For the complete results, see each paper appended in this thesis respectively; **paper 1**, **paper 2**, **paper 3**, and **paper 4**.

HOME-BASED PHYSICAL ACTIVITY AND EXERCISE IMPROVES PAIN AND FUNCTION (PAPER 1)

The main results of **paper 1**, were that the long term home-based PA&E intervention did improve both pain intensity and function in both intervention groups (STRENGTH and STRETCH). However, no differences between the two different PA&E groups could be identified neither due to statistical nor to clinically important improvements. That is, in this study both specific neck strength exercises and specific stretching exercises, led to decreased pain intensity and increased function.

Pain intensity, function, strength and range of motion were measured at 4-6 month follow-up, and after 12 months of exercise. Baseline values and outcomes at 4-6 month- and 12 month follow-ups for the two exercise groups are shown in table 1. During the 12 months intervention, 12 STRENGTH participants and four STRETCH participants discontinued, see figure 4.

Table 1. Pain intensity (NRS = numeric rating scale), function measured by Neck disability index (NDI), range of motion in the neck, and strength in the neck and shoulders at baseline after 4-6 months of training and 12 months of training.

STRENGTH TRAINING GROUP (STRENGTH)						STRETCHING GROUP (STRETCH)					
		Baseline Median (25, 75 percentile)	4-6 months **** Median (25, 75 percentile)	n	12 months Median (25, 75 percentile)	n	Baseline Median (25, 75 percentile)	4-6 month follow-up Median (25, 75 percentile)	n	12 months Median (25, 75 percentile)	n
Primary outcomes											
Pain in the neck and shoulders (NRS)											
Pain neck (NRS)		6 (4, 7)	5 (2, 7)	25	2.5 (0, 7)	20	5 (4, 6)	4 (3, 8)	19	3 (2, 6)	19
Pain shoulder (NRS)		4 (3, 6)	4 (1, 7)	25	2.5 (0, 7)	20	5 (3, 8)	3 (0, 5)	19	3 (1, 5)	19
Function (NDI)											
Function (NDI)		13 (10, 18)	11 (7, 14)	25	10 (4, 12)	20	13.5 (11, 18)	11.5 (9.5, 15)	18	9 (4.5, 11.5)	17
Secondary outcomes											
Range of motion in the neck (degrees)											
Neck flexion		48 (38, 53)	54 (40, 60)	26	50 (47, 60)	22	48 (38, 50)	50 (42, 52)	19	48 (38, 62)	19
Neck extension		56 (46, 68)	70 (52, 79)	26	70 (63, 75)	22	60 (50, 68)	68 (56, 80)	19	70 (50, 78)	19
Lat. flex. right		30 (28, 38)	40 (36, 48)	26	40 (35, 42)	22	32 (22, 40)	38 (32, 42)	19	40 (34, 48)	19
Lat. flex. left		32 (30, 38)	39 (32, 43)	26	40 (37, 47)	22	38 (28, 40)	40 (32, 48)	19	42 (36, 52)	19
Rotation right		62 (57, 66)	69 (60, 75)	26	66 (60, 70)	22	64 (58, 68)	64 (54, 74)	19	68 (60, 70)	19
Rotation left		59 (52, 65)	68 (60, 73)	26	69 (60, 74)	22	62 (52, 72)	66 (58, 74)	19	68 (62, 72)	19
Strength in neck and shoulders (N) = Newton, (#) = numbers of repetition											
Neck flex, (N)		56 (46, 63)	76 (68, 81)	26	75 (67, 82)	22	63 (55, 72)	75 (60, 85)	19	70 (59, 80)	19
Neck ext, (N)		92 (76, 110)	132 (118, 154)	26	123 (111, 149)	22	100 (74, 110)	121 (109, 146)	19	121 (102, 132)	19
Shod. abd. kg, (#)	4	9 (5, 12)	15 (12, 18)	25	20 (14, 22)	22	9 (3, 13)	10 (7, 13)	16	11 (6, 12)	16
Stand. Row kg, (#)	4	18 (13, 25)	34 (26, 49)	26	38 (29, 50)	22	16 (14, 20)	20 (16, 30)	17	26 (20, 30)	17

4-6 MONTH FOLLOW-UP COMPARED TO BASELINE

Within group changes

No significant changes in the primary outcome pain intensity were found between baseline and 4-6 month follow-up in either STRENGHT or STRETCH. However, STRENGTH showed an overall increase of neck ROM, whereas STRETCH only improved neck extension and lateral flexion to the right (table 2). Both groups showed significant increases in neck and shoulder strength.

Differences between groups

No significant differences between the two groups were found in changes in the primary outcome pain intensities (p=0.59-0.93) and function (NDI) (p=0.50) at the 4-6 month follow-up.

Significant increases were found in favour of STRENGTH for the following secondary outcome variables: shoulder abductions ((median) STRENGTH: 4.0 vs. STRETCH: 1.0; $p=0.04$) and standing row ((median) STRENGTH: 12.5 vs. STRETCH: 5.0; $p=0.02$). In addition, significant differences in favour for STRENGTH were found for ROM neck rotation left ((median) STRENGTH: 9.0 vs. STRETCH: 0.0; $p=0.01$) and strength of the neck ($p=0.09-0.52$).

12-MONTH FOLLOW-UP COMPARED TO BASELINE

Within group changes

STRETCH reported significant reduced pain intensities in neck and shoulders. Both groups improved their function significant according to the NDI (table 2). STRENGTH improved ROM significant in all directions except neck flexion and STRETCH improved ROM significant in all directions except neck flexion and rotation to the right. STRENGTH showed overall significant increases in neck and shoulder strength, whereas STRETCH significantly improved strength in neck extension and standing row.

Differences between groups

No significant differences between the two groups were found in changes in the primary outcomes pain intensities ($p=0.50-0.91$) and function NDI ($p=0.71$) at the 12-month follow-up.

Significant increases were found in favour of STRENGTH for the following secondary outcome variables: flexion strength of the neck ((median) STRENGTH: 17.1 vs. STRETCH: 5.1; $p=0.031$); shoulder abductions ((median) STRENGTH: 8.0 vs. STRETCH: 2.0; $p=0.01$); and standing row ((median) STRENGTH: 17.5 vs. STRETCH: 5.5; $p\leq 0.00$). No differences between groups existed in changes in ROM variables ($p: 0.15-0.65$) or extension strength of the neck ($p=0.09$).

Table 2. Changes within the groups: Differences in pain intensity (NRS = numeric rating scale), function measured by Neck disability index (NDI), range of motion in the neck, and strength in the neck and shoulders. Baseline compared to 4-6 month follow-up of training and baseline compared to 12 months of training. Statistical analysis is performed with Wilcoxon signed rank test.

	STRENGTH TRAINING GROUP (STRENGTH)				STRETCHING GROUP (STRETCH)			
	Difference BL - 4-6 month follow-up Median (25, 75 percentile)	p- value	Difference BL - 12 months Median (25, 75 percentile)	p- value	Difference BL - 4-6 month follow-up Median (25, 75 percentile)	p- value	Difference BL - 12 months Median (25, 75 percentile)	p- value
Primary outcomes								
<i>Pain in the neck and shoulders (NRS)</i>								
Pain neck (NRS)	1 (-0.75, 3)	NS	2 (-1, 5)	NS	1 (-2, 2)	NS	1 (0, 2)	0.009
Pain shoulder (NRS)	1 (-2.75, 2.75)	NS	1 (-1, 3)	NS	1 (-1, 4)	NS	1 (0, 2)	0.017
<i>Function (NDI)</i>								
Function (NDI)	2 (0, 5.5)	0.036	4 (2, 8)	0.002	1 (-2, 4)	NS	4 (-1, 10)	0.015
Secondary outcomes*								
<i>Range of motion in the neck (degrees)</i>								
Neck flexion	-4 (-12.25, 2)	0.043	-2 (-9, 3)	NS	-2 (-12, 0)	NS	-6 (-16, 4)	NS
Neck extension	-9 (-15, -1.5)	0.004	-11 (-25, -2)	0.002	-6 (-19, -2)	0.002	-12 (-14, 0)	0.003
Lat. flex. right	-8 (-12, -2)	<0.001	-6 (-12, -2)	<0.001	-6 (-10, -2)	0.003	-6 (-14, 4)	<0.001
Lat. flex. left	-3.5 (-8.5, 0)	0.002	-8 (-10, 0)	0.002	-2 (-12, 4)	NS	-10 (-16, -2)	0.001
Rotation right	-6 (-10, 1)	0.002	-2 (-8, 1)	0.006	-2 (-10, 4)	NS	-4 (-14, 0)	NS
Rotation left	-9 (-12, -4)	<0.001	-10 (-13, -2)	<0.001	0 (-8, 4)	NS	-6 (-10, 2)	0.026
<i>Strength in neck and shoulders (N) = Newton, (#) = numbers of repetition</i>								
Neck flex, (N)	-17 (-29, -9)	<0.001	-17 (-29, -12)	<0.001	-11 (-20, -1)	0.011	-5 (-22, 3)	NS
Neck ext, (N)	-30 (-55, -16)	<0.001	-40 (-57, -17)	<0.001	-28 (-44, -15)	0.002	-25 (-30, -12)	0.001
Shod. abd. 4 kg, (#)	-5 (-10, -1)	0.001	-8 (-16, -4)	<0.001	-1 (-4, 0)	0.044	-2 (-6, 0)	NS
Stand. Row4 kg, (#)	-13 (-23, -5)	<0.001	-18 (-25, -6)	<0.001	-5 (-10, 0)	0.001	-6 (-13, -4)	0.003

*An improvement in secondary outcomes is shown by a negative number (contrary to primary outcomes).

ADHERENCE TO THE PHYSICAL ACTIVITY AND EXERCISE INTERVENTION

There was a large variation in PA&E frequency in both groups during the whole intervention period. From baseline to the 4-6 month follow-up, the STRENGTH group performed the exercise 1.5-2.5 times a week, and the STRETCH group performed the exercise at least two times a week. After 4-6 months, the STRENGTH exercise frequency in STRENGTH was 1.5 times a week or less. STRETCH reported exercise frequency of 1.5 times a week or more until month 10. During the last two months of the trial, the STRETCH group performed the exercises less than 1.5 times a week. Adherence to STRENGTH and STRETCH PA&E during the one year intervention period is shown in figure 8.

Figure 8: Training frequency during the trial showed in weekly mean frequency for each month for the strength training group (STRENGTH) and the stretching group (STRETCH). Data are presented as mean and standard deviation.

COMPLETERS AND RESPONDERS

4-6 MONTH FOLLOW-UP FOR THE COMPLETERS AND RESPONDERS

Within group changes

At 4-6 month follow-up, there were 19 (79%) participants that were completers and 5 (21%) non-completers in the STRENGTH group. Corresponding numbers for the STRETCH group were 17 (89%) completers and 2 (11%) non-completers. In the STRENGTH completers, there were 9 (47%) responders for neck pain, 9 (47%) responders for shoulder pain, and 7 (37%) responders for function. The corresponding numbers for STRETCH were 7 (41%) responders for neck pain, 8 (47%) responders for shoulder pain, and 5 (29%) responders for function.

Differences between groups

At 4-6 month follow-up, there was no significant difference in proportions of completers between the groups ($p=0.28$). Among the completers, there was no significant difference in proportions between the two intervention groups in responders for neck pain ($p=0.75$), shoulder pain ($p=0.71$), or function ($p=0.44$).

12-MONTH FOLLOW-UP FOR THE COMPLETERS AND RESPONDERS

Within group changes

At 12 month follow-up, there were 11 (55%) participants that were completers and 9 (45%) non-completers in the STRENGTH group. Corresponding numbers for the STRETCH group were 10 (53%) completers and 9 (47%) non-completers. In the STRENGTH completers, there were 5 (45%) responders for neck pain, 6 (55%) responders for shoulder pain, and 6 (55%) responders for function. The corresponding numbers for STRETCH were 4 (40%) responders for neck pain, 5 (50%) responders for shoulder pain, and 2 (20%) responders for function.

Differences between groups

At 12 month follow-up, there was no significant difference in proportions of completers between the groups ($p=0.90$). Among the completers, there was no significant difference in proportions between the two intervention groups in responders for neck pain ($p=0.41$), shoulder pain ($p=0.64$), or function ($p=0.07$).

PHYSICAL ACTIVITY AND EXERCISE ALTERS PAIN MODULATORY SUBSTANCES IN PAINFUL TRAPEZIUS MUSCLES (PAPER 2)

As no significant differences in pain intensity or function were found between the two groups (STRENGTH or STRETCH) in **paper 1**, all participants with chronic neck- and shoulder pain were analysed as one group in **paper 2** in order to increase the power of the statistical analyses. The results for women with neck- and shoulder pain were compared with the pain-free women, as well as before and after the PA&E intervention.

The main results of alterations in the pain modulatory substances were that higher concentrations of glutamate and beta-endorphin as well as lower levels of cortisol were found in the participants with chronic neck- and shoulder pain, compared to the pain-free controls before the PA&E intervention (baseline, microdialysis number one). After 4-6 months PA&E intervention (follow up, microdialysis number two), decreased levels of substance P, and possibly glutamate together with increased levels of beta-endorphin and cortisol were found in the participants with chronic neck- and shoulder pain, compared to the levels before PA&E. Furthermore, pain intensity had decreased and pain thresholds for pressure had increased significantly after the PA&E intervention.

RESULTS - TRADITIONAL STATISTICS

SUBSTANCE P, BETA-ENDORPHIN, AND CORTISOL

Between group analyses

Participants with chronic neck- and shoulder pain vs. pain-free controls

No differences between the groups were found for substance P at baseline.

Concentrations of beta-endorphin were significantly higher in the participants with neck- and shoulder pain compared to pain-free controls at 100 min ($p=0.007$); no difference was found at 200 min. No group differences were found for cortisol (Figure 9).

Within group analyses

Participants with chronic neck- and shoulder pain

Concentrations of substance P were significantly lower at follow-up after 4-6 months PA&E intervention compared to baseline at 200 min ($p=0.001$). Beta-endorphin was significantly higher after 4 – 6 months of PA&E, both at time point 100 min ($p=0.003$) and 200 min ($p=0.001$). Concentrations of cortisol were significantly higher after 4 – 6 months of PA&E compared to baseline at 100 min ($p=0.033$) and at 200 min ($p<0.001$) (Figure 9).

Figure 9: Concentrations in picogram/ml (pg/ml) for (a) substance P, (b) beta endorphin, and (c) cortisol for pain-free participants at baseline (BL) and for participants with chronic neck- and shoulderpain at baseline (BL) and follow up (FU) at four to six months. Data are presented as median, percentiles and max and min. Circles and stars mark outliers and extremes. Statistically significant differences are marked with Δ .

GLUTAMATE, LACTATE, AND PYRUVATE

Between group analyses

Participants with chronic neck- and shoulder pain vs. pain-free controls

At baseline, concentrations of glutamate were significantly higher for the participants with neck- and shoulder pain, compared to the pain-free controls at 140 min ($p=0.008$), 160 min ($p=0.025$), and 180 min ($p=0.025$) (Table 3). A significant lower concentration of lactate in the participants with neck- and shoulder pain was found at 220 min ($p=0.040$). No significant differences between the two groups were found for pyruvate. After 4-6 months of PA&E, no significant differences were found between the two groups of participants at any time point except for a significantly lower level of pyruvate in the participants with neck- and shoulder pain at 180 min ($p=0.041$).

Within group comparisons

Participants with chronic neck- and shoulder pain

There were no statistically significant differences in concentrations of glutamate, lactate, or pyruvate for any time point between baseline and follow-up after 4-6 months of PA&E (Table 3).

The pain-free controls

Glutamate was significantly higher at follow-up after 4-6 months, compared to baseline at 180 min ($p=0.026$) and 200 min ($p=0.009$). Lactate did not differ between follow-up and baseline at any time point. Pyruvate was significantly higher at follow-up compared to baseline at 200 min ($p=0.018$) (Table 3).

Table 3. Concentrations of glutamate (millimol/l), lactate (millimol/l), and pyruvate (micromol/l) for subjects with pain (CNSP) and pain-free subjects (CON) at baseline and follow up at four to six months for the following time points: 140, 160, 180, 200, and 220. Missing data are due to insufficient quantities of samples. Hence, in CNSP 39–41 samples were analysed for each substance and time point at baseline and 32–33 samples at follow up. Corresponding figures for CON were 24 samples both at baseline and at follow up. Statistical analyses of between group differences are reported at baseline and at follow up. Furthest to the right is reported the within group differences (baseline vs follow up) for CNSP and for CON; * denotes significant difference (p-value reported), ns denotes not significant.

Substance, time point	Baseline			Follow up, 4 to 6 months			
	CNSP n = 41 Median (25, 75 percentile)	Statistics CNSP vs. CON p-value	CON n = 24 Median (25, 75 percentile)	CNSP (exercise intervention) n = 33 Median (25, 75 percentile)	Statistics CNSP vs. CON p-value	CON (no intervention) n = 24 Median (25, 75 percentile)	Statistics within CNSP p-value
Glutamate, 140	48.9 (33.7, 60.2)	0.008*	32.5 (20.1, 44.5)	35.6 (24.9, 58.7)	ns	42.4 (32.4, 71.2)	ns
Glutamate, 160	64.6 (49.5, 86.5)	0.025*	50.6 (36.5, 62.3)	45.0 (32.7, 89.6)	ns	61.0 (42.5, 74.8)	ns
Glutamate, 180	55.0 (40.1, 74.4)	0.025*	33.1 (21.5, 66.3)	45.2 (29.7, 72.7)	ns	59.4 (42.8, 87.8)	ns
Glutamate, 200	39.3 (25.6, 57.8)	ns	31.3 (23.4, 56.7)	36.0 (26.5, 70.9)	ns	52.5 (32.9, 68.7)	ns
Glutamate, 220	36.5 (26.9, 53.5)	ns	40.2 (29.8, 61.8)	36.6 (26.3, 64.2)	ns	41.7 (33.5, 55.4)	ns
Lactate, 140	1.9 (1.6, 2.6)	ns	2.1 (1.7, 3.4)	2.0 (1.6, 2.4)	ns	2.2 (1.7, 3.0)	ns
Lactate, 160	2.1 (1.7, 2.7)	ns	2.0 (1.7, 3.3)	2.1 (1.6, 2.9)	ns	2.4 (1.7, 3.8)	ns
Lactate, 180	2.0 (1.6, 2.9)	ns	2.3 (2.0, 2.9)	1.9 (1.6, 2.8)	ns	2.5 (1.6, 3.5)	ns
Lactate, 200	2.1 (1.6, 2.6)	ns	2.3 (1.9, 2.7)	2.0 (1.5, 3.0)	ns	2.9 (1.6, 3.7)	ns
Lactate, 220	2.0 (1.6, 2.4)	0.040*	2.5 (1.8, 3.8)	2.3 (1.7, 3.1)	ns	2.3 (1.7, 3.7)	ns
Pyruvate, 140	82.7 (61.5, 101.6)	ns	70.0 (48.6, 113.3)	74.1 (64.3, 102.6)	ns	91.4 (71.2, 114.1)	ns
Pyruvate, 160	97.5 (79.6, 122.3)	ns	92.3 (68.8, 126.4)	88.4 (78.8, 135.4)	ns	92.1 (73.9, 150.8)	ns
Pyruvate, 180	93.8 (76.7, 118.7)	ns	89.5 (58.1, 119.9)	85.4 (66.7, 119.0)	0.041*	117.2 (96.8, 156.2)	ns
Pyruvate, 200	90.7 (76.7, 109.8)	ns	72.7 (50.6, 116.5)	89.9 (67.4, 126.6)	ns	104.3 (83.5, 173.8)	ns
Pyruvate, 220	81.3 (62.8, 112.6)	ns	87.7 (47.8, 122.3)	83.9 (68.6, 130.4)	ns	100.2 (78.6, 121.4)	ns
							0.018*
							ns

PAIN INTENSITY

Between group analyses

Participants with chronic neck- and shoulder pain vs. healthy controls

Pain intensity ratings were, as expected, significantly higher for the participants with neck- and shoulder pain compared to the pain-free controls pre-insertion ($p<0.001$) and for time points 140 (baseline) ($p<0.001$), 160 ($p<0.001$), 180 ($p<0.001$), 200 ($p<0.001$), and 220 minutes ($p<0.001$) at both baseline and follow-up.

Within group analyses

Participants with chronic neck- and shoulder pain

There were significantly higher pain ratings at baseline than at follow-up for time points 160 minutes ($p=0.018$), 180 minutes ($p=0.022$), and 220 minutes ($p=0.047$) (Figure 10).

The pain-free controls

There were no significant differences in pain ratings between baseline and 4-6 month follow-up at any time point.

Figure 10: Pain intensity ratings (Numeric rating scale, NRS) for participants with neck and shoulder pain (CNSP) at baseline (baseline) and follow-up (FU) at four to six months pre insertion and at time points 140, 160, 180, 200, and 220. Statistical significant differences between baseline and FU are marked with *; clinically significant differences between baseline and FU are marked with ★.

PRESSURE PAIN THRESHOLDS

Between group analyses

Participants with chronic neck- and shoulder pain vs. pain-free controls

At baseline, participants with neck- and shoulder pain had a median PPT of 255 kPa (25th percentile (perc): 208 kPa; 75th perc: 321 kPa) for trapezius (figure 10). The pain-free controls had a median PPT of 600 kPa (25th perc: 410 kPa; 75th perc: 600 kPa). The difference between the groups was statistically significant ($p<0.001$). A similar significant difference was also found for PPT over tibialis anterior (participants with neck- and shoulder pain: 423 vs. pain-free controls: 600 kPa; $p<0.001$).

Within group analyses

Participants with chronic neck- and shoulder pain

Between baseline and follow-up after 4 – 6 months, the PPT of the trapezius had increased significantly ($p=0.006$), from 255 to 277 kPa (figure 11).

Figure 11: Pressure pain thresholds (kilopascal, kPa) for the pain-free participants (CON) at baseline and participants with chronic neck- and shoulder pain (CNSP) at baseline (BL) and follow-up after four to six months (FU). Data are presented as median, percentiles, max and min. Circles mark outliers. Statistically significant differences are marked with Δ .

RESULTS - MULTIVARIATE DATA ANALYSES

Area under curve (AUC) of glutamate, lactate and pyruvate were calculated and used in the multivariate analyses together with the mean of the two time points measured for substance P, beta-endorphin, and cortisol.

REGRESSION OF GROUP MEMBERSHIP AT BASELINE

Group membership (participants with chronic neck- and shoulder pain, and pain-free participants) was regressed in order to understand which biochemical variables in the multivariate context that best separated the two groups.

The following variables were identified (from most to least important): glutamate (VIP=1.48 +), cortisol (VIP=1.23-), and beta-endorphin (VIP=1.10+). Hence, belonging to participants with chronic neck and shoulder pain was multivariately associated with higher glutamate and beta-endorphin levels and lower cortisol levels.

REGRESSION OF PAIN INTENSITY IN PARTICIPANTS WITH NECK- AND SHOULDER PAIN AT BASELINE

It was not possible to regress pain intensity using the biochemical substances for AUC of pain intensity or for pain intensity at the five time points.

REGRESSIONS OF CHANGES IN ASPECTS OF PAIN

Changes in glutamate, lactate, and pyruvate levels were calculated as the difference between AUCs of baseline and FU. Changes in substance P, beta-endorphin, and cortisol levels were calculated as differences in mean levels of 4-6 month follow-up and baseline.

Regression of changes in pain intensity

The regression ($R^2=0.20$) identified substance P (VIP=2.29+) as the most important regressor at baseline, which means that a prominent change in pain intensity after PA&E was associated with high levels of substance P at baseline. When regressing the changes in pain intensity as a consequence of PA&E using the changes in the biochemical substances ($R^2=0.15$), we found that cortisol (VIP=1.84+) and glutamate (VIP=1.15-) were important. In other words improvements in pain intensity after PA&E was associated with increases in cortisol and a small decrease in glutamate.

REGRESSION OF PPT OF TRAPEZIUS AT BASELINE

All participants taken together

In the regression ($R^2=0.18$), glutamate (VIP=1.99-) and cortisol (VIP=1.34+) were identified as most important. Hence, low PPTs of trapezius were associated with high glutamate levels and low cortisol levels.

Participants with chronic neck- and shoulder pain

In the regression ($R^2=0.06$), the following substances were most important: beta-endorphin (VIP=1.57+) and glutamateAUC (VIP=1.74-). Hence, low PPTs of trapezius were associated with high levels of beta-endorphin and low glutamate levels.

Pain-free controls

No significant model was obtained of regression of PPT of trapezius in the pain-free participants using AUC of the metabolic variables as regressors together with the two time points measured for substance P, beta-endorphin, and cortisol.

REGRESSION OF CHANGES IN PPT OF TRAPEZIUS IN PARTICIPANTS WITH CHRONIC NECK- AND SHOULDER PAIN

The difference between PPT values at 4-6 month follow-up and baseline was calculated (that is, a positive value indicated an increase in PPT after the PA&E intervention). Negative correlations between the changes in PPT were associated with levels of glutamate (VIP=1.47-), lactate (VIP=1.30-), and pyruvate (VIP=1.13-) at baseline according to the regression ($R^2=0.12$). Hence, prominent increases in PPT after PA&E were associated with low concentrations of glutamate, lactate, and pyruvate at baseline.

PSYCHOLOGICAL FACTORS ARE ASSOCIATED WITH THE RESULTS OF PHYSICAL ACTIVITY AND EXERCISE AS TREATMENT FOR CHRONIC PAIN (PAPER 3)

Paper 3 addressed associations between psychological factors and changes in pain intensity and disability as well as associations between psychological factors and adherence to the PA&E intervention. All the participants with chronic neck- and shoulder pain were analysed as one group. The main results of **paper 3** were that associations were found between decreases in pain intensity and disability and low fear avoidance beliefs and low pain self-efficacy at baseline. In addition, fear avoidance beliefs at baseline were higher for the participants who dropped out of the intervention than in those who continued. Pain acceptance at baseline were higher for the participants who completed the PA&E intervention at end of the trial after 12 months of PA&E.

DROP-OUTS, COMPLETERS AND RESPONDERS

Of the included 57 participants with neck-and shoulder pain, 45 remained in the trial until the follow-up after 4-6 months and 41 remained until the end of the trial (after one year). At 4-6 month follow-up, 37 participants were defined as completers and eight as non-completers. At end of the trial, 22 participants were defined as completers and 19 as non-completers.

PAIN INTENSITY, FUNCTION, AND PSYCHOLOGICAL VARIABLES AT BASELINE, 4-6 MONTH FOLLOW-UP, AND AT 12 MONTH FOLLOW UP

All outcome variables showed improvements after 12 months of the PA&E intervention (Table 4).

Table 4. Pain intensity ratings, disability scores, and psychological factors at baseline (BL), follow-up at 4-6 months (FU₄₋₆), and end of the trial after one year (END₁₂). Statistically significant differences between BL and FU₄₋₆ and BL and END₁₂ were analysed with Wilcoxon Signed Rank Test. * denotes statistical change. The median change for pain intensity ratings, disability scores, and psychological factors at FU₄₋₆ and END₁₂ are also shown. Positive values in the changes columns implies improvement.

	BL-values Median (25 th , 75 th percentile), n	FU ₄₋₆ -values Median (25 th , 75 th percentile), n	p-value (BL- FU ₄₋₆)	Changes BL-FU ₄₋₆ Median (25 th , 75 th percentile), n	END ₁₂ -values Median (25 th , 75 th percentile), n	p-value (BL- END ₁₂)	Changes BL-END ₁₂ Median (25 th , 75 th percentile), n
Pain in the neck	5 (4, 7), 56	5 (2, 7), 44	p=0.13	1 (-1, 2), 43	3 (2, 7), 39	p=0.003*	2 (0, 4), 38
Pain in the shoulders	4 (3, 6), 56	4 (0, 7), 44	p=0.15	1 (-1, 3), 43	3 (0, 6), 39	p=0.016*	1 (0, 2), 38
Disability	13 (10, 18), 55	11 (7, 15), 43	p=0.021*	2 (-1, 4), 42	10 (4, 12), 37	p<0.001*	4 (1, 9), 36
Anxiety	5 (3, 8), 55	5 (3, 9), 44	p=0.85	0 (-1, 2), 42	4 (2, 6), 38	p=0.027*	2 (-1, 3), 36
Depression	4 (1, 6), 56	3 (1, 7), 45	p=0.21	0 (-1, 2), 44	2 (1, 5), 39	p=0.007*	1 (-1, 2), 38
Pain catastrophizing	12 (7, 20), 54	8 (6, 16), 45	p=0.16	0 (-2, 5), 42	11 (5, 17), 39	p=0.014*	3 (-2, 6), 36
Fear-avoidance	21 (15, 28), 56	15 (8, 26), 42	p=0.010*	2 (-1, 10), 42	13 (8, 21), 37	p<0.001*	4 (0, 10), 36
General self-efficacy	31 (28, 33), 55	31 (29, 35), 45	p=0.022*	1 (-1, 4), 43	33 (28, 36), 38	p=0.009*	2 (-1, 5), 36
Pain self-efficacy	49 (42, 55), 56	51 (47, 58), 44	p=0.005*	3 (0, 6), 43	53 (46, 59), 38	p=0.011*	4 (-1, 8), 37
Pain acceptance	77 (67, 87), 52	85 (77, 94), 43	p<0.001*	7 (3, 16), 39	88 (76, 97), 39	p=0.001*	9 (-1, 23), 35

CORRELATION ANALYSES

Associations of psychological variables at baseline with pain and disability and their changes.

Pain acceptance at baseline was negatively correlated with pain intensity in the neck at baseline ($\rho=-0.30$, $p=0.033$). Fear-avoidance beliefs at baseline were negatively correlated with changes in pain intensity in the shoulders at 4-6 month follow-up ($\rho=-0.33$, $p=0.029$). Pain self-efficacy at baseline was negatively correlated with changes in pain intensity in the neck at end of the trial ($\rho=-0.38$, $p=0.019$). Fear-avoidance beliefs at baseline were positively correlated with disability at baseline ($\rho=0.39$, $p=0.003$), and pain self-efficacy ($\rho=-0.39$, $p=0.003$), and pain acceptance ($\rho=-0.46$, $p=0.001$) at baseline were negatively correlated with disability at baseline.

Associations of changes in psychological variables and changes in pain intensity and disability.

Changes in depression symptoms were positively correlated with changes in pain intensity in the neck ($\rho=0.39$, $p=0.009$) at 4-6 month follow-up. In addition, changes in depression symptoms were positively correlated with changes in pain intensity in the neck ($\rho=0.47$, $p=0.003$,) and shoulders ($\rho=0.60$, $p<0.001$) at end of the trial. Changes in depression symptoms ($\rho=0.43$, $p=0.008$) and changes in pain self-efficacy ($\rho=0.39$, $p=0.019$) were positively correlated with changes in disability after 12 months of PA&E.

REGRESSION ANALYSES

Multivariable bivariate linear regression analyses on psychological factors and changes in disability and on changes in psychological variables and changes in disability

Baseline scores on fear-avoidance beliefs, pain self-efficacy, and pain acceptance significantly influenced disability at baseline (Table 5). Furthermore, baseline scores on pain self-efficacy significantly influenced changes in disability after 12 months of PA&E.

Table 5. Linear regression analyses of disability measured by the Neck Disability Index at baseline (BL), of changes in disability from BL to follow-up at 4 – 6 months (FU₄₋₆) and of changes in disability from BL to end of the intervention after one year (END₁₂) as dependent variables and the psychological factors at BL as separate independent variables. Un-adjusted data. * denotes significance.

Psychological factors BL	Disability BL			Changes in disability BL – FU ₄₋₆			Changes in disability BL – END ₁₂		
	Parameter Estimate	Confidence interval	p-value	Parameter estimate	Confidence interval	p-value	Parameter estimate	Confidence interval	p-value
Anxiety	0.036	-0.454; 0.527	0.88	0.024	-0.425; 0.474	0.91	-0.156	-0.636; 0.324	0.51
Depression	0.297	-0.234; 0.791	0.28	-0.298	-0.866; 0.271	0.30	-0.197	-0.876; 0.481	0.56
Pain catastrophizing	0.141	-0.078; 0.359	0.20	-0.010	-0.219; 0.199	0.92	0.147	-0.112; 0.405	0.26
Fear-avoidance	0.232	0.102; 0.363	0.001*	0.047	-0.087; 0.181	0.48	0.002	-0.182; 0.185	0.98
General self-efficacy	-0.014	-0.302; 0.274	0.92	-0.015	-0.340; 0.390	0.92	0.051	-0.323; 0.424	0.78
Pain self-efficacy	-0.307	-0.441; -0.172	<0.001*	-0.044	-0.202; 0.113	0.57	-0.268	-0.482; -0.053	0.016*
Pain acceptance	-0.218	-0.323; -0.114	<0.001*	-0.005	-0.114; 0.105	0.93	-0.071	-0.210; 0.067	0.30

Changes in fear-avoidance beliefs scores at 4-6 month follow-up, as well as at end of the trial significantly influenced changes in disability at the corresponding times (Table 6). In addition, changes in pain self-efficacy significantly influenced changes in disability after 12 months of PA&E.

Table 6. Linear regression analyses of changes in disability measured by the Neck Disability Index from baseline (BL) to follow-up at 4 – 6 months (FU₄₋₆) and of changes in disability from BL to end of the intervention after one year (END₁₂) as dependent variables and changes in the psychological variables for corresponding periods as separate independent variables. Un-adjusted data. * denotes significance.

Changes in psychological factors BL- FU ₄₋₆	Changes in disability BL – FU ₄₋₆			Changes in psychological factors BL- END ₁₂	Changes in disability BL – END ₁₂		
	Parameter estimate	Confidence interval	p-value		Parameter estimate	Confidence interval	p-value
Anxiety	0.422	-0.170; 1.015	0.16	Anxiety	0.371	-0.267; 1.010	0.25
Depression	0.056	-0.630; 0.743	0.89	Depression	0.885	0.207; 1.563	0.012*
Pain catastrophizing	0.111	-0.147; 0.369	0.39	Pain catastrophizing	0.227	-0.074; 0.528	0.13
Fear-avoidance	0.285	0.084; 0.486	0.007*	Fear-avoidance	0.200	0.000; 0.401	0.05*
General self-efficacy	-0.086	-0.541; 0.368	0.70	General self-efficacy	0.010	-0.440; 0.460	0.96
Pain self-efficacy	0.156	-0.038; 0.350	0.11	Pain self-efficacy	0.236	0.018; 0.454	0.035*
Pain acceptance	0.009	-0.146; 0.164	0.91	Pain acceptance	0.073	-0.049; 0.196	0.23

Multivariate regression analyses

Partial least squares regression was used to investigate which baseline variables best predicted changes in disability at 4-6 month follow-up, and at end of the trial. The regression of changes in disability at end of the trial (R²=0.24, Q²=0.09) revealed that the following baseline variables were significant regressors: pain self-efficacy (VIP=2.09 (-) and disability (VIP=1.72 (+)). Hence, low pain self-efficacy and high disability at baseline were associated with positive changes in disability after 12 months of PA&E.

DIFFERENCES IN PAIN INTENSITY, DISABILITY, AND PSYCHOLOGICAL VARIABLES AT BASELINE BETWEEN PARTICIPANTS WHO DISCONTINUED VS. PARTICIPANTS WHO REMAINED IN THE TRIAL

Participants who discontinued vs. participants who remained in the trial

Baseline values of disability ($p=0.037$) and fear avoidance beliefs ($p=0.048$) were higher among the participants who discontinued the trial within four to six months. In the discontinued group, the median (25th – 75th percentiles) value for disability was 17 (13 – 22) and the median value for fear avoidance beliefs was 24 (21 – 31). Among the participants who remained in the trial, the median values for disability and fear avoidance were 13 (10 – 17) and 19 (11 – 28), respectively.

Completers vs. non-completers

Baseline values of pain acceptance were higher ($p=0.018$) among those who had completed the PA&E intervention after 12 months (pain acceptance median 81; 25th – 75th percentiles 72 – 92), compared to the respective values of the non-completers (67; 58 – 84).

PHYSICAL ACTIVITY AND EXERCISE ARE VALUABLE, BUT
DIFFICULT TO ACHIEVE (PAPER 4)

Paper 4 was a qualitative interview study witch aimed to describe experiences and attitudes about PA&E in patients with chronic pain. The analysis of the interviews resulted in one main theme: To overcome obstacles and to seize opportunities to be physically active despite chronic pain. This main theme was abstracted from five themes: “Valuing a life with physical activity and exercise”; “Physical activity and exercise – before and after pain; “A struggle – difficulties and challenges”; “The enabling of physical activity and exercise”; and “In contact with health care providers”. The themes were derived from categories (figure 12). For a detailed result description, see appended **paper 4**.

Figure 12: Overview of the results in paper 4: The main theme, themes, and categories.

VALUING A LIFE WITH PHYSICAL ACTIVITY AND EXERCISE

Physical activity and exercise were highly valued and desirable in daily life, but the actual performance of PA&E were often difficult and most patients were less physically active than they wanted.

Some patients described physical activity as a basic need, and PA&E were seen as a prerequisite for other activities leading to a high quality of life. Expectations of decreased pain was a reason for being physically active for many patients. Similarly, many patients noted that mental wellness was an important reason for being physically active. Several patients believed that regular PA&E would help prevent diseases and illnesses. To experience well-being was also viewed as a reason to be physically active. PA&E also contributed to an experience of freedom and autonomy to make choices about daily life. Several patients assigned being physically active to an important part of their identity, and not being able to perform PA&E led to distress.

Most of the patients experienced a lack of PA&E, and they believed this lack of PA&E decreased their quality of life and was associated with a negative state of mind. Sorrow, resignation, emotions of loss, and feelings of having limited freedom were also common. Several patients described that the difficulties with being physically active led to frustration and disappointment, feelings of hopelessness, and altogether this negatively affected one's mental and emotional state.

PHYSICAL ACTIVITY AND EXERCISE – BEFORE AND AFTER PAIN

All the patients described a major distinction between experiences of physical activities before the pain and at present, even if a few only had limited experiences of regular PA&E before pain. Before the pain, many of the patients could choose their desired type of PA&E without limitations. The choice was often activities that were enjoyable and resulted in a sense of well-being. The patients described a transformation towards less PA&E once the chronic pain was established. Additionally, the difficulties with performance of PA&E in contrast to before the pain led to a sense of failure.

A STRIVE – DIFFICULTIES AND CHALLENGES

Many patients expressed a hesitance towards PA&E based on experiences of increased pain due to PA&E, which often led to self-directed restrictions. Many patients also perceived that their body did not function properly, so it was impossible to perform certain PA&E despite how much effort they put into the performance. Also, experience of energy deficiency was tough to tackle for several of the patients. In addition, many patients described difficulties in identifying their physical limits, which led to experiences of failure and incapability when, for example, they were

unable to finish PA&E as planned. An inability to adjust the dose and content of the PA&E was also noted.

A lack of anticipated improvement and the impression of failure, especially in combination with increased pain after PA&E, made it less appealing to perform PA&E for several patients. Worries that PA&E would enhance pain and physical harm were expressed by many patients.

This view was reinforced by experience of increased pain related to PA&E and caused ambivalence and reluctance towards performance of PA&E for many patients. A few patients also highlighted difficulties performing PA&E even though the benefits were obvious and no hindrance was present. Lack of volition to challenge the pain and energy deficiency, comfort, the mental status, and difficulties getting used to new behaviours were brought up as reasons for not carrying out the plans.

ENABLING PHYSICAL ACTIVITY AND EXERCISE

To choose an appropriate type and dose of PA&E and to adjust the PA&E when needed were crucial components for enabling PA&E. To pay attention to and to respect their own physical limits were seen as prerequisites for proper adjustments of the PA&E. Several patients described that mental focus was essential for accomplishing PA&E.

To make choices in the daily life such as prioritizing PA&E was brought up as one aspect of the mental focus on PA&E, important for the enabling of PA&E. The willpower to perform PA&E and the willpower to venture to perform PA&E was essential. It was important to make doable goals for PA&E and to have a positive approach.

To reinforce the feeling of doing something good and to be satisfied with the performance was stressed by several patients. Furthermore, a few patients found that a reinforcing strategy, such as recording the planned and performed PA&E in a diary, was important. Social aspects were described by several patients. PA&E was considered an obligation for some patients and implied a sense of demand and increased the likelihood of accomplishing the planned activities. A strong factor for enabling PA&E was to have positive experiences with decreased pain. Furthermore, to perform PA&E with a personal and positive attitude is something desirable and strengthens the likelihood of accomplishing PA&E.

IN CONTACT WITH HEALTH CARE PROVIDERS

Almost all patients had experiences with physiotherapy interventions, which mostly focused on local body regions. Only a few patients had experienced interventions intended to improve general function, performance of and adherence to regular PA&E, or for other health-promoting behaviours. Many patients had received advice on how to manage pain. Often, the patients carefully considered the advice based on who gave them the advice and if the advice seemed reasonable and fell within their own preferences. Often the advice further strengthened their existing attitude towards PA&E, but rarely affected the PA&E performed. Many patients had tried several treatments with slight improvement and described lack of explanation and information about the pain and possible treatment options.

Often, the patients experienced a worsening of the pain after the treatment. Several patients reported lack of individualized treatment and evaluation and about misunderstandings from the health care providers, who did not seem to care about the patients' explanations.

Several patients noted the importance of receiving continuous extensive support from the health care providers. Furthermore, it was important that the health care providers were skilled in explaining various aspects related to the pain and the treatment. Most patients expressed that a high level of knowledge in combination with an understanding, responsive, and empathetic attitude were important for their trust. The trust was especially required when it was necessary to involve both physical and mental aspects in the treatment.

DISCUSSION

The overall aim of this thesis is to increase the knowledge about PA&E as treatment for chronic pain. It takes its start in the biopsychosocial model [10], and in PA&E as treatment for chronic pain. The thesis is addressing chronic pain and PA&E in relation to biological factors, psychological factors, and the interaction there between. Consequently, the discussion will be based on two of the domains included in the biopsychosocial model; *physiology* (the biological domain), and *behaviour* (the psychological domain) in relation to PA&E as treatment for chronic pain. This means that the social domain in the biopsychosocial model not is covered in the thesis, as mentioned in the background, and not either in the discussion. An outline of the discussion is illustrated in figure 13.

Figure 13: Chronic pain and PA&E will be discussed related to two of the domains within the biopsychosocial model; physiology and behaviour. The aim of the thesis is to increase the knowledge about PA&E as treatment for chronic pain.

Paper 1 – 3 in this thesis were based on a clinical trial which comprised a home-based PA&E intervention for women suffering chronic neck- and shoulder muscle pain. The PA&E intervention focused on specific PA&E for the neck- and shoulder muscles (either strength-, or stretching exercise) in combination with the advice to perform optional aerobic activity. The PA&E in this trial were based and modified from previous studies [193, 216] which reported improvements in pain intensity and strength for women with pain in the neck- and shoulder muscles. PA&E in various combinations are often used for the treatment of chronic pain [3, 33-39]. However, despite the large amount of research on PA&E as treatment for chronic pain, there is still a lack of knowledge on physiological effects mechanisms behind the positive effects. In addition, there is still a lack of conclusive knowledge about most efficient types, combinations and doses of PA&E.

Strength exercise have been recommended to be included in PA&E interventions for chronic pain [38, 217]. In **paper 1**, improved strength was a result particularly evident in the STRENGTH group. This is in line with other studies on strength exercise, which often show improvements in strength as a positive outcome of the intervention [3, 193, 216, 218]. Increase in strength has earlier been shown in addition to decreased pain [193, 216, 219, 220]. Consequently, it has been argued that increase in strength could be a physiological mechanism underpinning decreased pain [193]. This argument is derived from the assumption that increased muscle strength entail decreased every-day loading on the muscles, that is daily activities require less muscular strain if the muscle is strong.

The speculation of an association between increase in strength and a decrease in pain intensity is however not supported by the results of the slightly underpowered trial in **paper 1**. In this trial one hypothesis was that the STRENGTH group should report decreased pain intensity and improved function compared to the STRETCH group, but unexpected results were found in the STRETCH group with improvements in strength, as well as in the primary outcomes pain intensity and function.

The fact that both groups increased their strength is not congruent with the knowledge that the effects of muscle exercise are specific [137]. Contrariwise, no statistical significant differences between the two PA&E groups (STRENGTH and STRETCH) in pain intensity and function were found after the PA&E intervention in **paper 1**. Furthermore, similar results of no differences in pain intensity or function between a strength and stretching PA&E intervention has however also been shown earlier [221].

Except for an explanation based on the lack of power (type II-error), it is possible to speculate on that the results of similar improvements in pain intensity and function in STRENGTH and STRETCH in our trial might depend on the combination of PA&Es in the two groups, or the length of the intervention leading to an successive overall increase in PA&E. For example, both groups did get advice about to perform an optional aerobic PA&E three times a week, during the intervention period.

The aerobic exercise could speculatively have had a positive influence on the effects on pain and function. Beneficial effects of aerobic exercise on the chronic pain condition fibromyalgia syndrome have been reported earlier [222]. However, in our present trial, the dose of aerobic PA&E were not controlled, nor measured, and thus we cannot present any reliable results associated to the aerobic activity. Furthermore, it might be reasonable to assume that an increase in PA&E during a long time could have been important and entailed a stable perception and experience of increased physical capacity. In fact, several of the participants in both STRENGTH and STRETCH told us that they successively were able to perform more intense every-day physical activities such as gardening, walking long distances, painting outside walls and stay cleaning; activities they did not manage before the trial because of pain in the neck- and shoulder muscles. Thus, the possibly overall increase in PA&E during a long time period might have been enough beneficial to lead to the result of our study that is similar improvements in both STRENGTH and STRETCH group. In addition to the primary outcomes pain intensity and function, an increase in PPT in painful muscles were found after 4-6 months of PA&E in **paper 2**. The increase in PPT might be interpreted as a decrease in hypersensitivity and sign of improved pain modulatory system in the central nervous system, thus a central nervous long-term effect of the PA&E intervention.

On a cellular level, one previous study indicate a strong myogenic response to strength training in chronically painful trapezius muscles, as the satellite cell pools expands in chronically painful muscles after PA&E [223]. This is interesting results because it indicate a response to PA&E in painful muscles, similar to the response in a pain free muscle [224]. Knowledge on physiological responses to PA&E in chronic pain is essential to improve the research field and enable relevant study designs in future research on PA&E as treatment for chronic pain. This thesis does however not address morphological alterations. Instead, **paper 2** examine pain modulatory substances before and after PA&E in women with chronic neck- and shoulder muscle pain using microdialyse in the trapezius muscle, and alterations in both pain inducing, as well as in pain reliving substances after PA&E were found.

Decreased levels of glutamate and substance P, both algescic substances, were found after four to six months of PA&E compared to before PA&E. Similar results of decreased glutamate in painful muscles (m. vastus lateralis) and decreased pain after PA&E has also recently been reported in another study on PA&E as treatment for fibromyalgia syndrome [167]. The decrease of glutamate in participants with chronic neck- and shoulder pain in **paper 2** should though be interpreted with caution because of an unexpected variation of glutamate also were found in the pain-free group which did not PA&E. The variation of glutamate in the pain-free group in paper 2 is difficult to explain. There might be a spontaneous normal variation of glutamate in pain-free muscles. In fact, there are no studies on variation over time of glutamate in pain-free muscles to either strengthen or dismiss that reasoning. Another explanation could be that the follow-up microdialysis were performed late in

the spring just before vacation time, at a time where many individuals are more stressed, speculatively more tensed in the muscles and thus also possibly increased peripheral nociceptive activity.

Beta-endorphin, an analgesic substance analysed in **paper 2**, has earlier been found to be released as a direct response after PA&E [102]. Increase of beta-endorphin has foremost been related to PA&E intensity increasing the level of serum lactate [155], or after PA&E with an intensity exceeding 60 % VO₂max [225]. In **paper 2** however, increased levels of beta-endorphin in muscle interstitium in participants with regional pain, after long-term strength and stretching PA&E were found. Thus, the finding in **paper 2** of increased levels of beta-endorphin in muscle interstitium of m. trapezius after four to six months of strength and stretch PA&E is especially interesting, as it indicates a long-term response of neck PA&E in participants with regional neck muscle pain.

Previous microdialysis studies report alterations of biochemical substances such as glutamate, lactate, pyruvate and cytokines in painful muscles compared to pain-free muscles, even though the results are not completely, and in detail conclusive, for example there are some differences in which substances alterations are found [194]. The heterogeneity of the microdialysis results might be explained by several factors, for example; different pain conditions, differences in muscles investigated, methodological aspects and differences in reporting of the results. In addition there is a lack of microdialysis studies investigating alterations of the biochemical substances in muscles after a PA&E intervention. Nevertheless, despite the differences and sparsity of research, it appears like there in fact are alterations in several pain modulatory substances in painful muscle compared to pain-free muscles [194]. Furthermore, alterations of inflammatory biomarkers and genes involved in neurotransmission have been found in blood sources and saliva after PA&E in chronic pain conditions [62]. Moreover and importantly, there are a few microdialysis studies [85, 168], including **paper 2**, indicating an altering effect on pain modulatory substances in muscle interstitium as a result of long term PA&E.

Stretching exercise is assumed to improve range of motion and flexibility. In such terms stretching shares some physiological similarities with yoga, which also includes flexibility exercise and which has been suggested to be an alternative PA&E in the treatment of chronic pain [226, 227]. In **paper 1**, improvements in both the STRENGTH and STRETCH group were found. In addition, stretching improves range of motion due to increased flexibility in muscles and tendons, as well as neural adaptations leading to an improved stretch tolerance [150]. Hence, even if stretching earlier has been interpreted to not be beneficial for chronic pain conditions [39], there is interest to speculate about possible physiological effects as results of stretching exercise in painful muscles. Furthermore, a physiological mechanism possibly underpinning a positive effect of stretching or flexibility exercise for chronic pain could speculatively be the effect of countering tension in the muscles. Increased muscle tension in chronically painful muscles has in fact been reported earlier [228,

229], and muscle tension might enhance the nociceptive activity and thus, in a sensitized nervous system lead to increased pain perception. If stretching diminish the nociceptive activity [150, 151] by reducing the muscle tension, stretching could consequently possibly lead to decreased pain perception.

There are also other possible physiological mechanisms earlier proposed to be involved in pain inhibition as a result of PA&E, for example conditioned pain modulation [230, 231], blood pressure [156-158], and the endocannabinoid system [232-234]. However, these physiological mechanisms are not examined in this thesis.

It has been suggested that if the central nervous system has changed towards a sensitized state, the acute analgesic effect of PA&E is diminished or altered compared to healthy individuals [153, 154, 235]. However, in accordance with the suggestion that chronification of pain might be related to an imbalance between facilitating and inhibitory neurobiological systems [47, 236], it is important to highlight the potential of PA&E to impact both ascending pain inducing activities as well as pain modulatory and descending activities in the nervous system. In future studies, the clinical effect on pain intensity and function as a result of different types of PA&E might not be of main interest to evaluate further, as several reviews [3, 33, 34, 36-39] and a meta-analyse [35] consistently shows that PA&E of different types are beneficial for chronic pain. To advance the research field, it might instead be interesting to add a focus on the physiological and neurobiological effect mechanisms associated to acute and long-term effects of PA&E in chronic pain. Up to now, there are results from both animal [237], and human studies [62, 153, 154, 168], including the results presented in **paper 2**, converging at PA&E induced alterations of physiological mechanisms and biochemical substances with a pain modulatory function. However, the details in this field of research are left to uncover, primarily regarding long term effects of PA&E on chronic pain and identification of types and doses of PA&E required to optimize the pain inhibitory effect.

However, PA&E as treatment for chronic pain requires a voluntary action, that is a behavioural performance from the individual who suffer from chronic pain, preferable in line with prescribed PA&E regimen. Consequently, behavioural factors should be essential to target in order to optimize PA&E as treatment for chronic pain.

Physical activity and exercise are per se behaviours [171], modifiable by several other psychological components. In **paper 3** and **paper 4**, a range of overt and covert behavioural and psychological factors related to PA&E were investigated. In addition, adherence to prescribed and desired PA&E are emphasized in the **papers 1, 3 and 4** providing in this thesis Adherence will be discussed below in relation to psychological and behavioural aspects, as high adherence to prescribed PA&E regimen is important in order to optimize the effect of PA&E treatment. The concepts included in the discussion about adherence in this thesis are outlined in figure 14.

Figure 14: Overview of the concepts related to adherence which are discussed in this thesis.

Adherence to PA&E as treatment is troublesome [7, 174], and possibly even more troublesome in home-based PA&E interventions [238]. Also in **paper 1**, limited adherence to the PA&E intervention were reported and a successive decline in adherence during time period was obvious. Poor adherence might diminish the possible outcomes of a PA&E intervention. In addition, poor adherence diminish the potential to draw firm conclusions from the research results on PA&E as treatment. Thus, adherence to prescribed PA&E is a key factor for high quality treatment as well as research on PA&E in performed by individuals with chronic pain. Nevertheless, there is a lack of conclusive knowledge about the underlying mechanisms behind poor adherence, as well as about effective interventions to improve adherence [7, 239].

Self-efficacy is a core component in the *Social Cognitive Theory* [127, 128], proposed to antedate successful behaviour change, and is thus probably important for a high adherence. Self-efficacy describes an individual's perceived confidence in performing a certain behaviour, or behaviours during certain circumstances. Pain self-efficacy, an individuals confident in performing activities in presence of pain [130], has earlier been studied in research on chronic pain and PA&E, and associations to pain severity, disability and psychological distress has been proposed [131], as well as an association between low self-efficacy and poor adherence to PA&E as treatment [174, 238]. However, there are conflicting evidence for the impact of self-efficacy on adherence to treatment in chronic pain [240]. In **paper 3**, no difference in pain-self efficacy in participants who adhered to the PA&E intervention compared to those who did not was found. The non-difference in pain self-efficacy between participants who adhered to the PA&E intervention and those who did not, might be explained by the fact that participants in **paper 3** scored their pain self-efficacy relatively high. On the other hand, in **paper 4**, participants described that insecurity about how to perform PA in presence of pain was a troublesome obstacle. The experienced insecurity could be interpreted as similar to low self-efficacy which negatively affected the adherence to PA&E in **paper 4**.

Fear-avoidance [123, 124], is included in **paper 3** and **paper 4**, and fear-avoidance has also gained extensive attention also in previous research on chronic pain [121, 125, 126]. The fear-avoidance model is an established model for explaining behavioural consequences of pain. Even if some components of the model has been critically discussed in the literature such as the assumption of catastrophizing preceding avoidance [241], the model is still used and continues to be included in resent research. Avoidance, or reduction of PA&E, is according to the model a probable negative outcome if the perception of pain include fear. Consequently, poor adherence to PA&E could theoretically be related to high fear-avoidance. This is in accordance with quantitative and qualitative data in our research showing that higher fear-avoidance was associated to higher drop-out rate early in the intervention in paper 3, and also that fear of pain and harm was a prominent obstacle to perform desired PA&E paper 4.

The opposite of avoidance of activity could be described in terms of *acceptance and commitment* as included in Acceptance and Commitment Therapy (ACT) [132, 133, 135], a method earlier applied on chronic pain research [242, 243]. Adherence to prescribed and desired PA would from an ACT point of view, speculatively be facilitated by high acceptance, and accompanied by a strong commitment. This is in line with the results in **paper 3**, where it was found that participants who completed the whole intervention of 12 months PA&E had higher chronic pain acceptance at the beginning of the study compared to those who did not complete the PA&E intervention.

We did not measure the factor commitment in **paper 3**, but in **paper 4** participants described a high determination to complete with PA&E. This was an important aspect for the enabling of PA&E and could be interpreted in line with high commitment.

The research field of health psychology addresses for example health behaviour change. PA&E are health behaviours. However, health behaviour change theories are surprisingly rarely included in studies on PA&E as treatment for chronic pain, even though recently one study reports relations between core constructs within the SDT and the Theory of Planned Action applied on individuals with chronic pain [239], and one study showed that interventions based on the Transtheoretical Model [244] increased recreational PA&E in patients with chronic low back pain [245].

The SDT include motivation as central and highly important, preceding the performance of PA&E behaviours [179]. In the SDT, motivation is understood in relation to extrinsic and intrinsic motivational factors, where intrinsic motivation is thought to be most important for long-term adherence. External motivation is depending on reinforcement from external sources and intrinsic motivation entails the performance of the behaviour is wanted and enjoyed in itself. Extrinsic and intrinsic motivation are however not dichotomous, motivation is described as ranging from no motivation at all (amotivation), via stages of extrinsic and intrinsic motivation to a fully intrinsic motivation state. In **paper 4**, motivation was highlighted and included in the interview guide. The participants brought up several aspects which could be interpreted as external motivational factors, which might have diminished the strength of the motivation.

Motivation, or an intention to perform PA&E, is according to behaviour change theories seen as the most proximal state preceding the PA&E behaviour [246]. Motivation were not measured as outcomes in **papers 1 – 3**, but motivation to engage in the prescribed PA&E intervention was an inclusion criteria for the participants with neck- and shoulder pain. All of the participants in **paper 1 – 3** verbally confirmed their motivation and intention to adhere to the PA&E intervention, nevertheless the adherence was limited. Also in **paper 4** discordance between desired and performed PA&E was evident. Even if the PA&E was perceived as a highly valued action, accompanied by several external and sometimes internal motives, the participants were often not satisfied with the PA&E they accomplished. The discordance between motivation and behaviour has also been evaluated meta-analysis which showed that an increase in motivation only resulted in a small change in PA&E behaviour [247]. Thus, even if intention to perform PA&E is important, it is often not enough to reach a high adherence.

The difficulty with accomplishing a beforehand decided PA&E behaviour, even if the individual is motivated, is well known in studies on health behaviour change, and is described as the intention-behaviour gap [246, 248]. It is proposed that several components are essential for an improved concordance between intention and behaviour, such as motivational components, as well as behavioural control and habitual components [249].

A health behaviour change model that might theoretically bridge a part of the gap between intention and behaviour is the *Health Action Process Approach* (HAPA) [177, 178]. The HAPA includes both an intention (motivational, goal setting) phase and an action (volition, goal pursuit) phase, where the action phase highlights goal pursuit, that is performance of intended PA&E. However, the action phase in HAPA is constructed of cognitive components such as planning (action- and coping planning), and maintainence self-efficacy, which all could be interpreted as covert behaviours. To reach the conduction of PA&E, overt behaviour is required, and the transfer from covert cognitions to overt PA&E behaviour is still complicated to predict and promote. In **paper 4**, the participants described several cognitions and thoughts which according to HAPA should be beneficial for the performance of PA&E such as intention, motivation, action planning and PA&E self-efficacy, but still; there was often troublesome to conduct desired PA&E.

Earlier research on the transition from intention to behaviour has highlighted automaticity and cross-behaviour regulation as important for the performance of PA&E [250]. Automaticity can be described as a habit or an action that is performed without preceding elaborating thoughts, planning or rumination. Instead, the action is performed without forgoing thought as a result of learned behaviour which were once motivational based. Cross-behaviour regulation refers to a prioritization between different behaviours, that is the strength of commitment is crucial for which behavior that is choosed and performed. Both automaticity and cross-behaviour regulation can be found in the experiences described in **paper 4**. Furthermore, it is possible to speculate on similarities between intention - behaviour and ACT. That is, the intention phase (HAPA) could speculatively be similar to acceptance and values constructs (ACT), and the action phase (HAPA) could speculatively be similar to committed action (ACT).

Thus, when summarizing the result of adherence to PA&E in **paper 1, 3, and 4**, commitment and committed action emerges as essential for the application of PA&E as treatment for chronic pain.

Behavioural interventions for the treatment of chronic pain can include for example CBT, operant behavioural therapy, and progressive relaxation [251]. It is reasonable to assume that adding two moderately effective interventions, such as PA&E and behavioural interventions, would enhance the effect on chronic pain conditions. However, several studies show no difference in effect if the two treatment approaches are combined [252]. Although the quality of the recent studies on combined treatment (PA&E and CBT) could be improved, the current evidence might be interpreted as indicating that adding behavioural treatment such as CBT to PA&E interventions are no more effective than PA&E alone as treatment of chronic pain [252].

Except for behavioural interventions targeting chronic pain, adherence to PA&E is also a behavioural aspect of importance, however much less studied in chronic pain research. Adherence to prescribed PA&E are often troublesome [7, 172], which also were shown in **paper 1** and **paper 4**. Because PA&E are beneficial for chronic pain [3, 33-39], and that the physiological responses of the PA&E normally are depending on the dose and frequency [137], it should reasonably be important to strive after higher adherence to prescribed PA&E in order to optimize the effect of the PA&E. Adherence is targeted in models of health behaviour change, but such models are seldom included in research on PA&E interventions for chronic pain. In future studies and clinical application of PA&E as treatment, it is therefore interesting to further emphasize behavioural strategies for increased adherence to the prescribed PA&E, separate from and parallel to behavioural approaches focusing on the chronic pain. This speculation of the importance of behavioural strategies to enhance adherence to prescribed PA&E is in line with the conclusion in **paper 4**, and to the results of one recent study showing improved adherence to recreational PA&E as well as improved pain related outcomes when behaviour change strategies were included in the intervention design [245].

METHODOLOGICAL CONSIDERATIONS

The biopsychosocial model as a backdrop of this thesis forms the basis for increased knowledge about PA&E as treatment for chronic pain. A strength of the thesis is the design of the four papers including physiological-, as well as psychological aspects important for PA&E interventions. Especially the biochemical evaluation in **paper 2** using the method microdialysis is an important strength in this thesis because it was the first study addressing alterations in biochemical substances in painful muscles after a PA&E intervention. However, the design and conduction of **papers 1 – 4** has several limitations.

First of all it is possible to speculate on that the participants who agreed to be included in **paper 1 – 3** and **4** to some extent were interested in PA&E. This would imply that the results might not fully be applicable on groups of individuals who not are interested in PA&E at all.

The design of the PA&E intervention, and also the slightly too small sample size affects the reliability of the interpretation of the results on pain intensity and function after the PA&E intervention. It is possible that the non-difference between the PA&E groups depends on a type II error, thus showing no difference because of insufficient sample size. The goal was to include 50 participants in each group (STRENGTH and STRETCH), but it was not possible due to limited resources and logistical reasons.

Inclusion of aerobic PA&E in the home-based PA&E intervention evaluated in **paper 1** was inspired from another study showing decreased pain after home-based PA&E [193]. That PA&E intervention was successful, and thus represented a PA&E model for this present thesis which also include the biochemical design. That is, it was essential to strive after a successful home-based PA&E intervention in order to enable a biochemical evaluation as well. Thus the design of the PA&E intervention included aerobic PA&E in both groups, however the design did not fully capture crucial aspects of the aerobic PA&E such as intensity of the PA&E. Intensity of aerobic activity is probably essential for the physiological effects of the PA&E, thus it is not possible to evaluate the influence of aerobic PA&E on the results of the PA&E intervention in this thesis.

The follow-up measurement were because of practical reasons performed after 4-6 months of PA&E. The two months follow-up period could also be seen as a limitation because of the inconsistency of length of the PA&E. However, the circumstances were the same for all participants.

When evaluating biochemical alterations in trapezius muscles at follow-up, unexpected alterations in glutamate in the pain-free group were found in **paper 2**. This finding is difficult to explain. A clinical examination and PPT-measurement of the participant with pain as well as the pain-free participants before the first microdialysis experiment were performed. It might have been beneficial for the interpretation of the data if the same clinical examination and PPT-measurement at follow-up had been performed as well for both groups. It could also be considered a limitation that the two PA&E groups were merged into one when analyzing the results in **paper 2**, as it hypothetically could be different physiological mechanisms involved in pain inhibition after strength and stretching PA&E. However, there were no statistical significant differences in pain intensity and function after PA&E between the two PA&E groups (STRENGTH and STRETCH), thus not possible to evaluate and interpret the biochemical status based on subjective perception of pain. In addition, there are no available reference values on normal variability of the examined biochemical substances in painful and pain-free trapezius muscles. Furthermore, an additional reason for the merge of the two PA&E groups (STRENGTH and STRETCH) into one was to increase the sample size in order to increase the power.

Associations between psychological factors and the effect of the PA&E intervention were found in **paper 3**. However, the severity of pain intensity, disability and psychological symptoms were moderate. Consequently the clinical importance of the findings could be questioned. In **paper 4**, all patients who were asked to participate in multimodal pain rehabilitation at Pain and Rehabilitation centre, Linköping, were invited to the study. However, no participant younger than 31 years agreed to participate in the study. Thus, the result is lacking descriptions of experiences from young adults which is a limitation.

It is also necessary to mention the gender perspective as a limitation. In **papers 1 – 3**, all participants were women, thus the results might not be valid for men. In **paper 4**, only two men agreed to participate, which means that there is mainly experiences expressed by women that form the basis for the qualitative content analyse.

CONCLUSIONS

1. Strength-, and stretch PA&E during a long time-period might be beneficial for chronic pain in the neck and shoulders. Adherence to prescribed intervention should be supported in application of PA&E as treatment for chronic neck and shoulder pain.
2. Higher concentrations of glutamate and beta-endorphin, and lower levels of cortisol in painful trapezius muscle compared to pain free trapezius muscle indicate peripheral alterations of pain modulatory substances in chronic pain. PA&E possibly results in a peripheral long-term physiological effect (alterations of pain modulatory substances) related to decrease in pain.
3. Psychological factors might be associated to the effects on pain intensity and function, as a result of a PA&E intervention. In addition, high pain acceptance could be valuable for increased adherence to prescribed PA&E.
4. The underlying mechanisms of an intention-behaviour gap regarding desired and accomplished PA&E identified in interviews might be related to motivational aspects and committed action. Interventions aimed to recognize and decrease an intention-behaviour gap in connection to PA&E as treatment for chronic pain should be investigated in future research.

In summary; this thesis strengthens the importance of PA&E as treatment for chronic pain. This thesis increases the knowledge about; possible peripheral pain inhibitory effects after long-term exercise; how psychological factors might affect the results of PA&E; and also about important behavioural aspects that might affect adherence to prescribed PA&E.

CLINICAL IMPLICATIONS

Long term PA&E are beneficial for chronic neck and shoulder pain with improvements in subjective perception of pain and function as well as for biochemical substances indicating more efficient pain modulatory mechanisms. It is probably important to insert a behavioural approach in PA&E interventions to optimize adherence. For example, motivation and committed action might to be relevant to explicitly consider and include in analysis and designs of PA interventions.

FUTURE RESEARCH

It is essential that future studies take pain physiology as well as PA&E physiology into consideration when designing trials on PA&E as treatment for chronic pain. To advance the research field further it is important to understand more about which physiological and neurobiological mechanisms that can be associated to long term effects of PA&E in chronic pain. It is also of importance to know more about optimal dose and types of PA&E, most beneficial for chronic pain treatment.

Moreover, adherence to prescribed and agreed PA&E should be highlighted in future research on PA&E as treatment for chronic pain. For example outcome measurements of motivation, commitment and adherence could be included. Preferable, PA&E interventions for chronic pain should comprise not only a design of the PA&E, but also an adherence design for example by including theories and models of health behaviour change in research on PA&E as treatment for chronic pain.

Finally, it is important to investigate the interplay between physiological mechanisms, psychological and behavioural aspects and subjective pain perception. Future research should strive to include all these aspects.

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APPENDIX

Description of the physical activity and exercise intervention

- **the STRENGTH and STRETCH exercises**

STRENGTH exercises for the neck- and shoulder muscles to be performed three times per week.

- Neck lift up from supine; 20 repetitions, 3 sets during the whole intervention period
- Dumbbell exercises; 2 kg weight – 20 repetitions, 3 sets first eight weeks of the intervention. The remaining intervention period; max weight to perform 10 repetitions, 3 sets during three weeks, altering with one week of exercising with 2 kg dumbbells, 20 repetitions, 3 sets.
- Exercise for core muscles and legs (without dumbbells); 20 repetitions, 3 sets during the whole intervention period.

The STRENGTH group did additionally perform the same stretch exercises as the STRETCH group. Both groups (STRENGTH and STRETCH) were advised to perform 30 minutes of aerobic exercise three times per week.

STRETCH exercises for the neck- and shoulder muscles and upper extremities to be performed three times per week.

- Approximately 30 seconds, 2 times bilaterally for each exercise.

The STRENGTH group did perform the same stretch exercises as the STRETCH group after the STRENGTH exercises. Both groups (STRENGTH and STRETCH) were advised to perform 30 minutes of aerobic exercise three times per week.

Papers

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