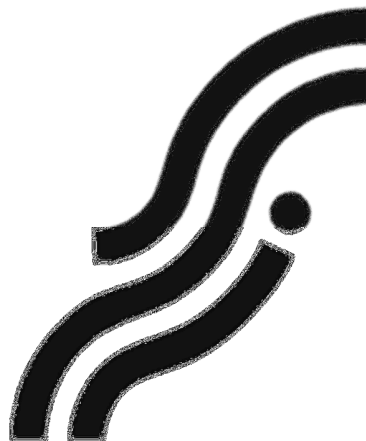


# **Temporal and Spatial Manifestations of Exercise-induced Hypoalgesia and Conditioned Pain Modulation**

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## PREFACE

The primary objective of this PhD thesis was to investigate the temporal and spatial manifestations of exercise-induced hypoalgesia (EIH) and conditioned pain modulation (CPM) in healthy subjects and in patients with chronic musculoskeletal pain. The thesis is based on the four peer-reviewed papers, introduced below, which are referred to in the text as I-IV. The papers are based on three separate experiments, which have been conducted in the period 2011-2014 at Pain Center South, Department of Anesthesiology and Intensive Care Medicine, University Hospital Odense (OUH), Denmark. This PhD has been a collaboration between Pain Center South and Center for Sensory-Motor Interaction (SMI), Faculty of Medicine, Aalborg University.

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## ABBREVIATIONS AND ACRONYMS

**CPM** Conditioned pain modulation

**EIH** Exercise-induced hypoalgesia

**QST** Quantitative sensory testing

**CONDITIONED PAIN MODULATION:** The term '*conditioned pain modulation*' is not defined in the IASP terminology. It has been used throughout this thesis to denote the effect (i.e. inhibitory or facilitatory) on the pain test stimulus (i.e. pressure pain) after applying a painful conditioning stimulus (i.e. cold pressor test).

**HYPOALGESIA:** The term '*hypoalgesia*' has been used throughout this thesis in agreement with the IASP taxonomy to denote *Diminished pain in response to a normally painful stimulus*.

**PAIN THRESHOLD:** The term '*pain threshold*' has been used throughout this thesis in agreement with the IASP taxonomy to denote *The minimum intensity of a stimulus that is perceived as painful*.

**PAIN TOLERANCE:** The term '*pain tolerance*' has been used throughout this thesis in agreement with the IASP taxonomy to denote *The maximum intensity of a pain-producing stimulus that a subject is willing to accept in a given situation*.

**TEMPORAL SUMMATION OF PAIN:** The term '*temporal summation of pain*' is not defined in the IASP terminology. It has been used throughout this thesis to denote an increase in subjective pain ratings during application of repetitive painful pressure stimulations.

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## 1. INTRODUCTION

Pain is defined by the International Association for the Study of Pain (IASP) as ‘*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*’ (Merskey and Bogduk, 1994). However, the experience of pain is not static, and a variety of conditioning stimuli can modulate the way pain is perceived. This phenomenon has for instance been observed during combat in wounded soldiers reporting little or no pain (Beecher, 1956). Similarly, there are anecdotes about absence of pain associated with injuries sustained during running (Egger, 1979). Thus, pain is a complex and highly subjective phenomenon that can be influenced by several factors, which can modulate the experience of pain.

Previous pain research has demonstrated that modulation of pain is an important determinant of the pain experience (Yarnitsky, 2010) and may therefore be an important factor in understanding pain conditions and potentially improving treatment strategies. Furthermore, reduced pain inhibition has been associated with several chronic pain conditions (Lewis et al., 2012b) and may predict who develop chronic pain (Yarnitsky et al., 2008; Wilder-Smith et al., 2010), and who will benefit from pharmacological pain treatment (Yarnitsky et al., 2012). In humans, assessment of the pain inhibitory pathways is recommended through the paradigm known as *conditioned pain modulation* (CPM) (Yarnitsky et al., 2014), frequently demonstrated as a reduction in pain sensitivity by a painful conditioning stimulus (e.g. cold pressor test).

Recently, the paradigm of *exercise-induced hypoalgesia* (EIH) has also been proposed to reflect the efficiency of the pain inhibitory pathways (Lannersten and Kosek, 2010). EIH is also frequently demonstrated as a reduction in pain sensitivity after aerobic or isometric exercises (Koltyn, 2000; Naugle et al., 2012). Similarities between CPM and EIH in their interaction with the opioid system after noxious thermal stimuli (Le Bars et al., 1981c; Willer et al., 1990) and after exercise (Janal et al., 1984; Bertolini et al., 2012) indicate similar mechanisms underlying CPM and EIH, and the paradigms may reflect somewhat similar aspects of pain inhibition. This hypothesis is furthermore supported by a recent study demonstrating that the EIH response was predictive of pain severity following nerve injury in rats (Khan et al., 2014). Yet, the spatial and temporal manifestations of the two paradigms have never been directly compared, and it is currently unknown whether they provide equivalent data on the pain inhibitory systems. A comparison of the two paradigms will clarify whether they represent similar or different aspects of pain inhibition, which is necessary if the two phenomena are to be used

interchangeably as a method to evaluate the efficiency of the pain inhibitory systems. Additionally, similarities between CPM and EIH may also be related with the influence of gender and age on the CPM and EIH responses. Recent studies have shown significant differences in both CPM and EIH in relation to gender (Sternberg et al., 2001; Popescu et al., 2010) and age (Edwards et al., 2003a; Lariviere et al., 2007; Hoeger Bement et al., 2011). However, other studies showed no differences (Baad-Hansen et al., 2005; Umeda et al., 2010; Oono et al., 2011; Lemley et al., 2014b), and the gender and age effects on the CPM and EIH responses in healthy subjects are still unclear.

Physical exercise is, besides its potential ability to assess pain inhibition, an important component in the treatment and rehabilitation of many patients with chronic musculoskeletal pain (Mannerkorpi and Henriksson, 2007; Hassett and Williams, 2011). A comprehensive understanding of how exercise influences pain perception is necessary to optimize the clinical utility of exercise as a method of pain management. Nevertheless, very little research has compared whether acute aerobic or isometric exercise has a greater effect on reducing pain sensitivity (Drury et al., 2004). Furthermore, the exercise intensity and duration to best inhibit pain are not clear. In addition, research on the effect of exercise on central pain mechanisms, like temporal summation of pressure pain, is sparse (Meeus et al., 2014).

Regular exercise has been linked to alterations in pain perception with athletes demonstrating significantly higher pain tolerance compared with normally active controls (Tesarz et al., 2012). Current research comparing the CPM response in athletes and normally active controls during a cold pressor test showed equivocal results, with one study showing increased CPM (Geva and Defrin, 2013), and one study showing decreased CPM (Tesarz et al., 2013) in athletes compared to controls. A recent study found that greater amount of self-reported physical activity, as well as greater amount of vigorous physical activity, predicted a greater CPM response, assessed as change in thermal pain sensitivity during cold pressor test (Naugle and Riley, 2014). So far, two small studies have investigated the relationship between physical activity and EIH (Øktedalen et al., 2001; Sternberg et al., 2001), but no studies have investigated CPM and EIH responses between active and inactive subjects.

In patients with chronic pain, studies have indicated that a large subset of patients demonstrate impaired CPM and EIH responses compared with asymptomatic controls (Lewis et al., 2012b; Naugle et al., 2012). It has been hypothesized that an impaired CPM response or an impaired EIH response may indicate a dysfunction of the pain inhibitory systems (Yarnitsky et al., 2014; Lannersten and



Kosek, 2010). In patients, the degree of CPM has been linked with clinical pain (Nahman-Averbuch et al., 2011; Pickering et al., 2014) and psychological factors (Goodin et al., 2009), with both factors having a negative impact on the degree of pain inhibition. In addition to impaired pain inhibition, increased pain sensitivity has also been demonstrated in patients with chronic pain compared with asymptomatic controls (Staud et al., 2003a; Arendt-Nielsen et al., 2010; Kosek et al., 2013). Still, no studies have compared the degree of pain inhibition in chronic musculoskeletal pain patients with high and low pain sensitivity. It may be hypothesized that low pain sensitivity in sub-groups of patients could be due to adequate pain inhibitory pathways. Improving knowledge about the efficiency of the pain inhibitory pathways in patients with chronic pain is important for optimal treatment. As mentioned earlier, reduced pain inhibition may be predictive of acute and chronic postoperative pain and drug efficacy, which highlights the importance of pain mechanisms in clinical decision-making.

In the current PhD study (Fig. 1.1), CPM and EIH responses were investigated in healthy subjects (experiment 1 and 2) and in patients with chronic musculoskeletal pain (experiment 3), to characterize the temporal and spatial manifestations of the two phenomena and to study the influence of age, gender, regular physical activity, exercise modality, intensity and duration as well as experimental pain sensitivity on the CPM and EIH responses. Standardized quantitative sensory testing (QST) was used to assess pressure pain sensitivity (pain thresholds, pain tolerance, pain ratings and temporal summation of pain) in the deeper musculoskeletal structures in relation to cold pressor tests (CPM paradigm) and different exercise protocols (EIH paradigms).

## **1.1 Aims of the PhD thesis**

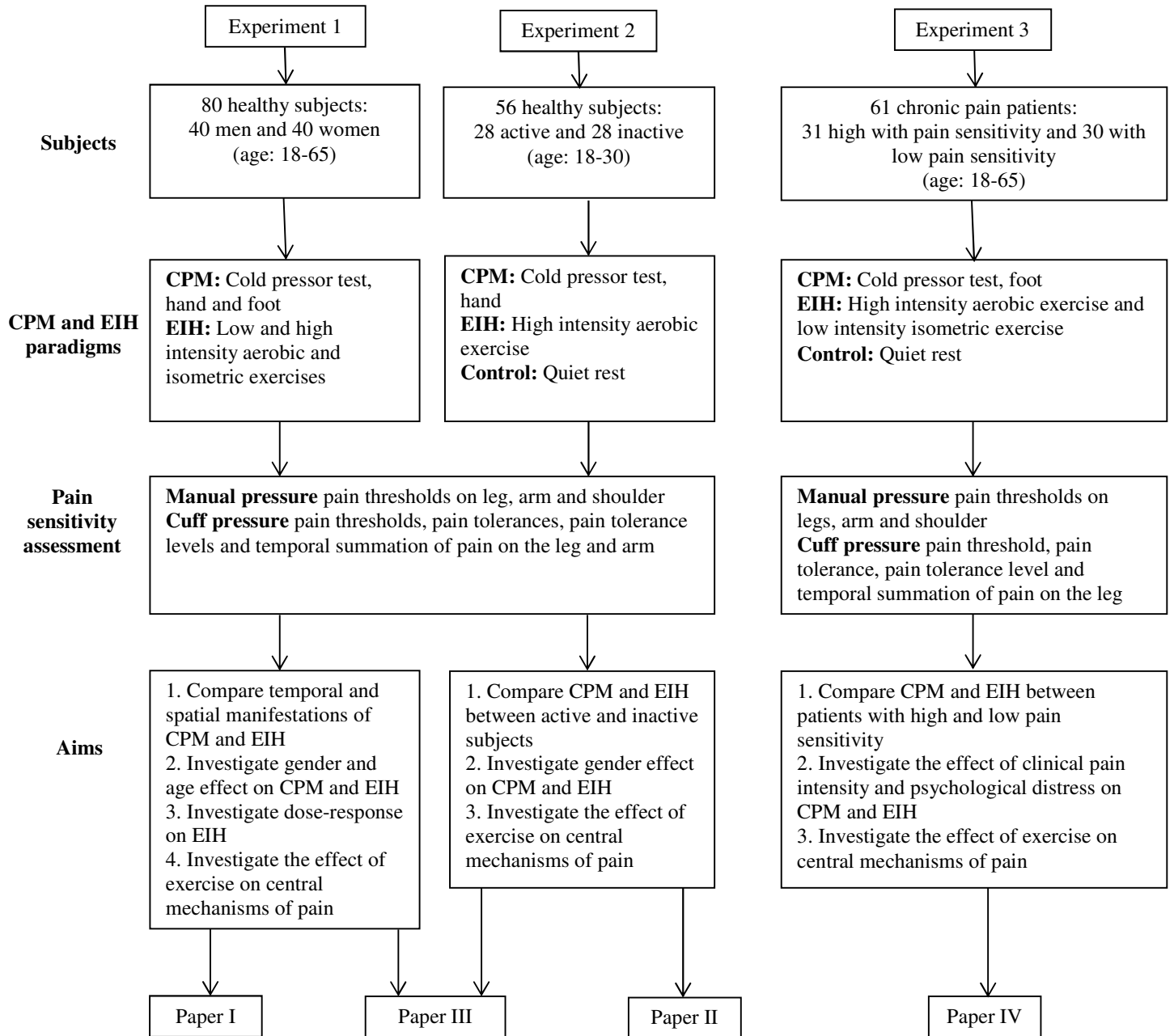
The aims of this PhD thesis were (Fig. 1.1):

- i. To compare the temporal and spatial manifestations of conditioned pain modulation and exercise-induced hypoalgesia in healthy subjects.
- ii. To investigate the influence of age, gender and level of regular physical activity on conditioned pain modulation and exercise-induced hypoalgesia in healthy subjects.
- iii. To investigate dose-response of exercise-induced hypoalgesia after different exercise modalities, intensities and durations in healthy subjects.
- iv. To investigate the effect of exercise on central mechanisms of pain in healthy subjects and patients with chronic musculoskeletal pain.

- v. To investigate the influence of pain sensitivity, clinical pain intensity and psychological distress on conditioned pain modulation and exercise-induced hypoalgesia in patients with chronic musculoskeletal pain.

## 1.2 Hypothesis

The hypotheses in relation to the CPM and EIH responses in healthy subjects were that cold pressor tests, as well as aerobic and isometric exercises would cause a multisegmental decrease in pain sensitivity and the CPM and EIH responses would be correlated. It was also hypothesized that the CPM and EIH responses would be influenced by age, gender and level of regular physical activity. For the exercise conditions in healthy subjects, it was hypothesized that greater reduction of pain sensitivity would be observed after higher intensity exercise, compared with lower intensity exercise, and that aerobic and isometric exercise would reduce central mechanisms of pain. In the clinical experiment, it was hypothesized that the CPM and EIH responses would be reduced in chronic musculoskeletal pain patients with high pain sensitivity compared with pain patients with low pain sensitivity, and that the CPM and EIH responses would be correlated, as well as influenced by, clinical pain sensitivity and psychological distress.



**Fig. 1.1:** Illustration of the methodologies and aims of the experiments.

‘MSK’: Musculoskeletal. ‘CPM’: Conditioned Pain Modulation. ‘EIH’: Exercise-induced Hypoalgesia.

## 2. ASSESSMENT OF PAIN SENSITIVITY AND PAIN MODULATION

In the current PhD study, QST was used to assess experimental pressure pain sensitivity in relation to paradigms of CPM and EIH in healthy subjects and in patients with chronic musculoskeletal pain. An overview of the options available for assessment of pain sensitivity and pain modulation is presented in this chapter. Procedures used in experiment 1-3 are summarized in Table 2.1.

### 2.1 Assessment of pain sensitivity

Different methodologies for assessment of pain sensitivity have been used before and after CPM and EIH paradigms in humans, including assessment of pressure pain thresholds (Goodin et al., 2009; Hoeger Bement et al., 2009), pressure pain ratings (Rezaii et al., 2012; Lemley et al., 2014a), pressure pain tolerance (Gurevich et al., 1994; Sowman et al., 2011), temporal summation of pressure pain (Cathcart et al., 2009; Meeus et al., 2014), electrical pain thresholds (Drury et al., 2005; Rosen et al., 2008), heat pain thresholds (Talbot et al., 1987; Kodesh and Weissman-Fogel, 2014), heat pain ratings (Lariviere et al., 2007; Ellingson et al., 2014), temporal summation of heat pain (Edwards et al., 2003a; Koltyn et al., 2013), and the spinal nociceptive flexion reflex (RIII reflex) (Guieu et al., 1992; France and Suchowiecki, 1999).

A standardized battery of pressure pain tests was used in experiment 1-3 to assess deep tissue pain sensitivity (I, II, III, and IV). Assessment of deep tissue pain sensitivity was chosen for three reasons. 1) The deeper tissues play an important role in many musculoskeletal pain conditions (Arendt-Nielsen and Graven-Nielsen, 2002), 2) pressure pain tends to give large and robust CPM responses (Ge et al., 2004; Arendt-Nielsen et al., 2008; Wang et al., 2010) and EIH responses (Koltyn, 2000), and 3) assessment of pressure pain sensitivity is a reliable method (Brennum et al., 1989). Though pressure stimulation applied on the skin could reflect the pain sensitivity of both the superficial and deep structures, deep-tissue nociceptors mediate a major component of the pressure-induced pain during pressure algometry (Kosek et al., 1995; Graven-Nielsen et al., 2004).

Assessment of deep tissue pain sensitivity included assessment with manual pressure algometry and computer-controlled cuff algometry. Manual algometry (Somedic Sales AB, Sweden) was used for assessment of pressure pain thresholds with a standardized rate of pressure increase (30 kPa/s), applied at each assessment site with a stimulation probe of 1 cm<sup>2</sup>. Pressure pain thresholds were assessed at

standardized anatomical muscular sites (leg, arm and shoulder). Manual pressure algometry has been extensively used and validated in clinical and experimental research as a quantitative method of assessing deep tissue pain sensitivity (Jensen et al., 1986a). Previous studies (Reeves et al., 1986; Brennum et al., 1989; Delaney and McKee, 1993; Nussbaum and Downes, 1998; Geber et al., 2011; Walton et al., 2011) on manual pressure algometry have demonstrated high levels of reliability with ICC values above 0.7 for test-retest data. These findings were supported by the current experiments, which showed substantial ICC values above 0.8 in healthy subjects (Table 2.2) and in patients with chronic musculoskeletal pain (IV).

Cuff algometry (Nocitech, Denmark and Aalborg University, Denmark) was used for assessment of pressure pain thresholds, pressure pain tolerance, pain tolerance level (pain rating when pain tolerance was reached), and pain ratings during repeated pressure stimulations as a measure of temporal summation of pain. Assessment with cuff algometry was performed at standardized anatomical muscular sites (lower leg and upper arm) with a 13-cm wide silicone tourniquet cuff (VBM, Sulz, Germany). A 10 cm electronic visual analogue scale (VAS) anchored 'no' pain at the left hand end and 'maximal pain' at the right hand end was used to record pain during cuff inflation. VAS ratings have been shown to provide useful information in pain research (Jensen et al., 1986b; Staud et al., 2003b). In contrast to manual pressure algometry, a larger tissue volume can be assessed by computer-controlled cuff algometry (Polianskis et al., 2001). In cuff algometry, the pain intensity related to inflation of a tourniquet cuff applied around an extremity is used to establish stimulus-response curves, allowing assessment of deep-tissue pain sensitivity. Moreover, cuff algometry is less likely to be influenced by local variations in pain sensitivity and is also an examiner-independent technique reducing the potential measurement bias. Cuff algometry has shown less variability compared with manual algometry (Polianskis et al., 2001) and is sensitive to hypoalgesia and hyperalgesia in the deep tissues (Polianskis et al., 2002b). Furthermore, cuff algometry has been used previously to assess pain sensitivity in healthy subjects (Polianskis et al., 2001, 2002a, b, c), in patients with regional pain conditions (Lemming et al., 2012; Jespersen et al., 2013; Skou et al., 2013, 2014), and widespread pain conditions (Jespersen et al., 2007). In the current experiments, moderate to high ICC values (0.65 - 0.90) for test-retest data were found with cuff algometry in healthy subjects (Table 2.2) and in patients with chronic musculoskeletal pain (IV). Test-retest reliability for cuff algometry has not previously been determined.

<b>Table 2.1.</b> Experimental methods and standardization procedures used in the current studies on CPM and EIH.		
<b>Experimental parameters</b>	<b>Method</b>	<b>Standardization procedures</b>
Deep tissue sensitivity	<p>1. Pain threshold, pain tolerance, pain tolerance level and pain ratings during repeated stimulations measured at the lower leg and upper arm (experiment 1 and 2) and lower leg (experiment 3) with computer-controlled pressure algometry (Nocitech, Denmark and Aalborg University, Denmark)</p> <p>2. Pain thresholds measured at the thigh, upper arm and shoulder (experiment 1 and 2) and thighs, upper arm and shoulder (experiment 3) with manual pressure algometry (Somedic Sales AB, Sweden)</p>	<p>1. <u>Stimulation area</u>: 13-cm wide silicone tourniquet cuff <u>Rate of application</u>: 1 kPa/s and the maximal pressure limit was 80 kPa</p> <p>2. <u>Stimulation area</u>: 1.0 cm<sup>2</sup> <u>Rate of application</u>: 30 kPa/s <u>Peak value</u>: Average of 2 measurements per site</p>
Pain intensity during cuff stimulation	Electronic VAS	Computer-controlled data collection
Cold pressor test	Tank containing circulating cold water	Standardized temperature, time and immersion depth
Aerobic exercise	Stationary ergometric bicycle (Ergomedic 928E)	Standardized pedal frequency and time of bicycling
Intensity of aerobic exercise	Electronic digital heart rate belt (Monark Heart Rate Monitor)	Standardized determination of age-related heart rate Standardized increase and adjustment of resistance
Maximal knee extension and elbow flexion force	Electronic digital hand dynamometer (Commander Muscle Tester, Powertrack II)	Standardized body positions <u>Peak values</u> : Average of two measurements
Sub-maximal knee extension and elbow flexion force	Electronic digital hand dynamometer (Commander Muscle Tester, Powertrack II)	Standardized body positions and time of contractions Visual feedback during contractions

Assessment site	Pain sensitivity parameter	ICC		
		1 <sup>st</sup> session Mean ± SD	2 <sup>nd</sup> session Mean ± SD	ICC <sub>3,1</sub> (95 % CI)
Leg	Manual pressure pain threshold	543 ± 264 kPa	509 ± 243 kPa	0.89 (0.84-0.92)
	Cuff pressure pain threshold	26.7 ± 12.9 kPa	27.4 ± 11.8 kPa	0.79 (0.70-0.85)
	Cuff pressure pain tolerance	58.4 ± 18.4 kPa	60.6 ± 19.5 kPa	0.87 (0.81-0.91)
	Cuff pain tolerance level	6.5 ± 2.5 cm	6.7 ± 2.9 cm	0.74 (0.63-0.82)
	Cuff pain ratings during repeated stimulations (VAS-I)	3.7 ± 2.1 cm	3.9 ± 2.9 cm	0.73 (0.62-0.81)
	Cuff pain ratings during repeated stimulations (VAS-II)	4.7 ± 2.4 cm	4.9 ± 2.4 cm	0.70 (0.58-0.79)
	Cuff pain ratings during repeated stimulations (VAS-III)	5.1 ± 2.5 cm	5.1 ± 2.5 cm	0.71 (0.59-0.80)
Arm	Manual pressure pain threshold	367 ± 160 kPa	334 ± 162 kPa	0.87 (0.82-0.91)
	Cuff pressure pain threshold	30.4 ± 15.1 kPa	34.5 ± 15.8 kPa	0.85 (0.79-0.90)
	Cuff pressure pain tolerance	69.1 ± 16.1 kPa	70.6 ± 15.4 kPa	0.90 (0.87-0.93)
	Cuff pain tolerance level	6.1 ± 2.6 cm	5.6 ± 2.9 cm	0.82 (0.75-0.87)
	Cuff pain ratings during repeated stimulations (VAS-I)	3.2 ± 2.1 cm	3.2 ± 2.3 cm	0.65 (0.51-0.75)
	Cuff pain ratings during repeated stimulations (VAS-II)	4.0 ± 2.3 cm	3.9 ± 2.5 cm	0.66 (0.52-0.76)
	Cuff pain ratings during repeated stimulations (VAS-III)	4.2 ± 2.3 cm	4.1 ± 2.6 cm	0.65 (0.51-0.75)

**Table 2.2:** Test-retest reliability of manual pressure algometry and computer-controlled cuff algometry in healthy men and women. The mean and standard deviation (SD) at baseline for each of the two sessions were calculated for the leg and arm. Intraclass correlations (ICCs) and 95 % confidence intervals (CI) based on a single rating, consistency and 2-way mixed effect model (ICC<sub>3,1</sub>) was used for analysis of reliability. VAS scores during repeated pressure stimulations are presented as mean values from stimulations 1-4 (VAS-I), 5-7 (VAS-II), and 8-10 (VAS-III). (Unpublished data from experiment 1 and 2).

## 2.2 Assessment of pain modulation

Efficiency of the pain inhibitory pathways is typically assessed by paradigms of CPM (Yarnitsky et al., 2008; Pud et al., 2009; Yarnitsky, 2010; Wilder-Smith et al., 2010) or EIH (Koltyn et al., 1996; Cook et al., 2010; Meeus et al., 2014) with recordings of pain sensitivity before and during a painful conditioning stimulus or before and after an exercise condition.

### 2.2.1 Conditioned pain modulation – methodological parameters

The clinical observation that pain in one area of the body can be reduced by painful stimuli, applied to distant parts of the body has been known for centuries (Wand-Tetley, 1956; Melzack, 1975). Le Bars et al. (1979a, 1979b) first investigated the phenomenon of '*pain inhibits pain*', and they observed that the electrophysiological responses of dorsal horn neurons to somatic noxious stimuli were inhibited when a second noxious stimulus was applied to an extrasegmental site. These observations led to a formulation of the concept of *diffuse noxious inhibitory control* (DNIC) (Le Bars et al., 1979b, a). Various other terms have been used including '*counterirritation*' (Le Bars et al., 1979a; Michaux et al., 2010), '*endogenous analgesia*' (Pud et al., 2005; Granot et al., 2008), and '*heterotopic noxious conditioning stimulation*' (Kosek and Ordeberg, 2000b; Tuveson et al., 2007). Recently, the term '*conditioned pain modulation*' (CPM) has been recommended (Yarnitsky et al., 2010).

In humans, CPM is typically assessed by recordings of a pain test stimulus (e.g. pain thresholds) before, during or after applying a conditioning painful stimulus (e.g. cold pressor test). To demonstrate CPM, various modes of conditioning stimulus have been used, including painful cold (Chalaye et al., 2013), painful hot (Nir et al., 2011), painful ischemic (Cathcart et al., 2009), chemical (Graven-Nielsen et al., 1998), and electrical (Vo and Drummond, 2014). CPM can be either inhibitory (*i*CPM) or facilitatory (*f*CPM) (Yarnitsky et al., 2010). As illustrated in Appendix 1, the experimental phenomenology of CPM is well established in healthy subjects and typically reported as reduced pain sensitivity in response to a painful conditioning stimulus. CPM causes an acute heterotopic decrease in the pain sensitivity (Graven-Nielsen et al., 1998), although homotopic hypoalgesia have been reported (Pud et al., 2005).

As illustrated in Appendix 2, several studies have demonstrated impaired CPM responses in patients with chronic pain. A recent systematic review and meta-analysis concluded that reduced CPM



is common in patients with chronic pain. In 29 out of 42 included studies, patients with chronic pain demonstrated reduced CPM compared to asymptomatic controls and a reduced CPM response was a common feature across different pain conditions (Lewis et al., 2012b). Nonetheless, CPM response similar to asymptomatic controls (Chua et al., 2011; Garrett et al., 2013) has also been reported, indicating that a subgroup of patients may have preserved inhibitory pain modulation. CPM responses may be impaired at painful body sites, but not at non-painful body sites (Oono et al., 2014). This indicates systemic effects of CPM and highlights the importance of several pain assessment sites when assessing the CPM response, but it also illustrates the influence of clinical pain on the CPM response. In the current experiments, circulating cold water at 1-2°C (cold pressor test) was chosen as conditioning stimulus (I, II, and IV). Cold pressor test is often used for investigation of CPM in healthy subjects (Appendix 1) and in patients with chronic pain (Appendix 2) and produced the greatest inhibitory effect when compared with muscle pain (Arendt-Nielsen et al., 2008). Several standardized assessment sites including the body part immersed in cold water and distant body sites were used in the experiments (I, II, and IV).

### **2.2.2 Exercise-induced hypoalgesia – methodological parameters**

Black and colleagues (1979) investigated the phenomenon of pain relief in response to exercise. Yet, the term '*exercise-induced hypoalgesia*' was coined more than twenty years later (Koltyn, 2002). Various other terms have been used including '*exercise analgesia*' (Fuller and Robinson, 1993) and '*exercise-induced analgesia*' (Kemppainen et al., 1990). Exercise rarely causes complete analgesia and the term '*exercise-induced hypoalgesia*' is preferred, as it avoids the implication of complete pain relief.

Early research in this area was limited by significant methodological flaws (e.g. no control condition), leading some to conclude that reduced pain sensitivity following exercise was simply a phenomenon of pre-exposure to painful stimuli (Padawer and Levine, 1992). Subsequent research has clearly demonstrated that reduced pain sensitivity occurs following acute exercise when compared to non-exercise control conditions (Gurevich et al., 1994; Koltyn et al., 1996). The experimental phenomenology of EIH is now well established in healthy subjects and typically reported as 'reduced pain sensitivity in response to an exercise condition' (Koltyn, 2002; Naugle et al., 2012), but no

hypoalgesic effect (Dannecker et al., 2001; Ruble et al., 2005) and hyperalgesia following exercise have been demonstrated (Vecchiet et al., 1984; Sternberg et al., 2001). A summary of experimental studies on EIH in healthy subjects are presented in Appendix 3. The effect of exercise on pain sensitivity in subjects with chronic pain is still controversial, since both hyperalgesia (Cook et al., 2010) and hypoalgesia (Lannersten and Kosek, 2010) have been reported. A summary of experimental studies on EIH in patients with chronic pain are presented in Appendix 4.

To demonstrate EIH, various modes of exercise have been used, including aerobic exercises (e.g. cycling and running) (Dannecker et al., 2002; Hoffman et al., 2007), isometric exercises (i.e. a muscle contractions without joint movement) (Kosek and Lundberg, 2003) and resistance exercises (i.e. a muscle contractions with joint movement) (Focht and Koltyn, 2009). Changes in pain sensitivity occur not only in the exercising body part or within a few segmental levels, but also at distant sites, which indicate systemic effects, which further highlights the importance of several pain assessment sites when assessing EIH. In the current experiments, aerobic exercise (I, II, III, and IV) and isometric exercises (I, III, IV) were used to investigate EIH. Bicycling was performed on a stationary bicycle (Ergomedic 928E, Monark Exercise AB, Vansbro, Sweden) at age-related target heart rate corresponding to 75 %  $VO_{2max}$  and 50 %  $VO_{2max}$  (Swain et al., 1994), which has previously demonstrated robust EIH responses (Naugle et al., 2014). Isometric muscle contractions were performed against a force transducer on a handheld dynamometer (Commander Muscle Tester, Powertrack II, JTECH Medical, Utah, USA) at intensities of 30 % and 60 % of maximal voluntary contraction (MVC). During the sustained sub-maximal isometric contractions, each subject was required to match the target force as displayed on the monitor of the force transducer. Handheld dynamometry has demonstrated high inter-rater reliability (Whiteley et al., 2012), good construct validity (Roy et al., 2009) and showed medium to high correlation with isokinetic measures of isometric muscle strength for isometric knee extension and elbow flexion (Stark et al., 2011). Several standardized assessment sites including the exercising body part and distant body sites were used for evaluation of the EIH response (I, II, III, and IV).

### **2.2.3 Subgrouping of patients with chronic musculoskeletal pain**

61 patients with chronic musculoskeletal pain participated in experiment 3: 37 patients presented with low back pain as their primary complaint, 16 with neck pain, 7 with shoulder pain, and 1 with elbow pain. Based on widespread manual pressure pain thresholds assessed at the legs, arm and shoulder at baseline, patients were sub-grouped into patients with high pain sensitivity (HPS) and low pain sensitivity (LPS), respectively. The median of the averaged pressure pain thresholds for men and women, respectively were used for subgrouping. The median pressure pain threshold was chosen as the cut-off point, since this divides the groups in equally sized subgroups with distinguishable degrees of pain sensitivity. A similar approach has recently been demonstrated useful (Skou et al., 2014). Patients with high pain sensitivity demonstrated decreased cuff pain threshold and tolerance as well as facilitated temporal summation of pain. They also reported more pain during cold pressor test compared with patients with low pain sensitivity, indicating that subgrouping, based on widespread pain sensitivity, was relevant (IV). The difference in pain sensitivity between subgroups of patients is in agreement with a previous study on lateral epicondylgia, which also found subgroups of patients with more or less temporal summation of pain (Jespersen et al., 2013). The relevance of the subgrouping is furthermore supported by previous research, demonstrating differences in pain reporting during cold pressor test between subgroups (Chen et al., 1989; Zheng et al., 2014).

### **3. CURRENT PERSPECTIVES ON EXERCISE-INDUCED HYPOALGESIA**

This chapter describes the current perspectives on exercise-induced hypoalgesia in healthy subjects and in patients with chronic pain.

#### **3.1 Temporal and spatial manifestations of EIH in healthy subjects**

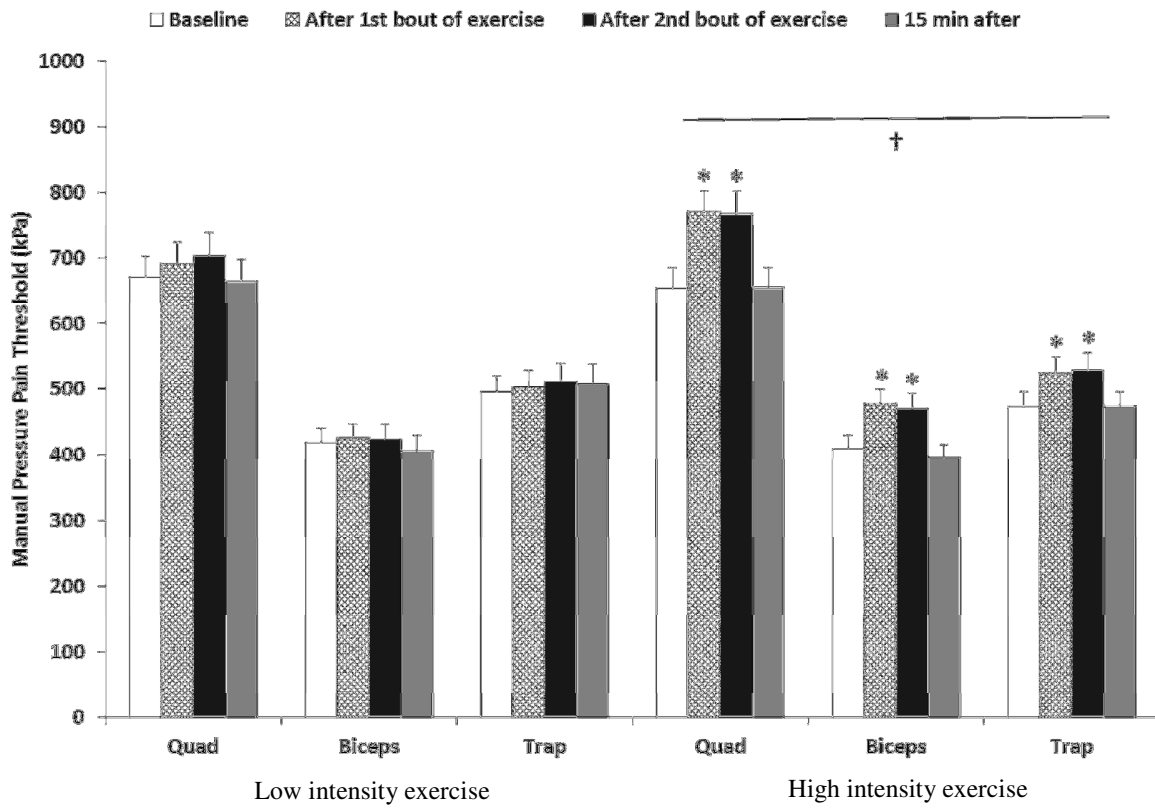
The first part of the chapter describes the current perspectives on EIH in healthy subjects.

##### **3.1.1 Aerobic exercise and EIH**

In agreement with previous research (Koltyn et al., 1996; Hoffman et al., 2004; Naugle et al., 2014) the current experiments demonstrated multisegmental increases in manual pressure pain thresholds immediately after high intensity aerobic exercise (I and II; Fig. 3.1). In contrast with these findings, earlier studies have also demonstrated a lack of EIH response after high intensity aerobic exercise (Padawer and Levine, 1992; Ruble et al., 2005). However, these studies used heat and cold pain thresholds to assess pain sensitivity on the skin, which may not be subject to as strong pain inhibition as input from deep structure nociceptors (Yu and Mense, 1990).

The duration of the EIH response differed between experiments, with one experiment demonstrating short-lasting (< 15 min) effects (I), and one demonstrating significant increases in pain thresholds immediately after and 15 min after exercise (II). The duration of the EIH response is in agreement with previous research demonstrating hypoalgesia for a maximum of 10-15 min following aerobic exercise, but results on the duration of the EIH response are inconsistent. A previous study found a significant decrease in pressure pain sensitivity 5 min after high intensity aerobic exercise, which was not sustained after 10 min (Hoffman et al., 2004), while hypoalgesic effects on ischemic pain test 20 min after high intensity aerobic exercise in runners (Janal et al., 1984) and hypoalgesic effects on electrical dental pain thresholds 30 min after high intensity aerobic exercise (Kemppainen et al., 1990) have been reported.

The increase in manual pressure pain thresholds was significantly larger in the exercising body part compared with non-exercising body parts (I). This indicates that local or segmental mechanisms play an important role in the EIH response after aerobic exercise. The effect of aerobic exercise on the EIH response in exercising and non-exercising body parts has not previously been investigated.



**Fig. 3.1:** Mean (+SEM) manual pressure pain threshold at the quadriceps muscle, biceps muscle and trapezius muscle before, immediately after 1<sup>st</sup> bout, immediately after 2<sup>nd</sup> bout, and 15 min after low and high intensity aerobic exercises (\*, significant difference compared with baseline. †, significant difference between low and high intensity exercise conditions; NK: P < 0.05; Raw data from I).

In the current experiments, the effect of aerobic exercise on pain tolerance was mixed. When compared with a control condition, high intensity exercise increased pain tolerance in subjects aged 18-30 years compared with baseline and quiet rest (III). However, when high and low intensity aerobic exercises were compared in subjects aged 18-65, pain tolerance was not significantly different after exercise compared with baseline (III). The increase in pain tolerance, which was found in the younger subjects, is in agreement with previous findings of the effect of aerobic exercise on pain tolerance (Gurevich et al., 1994; Bartholomew et al., 1996). The mixed results in the current experiments were somewhat unexpected. The same protocol for the aerobic exercises, as well as for the assessment of pain tolerance, was used in both experiments. One possible reason for the mixed results may be related with the different age groups included in the experiments. This is supported by the negative correlation between age and the EIH response after aerobic exercise, indicating that older subjects may have less EIH response after aerobic exercise (III). This hypothesis is also supported by a study in pain patients (Bement et al., 2011) demonstrating increased EIH responses after isometric exercise in younger patients. Nevertheless, a recent study in healthy subjects found no difference in the EIH response after isometric exercise between younger and older healthy subjects (Lemley et al., 2014b).

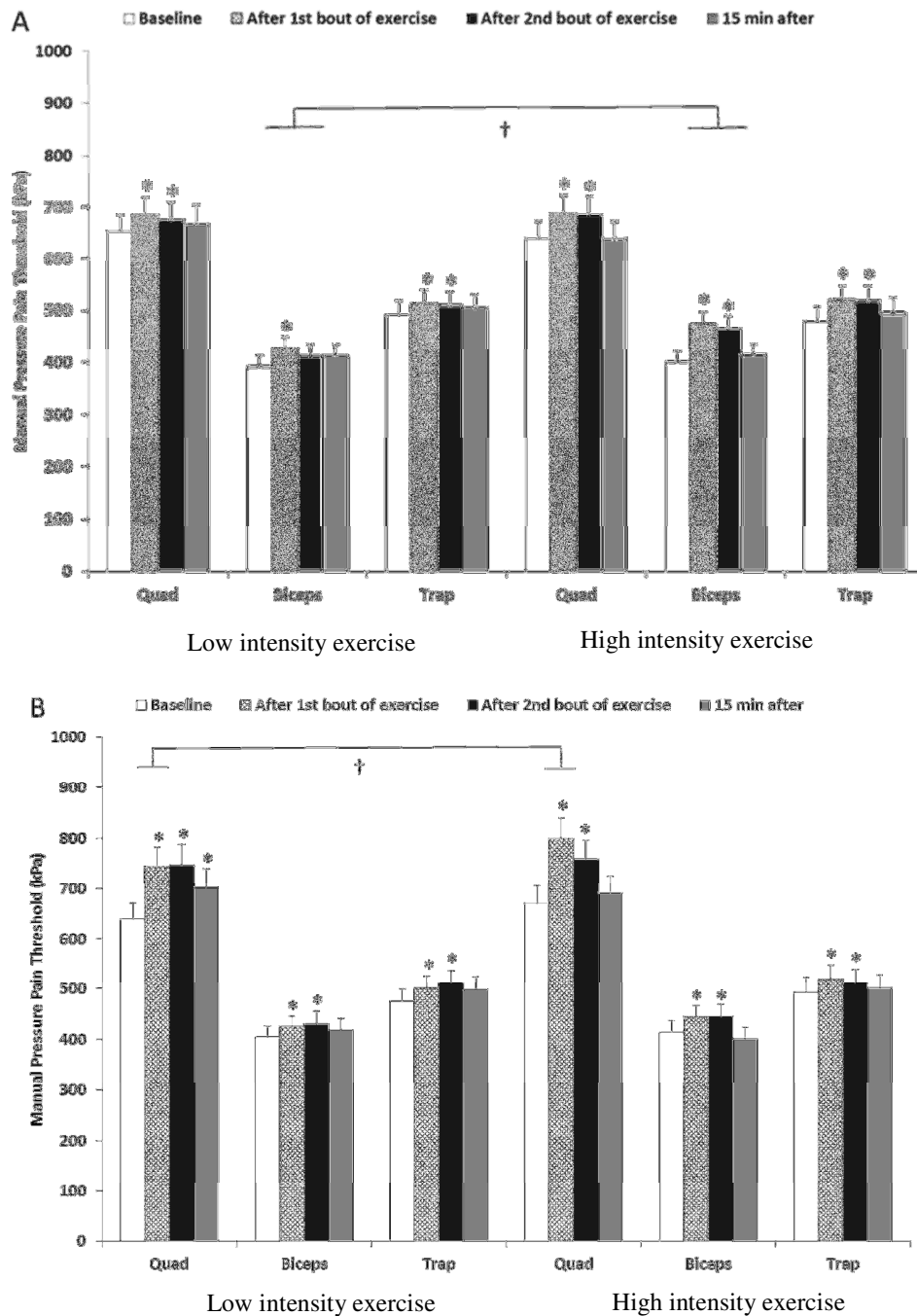
Temporal summation of pain was reduced after aerobic exercise compared with baseline in subjects aged 18-30 years, but when compared with the quiet rest condition, the reduction in temporal summation of pain failed to reach significance. When high and low intensity aerobic exercises were compared in subjects aged 18-65, temporal summation of pain was not significantly influenced (III). This indicates that the aerobic exercises used in these experiments did not target the central mechanisms of pain summation. Recently, low and high intensity aerobic exercises were found to reduce temporal summation of heat pain in 27 healthy subjects (Naugle et al., 2014b), however pain ratings to suprathreshold pressure stimuli were not affected, highlighting the importance of pain sensitivity assessment methodology.

### **3.1.2 Isometric exercise and EIH**

Previous findings of increased pressure pain thresholds after isometric exercises (Kosek and Ekholm, 1995; Koltyn et al., 2001; Kosek and Lundberg, 2003; Koltyn and Umeda, 2007; Bement et al., 2008; Bement et al., 2009; Umeda et al., 2010; Naugle et al., 2013; Bement et al., 2014; Lemley et al., 2014a; Koltyn et al., 2014) were supported by the findings in the current experiments (I). Low and high

intensity isometric exercises induced short-lasting (< 15 min) multisegmental increases in manual pressure pain thresholds immediately after exercise. The increase in pressure pain thresholds was larger in the exercising body part compared with non-exercising body parts (I; Fig. 3.2). This indicates that local or segmental mechanisms also play an important role in the EIH response after isometric exercise. The multisegmental pain inhibitory effects after isometric exercise are also in agreement with previous findings on EIH (Kosek and Lundberg, 2003; Koltyn and Umeda, 2007; Bement et al., 2008). More pronounced EIH responses at the contracting thigh muscle compared with the contralateral non-contracting thigh muscle has previously been demonstrated (Kosek and Lundberg, 2003). The duration of EIH after isometric exercise is in agreement with previous research demonstrating hypoalgesia immediately after isometric exercise (Kosek and Ekholm, 1995).

Low and high intensity isometric arm and leg exercises produced multisegmental increases in pain tolerance immediately after and also 15 min after exercise, without significant difference between assessment sites (III). Low and high intensity isometric leg exercises reduced temporal summation of pain, whereas only high intensity isometric arm exercise reduced temporal summation of pain immediately after and 15 min after exercise (III). This indicates that isometric exercise, in contrast to aerobic exercise, also target the central mechanisms of pain summation. Previous research have demonstrated that isometric exercise reduce temporal summation of heat pain in healthy subjects (Koltyn et al., 2013; Koltyn et al., 2014; Naugle et al., 2014), but the effect of isometric exercises on pressure pain tolerance and temporal summation of pressure pain has not previously been investigated.



**Fig. 3.2:** Mean (+SEM) manual pressure pain threshold at the quadriceps muscle, biceps muscle and trapezius muscle before, immediately after 1<sup>st</sup> bout, immediately after 2<sup>nd</sup> bout, and 15 min after low and high intensity isometric arm (A) and isometric leg (B) exercises (\*, significant difference compared with baseline. †, significant difference between low and high intensity exercise conditions; NK: P < 0.05; Raw data from I).



Few studies have previously compared the effect of different exercise modalities on the EIH response. A small study including 12 healthy men compared the effect of high intensity aerobic exercise and repeated maximal isometric exercise on pressure pain threshold. Both exercise conditions caused hypoalgesia with aerobic exercise, resulting in greater hypoalgesia compared with isometric exercise (Drury et al., 2004). A recent meta-analysis by Naugle et al. (2012) examined the effect of aerobic, isometric, and resistance exercise on pain threshold and pain intensity, suggesting that all included exercise modalities reduced pain sensitivity. The mean effect size for aerobic exercise was moderate, while the mean effect sizes for isometric and resistance exercises were large. In the current experiment, no significant difference in the EIH responses was found between aerobic and isometric exercises (I), yet only isometric exercises reduced temporal summation of pain (III), and it appears that isometric exercises can be performed at lower intensities than aerobic exercises to produce an EIH response (I and III). A possible reason for this discrepancy is that the EIH responses after aerobic and isometric exercise are due to partly different mechanisms (See section 3.6).

### **3.2 Influence of exercise intensity and exercise duration on EIH**

Previous research investigating the influence of aerobic exercise intensity on pressure pain sensitivity has demonstrated larger effects after high intensity exercise compared with low intensity exercise (Hoffman et al., 2004; Naugle et al., 2014b), which is supported by the current findings (I). Naugle et al. (2014b) assessed pain thresholds before and after low and high intensity exercises and found that pain thresholds increased after high intensity exercise only. An interaction between intensity and duration after aerobic exercise has been demonstrated. Hoffman et al. (2004) assessed pressure pain sensitivity in healthy subjects before and after aerobic exercise and discovered that pain sensitivity only decreased after exercise at high intensity (75 %  $VO_{2max}$ ) and longer duration (30 min) and not after shorter time (10 min) at same intensity or same duration at a reduced exercise intensity. This is in contrast with the current findings on manual pressure pain thresholds, where no difference in the EIH response after 10 min of high intensity aerobic exercise compared with 2 x 10 min of high intensity aerobic exercise was observed (I). No systematic differences in pain tolerance and temporal summation of pain after aerobic exercise were found between low and high intensity exercises.

Bement et al. (2008) investigated the influence of isometric exercise intensity on pressure pain sensitivity and demonstrated that isometric contractions at lower intensity and longer duration caused greater decrease in pain sensitivity compared with contractions at low and high intensity and shorter duration. This is in contrast to the current findings, which showed that high intensity isometric exercise had larger effects on manual pressure pain thresholds compared with low intensity isometric exercise (I). However, the larger EIH response after high intensity isometric exercises was only in the exercising body part (I). Bement et al. (2008) assessed pain sensitivity at the finger in relation to elbow exercises, not at the exercising body part, which may explain the equivocal results. Earlier research investigating the influence of isometric exercise intensity on heat pain sensitivity and electrical pain stimulation has demonstrated larger effects after high intensity exercises compared with low intensity exercise (Ring et al., 2008; Misra et al., 2014). No systematic differences in pain tolerance and temporal summation of pain after isometric exercise were found between low and high intensity exercises, although only high intensity isometric biceps contractions reduced temporal summation of pain (III).

EIH occurred after low and high intensity isometric exercises performed for duration of both 90 s and 2 x 90 s, but in general without significant difference in the EIH response between the first and second bout of exercises. This is in agreement with a previous study, failing to find a dose-response relationship for the EIH response after isometric handgrip exercises performed at 25 % MVC for 1, 3 and 5 min (Umeda et al., 2010).

### **3.3 Gender and age related differences in EIH**

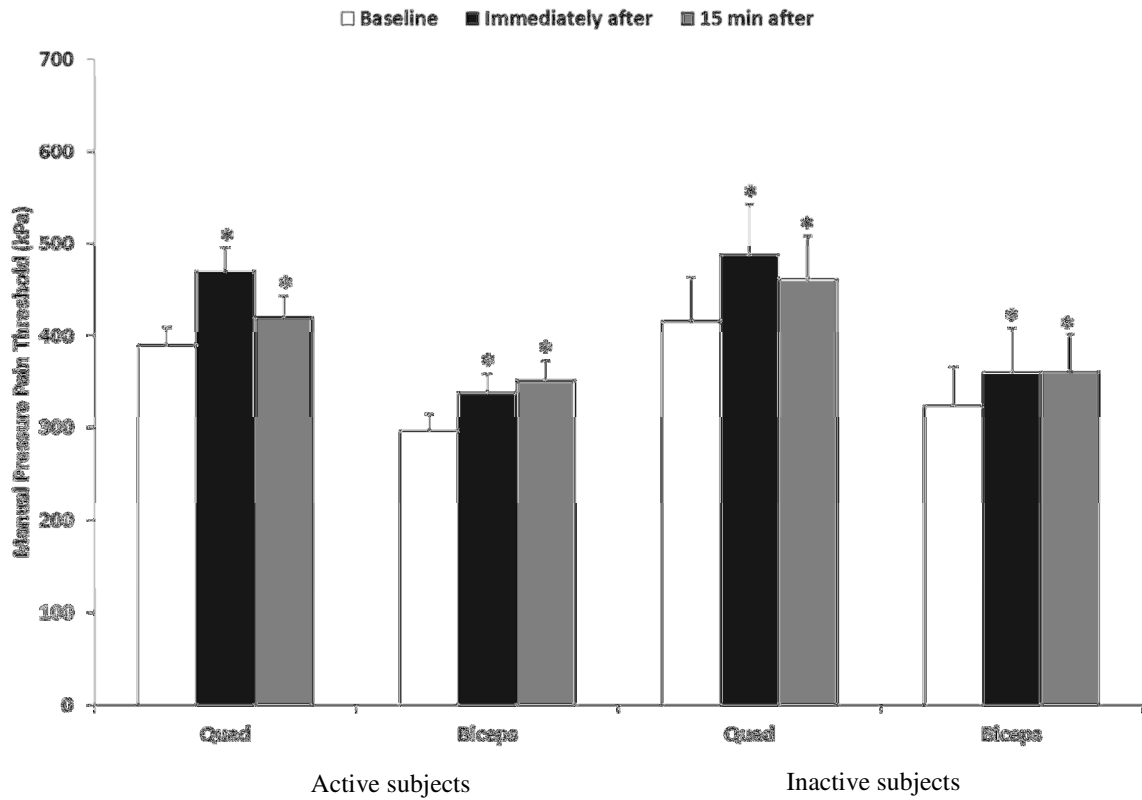
Recent studies on the influence of gender on the EIH response have demonstrated mixed results. Some studies have shown comparable EIH responses in men and women (Kosek and Lundberg, 2003; Hoffman et al., 2004; Umeda et al., 2010; Koltyn et al., 2014), while other studies have shown larger effects in women (Koltyn et al., 2001; Sternberg et al., 2001). Mixed results were also found in the current experiments. No gender differences were found after isometric exercises (I). The increase in manual pressure pain thresholds after aerobic exercise was increased in women compared with men (I), but no gender differences were found after aerobic exercise in younger subjects (II). Limitations regarding the gender effects should be considered. Although different phases of the menstrual cycle do not appear to influence the magnitude of the EIH response in women (Bement et al., 2009), data were

not collected in the current experiments on the use of contraceptives, status of menopause or menstrual cycle, which may affect the pain perception in the female participants (Riley et al., 1999), and the complexity of the gender, pain and exercise relationship deserves more systematic study.

In the current experiment (I), the increase in manual pressure pain thresholds after isometric exercises were not affected by age, which is in agreement with previous research on age and EIH after isometric exercise (Lemley et al., 2014b; Burrows et al. 2014). Nonetheless, a negative correlation between age and the EIH response after aerobic exercise was found (III), indicating that older subjects may have less EIH response after aerobic exercise. This hypothesis is also supported by the mixed effects of aerobic exercise on pain tolerance (III) as previously mentioned.

### **3.4 Influence of regular physical activity on EIH**

Regular exercise has been linked with alterations in pain sensitivity and athletes have significantly higher pain tolerance (Tesarz et al., 2012), report less pain intensity during experimental pain (Sternberg et al., 2001), and demonstrate higher nociceptive withdrawal reflex threshold compared with normally active controls (Guieu et al., 1992). The influence of regular exercise on EIH has previously been investigated in two small studies with 20 active subjects and 9 inactive subjects (Øktedalen et al., 2001) and 10 athletes and 10 nonathletes (Sternberg et al., 2001). Pressure pain ratings during an ischemic tourniquet test were assessed before and after maximal treadmill exercise and no difference in the EIH response between active and inactive subjects were found (Øktedalen et al., 2001). Pain ratings during cold pressor test were assessed before and after a submaximal running exercise and no difference in the EIH response between athletes and nonathletes were discovered (Sternberg et al., 2001). These findings are supported by the current experiment (II), which demonstrated a robust increase in manual pressure pain thresholds after aerobic exercise in both active and inactive subjects, with no significant difference between the groups (Fig. 3.3).



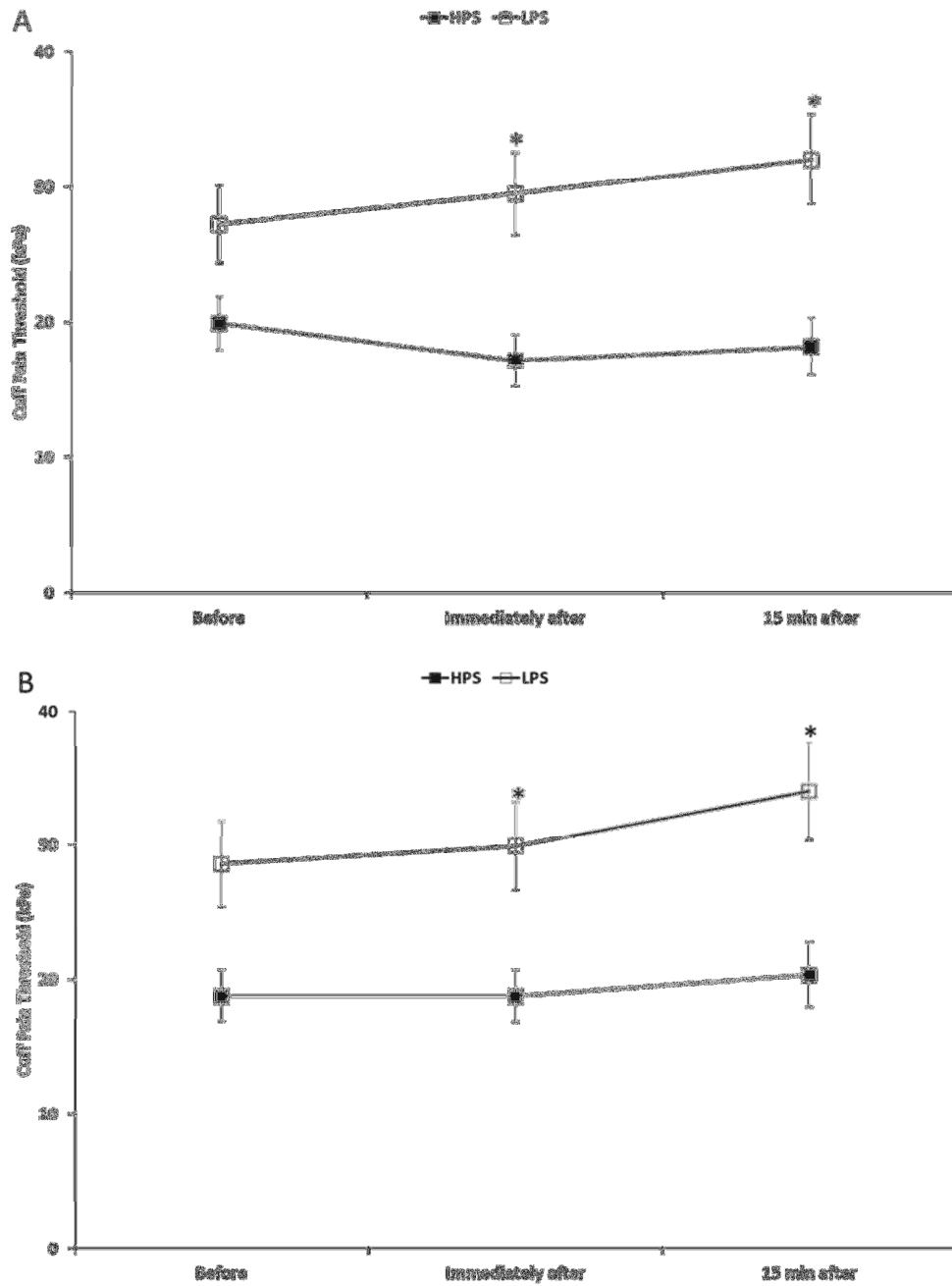
**Fig. 3.3:** Mean (+SEM) manual pressure pain threshold at the quadriceps and biceps muscles before, immediately after, and 15 min after high intensity aerobic exercise in active and inactive men and women (\*, significant difference compared with baseline; NK:  $P < 0.05$ ; Raw data from II).

### 3.5 EIH in patients with chronic pain

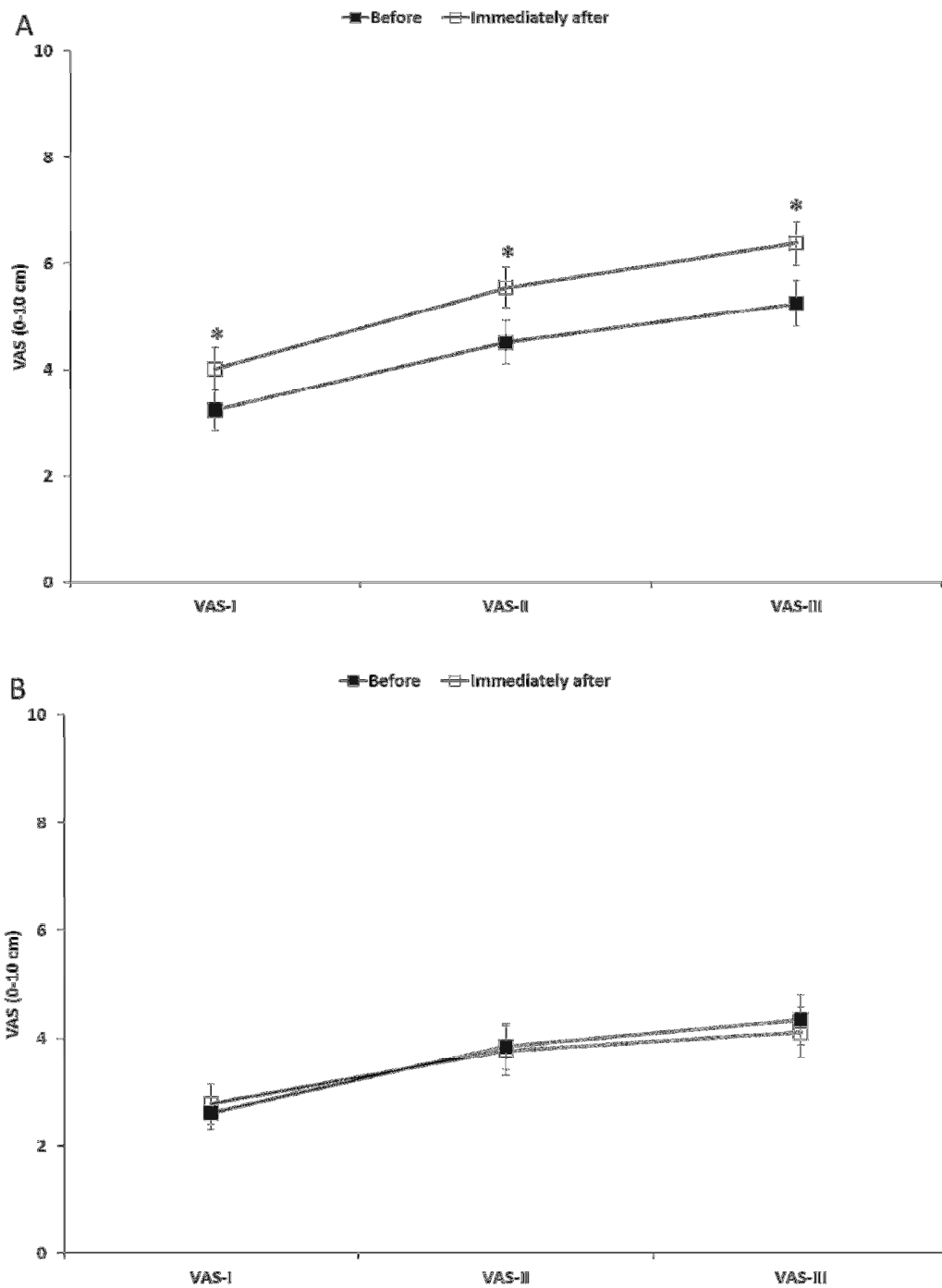
The results from a recent meta-analysis indicate that a subset of patients with chronic pain demonstrates impaired EIH responses compared with asymptomatic controls (Naugle et al., 2012). A hyperalgesic response after submaximal isometric exercise and vigorous aerobic exercise have also been demonstrated in patients with fibromyalgia (Vierck et al., 2001; Staud et al., 2005; Lannersten and Kosek, 2010) and after vigorous aerobic exercise in patients with widespread chronic pain (Cook et al., 2010; Meeus et al., 2010). Even so, a hypoalgesic response was elicited at multiple body sites after aerobic exercise in patients with chronic low back pain similar to healthy controls (Hoffman et al., 2005; Meeus et al., 2010) and after isometric contractions at non-painful muscles in patients with shoulder myalgia (Lannersten and Kosek, 2010). An EIH response was also elicited in patients with fibromyalgia after aerobic exercise performed at moderate intensity (Newcomb et al., 2011) and after isometric contractions performed at low intensity (Kadetoff and Kosek, 2007).

The current clinical experiment on patients with chronic musculoskeletal pain (IV) showed that the EIH response was partly impaired in patients with high pain sensitivity compared with patients with low pain sensitivity. Only patients with low pain sensitivity demonstrated an increase in cuff pressure pain threshold and a decrease in pain ratings after aerobic and isometric exercises (IV; Fig. 3.4). Furthermore, patients with high pain sensitivity showed facilitated temporal summation of pain following high intensity aerobic exercise (IV; Fig. 3.5). Clinically, it is well known that some chronic pain patients report increasing pain after exercise and this finding is in agreement with previous studies demonstrating a hyperalgesic response after aerobic exercise (Vierck et al., 2001; Whiteside et al., 2004; Cook et al., 2010; Meeus et al., 2010). These findings support the hypothesis that low pain sensitivity in subgroups of patients could be due to adequate pain inhibitory pathways.

Change in cuff pain threshold after cold pressor test (CPM response) predicted the change in cuff pain threshold after aerobic exercise (EIH response), and change in pain tolerance level after cold pressor test (CPM response) predicted the change in pain tolerance level after aerobic (EIH response) exercise, suggesting that individuals who demonstrated a greater ability to activate the descending inhibitory systems reported greater hypoalgesia following aerobic exercise (IV).



**Fig. 3.4:** Mean ( $\pm$  SEM) cuff pressure pain threshold at the non-dominant lower leg before, immediately after, and 15 min after high intensity aerobic exercise (A) and low intensity isometric leg exercise (B) in chronic musculoskeletal pain patients with high pain sensitivity (HPS,  $n = 30$ ) and low pain sensitivity (LPS,  $n = 30$ ) (\*, significant difference compared with baseline; NK:  $P < 0.05$ ; Raw data from IV).



**Fig. 3.5:** Mean ( $\pm$ SEM) VAS scores during 10 repeated cuff stimulations at PTT level at the non-dominant lower leg indicating temporal summation of pain in chronic pain patients with high pain sensitivity (A) and low pain sensitivity (B) before and immediately after aerobic exercise. VAS scores are presented as mean values from stimulations 1-4 (VAS-I), 5-7 (VAS-II), and 8-10 (VAS-III) (\*, significant difference from baseline; NK:  $P < 0.05$ ; Raw data from IV).

### 3.6 Mechanisms of EIH

The most studied mechanism of the EIH response involves the endogenous opioid system, which may account for the multisegmental manifestations of EIH. Aerobic exercise results in an increased level of systemic  $\beta$ -endorphin (Janal et al., 1984; McMurray et al., 1987) although not directly correlated to the reduction in pain sensitivity (Janal et al., 1984; Droste et al., 1991). Several studies have investigated the contribution of an opioid mechanism by administering naloxone, an opioid antagonist prior to aerobic exercise (Black et al., 1979; Haier et al., 1981; Janal et al., 1984; Droste et al., 1991). In two studies (Black et al., 1979; Droste et al., 1991) naloxone did not affect hypoalgesia. In one study (Haier et al., 1981), a dose-dependent effect of naloxone was found with only high dose (10 mg) naloxone blocking the hypoalgesic response. In another study (Janal et al., 1984), naloxone blocked hypoalgesia to ischemic pain but not thermal pain. These findings implicate that the endogenous opioid system is involved in some of the hypoalgesic response after aerobic exercise, but not all of the exercise-induced alterations in pain sensitivity.

In addition to an opioid mechanism, it has been suggested that non-opioid mechanisms may also be involved in the hypoalgesic response produced by exercise, and several non-opioid mechanisms have been proposed. A non-opioid mechanism potentially contributing to EIH after aerobic exercise is the Gate Control Theory (Melzack and Wall, 1965), where limb movement during exercise may excite large diameter afferent nerve fibers inhibiting nociceptive processes in the dorsal horn. Interestingly, in healthy subjects, passive movements induced hypoalgesia compared with a control condition, indicating a potential role of joint movement or proprioception in EIH (Nielsen et al., 2009). Still, if this was a main mechanism, low intensity aerobic exercise should have produced an EIH response in the exercising body parts, which was not the case (I). The Gate Control Theory does not explain the distant effects on pain sensitivity demonstrated in the current experiments (I, II, III, and IV), but could account for part of the hypoalgesic response in the exercising body part.

Vigorous aerobic exercise has been shown to increase circulating plasma levels of catecholamines, particularly norepinephrine, which can remain elevated for hours after exercise (Bahr et al., 1991). Similarly, serotonin has been shown to be affected by exercise with increased levels of serotonin in active subjects (Soares et al., 1994), and with an increase in serotonin after aerobic exercise in active subjects, compared with inactive subjects (Steinberg et al., 1998).



Aerobic exercise of moderate intensity activates the endocannabinoid system (Sparling et al., 2003), and antinociception after aerobic exercise is partly mediated by the endocannabinoid system in rats (Galdino et al., 2014). The hypothesis of involvement of the endocannabinoid system in the EIH response is further supported by a recent study in humans, demonstrating a significant decrease in temporal summation of heat pain after isometric exercise in conjunction with a significant increase in circulating endocannabinoids (Koltyn et al., 2014).

Exercise causes changes in the cardiovascular response and changes in blood pressure, which have been suggested as a possible mechanism (Koltyn and Umeda, 2006). Even so, there is no consistent dose-response correlation between changes in blood pressure and pain perception following isometric exercise (Umeda et al., 2009; Umeda et al., 2010).

The EIH response has also been linked to the CPM response. Recently, a study in 39 healthy subjects found that subjects with a greater CPM response were more likely to report a greater EIH response after isometric exercise (Lemley et al., 2014b). To support the link between EIH and CPM, another study including 16 healthy women found that the hypoalgesic response after aerobic exercise was greater following painful exercise than non-painful exercise (Ellingson et al., 2014). Although the relation between the CPM and EIH responses was not strong, the EIH response after aerobic exercise was predicted by the CPM response after cold pressor test (IV), suggesting that patients who demonstrated a greater ability to activate the descending inhibitory systems, reported greater hypoalgesia following aerobic exercise. This relationship could also indicate that the increase in temporal summation of pain after aerobic exercise in patients with high pain sensitivity may be due to impaired descending inhibition. The connection between the CPM and EIH responses could indicate similar mechanisms underlying the hypoalgesic response; yet, hypoalgesia has also been demonstrated after non-painful aerobic exercise (Ellingson et al., 2014), indicating that the CPM response may work as an additive effect after painful exercise. Pain during exercise was not assessed in the current experiments to confirm this.

In summary, high intensity aerobic exercise as well as low and high intensity isometric exercises produced short-lasting, multisegmental increases in manual pressure pain thresholds in healthy subjects, with significantly larger effects in the exercising body part compared with non-exercising body parts. Exercise intensity influences the magnitude of the EIH response, but the duration of exercise appears to be of less importance. Isometric exercises also increased cuff pain tolerance and

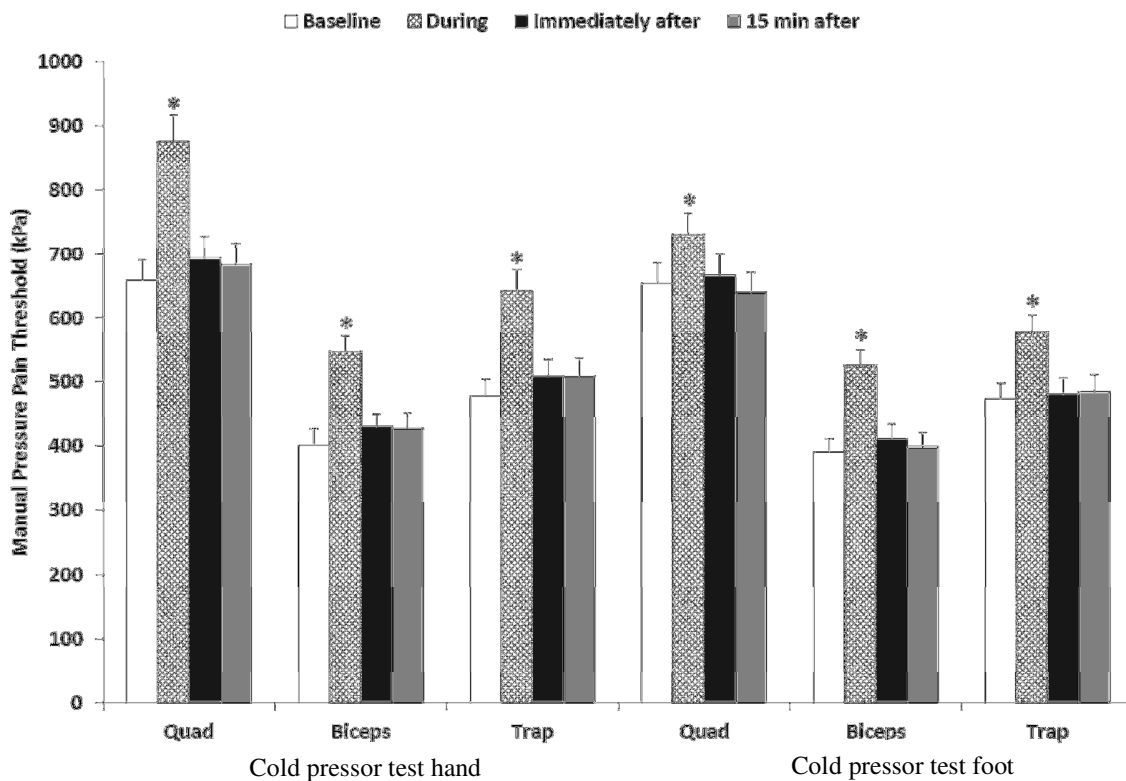
reduced temporal summation of pain, illustrating the potential for isometric exercise as a rehabilitation procedure, also targeting the central mechanisms of pain. The effect of aerobic exercise on pain tolerance was less consistent and no effect was demonstrated on temporal summation of pain. The EIH response after aerobic exercise was increased in women and negatively correlated with age, however no influence of level of regular physical activity was found. The EIH response after isometric exercise was not influenced by age or gender. Patients with high pain sensitivity demonstrated reduced EIH responses after aerobic and isometric exercises and facilitated temporal summation of pain following high intensity aerobic exercise compared with patients with low pain sensitivity. Differences in mechanisms for the EIH responses after aerobic and isometric exercises may explain the different effect on central mechanisms of pain summation as well, as the difference in the EIH response after low intensity exercises demonstrated (I and III).

## 4. CURRENT PERSPECTIVES ON CONDITIONED PAIN MODULATION

This chapter describes the current perspectives on conditioned pain modulation in healthy subjects and in patients with chronic pain.

### 4.1 Temporal and spatial manifestations of CPM in healthy subjects

In the current experiments, cold pressor test induced heterotopic and homotopic increases in manual pressure pain thresholds during immersion of the hand and foot (I and II; Fig. 4.1) in agreement with previous studies (Pud et al., 2005; Oono et al., 2011).

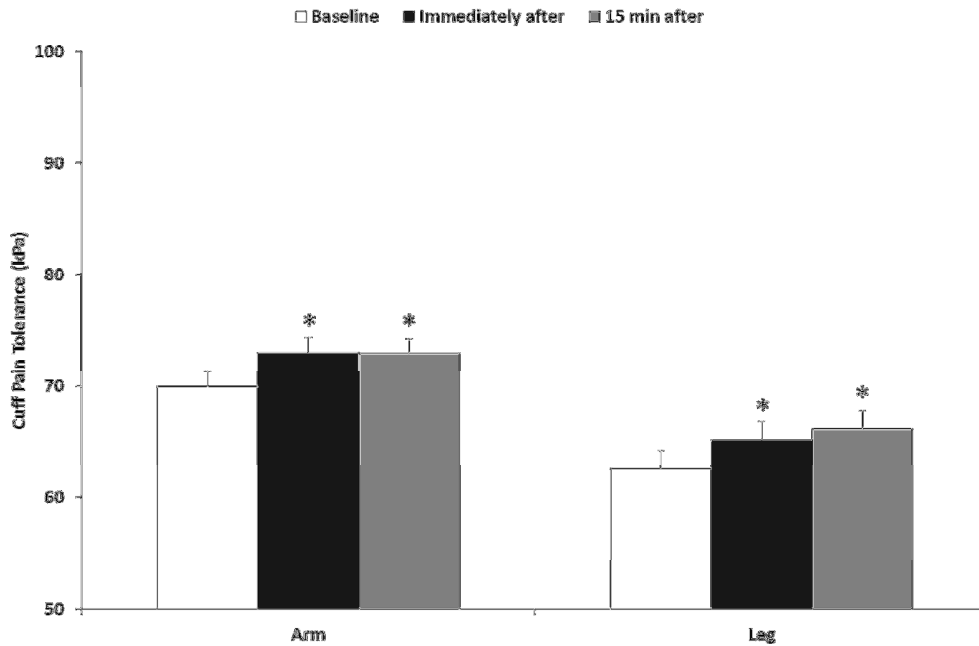


**Fig. 4.1:** Mean (+SEM) manual pressure pain threshold at the quadriceps muscle, biceps muscle and trapezius muscle before, during, immediately after, and 15 min after cold pressor test at the dominant hand and foot (\*, significant difference compared with baseline; NK:  $P < 0.05$ ; Raw data from I).

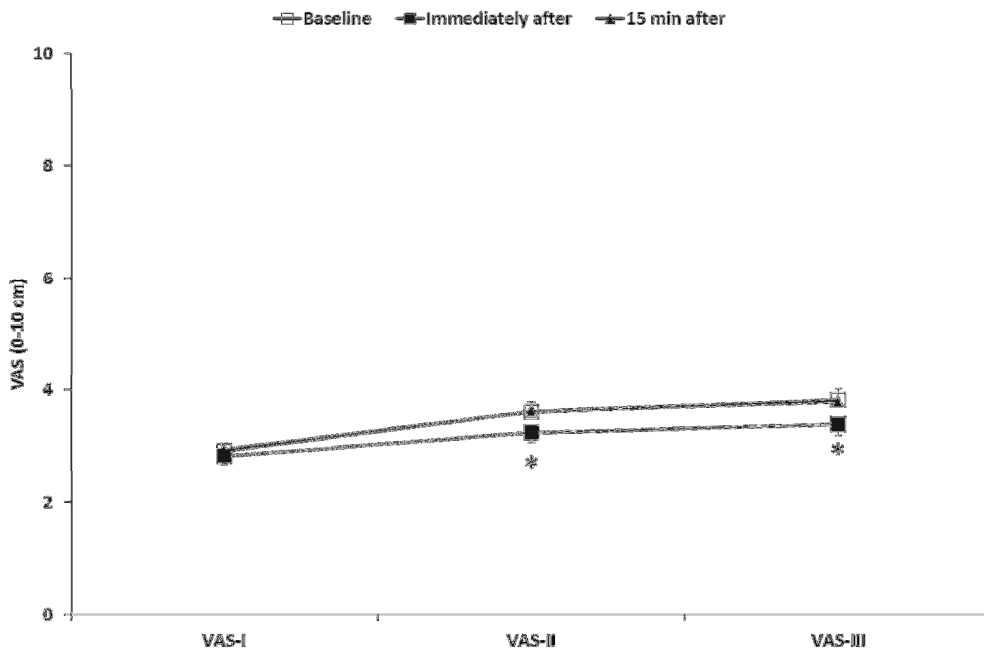
Pain tolerance increased (Fig. 4.2), and temporal summation of pain decreased significantly in both the arm and leg after cold pressor test on the hand (Fig. 4.3). A previous study reported similar findings in decreased cuff pain sensitivity assessed on the leg when conditioning stimulus was applied on the arm (Graven-Nielsen et al., 2012). Reduction in temporal summation of mechanical pain (Cathcart et al., 2009; Streff et al., 2011) and heat pain (Edwards et al., 2003a; Edwards et al., 2003b) has previously been demonstrated after CPM paradigms. However, in the current experiments, the stimulation intensity used for the temporal pain summation was increased after the cold pressor test, as an attempt to account for the pain sensitivity changes, and still the temporal summation effect was reduced.

The cold pressor tests used in the current experiments were perceived as painful by all subjects, with most subjects reporting moderate to severe pain during cold water immersion (I and II). A significant positive correlation between the intensity of pain during cold pressor test on the foot and increase in heterotopic pressure pain threshold was found (I), but no association was found between the intensity of pain during cold pressor test on the hand and increase in pressure pain thresholds (I and II). This difference between cold pressor test on the hand and foot was unexpected. Having said that, this is the first study to compare cold pressor test on different limbs and further research is warranted. Although a clear relationship between the intensity of the conditioning stimulus and the strength of the resultant CPM has been reported (Villanueva and Le Bars, 1995), the influence of the intensity of perceived pain induced by a conditioning stimulus has been mixed. Some studies demonstrated a correlation with the magnitude of the CPM response (Treister et al., 2010; Nir et al., 2012) and some demonstrated no correlation with the magnitude of the CPM effect (Granot et al., 2008; Weissman-Fogel et al., 2008; Nir et al., 2011).

A significant increase in manual pressure pain thresholds was in general only observed *during* the cold pressor stimulation. This is in agreement with previous studies, reporting an increase in pressure pain thresholds during noxious thermal stimulation, but not after (Kosek and Ordeberg, 2000b; Leffler et al., 2002a; Oono et al., 2011). Other investigators have, however, found a significant CPM response immediately after noxious stimulation (Pud et al., 2005) and up to 60 min after cold pressor test (Washington et al., 2000), indicating longer-lasting effects.



**Fig. 4.2:** Mean (+SEM) pain tolerance at the arm and leg before, immediately after, and 15 min after after cold pressor test on the hand (\*, significant difference from baseline; NK:  $P < 0.05$ ; Unpublished data from experiment 1 and 2).



**Fig. 4.3:** Mean ( $\pm$ SEM) VAS scores during 10 repeated cuff stimulations at PTT level before, immediately after, and 15 min after cold pressor test on the hand. VAS scores are presented as mean values from stimulations 1-4 (VAS-I), 5-7 (VAS-II), and 8-10 (VAS-III) (\*, significant difference from baseline; NK:  $P < 0.05$ ; Unpublished data from experiment 1 and 2).

The increase in manual pressure pain thresholds was only observed *during* the cold pressor stimulation (I and II), whereas the increase in pain tolerance and decrease in temporal summation of pain was also observed *after* cold pressor test (Fig. 4.2 and 4.3). The equivocal results on the temporal manifestations of the CPM response between manual algometry and cuff algometry may be due to the different temporal and spatial aspects of assessment. First of all, cuff algometry was performed after cold pressor test and not during, as was the case with manual algometry. Secondly, the equivocal results suggest either that spatial integration is a major determinant in pain modulation, or that the integration between spatial summation and temporal summation of pain is more sensitive to pain modulation after cold pressor test. Finally, the CPM response may influence pain thresholds, pain tolerance and temporal summation differently and a difference in the response on pain threshold, and pain tolerance after a CPM paradigm has previously been demonstrated (Sowman et al., 2011).

#### **4.2 Gender and age related differences in CPM**

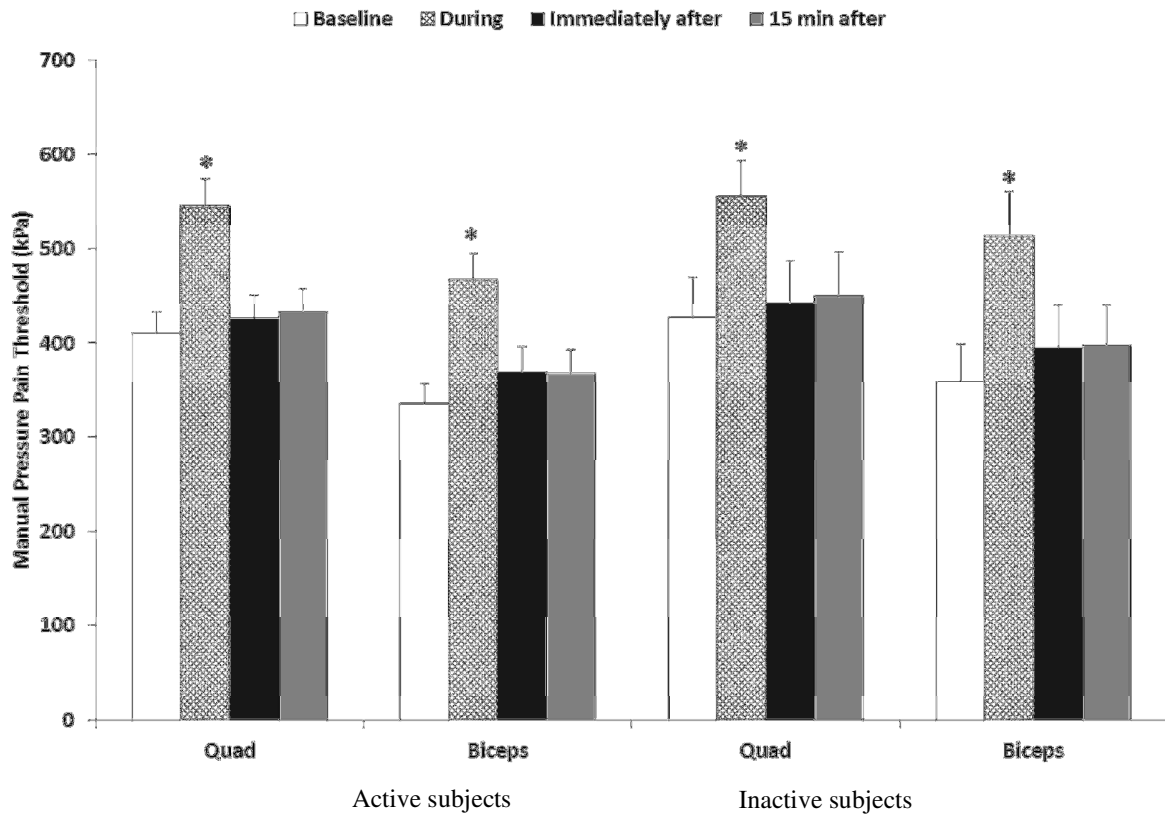
Recent human studies have shown significant gender differences in CPM response (Staud et al., 2003c; Ge et al., 2004; Serrao et al., 2004; Arendt-Nielsen et al., 2008, Granot et al., 2008; Goodin et al. 2009; Honigman et al., 2013) and, according to a recent review (Popescu et al., 2010), the majority of the studies report significantly more efficient CPM in men compared with women. However, several other studies (France and Suchowiecki, 1999; Baad-Hansen et al., 2005; Pud et al., 2005; Quiton and Greenspan, 2007; Tousignant-Laflamme et al., 2008; Rosen et al., 2008; Cathcart et al., 2009; Wang et al., 2010; Grashorn et al., 2013; Nahman-Averbuch et al., 2014; Zheng et al., 2014), as well as the current experiments (I and II) demonstrated no influence of gender on the magnitude of the CPM response. Yet, a gender difference in the temporal manifestation of the CPM response was demonstrated. Young women demonstrated increased manual pressure pain thresholds *during and immediately after* cold pressor test compared with men who only demonstrated increases in manual pressure pain thresholds *during* cold pressor stimulation (II).

Age was not significantly correlated with the CPM response (I), which is in agreement with a previous study (Nahman-Averbuch et al., 2014). Earlier studies using manual pressure pain (Lemly et al., 2014) or heat pain (Washington et al., 2000; Edwards et al., 2003a; Lariviere et al., 2007; Riley et al., 2010) as test stimuli, have established reduced CPM responses associated with ageing. The

conflicting results may be related to different pain sensitivity assessment methodology or due to the different age groups included in the studies. The study by Lemley et al. (2014) assessed pressure pain thresholds and pain ratings before and after cold pressor test in two groups of subjects with a mean age of 21.9 and 72.0 years, respectively, with only young subjects demonstrating a CPM response.

### **4.3 Influence of regular physical activity on CPM**

Few studies have examined the relationship between regular physical activity and CPM response. In this PhD study, the manifestations of the CPM response between normally active and inactive healthy subjects were compared, and a robust increase in manual pressure pain thresholds was found in both active and inactive subjects (II; Fig. 4.4). Although the effect size indicated that the inactive subjects had a larger CPM response compared with active subjects, there was no significant difference in the CPM response between groups. This was further supported by the lack of association between times spent on physical activity and the CPM response during cold pressor test (II). A similar trend has previously been demonstrated in endurance athletes demonstrating less reduction in heat pain after a cold pressor test compared with healthy controls (Tesarz et al., 2013). Chronic pain has been associated with an impaired CPM response (Lewis et al., 2012b, Appendix 2) and a reduced CPM response in athletes could be due to regular pain during training and due to exercise-induced injuries as an additional source of pain. In contrast, Geva and Defrin (2013) demonstrated an increased CPM response in triathletes compared with controls. This study also showed that triathletes demonstrated significantly less fear of pain compared with controls and that the CPM response was significantly correlated with fear of pain and mental stress during training. This indicates that the more efficient pain inhibition in triathletes may also relate to psychological factors. The relation between increased physical activity and a greater CPM response was supported by Naugle and Riley (2014), who showed that greater amount of self-reported physical activity, as well as greater amount of vigorous physical activity, predicted a greater CPM response during cold pressor test. The conflicting results may be due to different pain sensitivity assessment methodologies, with pressure pain used to evaluate the CPM response in the current experiment (II) and heat pain used in the previous studies (Geva and Defrin, 2013; Tesarz et al., 2013; Naugle and Riley, 2013).



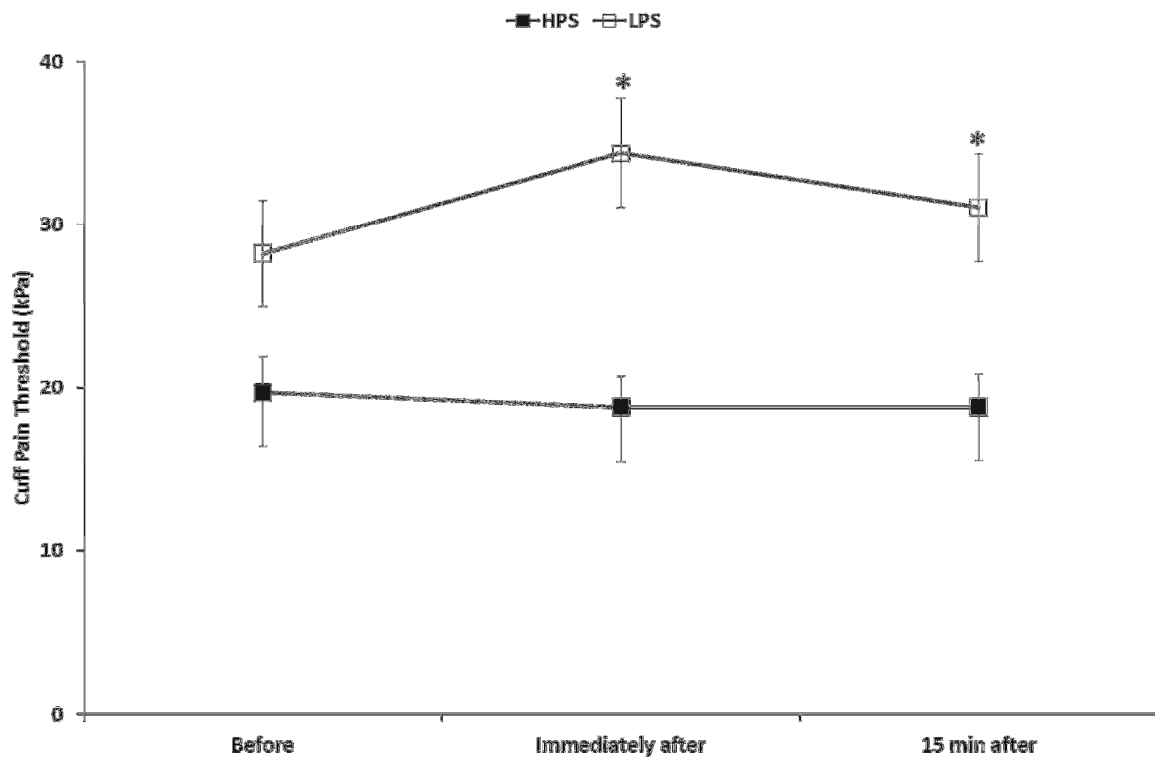
**Fig. 4.4:** Mean (+SEM) manual pressure pain threshold at the quadriceps muscle and biceps muscle before, during, immediately after, and 15 min after cold pressor test at the dominant hand in active and inactive subjects (\*, significant difference compared with baseline; NK:  $P < 0.05$ ; Raw data from II).



#### 4.4 CPM in patients with chronic pain

The assessment of the CPM response in clinical studies has provided insights into the function of the pain inhibitory systems in chronic pain. Impaired CPM responses have previously been shown in long-lasting pain conditions such as chronic pancreatitis (Olesen et al., 2010; Bouwense et al., 2013), irritable bowel syndrome (Heymen et al., 2010), tension-type headache (Pielsticker et al., 2005; Sandrini et al., 2006; Cathcart et al., 2010), fibromyalgia (Kosek and Hansson, 1997; Lautenbacher and Rollman, 1997; de Souza et al., 2009; Normand et al., 2011; Paul-Savoie et al., 2012), temporomandibular disorder (King et al., 2009), chronic whiplash associated disorder (Daenen et al., 2013; Ng et al., 2014), and osteoarthritis (Kosek and Ordeberg, 2000a; Graven-Nielsen et al., 2012) compared with asymptomatic controls. The present experiment extends these findings by showing a reduced CPM response in chronic musculoskeletal pain patients with high pain sensitivity, compared with patients with less pain sensitivity (IV; Fig. 4.5). Only patients with low pain sensitivity demonstrated an increase in cuff pressure pain threshold and a decrease in pain ratings after cold pressor test (IV; Fig. 4.5).

Cold pressor test did not affect temporal summation of pain in any of the pain sensitivity groups, highlighting potential differences in the effect of cold pressor test on central mechanisms of pain summation between healthy subjects (Fig. 4.3) and patients with chronic pain (IV). This finding is in agreement with a previous study on pain patients with chronic widespread pain (Staud et al., 2003a). A possible explanation is that patients with chronic musculoskeletal pain demonstrate facilitated temporal summation of pain making central mechanisms of pain summation less likely to be reduced by the competing mechanism of CPM. High pain sensitivity has recently been associated with impaired pain inhibition in 29 women subjects demonstrating a significant negative correlation between pain sensitivity assessed with the pain sensitivity questionnaire and pain modulation assessed by the offset analgesia paradigm (Honigman et al., 2013). Furthermore, the CPM response was negatively correlated with clinical peak pain intensity highlighting the importance of ongoing pain in the process of reduced CPM in chronic musculoskeletal pain (IV). The association between clinical pain intensity and the CPM response has previously been demonstrated in subjects with neuropathy (Nahman-Averbuch et al., 2011; Pickering et al., 2014) but not in temporomandibular disorder (Oono et al., 2014).



**Fig. 4.5:** Mean ( $\pm$  SEM) pressure pain threshold at the non-dominant lower leg before, immediately after, and 15 min after cold pressor test at the dominant foot in chronic musculoskeletal pain patients with high pain sensitivity (HPS,  $n = 30$ ) and low pain sensitivity (LPS,  $n = 30$ ) (\*, significant difference compared with baseline. NK:  $P < 0.05$ ; Raw data from IV).

## 4.5 Mechanisms of CPM

The specific mechanisms involved in the CPM response in humans are largely unknown, but is believed to represent the net outcome of multiple descending pain inhibitory mechanisms. The most commonly used hypothesis to explain the CPM response to a painful condition stimulus, is the activation of a spino-bulbo-spinal loop through the subnucleus reticularis dorsalis (SRD) in the medulla (Villanueva et al., 1988), leading to an inhibition of wide-dynamic-range neurons in the dorsal horn (Le Bars et al., 1979a; Le Bars et al., 1981a; Willer et al., 1984; Talbot et al., 1987; Price and McHaffie, 1988; De Broucker et al., 1990; Bouhassira et al., 1993). Activation of the opioid system has also been linked with the CPM response (Le Bars et al., 1981b; Le Bars et al., 1981c; Bouhassira et al., 1992; Le Bars et al., 1992) and injection of naloxone, in both animals and humans caused a reduction in the inhibitory response after noxious thermal stimuli (Le Bars et al., 1981c; Willer et al., 1990; Sprenger et al., 2011). A reduced CPM response has also been reported in patients treated with opioids (Ram et al., 2008). These findings indicate involvement of an opioidergic mechanism in CPM, which could explain the heterotopic and homotopic hypoalgesic response during cold water immersion (I, II, and IV). However, naloxone does not completely abolish the CPM response (Sprenger et al., 2011) providing evidence for a non-opioid mechanism.

Immersion of a body part in cold water produces sympathetically mediated heart rate and blood pressure increases (Weise et al., 1993; Chalaye et al., 2013). Interestingly, recent studies demonstrated a significant positive association between magnitude of the CPM response and increase in blood pressure during a cold pressor test in healthy subjects (Chalaye et al., 2013) and in patients with fibromyalgia (Chalaye et al., 2014), indicating that activation of a baroreceptor mechanism could be involved in the CPM response.

Recent animal studies have also shown that systemic or local administration of a  $\alpha$ 1-adrenoceptor agonist and systemic administration of a selective  $\alpha$ 2-adrenoceptor agonist inhibit the painful CPM response (Sanada et al., 2009, Makino et al., 2010) suggesting the involvement of adrenergic neurons in the CPM response. Involvement of a baroreceptor mechanism and adrenergic neurons could also explain the heterotopic and homotopic hypoalgesic response during cold water immersion (I, II, and IV).

In summary, cold pressor test applied to the hand and foot produced multisegmental increases in manual pressure pain thresholds during water immersion, as well as an increase in pain tolerance and

a decrease in temporal summation of pain after water immersion. A significant association between the CPM response and the perceived pain during water immersion was only found for cold pressor test on the foot. The CPM response was not affected by age or level of physical activity, and the CPM response during water immersion was comparable between men and women. Patients with high pain sensitivity demonstrated a reduced CPM response after cold pressor test compared with patients with low pain sensitivity. The CPM response was negatively correlated with the clinical peak pain intensity, highlighting the importance of ongoing pain in the reduced CPM response.

## 5. SIMILARITIES IN MANIFESTATIONS OF CPM AND EIH

Several similar manifestations between CPM and EIH were found in the current experiments (Table 5.1). Although the increase in manual pressure pain thresholds was larger during cold pressor tests, compared with exercise conditions (I and II), robust multisegmental increases in manual pressure pain thresholds were found in healthy men and women in relation to both paradigms (I and II). The CPM response and the EIH response after aerobic exercise were not affected by level of physical activity (II). The CPM response and the EIH response after isometric exercise were not affected by age and gender (I), and reduction in central mechanisms of pain summation was found after both paradigms (III, Fig. 4.3). Impaired CPM and EIH responses were found in patients with high pain sensitivity (IV). The similar manifestations between the CPM and EIH responses indicate a potential commonality in their underlying mechanisms. The CPM response may be involved in the EIH response after both isometric exercise (Lemley et al., 2014b) and aerobic exercise (Ellingson et al., 2013). To support this hypothesis, the clinical experiment (IV) demonstrated that the EIH response after aerobic exercise was predicted by the CPM response after cold pressor test, suggesting that individuals who demonstrated a greater ability to activate the descending inhibitory systems reported greater hypoalgesia following aerobic exercise. This relationship could also indicate that the increase in temporal summation of pain after aerobic exercise in patients with high pain sensitivity may be due to impaired descending inhibition. Ellingson et al. (2014) demonstrated a greater hypoalgesic response in 16 healthy women after painful aerobic exercise compared with non-painful aerobic exercise, supporting the link between the CPM and EIH responses. The relation between CPM and EIH could indicate similar mechanisms underlying the hypoalgesic response. However, hypoalgesia has also been demonstrated after non-painful aerobic exercise (Ellingson et al., 2014) indicating that the CPM response may work as an additive effect after painful exercise. Lemley et al. (2014) demonstrated that the CPM response predicted the EIH response after isometric exercise in healthy subjects, however this was not found in the current clinical experiment (IV). In the experiments on healthy subjects (I and II), a weak but significant correlation between the CPM and the EIH responses was demonstrated (II), supporting the hypothesis of similar mechanisms. This correlation was not demonstrated in a larger sample size (I), questioning the commonality of mechanisms underlying the CPM and EIH responses. These findings are in agreement with previous studies, comparing the CPM response with the response to the offset analgesia (OA) paradigm (Honigman et al., 2013; Nahman-Averbuch et al., 2014). Honigman et al.

(2013) demonstrated a significant correlation between the maximal inhibitory responses in relation to the CPM and OA paradigms. Interestingly, the study by Nahman-Averbuch et al. (2014) found no significant correlation between the pain inhibitory responses, although similar methodology was used. Although several similar manifestations between the CPM and EIH responses were found in the current experiments, differences in temporal and spatial manifestations were also established (Table 5.1). First of all, a significant increase in manual pressure pain thresholds was only observed *during* the cold pressor stimulation (I, II), whereas eloquent increases were also found following exercise conditions (I and II), signifying differences in the temporal manifestations. Secondly, a notable larger effect on manual pressure pain thresholds at the remote sites, compared with the local site, was found during cold pressor test on the foot, whereas the increase in manual pressure pain thresholds was significantly larger in the exercising body part compared with remote sites after exercise conditions (I), showing differences in the spatial manifestations. These differences in temporal and spatial manifestations of the CPM and EIH responses indicate that partially different mechanisms may be involved.

**Table 5.1:** A comparison of the temporal and spatial manifestations of CPM and EIH in healthy subjects and in patients with chronic musculoskeletal pain

		<b>CPM</b> <b>(cold pressor test)</b>	<b>EIH</b> <b>(aerobic exercise)</b>	<b>EIH</b> <b>(isometric exercise)</b>
<b>Healthy subjects</b>	Temporal and spatial manifestations	<u>Pain thresholds:</u> Multisegmental ↑ <i>during</i> Larger effects in heterotopic areas compared with homotopic area  <u>Pain tolerance:</u> Multisegmental ↑ <i>after</i>  <u>Temporal summation:</u> Multisegmental ↓ <i>after</i>	<u>Pain thresholds:</u> Multisegmental ↑ <i>after</i> Larger effects in exercising body part compared with remote areas  <u>Pain tolerance:</u> Multisegmental ↑ <i>after</i>  <u>Temporal summation:</u> No effect	<u>Pain thresholds:</u> Multisegmental ↑ <i>after</i> Larger effects in exercising body part compared with remote areas  <u>Pain tolerance:</u> Multisegmental ↑ <i>after</i>  <u>Temporal summation:</u> Multisegmental ↓ <i>after</i>
	Influence of age, gender and level of physical activity	<u>Age:</u> No influence <u>Gender:</u> No influence <i>during</i> conditioning stimuli, but ↑ duration in women  <u>Physical activity:</u> No influence	<u>Age:</u> ↓ EIH with ↑ age <u>Gender:</u> ↑ in women  <u>Physical activity:</u> No influence	<u>Age:</u> No influence <u>Gender:</u> No influence  <u>Physical activity:</u> Unknown
<b>Chronic MSK pain</b>	Temporal and spatial manifestations	<u>Manual pain thresholds:</u> Multisegmental ↑ <i>during</i> <u>Cuff pain threshold:</u> Increase in patients with low pain sensitivity. No effect in patients with high pain sensitivity  <u>Pain tolerance:</u> Segmental ↑ <i>after</i>  <u>Temporal summation:</u> No effect	<u>Manual pain thresholds:</u> Multisegmental ↑ <i>after</i> <u>Cuff pain threshold:</u> Increase in patients with low pain sensitivity. No effect in patients with high pain sensitivity  <u>Pain tolerance:</u> Segmental ↑ <i>after</i>  <u>Temporal summation:</u> Increase in patients with high pain sensitivity. No effect in patients with low pain sensitivity	<u>Manual pain thresholds:</u> Multisegmental ↑ <i>after</i> <u>Cuff pain threshold:</u> Increase in patients with low pain sensitivity. No effect in patients with high pain sensitivity  <u>Pain tolerance:</u> Segmental ↑ <i>after</i>  <u>Temporal summation:</u> No effect
	Influence of clinical pain and psychological distress	Predicted by clinical peak pain intensity	No significant relation was found The CPM response predicted the EIH response after aerobic exercise	No significant relation was found

## 6. CONCLUSIONS AND FUTURE PERSPECTIVES

Based on the results of the current PhD study, the following conclusions can be made (Fig. 6.1):

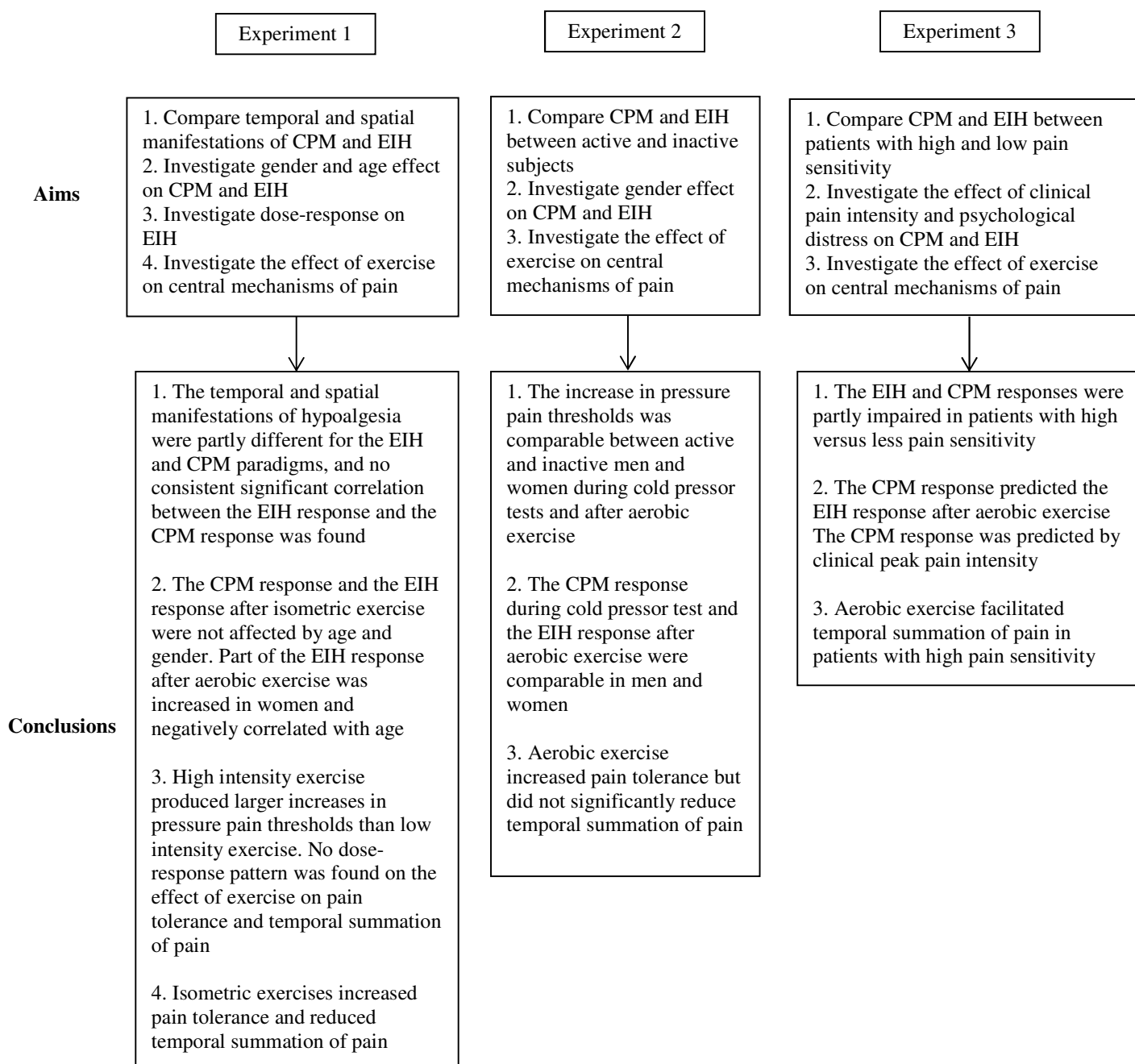
1. Cold pressor test (CPM response) as well as aerobic and isometric exercises (EIH responses) produced multisegmental increases in manual pressure pain thresholds in healthy men and women (I and II).
2. The CPM response and the EIH response after isometric exercise were not affected by age and gender. The EIH response after aerobic exercise was increased in women (I) and decreased with increasing age (III).
3. The increase in manual pressure pain thresholds was comparable between active and inactive men and women during cold pressor tests and after aerobic exercise (II).
4. The temporal and spatial manifestations of hypoalgesia were partly different for the EIH and CPM paradigms, and there was no consistent correlation between the maximal EIH response and the maximal CPM response in healthy subjects (I and II).
5. High intensity exercise produced larger increases in manual pressure pain thresholds than low intensity exercise (I).
6. Aerobic and isometric exercises increased pain tolerance, but only isometric exercises reduced temporal summation of pain, illustrating the potential for isometric exercise as a rehabilitation procedure, also targeting the central mechanisms of pain summation (III).
7. The EIH and CPM responses were partly impaired in chronic musculoskeletal pain patients with high pain sensitivity compared with patients with low pain sensitivity (IV).
8. Aerobic exercise further facilitated temporal summation of pain in chronic musculoskeletal pain patients with high pain sensitivity (IV).
9. The CPM response was predicted by clinical peak pain intensity, and the CPM response predicted the EIH response after aerobic exercise (IV).

These findings have implications for future evaluation of the pain inhibitory systems as well as for clinical practice. An impaired CPM response is commonly observed in clinical pain populations with chronic pain of musculoskeletal (Normand et al., 2011; Graven-Nielsen et al., 2012), neuropathic (Pickering et al., 2014) or visceral origin (King et al., 2009; Heyman et al. 2010). An impaired EIH response has primarily been demonstrated in chronic pain of musculoskeletal origin, and it is currently



unknown whether a reduced EIH response is also observed in other pain conditions. The evaluation of the pain inhibitory systems with multiple paradigms (e.g. CPM and EIH) may provide additional information about the pain inhibitory phenotype of the individual patient. For example, a patient may have an intact CPM response but a reduced EIH response and vice versa. The CPM paradigm alone may not be a sufficient paradigm to assess the wide scope of pain modulation, and multifaceted assessment might therefore have an important role in future pain assessment.

In clinical practice, it may be recommended that clinicians evaluate pain sensitivity, as well as the CPM and EIH responses, in addition to clinical pain, when considering treatment options utilizing the descending inhibitory pain control. The current results imply that chronic musculoskeletal pain patients with high pain sensitivity demonstrated less efficient pain inhibition. In conclusion, the present work on EIH and CPM has provided new information on assessment of the pain inhibitory systems as well as on the effect of different exercise modalities on the pain system. The results might be helpful to improve assessment and treatment of chronic musculoskeletal pain disorders in the future.



**Fig. 6.1:** Illustration of the aims and conclusions of the experiments.

‘CPM’: Conditioned Pain Modulation. ‘EIH’: Exercise-induced Hypoalgesia.

## SUMMARY

### **Temporal and Spatial Manifestations of Exercise-induced Hypoalgesia and Conditioned Pain Modulation**

**Introduction:** Impaired pain inhibition is believed to be involved in several chronic pain conditions. Efficiency of the pain inhibitory pathways is typically assessed by paradigms of conditioned pain modulation (CPM) or exercise-induced hypoalgesia (EIH). Still, the spatial and temporal manifestations of the two paradigms have never been directly compared, and it is unknown whether the paradigms provide equivalent data on pain inhibition. Furthermore, physical exercise is an important component in the treatment and rehabilitation of patients with chronic musculoskeletal pain and a comprehensive understanding of how exercise influences the nociceptive and pain inhibitory pathways is necessary to optimize the clinical utility of exercise.

The aims of this PhD project were 1) to compare the temporal and spatial manifestation of EIH and CPM, 2) to investigate the influence of age, gender and level of regular physical activity on CPM and EIH, 3) to investigate the influence of exercise modality, intensity and duration on the EIH response in healthy subjects, 4) to investigate the effect of exercise on central mechanisms of pain, and 5) to investigate the influence of pain sensitivity and clinical pain characteristics on CPM and EIH in patients with chronic musculoskeletal pain.

**Methods:** Three experiments were conducted. Experiment 1: 80 healthy subjects (40 women and 40 men) performed cold pressor tests on the hand and foot as well as aerobic and isometric exercises at the arm and leg with different intensities and durations. Experiment 2: 56 healthy subjects (30 active and 26 inactive) performed a cold pressor test, an aerobic exercise and a control condition. Experiment 3: 61 patients with chronic musculoskeletal pain (31 with high pain sensitivity and 30 with low pain sensitivity) performed cold pressor test, aerobic and isometric exercises and a control condition. In all three experiments, pressure pain thresholds, pressure pain tolerances and temporal summation of pain were assessed with manual algometry and computerized cuff algometry at local and distant body sites before and after conditions.

**Results:** Manual algometry and cuff algometry demonstrated good test-retest reliability.

Experiment 1 demonstrated robust multisegmental increases in manual pressure pain thresholds in men and women during cold pressor tests and after high intensity aerobic and low and high intensity isometric exercise conditions. The CPM response and the EIH response after isometric exercises were not affected by age or gender. Part of the EIH response after aerobic exercise was increased in women and decreased with increasing age. Differences in temporal and spatial manifestations between the EIH response and the CPM response were found, and there was no significant correlation between the maximal EIH response and the maximal CPM response, indicating partly different mechanisms. The increase in pressure pain thresholds was larger in the exercising body part compared with non-exercising body parts, and high intensity exercise produced larger increases in pressure pain thresholds than low intensity exercise. Isometric exercises also increased cuff pain tolerance and reduced temporal summation of pain, illustrating the potential for isometric exercise as a rehabilitation procedure, also targeting the central mechanisms of pain.

Experiment 2 demonstrated comparable multisegmental increases in manual pressure pain thresholds in active and inactive men and women during cold pressor tests and after aerobic exercise, indicating that physical inactivity does not alter the magnitude of the EIH and CPM responses compared to regular physical activity. Aerobic exercise also increased cuff pain tolerance, but did not affect temporal summation of pain.

Experiment 3 demonstrated partly impaired EIH and CPM responses in chronic musculoskeletal pain patients with high versus less pain sensitivity. Aerobic exercise facilitated temporal summation of pain in patients with high pain sensitivity. The CPM response was predicted by clinical pain intensity and the EIH response after aerobic exercise was predicted by the CPM response.

These findings have implications for future evaluation of the pain inhibitory systems as well as for clinical practice. The evaluation of pain inhibition with multiple paradigms (e.g. CPM and EIH) may provide additional information about the pain inhibitory phenotype of the patient. For example, a patient may have an intact CPM response but a reduced EIH response and vice versa. In clinical practice, clinicians should evaluate general pain sensitivity, as well as the CPM and EIH responses in addition to evaluating clinical pain when considering treatment options, utilizing the descending inhibitory pain control. In conclusion, the present work on EIH and CPM may help guiding the choice of exercise in future assessment and rehabilitation of chronic musculoskeletal pain patients.

## **SAMMENDRAG (Danish summary)**

### **Tids- og Rummæssige Manifestationer af Træningsinduceret Smertelindring og Betinget Smertemodulation**

**Indledning:** Nedsat smertehæmning menes at være involveret i flere kroniske smertetilstande. Effektiviteten af de smertehæmmende systemer vurderes typisk via den betingede smerte modulation (CPM) eller træningsinduceret smertelindring (EIH). De tids- og rummæssige manifestationer af CPM og EIH er aldrig tidligere blevet direkte sammenlignet, og det er fortsat uvist, om paradigmerne giver ækvivalent information om smertehæmning. Træning er desuden en vigtig komponent i behandlingen af patienter med kroniske smerter i bevægeapparatet, og en større forståelse af, hvordan træning påvirker smertesystemet og smertehæmning, er nødvendigt for at optimere den kliniske anvendelighed af træning.

Formålene med dette ph.d.-projekt var 1) at sammenligne de tids- og rummæssige manifestationer af EIH og CPM, 2) at undersøge betydningen af alder, køn og graden af habituel fysisk aktivitet på EIH og CPM, 3) at undersøge betydningen af trænings-type, -intensitet og -varighed på graden af EIH, 4) at undersøge effekten af træning på de centrale smertemekanismer, og 5) at undersøge hvilken indflydelse smertesensitivitet og kliniske smerte karakteristika har på CPM og EIH responsen hos patienter med kroniske smerter i bevægeapparatet.

**Metoder:** Tre eksperimenter blev udført. Eksperiment 1: 80 raske forsøgspersoner (40 kvinder og 40 mænd) udførte isvandstest på hånd og fod samt aerobe og isometriske træningsøvelser for arm og ben ved forskellige intensiteter og varigheder. Eksperiment 2: 56 raske forsøgspersoner (30 aktive og 26 inaktive) udførte isvandstest, aerob træning og en kontrolkondition. Eksperiment 3: 61 patienter med kroniske smerter i bevægeapparatet (31 med høj smertesensitivitet og 30 med lav smertesensitivitet) udførte isvandstest, aerob og isometrisk træning og en kontrolkondition. I alle tre eksperimenter blev tryksmertetærsklen, tryksmertetolerancen og tidsmæssig summation af smerte ved gentagne trykstimuli vurderet med håndholdt trykalgometri og computerstyret cuffalgometri på lokale og perifere steder på kroppen før og efter de forskellige konditioner.

**Resultater:** Håndholdt trykalgometri og computerstyret cuffalgometri viste god test-retest pålidelighed. Eksperiment 1 viste robuste, multisegmentalt øgede tryksmertetærskler hos mænd og kvinder under isvandstest samt efter højintensitets aerob og lav- og højintensitets isometrisk træning. CPM responsen og EIH responsen efter isometrisk træning var ikke påvirket af forsøgspersonernes alder eller køn. EIH responsen efter aerob træning var større hos kvinder, men aftagende med stigende alder. Forskelle i tids- og rummæssige manifestationer mellem EIH responsen og CPM responsen blev fundet, og der var ingen konsistent korrelation mellem den maksimale EIH respons og den maksimale CPM respons, hvilket indikerer forskellige mekanismer. Ændringen i tryksmertetærskel var størst på den kropsdel, hvor træningen blev udført sammenlignet med kropsdele, der ikke udførte træningen. Højintensitets træning resulterede i en større ændring i tryksmertetærsklen end lavintensitets træning. Isometrisk træning øgede også smertetolerancen og reducerede den tidsmæssige summation af smerte, hvilket illustrerer potentialet for at isometrisk træning kan reducere de centrale smertemekanismer. Eksperiment 2 viste sammenlignelige ændringer i tryksmertetærsklen hos aktive og inaktive mænd og kvinder under isvandstest og efter aerob træning, hvilket indikerer, at inaktivitet ikke reducerer smertehæmningen sammenlignet med regelmæssig fysisk aktivitet. Aerob træning øgede smertetolerancen, men påvirkede ikke den tidsmæssige summation af smerten. Eksperiment 3 viste delvist reduceret EIH og CPM i patienter med kroniske bevægeapparatsmerter og høj smertesensitivitet i forhold til patienter med lav smertesensitivitet. Aerob træning øgede den tidsmæssige summation af smerte hos patienter med høj smertesensitivitet. CPM responsen var prædikeret af den kliniske smerteintensitet, og EIH responsen efter aerob træning var prædikeret af CPM responsen.

Disse fund har implikationer for fremtidig undersøgelse af de smertehæmmende systemer og for klinisk praksis. Fremtidig undersøgelse af de smertehæmmende systemer med multiple paradigmer (ex. CPM og EIH) kan give yderligere information om det enkelte individs smertehæmmende fænotype. For eksempel kan en patient fremstå med en intakt CPM respons, men med en reduceret EIH respons eller omvendt. I klinisk praksis bør klinikere fremadrettet vurdere den generelle smertesensitivitet og CPM- og EIH-responsen i tillæg til vurdering af den kliniske smerteintensitet når behandlingsmuligheder, der påvirker de smertehæmmende systemer, overvejes. De indeværende studier om EIH og CPM har givet nye informationer om undersøgelse af de smertehæmmende systemer samt om effekten af forskellige

træningstyper på smertesystemet. Resultaterne kan bidrage til at optimere fremtidig undersøgelse og behandling af patienter med kroniske smerter i bevægeapparatet.

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## **APPENDIXES**

Appendixes 1-4 are summaries of experimental and clinical studies on CPM and EIH in humans. Ongoing literature searches in the following databases: PubMed, Web of Science, Embase, CINAHL and PEDro, has been conducted throughout the study period. The following keywords were used for searches on CPM: 'conditioned pain modulation', 'CPM', 'pain modulation', 'endogenous pain modulation', 'counterirritation', 'endogenous analgesia', 'heterotopic noxious conditioning stimulation', 'diffuse noxious inhibitory controls', 'DNIC'. The following keywords were used for searches on EIH: 'exercise-induced hypoalgesia', 'EIH', 'exercise-induced analgesia', 'EIA', 'exercise analgesia' and 'exercise hypoalgesia'. Furthermore, the reference list from each identified study and review was examined for studies that were not identified through the databases. However, the summaries are not part of a systematic literature review on CPM and EIH and thus may not be complete.



**Appendix 1:** A summary of experimental studies investigating conditioned pain modulation in healthy human adults, primarily organized according to the conditioning stimuli in the following order: ‘cold pressor test’, ‘cold pack’, ‘hot water’, ‘heat pain’, ‘tourniquet test’, ‘mechanical pressure’, ‘electrical stimulation’, ‘hypertonic saline’, ‘more than one paradigm’ and secondly after year of publication.

Reference	Healthy Subjects	Control condition	Conditioning stimulus <i>‘cold pressor test’</i> Intensity Location	Pain sensitivity parameters	Main findings
(Talbot et al., 1987)	10 healthy subjects (6/4) 19-36 years of age	Within-subject control condition	Cold pressor test (5°C) 5 min Hand	Heat pain threshold and rating on the upper lip during and after CPM	Heat pain intensity was reduced during CPM. Heat pain tolerance was increased during and after CPM
(Talbot et al., 1989)	10 healthy subjects (3/7) 19-37 years of age	Within-subject painful and non-painful CPM paradigms	Cold pressor test (5°C) 5 min Hand	Noxious heat stimuli detection changes on the face during CPM	Heat detection latencies were increased during the painful CPM paradigm
(Edwards et al., 2003a)	45 healthy young adults (25/20) 21.6 (18-25)  48 healthy older adults (32/16) 63.1 (55-67)	Different CPM paradigms	Cold pressor test (5°C or 22°C) 70 s Right hand	Temporal summation of heat at the left forearm or left ankle	<b>Younger subjects:</b> Temporal summation was decreased during painful CPM paradigm on both arm and leg <b>Older subjects:</b> Temporal summation was increased during painful CPM paradigm on both arm and leg
(Edwards et al., 2003b)	45 healthy young adults (25/20) 21.6 (18-25)  48 healthy older adults (32/16) 63.1 (55-67)	Different CPM paradigms	Cold pressor test (5°C or 22°C) 70 s Right hand	Temporal summation of heat at the left forearm or left ankle	CPM was not related to laboratory pain responses, psychological variables or physiological variables
(Serrao et al., 2004)	36 healthy subjects (20/16) 24-39 years of age	Within-subject painful and non-painful CPM paradigms	Cold pressor test (2-4°C) 5 min Hand	Nociceptive flexion reflex and pain rating elicited by sural nerve stimulation during and after CPM	Cold pressor test induced a significant reduction of the NFR. The reduction was larger in men compared with women
(Baad-Hansen et al., 2005)	54 healthy subjects (34/20) 25.7 (4.4)	Control CPM paradigm with 30°C water	Cold pressor test (1-2°C) 3 min Non-dominant hand	Pain intensity and unpleasantness during capsaicin-evoked pain intra orally during and after CPM	Pain intensity and unpleasantness decreased during CPM No gender differences
(Pud et al., 2005)	40 healthy subjects (17/23) 24.3 (0.6)	None	Cold pressor test (1°C) 30 s Fingers at right hand	Pain rating to mechanical punctate stimuli on the thenar eminence on both hands after cold pressor test	Both hands demonstrated CPM with no difference between hands. No difference was found between men and women

(Lariviere et al., 2007)	20 healthy young adults (10/10) 25.4 (4.2)  20 middle-aged adults (10/10) 47.0 (4.5)  20 older adults (10/10) 68.1 (3.8)	None	Cold pressor test (7°C) 6 min Right hand	Heat pain ratings at the calf during CPM	<b>Young healthy adults:</b> Significant CPM response <b>Middle aged healthy adults:</b> significant CPM response <b>Older healthy adults:</b> No CPM response
(Smith et al., 2007)	32 healthy subjects (32/0) 26 (5)	Randomized to 3 different sleep patterns	Cold pressor test (4°C) 20 s Left hand	Pressure pain threshold on the trapezius, masseter and brachioradialis muscles during CPM	CPM was reduced in the forced awakening group
(Rosen et al., 2008)	30 healthy subjects (15/15) 25 (4.5)	None	Cold pressor test (2-4°C) 5 min Hand	Electrical pain thresholds at the orofacial region and finger Pressure pain threshold at the masseter muscle and the finger during and after the CPM paradigm	Pressure pain thresholds increased during and immediately after the CPM paradigm No difference was found between men and women Electrical pain threshold at the finger increased during and after the CPM paradigm
(Goodin et al., 2009)	35 healthy subjects (19/16) 19.7 (1.9)	None	Cold pressor test (4°C) 30 s Right hand	Pressure pain threshold left forearm and trapezius during CPM.	Significant CPM response. Men had larger CPM response compared with women. CPM and catastrophizing was inversely correlated.
(Knudsen and Drummond, 2009)	32 healthy subjects (19/13) 17-51 years of age	Within-subject different CPM paradigms	Cold pressor test (10°C) for 1 min Dominant hand  Cold pressor test (2°C) 1 min Dominant hand  Repeated cold pressor test (4°C) 1 min Dominant hand	Pressure pain threshold and sharpness at the forehead after CPM	Cold pressor tests at 2°C and repeated cold pressor tests at 4°C produced CPM Cold pressor test at 10°C produced no CPM
(Riley et al., 2010)	27 younger healthy subjects (17/10) 25.3 (8.8) 22 older healthy subjects (18/4) 65.2 (6.9)	Within-subject painful and non-painful CPM paradigms.	Cold pressor test (8-16°C) 30-300 s Foot	Heat pain rating on the left palm	<b>Younger subjects:</b> Heat pain ratings were reduced during painful CPM paradigm <b>Older subjects:</b> Facilitation of heat pain rating during the painful CPM paradigm
(Treister et al., 2010)	191 healthy subjects (104/87) 24.5 (18-39)	Within-subject painful and non-painful CPM paradigms	Cold pressor test (12°C) 45 s Non-dominant hand	Heat pain rating on the thenar eminence of the left hand during and after CPM	Significant CPM effects during and immediately after painful and non-painful cold pressor test. Repeated pain testing also decreased pain ratings. The CPM effect for painful cold pressor test was significantly larger than the other two paradigms. The CPM response was correlated to conditioning pain scores in men

(Rezaii et al., 2012)	36 healthy subjects (36/0) 25.3 (4.2)	Different painful and non-painful CPM paradigms	Cold pressor test (3°C) 30-300 s Hand	Pressure pain rating on the masseter muscles during and after CPM	Pain rating decreased during and immediately after painful CPM paradigm Subjects in ovulatory phase had larger CPM response compared with the early follicular phase
(Bjorkedal and Flaten, 2012)	72 healthy subjects (36/36) (19-33 years of age)	1/3 of the subjects were told that the CPM paradigm would reduce pain, 1/3 that it would increase pain and 1/3 were not giving any information	Cold pressor test (8°C) 150 s Dominant hand	Heat pain ratings at the non-dominant hand during CPM	<b>In women:</b> Decrease in pain rating in analgesic group and increase in pain rating in hyperalgesic group <b>In men:</b> No difference in any of the groups
(Grashorn et al., 2013)	22 healthy young adults (12/10) 24.8 (2.8)  17 middle-aged adults (9/8) 48.7 (5.3)  25 older adults (13/12) 70.3 (5.2)		Cold pressor test (0°C) ? s Left foot	Heat pain ratings at the right forearm during and after CPM	<b>Younger subjects:</b> Significant CPM response <b>Middle aged subjects:</b> No CPM response <b>Older subjects:</b> No CPM response No difference in CPM between men and women
(King et al., 2013)	33 healthy subjects (16/17) 23.5 (3.89)	Within-subject placebo and naltroxen conditions	Cold pressor test (avg.: 12.9±2.7°C) 40 s Right foot	Heat pain ratings on left palm	CPM during placebo but not during naltroxen No difference in CPM based on catastrophizing scores
(Geva and Defrin, 2013)	19 triathletes (9/10) 39.6 (12)	17 non- athletes (10/7) 36.5 (11)	Cold pressor test (12°C) 30-60 s Right hand	Heat pain rating and temporal summation during CPM	<b>Athletes:</b> Significant CPM response <b>Non-athletes:</b> Significant CPM response The CPM effect on pain ratings was larger in the triathletes. A trend towards greater CPM with greater time spent on exercise
(Chalaye et al., 2013)	26 healthy subjects (13/13) 26.0 (20-41)	None	Cold pressor test (7°C) 5 min Right hand and forearm	Heat pain rating on left forearm after CPM	Pain ratings decreased after CPM Correlated with increase in blood pressure
(Goodin et al., 2013)	149 healthy subjects (78/71) 19.9 (2.9)	None	Cold pressor test (4°C) 30 s Right hand	Pressure pain threshold left forearm and trapezius during CPM	Significant CPM response during cold pressor test Greater optimism was associated with greater CPM
(Tesarz et al., 2013)	25 healthy endurance athletes (0/25) 27.8 (4.1)  26 normally active controls (0/26) 28.0 (4.5)	No within-subject control condition	Cold pressor test (12°C) 2 min Non-dominant hand	Heat pain rating on the dorsum of the hand after CPM	<b>Athletes:</b> Significant CPM response <b>Non-athletes:</b> Significant CPM response The CPM response was significantly larger in non-athletes
(Riley et al., 2014)	89 middle-aged subjects (61/28) 45-56 years of age 102 older-aged subjects (69/33) 57-76 years of age.	Different painful and non-painful CPM paradigms	.Repeated cold pressor test (8°C) 1 min Right hand	Heat pain rating and temporal summation on left forearm after CPM	No significant CPM responses in any group

(Naugle and Riley, 2014)	48 healthy subjects (24/24) 42 (21.25)	None	Cold pressor test (10-12°C) 45 s Right foot	Heat pain rating on the left forearm during CPM	Cold water produced CPM Greater self-reported vigorous physical activity predicted greater CPM
(Biurrun Manresa et al., 2014)	34 healthy subjects (0/39) 27.5 (6.8)	Between sessions reliability	Cold pressor test (2°C) up to 2 min (NRS = 7) Non-dominant hand	Nociceptive flexion reflex (NFR) and electrical pain threshold and pain intensity at the dominant sural nerve during CPM	Significant CPM effect for all measures NFR showed good reliability, although higher in session 1 compared with session 2
(Lemley et al., 2014b)	20 healthy young subjects (10/10)  19 healthy old subjects (9/10)	Within subject (exercise, rest and neutral water bath)	Cold pressor test (2°C) 80 s Foot	Pressure pain intensity at the right index finger	<b>Young subjects:</b> Significant CPM response <b>Old subjects:</b> No CPM response Greater CPM in more physical active subjects No relation between CPM and fear of pain/catastrophizing or pain attitude
<b>Reference</b>	<b>Healthy Subjects</b>	<b>Control condition</b>	<b>Conditioning stimulus 'cold pack' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Ladouceur et al., 2012)	31 healthy subjects (16/15) 24.5 (5.6)	Within-subject different painful and non-painful CPM paradigms	Cold pack 3 min Left forearm	Pain ratings and RIII reflex by stimulation on the sural nerve during the CPM paradigms	The painful paradigm reduced pain ratings and RIII reflex during the CPM paradigm The non-painful paradigm reduced pain rating when attention was focused on the conditioning stimulus. RIII was also reduced with the non-painful paradigm but to a smaller extent compared with the painful paradigm
<b>Reference</b>	<b>Healthy Subjects</b>	<b>Control condition</b>	<b>Conditioning stimulus 'hot water' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Willer et al., 1990)	9 healthy subjects (5/4) 23-36 years of age	Within-subject placebo and naloxone conditions	Hot water bath (46°C) 2 min Hand	Nociceptive flexion reflex of the sural nerve during and after the CPM paradigm	The NFR response was decreased during and after the CPM paradigm Naloxone completely abolished the inhibitory effects of the CPM paradigm
(Moont et al., 2010)	34 healthy subjects (16/18) 24.5 (3.9)	Different CPM paradigms with and without distraction	Hot water bath (46.5°C) 80 s Right hand	Heat pain and unpleasantness ratings during CPM	Hot water produced hypoalgesia in most of the subjects. The combined effects of CPM and distraction were larger than for CPM alone
(Nir et al., 2011)	30 healthy subjects (0/30) 24.6 (3.4)	Within-subject different CPM paradigms	Hot water bath (44.5°C) 1 min Non-dominant hand  Hot water bath (45.5°C) 1 min Non-dominant hand.  Hot water bath (46.5°C) 1 min Non-dominant hand.	Heat pain rating on the right forearm during CPM	Significant CPM response with 45.5°C and 46.5°C No significant correlation between CPM and conditioning pain levels

(Nir et al., 2012)	48 healthy subjects (0/48) 25.8 (3.2)	Between-subjects different paradigms manipulating subjects experience of the CPM paradigms	Hot water bath (45.5°C) 1 min Non-dominant hand	Heat pain rating on dominant forearm during CPM	The perceived magnitude of the conditioning pain affected the CPM response. Lower perceived pain decreased the CPM response
(Liebano et al., 2013)	60 healthy subjects (30/30) 25.84 (5.54)	Between subject different paradigms	Hot water bath (46.5°C) 2 min Right hand + active TENS  Hot water bath (46.5°C) 2 min Right hand + placebo TENS	Pressure pain threshold and heat pain threshold at the left extensor muscle of the left forearm during CPM	Pressure pain and heat pain thresholds increased in both groups No difference between groups with CPM + active versus placebo TENS
(Honigman et al., 2013)	29 healthy subjects (14/15) 27.6 (3.4)	Within-subject different CPM paradigms	Hot water bath (46°C) 1 min Non-dominant arm	Heat pain ratings at the dominant forearm during CPM	<b>Men:</b> Significant CPM response. <b>Women:</b> No CPM response
(Wilson et al., 2013)	34 healthy subjects (34/0) 27 (7)	Within-subject intersession test-retest reliability for the CPM paradigm. Tested in different phases of the menstrual cycle	Hot water bath (46.5°C) 1 min Non-dominant hand	Heat pain rating at the dominant forearm during the CPM paradigm	The CPM paradigm significantly reduced heat pain rating during the conditioning stimulus The inter session test-retest reliability was poor
<b>Reference</b>	<b>Healthy Subjects</b>	<b>Control condition</b>	<b>Conditioning stimulus 'heat pain' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Price and McHaffie, 1988)	7 healthy subjects (0/7) 22-45 years of age	Different painful and non-painful CPM paradigms	Painful and non-painful heat stimulations 10 s Ankle or the abdominal region	Electrical stimuli inducing first and second pain on the ankle during CPM	Short-lasting CPM was produced by painful CPM paradigms Degree of inhibition was largest on second pain compared with first pain
(Defrin et al., 2010)	17 healthy subjects (9/8) 27 (6)	Within-subject control condition with non-painful conditioning	Heat pain at different body regions	Heat pain rating on the forearm during CPM	CPM during conditioning stimulus The CPM response increased as the distance between the test and conditioning sites increased. However, non-noxious conditioning stimulus also reduced pain ratings when performed at the contralateral leg
<b>Reference</b>	<b>Healthy Subjects</b>	<b>Control condition</b>	<b>Conditioning stimulus 'tourniquet test' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(France and Suchowiecki, 1999)	83 healthy subjects (44/39) 18.9 (1.2)	None	Tourniquet test ? Right forearm	Nociceptive flexion reflex (NFR) at the left sural nerve during and after CPM	Reduced NFR during and 5 min after CPM in both men and women
(France and Suchowiecki, 2001)	113 healthy subjects (59/54) 18.9 (1.4)	None	Tourniquet test ? Right forearm	Nociceptive flexion reflex (NFR) at the left sural nerve during and after CPM	Reduced NFR during and 5 min after CPM in both men and women. No difference between offspring of hypertensive individuals compared with offspring of normotensive individuals

(Tuveson et al., 2006)	18 healthy subjects (10/8) 36 (20-54)	None	Tourniquet test ? Left arm	Pressure pain threshold and pain rating as well as heat pain threshold and pain rating on both thighs during and after CPM	Significant CPM responses on pressure pain threshold on both sides during CPM The CPM effect on pressure pain and heat pain intensity differed between first and second assessed thigh, with inhibitory effects on the first assessed thigh and facilitated effects on the second Heat pain threshold was not affected during CPM
(Cathcart et al., 2009)	20 healthy subjects (11/9) 27 (6.4)	Within-subject intrasession test-retest reliability for the CPM paradigm	Tourniquet test ? Left arm	Temporal summation to pressure pain on the right middle finger and trapezius muscle during the CPM paradigm	Temporal summation was reduced at both sites during the CPM paradigm No difference was found between men and women The CPM paradigm showed high to excellent reliability on the trapezius and moderate at the finger
(Bartley and Rhudy, 2012)	41 healthy subjects (41/0) 31 (8.86)	Different menstrual phases	Tourniquet test ? Right forearm	Electrical pain rating and nociceptive flexion reflex (NFR) at sural nerve during and after CPM	Pain ratings reduced during and after CPM paradigm NFR reduced during CPM paradigm No difference between mid-follicular or late-luteal menstrual phases
<b>Reference</b>	<b>Healthy Subjects</b>	<b>Control condition</b>	<b>Conditioning stimulus 'mechanical pressure' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Sowman et al., 2011)	11 healthy subjects (0/11) 22.5 (18-26)	Within-subject painful and non-painful CPM paradigms	A compression device 15 min Head	Pressure pain threshold and tolerance on the face, neck, finger, arm and leg during and after CPM	Significant CPM response on pain threshold at the leg and face during the painful paradigm. No effect on pain tolerance
(Oono et al., 2011)	40 healthy subjects (20/20) 24.1 (18-33)	Different painful and non-painful CPM paradigms	Pressure pain ? Head	Pressure pain thresholds at the right masseter muscle and left forearm	The most painful paradigm was associated with the largest CPM response
(Oono et al., 2012)	40 healthy subjects (20/20) 24.1 (18-33)	Within-subject session with and without additional painful stimuli	Pressure pain ? Head	Pressure pain thresholds at the right masseter muscle and left forearm	CPM in both sessions Acute pain induced during CPM did not alter the CPM response
<b>Reference</b>	<b>Healthy Subjects</b>	<b>Control condition</b>	<b>Conditioning stimulus 'electrical stimulation' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Quiton and Greenspan, 2007)	62 healthy subjects (30/32) 26.0 /2.5)	Different painful and non-painful CPM paradigms	Electrical stimulations. Stimulations were distracting, stressful or painful ? Left median nerve	Heat pain ratings on right leg during CPM	CPM was produced in men and women after distracting and painful CPM paradigms Some gender differences were detected for the distraction CPM paradigm
(Vo and Drummond, 2014)	68 healthy subjects (41/27) 18-51 years of age	Between-subject low and high frequency CPM paradigms	Low and high frequency electrical stimulation ? Forearm	Pressure pain thresholds at the forehead after CPM	Pressure pain threshold was increased after both CPM paradigms

Reference	Healthy Subjects	Control condition	Conditioning stimulus 'hypertonic saline' Intensity Location	Pain sensitivity parameters	Main findings
(Graven-Nielsen et al., 1998)	14 healthy subjects (0/14) 24.6 (21-34)	Within-subject isotonic saline injection	Hypertonic saline injection ? Tibialis anterior muscle	Pressure pain threshold at the tibialis anterior muscle, the arm	Pressure pain threshold increased at the arm during hypertonic saline injection
Reference	Healthy Subjects	Control condition	Conditioning stimulus 'more than 1 CPM paradigm' Intensity Location	Pain sensitivity parameters	Main findings
(Svensson et al., 1999)	14 healthy subjects (0/14) 27.5 (3.1)	Between-subject different painful and non-painful CPM paradigms	Intramuscular injection of hypertonic saline ? Arm and leg  Non-painful vibration ? Arm and leg	Electrical pain rating at the left tibialis anterior muscle during CPM	Both painful and non-painful CPM paradigms reduced pain ratings during CPM
(Lautenbacher et al., 2002)	20 healthy subjects (0/20) 27.5 (4.4)	Within-subject different CPM paradigms	Hot water bath (46.5°C) 1 min Hand  Hot water bath (42°C) 1 min Hand  Painful and non-painful heat stimulations 5 min Forearm	Heat pain ratings at the cheeks during CPM	Painful water and painful heat produced CPM. Non painful conditioning stimuli produced some inhibitory effects
(Arendt-Nielsen et al., 2008)	20 healthy subjects (10/10) 22.6 (20-30)	Different CPM paradigms	Hypertonic saline injection ? Tibialis anterior muscle  Cold pressor test (1-2°C) 5 min Left hand  Both paradigms induced simultaneously	Pressure pain thresholds around both knees during and after CPM	Men had higher CPM response during hypertonic saline injection Men and women had CPM response during cold pressor test The increase was largest in men
(Granot et al., 2008)	31 healthy subjects (10/21) 24.6 (4.6)	Within-subject control condition with non-painful conditioning	Cold pressor test (12, 15, 18°C) 1 min Non-dominant hand  Hot water (44, 44.6°C) 1 min Non-dominant hand	Heat pain ratings during CPM	CPM after 12°C and 46.5°C Greater CPM in men compared with women No effect of age was found

(Wang et al., 2010)	24 healthy subjects (12/12) 27 (1.5)	Within-subject different CPM paradigms	Mechanical headband 10 min Head  Cold headband 10 min Head	Pressure pain thresholds at the head, neck, elbow and finger during CPM	Both CPM paradigms increased pressure pain thresholds in both men and women
(Streff et al., 2011)	24 healthy subjects (12/12) 25 (21-54)	Between-subject different CPM paradigms	Hot water bath (47°C) 2 min Non-dominant hand  Pinch pressure 2 min Inter-digital web on hand	Temporal summation to heat and pressure on the left middle finger after CPM	Both CPM paradigms produced CPM on temporal summation for heat and pressure. The paradigms were equally effective
(Lewis et al., 2012a)	20 healthy subjects (13/7) 25 (8)	Within-subject different CPM paradigms	Tourniquet test ? Left arm  Cold pressor test (12°C) 2 min Left hand	Pressure pain threshold at the medial joint line on right knee during and after CPM	Pressure pain threshold increased during and 10 min after both CPM paradigms Intersession ICC was good for cold pressor test but poor for tourniquet test
(Razavi et al., 2013)	21 healthy subjects (12/9) 30 (19-55)	Within-subject different CPM paradigms	Painful heat stimulations 10 s Left or right forearm  Tourniquet test ? Left arm	Heat pain threshold and pain rating Pressure pain threshold and pain rating Temporal summation of pressure pain Test stimuli were delivered to the right thigh	Significant CPM effects on heat pain threshold, heat pain rating and pressure pain threshold. No effect on temporal summation Different effect of intensity and duration of conditioning stimulus depending on pain test stimulus
(Zheng et al., 2014)	41 healthy subjects (21/20) 27 (6.8)	Within-subject different CPM paradigms  Subjects were divided into pain adapters and pain non- adapters for analysis of CPM	Heat pain stimulation 7 min Under the foot  Cold pressor test (1-4°C) 5 min Left hand	Pressure pain threshold and pain rating at both forearm and the right calf during and after the CPM paradigms	<b>Pain adapters:</b> CPM response during both CPM paradigms <b>Pain non-adapters:</b> CPM response during both CPM paradigms Pain non-adapters rated pain intensity during CPM higher compared with pain adapters No difference in CPM response between men and women was found



**Appendix 2:** A summary of clinical studies investigating conditioned pain modulation in human adults, primarily organized according to conditioning stimuli in the following order: ‘cold pressor test’, ‘hot water’, ‘heat pain’, ‘tourniquet test’, ‘mechanical pressure’, ‘electrical stimulation’ and secondly after year of publication.

Reference	Pain subjects	Controls or control condition	Conditioning stimulus 'cold pressor test' Intensity Location	Pain sensitivity parameters	Main findings
(Leffler et al., 2002b)	11 subjects with rheumatoid arthritis for less than 1 year (7/4) 47 (20-68)  10 subjects with rheumatoid arthritis for more than 5 years (9/1) 53 (37-67)	11 healthy subjects (7/4) 46 (21-68)  10 healthy subjects (9/1) 52 (40-66)	Cold pressor test (3-4°C) Until pain intensity reached 7/10 Left hand and forearm	Heat and cold detection thresholds, pain thresholds and pain ratings as well as pressure pain threshold on the right thigh during and after CPM	<b>Rheumatoid arthritis for less than 1 year:</b> Heat pain threshold increased, and heat pain rating decreased during CPM Pressure pain threshold increased during CPM <b>Rheumatoid arthritis for more than 5 years:</b> Pressure pain threshold increased during CPM <b>Healthy controls:</b> Heat pain threshold increased and heat pain rating decreased during CPM Pressure pain threshold increased during CPM
(Sandrini et al., 2006)	24 subjects with migraine (12/12) 36 (12)  17 subjects with chronic tension-type headache (9/8) 32 (12)	20 healthy subjects (14/6) 32 (7)	Cold pressor test (5-6°C) 5 min Hand	Nociceptive flexion reflex on the sural nerve and pain rating elicited by sural nerve stimulation during and after CPM	<b>Migraine patients:</b> NFR was facilitated during CPM <b>Chronic tension-type headache:</b> NFR was facilitated during CPM <b>Healthy controls:</b> Significant reduction in NFR during CPM
(Johannesson et al., 2007)	20 subjects with vestibulodynia (20/0) 24.9 (20-33)	40 healthy subjects (40/0) 24.0 (18-34)	Cold pressor test (3°C) 1 min Dominant hand	Pressure pain thresholds on the non-dominant arm and leg during and after CPM	<b>Vestibulodynia patients:</b> Significant CPM response during the cold pressor test <b>Healthy controls:</b> Significant CPM response during the cold pressor test
(Ram et al., 2008)	110 subjects with chronic pain (52/58) 49.5 (16.5)	Between subject differences. 73 patients received opioids and 37 received non-opioids analgesics	Cold pressor test (12°C) 30 s Right hand	Heat pain intensity at the left thenar eminence during and after CPM	<b>Patients on opioids:</b> CPM was present during and after, with larger effects during CPM <b>Patients not on opioids:</b> CPM was present during and after, with larger effects during CPM Non-opioid subjects had larger CPM compared with opioid subjects No significant difference between men and women in CPM
(King et al., 2009)	14 subjects with irritable bowel syndrome (14/0) 26.8 (8.5)  14 subjects with temporomandibular disorder (14/0) 31.0 (10.2)	28 healthy subjects (28/0) 28.6 (10.8)  Within-subject control condition with non-painful conditioning	Cold pressor test (avg. 12.0°C) 40 s Right foot	Heat pain rating on the left hand during CPM	<b>Irritable bowel syndrome:</b> No CPM response <b>Temporomandibular disorder:</b> Hyperalgesic response during CPM <b>Healthy controls:</b> Significant CPM response
(de Souza et al., 2009)	52 subjects with fibromyalgia (52/0) 50.1 (6.9)	10 healthy controls (10/0) 49.7 (5.7)	Cold pressor test (12°C) 2 min Right hand and forearm	Pain intensity during different CPM trials	<b>Fibromyalgia patients:</b> FM with depression had less CPM compared with FM without depression <b>Healthy controls:</b> CPM response The amplitude of CPM was significantly smaller in FM compared with controls

(Leonard et al., 2009)	14 subjects with classical trigeminal neuralgia (5/9) 63.6 (9.6)  14 subjects with atypical trigeminal neuralgia (5/9) 65.4 (13.6)	14 healthy subjects (7/7) 64.6 (9.4)	Cold pressor test (10°C) 5 min Right hand	Heat pain rating over trigeminal area after CPM	<b>Classical trigeminal neuralgia:</b> Heat pain rating decreased after CPM <b>Atypical trigeminal neuralgia:</b> No CPM response <b>Healthy controls:</b> Heat pain rating decreased after CPM
(Heymen et al., 2010)	27 subjects with irritable bowel syndrome (27/0) 28.9 years of age	21 healthy subjects (21/0) 28.5  Within-subject control condition with non-painful conditioning	Cold pressor test (12°C) 2 min Right hand	Heat pain rating at the left hand during CPM	<b>Irritable bowel syndrome:</b> No CPM with painful paradigm. Reduced pain ratings after non-painful paradigm <b>Healthy controls:</b> Significant CPM with 12°C CPM paradigm. Reduced pain ratings after non-painful paradigm
(Olesen et al., 2010)	25 subjects with chronic pancreatitis (9/16) 52 (12)	15 healthy subjects (7/8) 40 (10)	Cold pressor test (2°C) 3 min Right hand	Pressure pain threshold at the quadriceps muscle after CPM	<b>Chronic pancreatitis:</b> Reduced CPM <b>Healthy controls:</b> CPM was impaired in CP compared with healthy subjects. There was no correlation between CPM and age in healthy subjects or CP subjects
(Normand et al., 2011)	29 subjects with fibromyalgia (22/7) 48.6 (7.1)  26 subjects with major depressive disorder (16/10) 46.5 (9.0)	40 healthy subjects (24/16) 45.2 (6.0)	Cold pressor test (12°C) 2 min Right arm and hand	Temporal summation of heat on the left forearm after CPM	<b>Fibromyalgia patients:</b> FM presented a significant deficiency of CPM compared to healthy subjects
(Roosink et al., 2011)	19 subjects with post-stroke shoulder pain (9/10) 57 (7)	29 subjects with pain-free stroke patients (8/21) 61 (10)  23 healthy subjects (13/10) 56 (7)	Cold pressor test (0.5°C) Up to 3 min Unaffected hand	Pressure pain and electrical pain threshold at both deltoids after CPM	<b>Post-stroke shoulder pain:</b> significant increase in pressure pain and electrical pain thresholds after cold pressor test <b>Pain-free stroke patients:</b> significant increase in pressure pain and electrical pain thresholds after cold pressor test <b>Healthy controls:</b> significant increase in pressure pain and electrical pain thresholds after cold pressor test
(Chua et al., 2011)	17 subjects with neck pain and cervicogenic headache (5/12) 50.6 (11.1)  10 subjects with neck pain (4/6) 54.5 (7.9)	27 healthy controls (8/19) 52.1 (10.4)	Cold pressor test (?°C) 3 min Dominant hand	Electrical pain tolerance on the thigh and forehead	<b>Neck pain and cervicogenic headache:</b> CPM response both in painful and non-painful areas <b>Neck pain:</b> CPM response both in painful and non-painful areas <b>Healthy controls:</b> CPM response
(Olesen et al., 2012)	62 subjects with chronic pancreatitis (24/38) 53 (11)	2 sessions with CPM to test reliability	Cold pressor test (2°C) 3 min Right hand	Pressure pain threshold at the quadriceps muscle after CPM	CPM was present at both sessions, but the test-retest reliability was poor

(Paul-Savoie et al., 2012)	50 subjects with fibromyalgia (50/0) 49.8 (10.5)	39 healthy subjects (39/0) 50 (7.4)	Cold pressor test (12°C) 2 min Right arm and hand	Heat pain rating on the left forearm after CPM.	<b>Fibromyalgia patients:</b> CPM was impaired in FM compared with healthy subjects. CPM was negatively correlated to sleep quality. There was no correlation between CPM and age.
(Sutton et al., 2012)	23 subjects with provoked vestibulodynia (23/0) 23.78 (5.04)	23 healthy subjects (23/0) 26.52 (8.56)	Cold pressor test (5°C) 18-? s Non-dominant hand	Heat pain tolerance and temporal summation to heat pain on the dominant forearm during and after CPM	<b>Provoked vestibulodynia:</b> CPM response on both pain tolerance and temporal summation <b>Healthy controls:</b> CPM response on both pain tolerance and temporal summation
(Valencia et al., 2012)	58 subjects with shoulder pain (17/41) 32.34 (11.55)	56 healthy subjects (16/40) 28.71 (8.44)	Cold pressor test (8°C) 1 min Hand	Heat pain intensity at the thenar eminence on the nonsurgical or non-dominant hand after CPM	<b>Shoulder pain:</b> Significant CPM after cold pressor test <b>Healthy controls:</b> Significant CPM after cold pressor test
(Garrett et al., 2013)	30 subjects with temporomandibular disorder (30/0) 36.3 (13.4)	30 healthy subjects (30/0) 36.7 (11.8) Within-subject control condition with non-painful conditioning.	Cold pressor test (5-16.5°C) 1 min Right hand	Temporal summation to pressure pain at the fingers	<b>Temporomandibular disorder:</b> reduction in temporal summation during cold pressor test <b>Healthy controls:</b> reduction in temporal summation during cold pressor test
(Valencia et al., 2013)	134 subjects with shoulder pain (47/87) 43.83 (17.8)	190 healthy subjects (116/74) 23.02 (6.04) Within-subject intrasession and intersession test-retest reliability for the CPM paradigm.	Cold pressor test (8°C) 1 min Hand	Heat pain intensity at the thenar eminence on the nonsurgical or non-dominant hand after CPM	<b>Shoulder pain:</b> Significant CPM response <b>Healthy controls:</b> Significant CPM response Both groups showed comparable CPM responses. CPM was relative stable between sessions, but not within sessions. CPM was not affected by change in pain intensity
(Edwards et al., 2013)	37 subjects with persistent postoperative pain after lumpectomy (37/0) 57.1 (8.4)	34 subjects without pain after lumpectomy (34/0) 59.0 (11.1)	Cold pressor test (4°C) 30 s Right hand	Pressure pain thresholds at both trapezius muscles during CPM	<b>Postoperative pain after lumpectomy:</b> Reduced CPM and enhanced temporal summation <b>No pain after lumpectomy:</b> Women without pain had larger CPM response compared with women with pain
(Martel et al., 2013)	55 subjects with chronic back pain (35/20) 49.0 (9.5)	2 different sessions of CPM	Cold pressor test (4°C) 1 min Left hand	Pressure pain threshold on the right trapezius muscle during CPM	Cold pressor test produced CPM in both men and women. The CPM response was significantly larger in men. The reliability of the CPM response in women were good
(Nahman-Averbuch et al., 2013)	26 subjects with migraine (26/0) 35.3 (11.6)	35 healthy subjects (36/0) 29.3 (9.3)	Repetitive cold pressor tests (10°C) 1 min Right foot	Heat pain rating at the lower left leg during and after CPM	<b>Migraine:</b> Significant CPM response, but the response decreased after repeated cold pressor tests <b>Healthy controls:</b> Significant CPM response
(Schliessbach et al., 2013)	464 subjects with chronic pain (Unknown) Unknown	None	Cold pressor test (1.5°C) 2 min Hand	Pressure pain tolerance at the second toe after CPM	In general CPM was present in pain patients 23.7% of the subjects had no CPM response
(Niesters et al., 2013)	10 subjects with chronic peripheral neuropathic pain (8/2) 54.4 (4.2)	CPM was performed on 3 different days with ketamine, morphine or placebo.	Cold pressor test (6-18°C corresponding to a VAS=30/100) 1 min Foot and lower leg	Heat pain intensity at the dominant forearm during CPM	No significant CPM response was found After the three treatments, a significant CPM response was found with no difference between the three treatments The magnitude of CPM correlated positively with pain relief from the treatments

(Bouwense et al., 2013)	48 subjects with chronic pancreatitis (13/35) 49 (42-52)	15 healthy controls (7/8) 38 (35-49)	Cold pressor test (1°C) 2 min Dominant hand	Electrical pain threshold and pain tolerance on neck and knee	<b>Chronic pancreatitis:</b> Reduced CPM <b>Healthy controls:</b> Healthy controls exhibited a significantly greater CPM response compared with CP patients
(Ng et al., 2014)	30 subjects with chronic whiplash associated disorder (14/16) 44.3 (9.6)	30 healthy subjects (14/16) 44.1 (10.2)	Cold pressor test (2°C) 1 min Non-dominant hand	Heat pain threshold at the midcervical spine after CPM	<b>Chronic whiplash:</b> Reduced CPM <b>Healthy controls:</b> CPM was significantly larger in healthy subjects compared with WAD
(Chalaye et al., 2014)	22 subjects with fibromyalgia (22/0) 49.3 (2.0)	25 healthy controls (25/0) 48.4 (1.7)	Cold pressor test (12°C) 2 min Right hand and forearm	Heat pain rating on left forearm after CPM	<b>Fibromyalgia patients:</b> Pain ratings decreased after CPM paradigm <b>Healthy controls:</b> Pain ratings decreased after CPM paradigm The decrease was significantly larger in controls
(Jarrett et al., 2014)	20 subjects with irritable bowel syndrome (20/0) 27.4 (6.6)	20 Healthy subjects (20/0) 27.6 (5.5)	Cold pressor test (12°C) 1 min Non-dominant hand	Heat pain rating at the dominant arm during CPM	<b>Irritable bowel syndrome:</b> Significant CPM response <b>Healthy controls:</b> Significant CPM response
(Ness et al., 2014)	14 subjects with bladder pain syndrome (14/0) (22-56 years old)	14 healthy subjects (14/0) (22-56 years old) Within-subject control with non-painful water.	Cold pressor test (0-5°C) 70 s Left hand	Heat pain threshold, tolerance and rating at the right ankle during and after CPM	<b>Bladder pain syndrome:</b> Heat pain tolerance decreased during CPM paradigm <b>Healthy controls:</b> Heat pain tolerance increased during CPM paradigm
(Grosen et al., 2014)	42 patients undergoing surgery for funnel chest (0/42) 19 years of age	None	Cold pressor test (1°C) 2 min Non-dominant hand	Pressure pain threshold at dominant quadriceps muscle	Significant CPM response CPM predicted morphine consumption postoperatively
(Pickering et al., 2014)	9 subjects with post herpetic neuralgia (4/5) 67 (4)	9 healthy subjects (4/5) 65 (5)	Cold pressor test (8°C) 2 min Hand	Heat pain intensity on volar forearm after CPM	<b>Post herpetic neuralgia:</b> Reduced CPM in patients compared with controls
(Smits et al., 2014)	24 subjects with cold intolerance after nerve lesion or amputation (8/16) 45 (14.4)	14 healthy subjects (6/8) 32 (11.4)	Cold pressor test (1.8°C) 30-180 s Hand	Pressure pain threshold at the affected site	<b>Cold intolerance after nerve lesion or amputation:</b> significant CPM response <b>Healthy controls:</b> Significant CPM response, The response was significantly larger in the healthy subjects
<b>Reference</b>	<b>Pain subjects</b>	<b>Controls or control condition</b>	<b>Conditioning stimulus 'hot water' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Staud et al., 2003b)	11 subjects with fibromyalgia (11/0) 52.9 (6.3)	22 healthy subjects (22/0) 35.8 (12) 11 healthy subjects (0/11) 40.2 (16.8)	Hot water test (46°C) 16 s Left hand	Temporal summation of heat at the right hand.	Men had a significant CPM response on temporal summation. Women and FM subjects had no CPM response.
(Meeus et al., 2008)	31 subjects with chronic fatigue syndrome and chronic pain (21/10) 44.8 (8.7)	31 healthy subjects (21/10) 44.2 (10.1)	Hot water test (46°C) 2 min a gradual spatial immersion paradigm	Pain ratings during cold pressor tests	<b>Chronic fatigue syndrome:</b> Significant CPM response <b>Healthy controls:</b> Significant CPM response

(Nahman-Averbuch et al., 2011)	27 subjects with neuropathy after chemotherapy (20/7) 56.6 (7.9)	None	Hot water test (46.5°C) 1 min Left hand	Heat pain threshold at the right forearm during CPM	Hot water produced CPM in pain patients CPM was inversely correlated with clinical pain intensity
(Defrin et al., 2014)	60 ex-soldiers (torture survivors) (0/60) 57.5 (3)	44 ex-soldiers (0/44) 58.8 (4)	Hot water test (46°C) 30 s Hand	Heat rating at the forearm during CPM	Larger CPM in subjects without pain compared with subjects with pain Pain intensity correlated with CPM
<b>Reference</b>	<b>Pain subjects</b>	<b>Controls or control condition</b>	<b>Conditioning stimulus 'heat pain' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Lautenbacher and Rollman, 1997)	26 subjects with fibromyalgia (26/0) 44.2 (11.8)	26 healthy subjects (26/0) 42.7 (8.2)	Painful and non-painful heat stimulations 5 min Under the foot	Electrical detection and pain threshold at the inner forearm	<b>Fibromyalgia patients:</b> No CPM response <b>Healthy controls:</b> Painful and non-painful heat increased electrical pain threshold
(Pielsticker et al., 2005)	29 subjects with chronic tension-type headache (13/16) 37.1 (13.5)	25 healthy subjects (11/14) 38.5 (12.9) Within-subject different painful and non-painful CPM paradigms.	Painful and non-painful heat stimulations 5 min Thigh	Electrical detection and pain thresholds at the forearm and temple region after CPM	<b>Chronic tension-type headache:</b> Significant CPM effect after the painful CPM paradigm <b>Healthy controls:</b> CPM was significantly larger in healthy subjects compared with CTTH
(Teepker et al., 2014)	32 subjects with migraine (32/0) 28.9 (8.8)	20 healthy subjects (20/0) 27.1 (6.6)	Painful and non-painful heat stimulations 5 min Left forearm	Electrical pain threshold to the right forearm during CPM	<b>Migraine patients:</b> Significant CPM response <b>Healthy controls:</b> Significant CPM response
<b>Reference</b>	<b>Pain subjects</b>	<b>Controls or control condition</b>	<b>Conditioning stimulus 'tourniquet test' Intensity Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Kosek and Hansson, 1997)	10 subjects with fibromyalgia (10/0) 41.4 (28-55)	10 healthy subjects (10/0) 43.6 (32-63)	Tourniquet test ? Left forearm	Heat and cold detection thresholds and pain thresholds as well as pressure pain threshold on the right quadriceps muscle during and after CPM	<b>Fibromyalgia patients:</b> Heat pain rating was decreased after CPM <b>Healthy controls:</b> Pressure pain threshold increased during. Heat pain rating was decreased after CPM
(Kosek and Ordeberg, 2000b)	15 subjects with painful osteoarthritis of the hip (6/9) 52 (29-66)	15 healthy subjects (6/9) 50 (30-67)  Both groups were reassessed 6-14 month after OA surgery	Tourniquet test ? Forearm ipsilateral to painful hip	Heat and cold detection thresholds and pain thresholds as well as pressure pain threshold on the painful hip and contralateral hip during and after CPM	<b>Painful osteoarthritis of the hip:</b> Before surgery: No CPM response After surgery: Significant CPM response <b>Healthy controls:</b> Significant CPM at both time of assessment.
(Leffler et al., 2002b)	10 subjects with long term trapezius myalgia (7/3) 38 (24-55)	10 healthy subjects (7/3) 38 (23-54)	Tourniquet test ? Left arm	Heat and cold detection thresholds and pain thresholds as well as pressure pain threshold on the right thigh during and after CPM	<b>Trapezius myalgia:</b> Heat pain and pressure pain threshold increased during CPM <b>Healthy controls:</b> Heat pain and pressure pain threshold increased during CPM

(Tuveson et al., 2007)	15 subjects with painful peripheral neuropathy (8/7) 42 (25-60)	15 Healthy subjects (8/7) 42 (25-59)	Tourniquet test ? Left arm	Pain intensity for ongoing pain. Pressure pain threshold and pain rating as well as heat pain threshold and pain rating on pain free thigh or arm during and after CPM	<b>Painful peripheral neuropathy:</b> The CPM paradigm reduced ongoing neuropathic pain Significant CPM response on pressure pain <b>Healthy controls:</b> Significant CPM response on pressure pain and heat pain
(Tuveson et al., 2009)	10 subjects with central post stroke pain (4/6) 60 (38-74)	10 healthy subjects (4/6) 59 (38-72)	Tourniquet test ? Left arm	Pain intensity for ongoing pain. Pressure pain threshold and pain rating as well as heat pain threshold and pain rating on pain free thigh or arm during and after CPM	<b>Central post stroke pain:</b> no change in ongoing pain during CPM. CPM response to pressure pain thresholds <b>Healthy controls:</b> CPM response to pressure pain thresholds
(Cathcart et al., 2010)	46 subjects with tension-type headache (30/16) 27.1 (7.4)	25 healthy controls (16/9) 27.1 (7.4)	Tourniquet test ? Left forearm	Pressure pain threshold and temporal summation at the right middle finger and trapezius muscle	<b>Tension-type headache:</b> Increased temporal summation and decreased CPM in headache patients compared with healthy controls
(Skou et al., 2013)	20 subjects with knee pain after revision of total knee arthroplasty (14/6) 61.5 (1.8)	20 subjects without knee pain after total knee arthroplasty (8/12) 65.7 (1.3)	Tourniquet test ? Left arm	Pressure pain threshold at the knee, tibialis anterior muscle and forearm during and after CPM	<b>Knee pain after knee revision:</b> Decreased pain threshold during CPM paradigm <b>No pain after knee revision:</b> Significant CPM response during the CPM paradigm
(Meeus et al., 2013)	15 subjects with chronic whiplash associated disorder (12/3) 41.63 (11.45)	16 healthy subjects (10/6) 40.88 (13.38)	Tourniquet test ? Left arm	Temporal summation of pressure pain on the right hand middle finger during CPM.	<b>Chronic whiplash:</b> <b>Healthy controls:</b> Comparable CPM responses.
(Daenen et al., 2013),  (Daenen et al., 2014)	30 subjects with acute whiplash associated disorder (14/16) 43.3 (10.98)  35 subjects with chronic WAD (26/9) 43.8 (9.59)	31 healthy controls (24/7) 43.19 (16.11)	Tourniquet test ? Left forearm	Pressure pain temporal summation at the right trapezius and the right quadriceps muscle during CPM	<b>Acute whiplash:</b> Significant CPM response <b>Chronic whiplash:</b> No CPM response <b>Healthy controls:</b> Significant CPM response The effect was largest in healthy controls
<b>Reference</b>	<b>Pain subjects</b>	<b>Controls or control condition</b>	<b>Conditioning stimulus 'mechanical pressure'</b> <b>Intensity</b> <b>Location</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Oono et al., 2014)	16 subjects with temporomandibular disorder (14/2) 43.0 (4.0)	16 healthy subjects (14/2) 38.9 (3.4)	Pressure pain (VAS = 5) 18 min Head	Pressure pain thresholds and tolerance at TMJ, masseter and forearm during and after CPM paradigm	<b>Temporomandibular disorder:</b> Pain thresholds increased at the forearm <b>Healthy controls:</b> Pain thresholds and pain tolerance increased at all assessment sites No significant correlation between CPM response and pain intensity or pain duration

Reference	Pain subjects	Controls or control condition	Conditioning stimulus <i>'electrical pain'</i> Intensity Location	Pain sensitivity parameters	Main findings
(Wilder-Smith et al., 2013)	34 subjects with functional dyspepsia (19/15) 39.7 (21-70)	42 healthy subjects (25/17) 39.1	Electrical pain ? Hand	Heat pain intensity at the foot during the CPM paradigm	<b>Functional dyspepsia:</b> No CPM response <b>Healthy controls:</b> Significant CPM response However, there was no between group difference in CPM

**Appendix 3:** A summary of experimental studies examining exercise-induced hypoalgesia in healthy human adults, primarily organized according to exercise modality in the following order: ‘aerobic’, ‘aerobic and isometric’, ‘isometric’, ‘resistance’, ‘mixed’, ‘passive movements’ and secondly after year of publication.

Reference	Subjects Total number Gender (F/M) Age (SD) or age range	Exercise protocol ‘aerobic’ Intensity Duration	Control condition	Pain sensitivity parameters	Main findings
(Black et al., 1979)	1 healthy subject (Unknown) Unknown	Aerobic running Unknown 40 min	Within-subject naloxone versus saline condition	Pain thresholds and pain ratings during ischemic arm pain test	Increased pain thresholds after exercise Naloxone did not affect the EIH response
(Haier et al., 1981)	15 healthy subjects (6/9) 27.3 (unknown)	Aerobic running Self-set pace 1 mile	Within-subject naloxone versus saline condition	Pressure pain threshold on the index finger	Pressure pain was increased after exercise in both the naloxone and the saline condition
(Vecchiet et al., 1984)	10 healthy subjects (0/10) 20-30 years of age	Aerobic bicycling 70 % of max HR 30 min	Within-subject rest condition with either 10% or 20% sodium chloride injections after exercise and after rest (4 conditions)	Pain intensities after injections	Increased pain ratings (hyperalgesia) to injections after exercise compared with rest
(Janal et al., 1984)	12 healthy subjects (0/12) 38.8 (12.1)	Aerobic running 85 % of VO <sub>2max</sub> 44 min	Within-subject naloxone versus saline condition	Heat withdrawal latencies and pain intensity Pain rating during ischemic pain test Pain rating and time tolerance during cold pressor test	Reduced pain ratings to thermal and ischemic pain following exercise. Naloxone reduced the hypoalgesic response to ischemic but not thermal pain
(Kemppainen et al., 1985)	7 healthy subjects (0/7) 22-46 years of age	Aerobic bicycling Increasing workload from 100-300 watt 15-30 min	None	Electrical dental pain threshold and thermal limen at the hand, forearm and leg	Dental pain threshold and thermal limen increased during and following the exercise session. Dental pain threshold increased from 250W
(Olausson et al., 1986)	11 healthy subjects (3/8) 21-40	Aerobic bicycling (Leg and arm) Heart rate 150 beats/min 20 min	Within-subject control TENS protocol	Electrical dental pain threshold	Dental pain threshold increased during and following both exercise sessions
(Kemppainen et al., 1986)	6 healthy subjects (0/6) 20-40 years	Aerobic bicycling Increasing workload from 200-300 watt Unknown	Within-subject cyproheptadine versus placebo condition	Electrical dental pain threshold	Increase in threshold with increasing exercise intensity. No effect of cyproheptadine on the EIH response
(Kemppainen et al., 1990)	6 healthy subjects (0/6) 24-36 years of age	Aerobic bicycling Increasing workload from 100-200 watt Unknown	Within-subject dexamethasone versus saline condition	Electrical dental pain threshold	Pain threshold was increased during and 30 min after exercise, but less in the dexamethasone condition compared with the saline condition
(Droste et al., 1991)	10 healthy subjects (0/10) 20-46 years of age	Aerobic bicycling Increasing workload from 100-250 watt Until exhaustion	Within-subject naloxone versus saline condition	Electrical dental pain and fingertip pain threshold	Increase in thresholds during and immediately after exercise No effect of naloxone on EIH
(Padawer and Levine, 1992)	91 healthy subjects (Unknown) Unknown	Aerobic bicycling 1:50 % APMHR 2:70 % APMHR 20 min	Between subject non-stressful coloring task	Pain ratings during 3 min cold pressor test with non-dominant hand	No EIH effects after exercise conditions compared with controls
(Guieu et al., 1992)	6 healthy subjects (athletes) (0/6) 18-27 years of age	Aerobic bicycling 200 watt 20 min	None	Nociceptive flexion reflex threshold at the biceps femoris	The threshold of the NFR increased following the exercise session



(Fuller and Robinson, 1993)	22 healthy subjects (endurance athletes) (0/22) 27-56 years of age	Aerobic running Unknown 6 miles (30 min)	Within subject rest condition	Heat pain and non-pain ratings applied to the volar site of the forearm	Heat non-pain ratings decreased after exercise, but heat pain ratings were not affected
(Gurevich et al., 1994)	60 healthy subjects (0/60) 22.9 (18-44 years of age)	Aerobic step exercise 63 % $VO_{2max}$ 12 min	Between subject non-stressful completion of two questionnaires	Pressure pain rating and pain tolerance at the dorsal surface of the dominant index finger	Pain tolerance increased and pain ratings decreased following exercise
(Koltyn et al., 1996)	16 healthy subjects (2/14) 29 (8)	Aerobic bicycling 75 % $VO_{2max}$ 30 min	Within-subject rest condition	Pressure pain threshold and pain rating on the right forefinger	Pain threshold increased and pain ratings decreased following exercise
(Øktedalen et al., 2001)	20 healthy trained subjects (0/20) 26-48 years of age  9 healthy untrained subjects (0/9) 38 (28-46)	Aerobic running $VO_{2max}$ test Unknown	Between subject comparison	Pain rating during ischemic pain test	Pain ratings decreased after exercise condition. No difference between trained and untrained in the EIH response
(Sternberg et al., 2001)	41 healthy college athletes (22/19) Unknown 22 healthy college non-athletes (11/11) Unknown	Subjects randomized to 3 experiments: 1: Sedentary videogame competition. 2: Track meet 3: Exercise condition with aerobic running at 85 % HR for 10 min.	Between subject comparison	Pain ratings during 90 s cold pressor test with non-dominant hand and heat pain thresholds on the fingertips and forearm	Track meet reduced cold pressor pain ratings. (Men > women) Athletes reduced pain ratings at baseline compared to non-athletes No difference between athletes and non-athletes in EIH Track meet and exercise run caused heat hyperalgesia
(Dannecker et al., 2002)	23 healthy subjects (11/12) Unknown	Aerobic bicycling 80 % of $VO_{2max}$ 30 min	Between subject comparison 27 subjects in video control group (15/12)	Pressure pain threshold at the biceps brachii after DOMS was induced 48 hours prior to exercise condition and video condition	No significant EIH response after exercise
(Hoffman et al., 2004)	12 healthy subjects (7/5) 32 (9)	Aerobic treadmill 1: 75 % $VO_{2max}$ for 10 min 2: 75 % $VO_{2max}$ for 30 min 3: 50 % $VO_{2max}$ for 30 min	Within-subject quiet rest control	Pressure pain ratings at the dorsal surface on the non-dominant index finger	Pain ratings were decreased 5 min after the exercise condition with 75 % $VO_{2max}$ for 30 min only. No EIH response 30 min after exercise
(Drury et al., 2005)	17 healthy subjects (17/0) 20.5 (0.9)	Aerobic bicycling Increasing workload from 30 watt - $VO_{2peak}$ Unknown	Within subject familiarization and reliability test	Electrical pain threshold and pain tolerance at the right index finger	Pain threshold increased at $VO_{2peak}$ . Pain tolerance was increased at 120 watt and $VO_{2peak}$ and 10 min after exercise. Largest effect at $VO_{2peak}$ .
(Ruble et al., 2005)	14 healthy subjects (8/6) 34 (3)	Aerobic treadmill 75 % $VO_{2max}$ 30 min	Within subject rest condition	Hot and cold pain thresholds and pain ratings on the thenar eminence of the non-dominant hand	No EIH effects on thermal pain thresholds or pain ratings 5 min and 30 min after exercise

(Hoffman et al., 2007)	21 healthy athletes (5/16) 46 (7)  9 healthy controls (1/8) 44 (11)	Aerobic running Unknown 100 mile	Between subject controls	Pressure pain ratings on the dorsal surface on the non-dominant index finger	Reduced pain ratings in the fastest runners only
(Wonders and Drury, 2011)	27 healthy subjects (0/27) 21.8 (Unknown)	Aerobic treadmill exercise 2 conditions near anaerobic threshold (HR monitored) 30 min	None	Pain threshold for cold pressor test and pain rating at the end of up to 5 min cold pressor test with non-dominant hand	Pain threshold for cold pressor test was increased after 30 min of exercise and 15 min after exercise
(Pokhrel et al., 2013)	41 healthy subjects (18/23) 18-25 years of age	Aerobic bicycling 70-75 % of $VO_{2max}$ 6 min	None	Pain threshold and pain tolerance during cold pressor test on non-dominant hand	Pain threshold and tolerance increased significantly after exercise in both men and women
(Ellingson et al., 2014)	21 healthy subjects (21/0) 30.6 (6.2)	Aerobic bicycling 1: 60 watt with painful cuffs on thighs 2: 60 watt without cuffs 10 min	Within subject rest condition	Heat pain ratings applied to the palm of the right hand	Heat pain ratings decreased during both exercise conditions. The size of the hypoalgesic response was greater following painful exercise than non-painful exercise
(Kodesh and Weissman-Fogel, 2014)	29 healthy subjects (0/29) 27.4 (2.7)	Aerobic bicycling continuous and interval conditions: 1: Continuous 70 % HR for 24 min 2: Interval 85 % HR for 4x4 min	Between subject different exercise protocols	Heat pain threshold and pain intensity and pressure pain threshold on non-dominant hand after exercise	Heat pain intensity was reduced after interval exercise. No effect on pressure or heat pain thresholds
(Naugle et al., 2014b)	27 healthy subjects (15/12) 21.78 (4.14)	Aerobic bicycling 1: 70 % HR reserve 2: 50-55 % of HR reserve 20 min	Within subject rest condition	Pressure pain threshold Suprathreshold pressure pain intensity Heat pain intensity Temporal summation to heat pain. Applied to both forearms	Pressure pain thresholds increased after high intensity exercise Heat pain intensity was reduced after both exercise conditions Reduced temporal summation after both exercise conditions
<b>Reference</b>	<b>Subjects Total number Gender (F/M) Age (SD) or age range</b>	<b>Exercise protocol 'aerobic and isometric' Intensity Duration</b>	<b>Control condition</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Drury et al., 2004)	12 healthy subjects (0/12) 20.5 (0.9)	1: Aerobic treadmill 65-75 % HR reserve 7 min 2: Isometric muscle contraction with hand dynamometer 100 % MVC every 2 <sup>nd</sup> s for 1 min	Within subject rest condition	Pressure pain thresholds applied to the forearm	Pressure pain was increased after both aerobic and isometric exercise compared with rest The effect after aerobic exercise was larger compared with the isometric exercise condition
<b>Reference</b>	<b>Subjects Total number Gender (F/M) Age (SD) or age range</b>	<b>Exercise protocol 'isometric' Intensity Duration</b>	<b>Control condition</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Kosek and Ekholm, 1995)	14 healthy subjects (14/0) 36.8 (Unknown) 20-54 years of age	Isometric muscle contraction m. quadriceps femoris 21 % MVC Until task failure	None	Pressure pain thresholds at the m. quadriceps femoris	Pain threshold increased during, and 5 min after the exercise condition

(Koltyn et al., 2001)	31 healthy subjects (16/15) 22	Isometric muscle contraction with hand dynamometer 1: Maximal (2 x 5 s.) and 2: Sustained 40-50 % MVC 2 min	Within-subject different intensities	Pressure pain thresholds and pain ratings at the right forefinger	Pain threshold increased and pain ratings decreased in women after maximal and sub-maximal contractions Pain ratings decreased in men after submaximal contractions
(Kosek and Lundberg, 2003)	24 healthy subjects (12/12) 20-27 years of age	Isometric muscle contractions m. quadriceps (1 kg) Isometric muscle contractions m. infraspinatus (0.5 kg). Until exhaustion (avg. 12 min)	None	Pressure pain threshold dominant and non-dominant m. quadriceps femoris and m. infraspinatus	Pain thresholds increased at both sites during and following contractions
(Koltyn and Umeda, 2007)	40 healthy subjects (40/0) 18-22 years of age	Isometric muscle contractions with hand dynamometer 40-50 % MVC 2 min	Within-subject opposite hand used as control	Pressure pain thresholds and pain intensity on the forefinger of both hands	Pain thresholds increased and pain ratings decreased bilaterally after the exercise session
(Ring et al., 2008)	24 healthy subjects (0/24) 21(3)	Isometric muscle contraction with hand dynamometer. 1: 1 % MVC 2: 15 % MVC 3: 25 % MVC Unknown	1 % MVC was used as within-subject control condition	Pain rating after electrical stimulation of the sural nerve. Nociceptive flexion reflex threshold at the sural nerve	Pain ratings decreased following 15 % and 25 % MVC No effect on NFR
(Bement et al., 2008)	40 healthy subjects (20/20) 18-42 years of age	Isometric muscle contractions with the elbow flexor muscles (2 experiments). 1: 3 maximum contractions 2: 3 sustained contractions 25 % MVC until task failure 3: 3 sustained contractions 25 % MVC for 2 min 4: 3 sustained contractions 80 % MVC until task failure	Within subject different exercise protocols + reliability experiment (quiet rest) for PPT measurement	Pressure pain threshold and pain rating on the right index finger	Pain threshold increased and pain ratings decreased following the 3 maximum contractions Pain threshold increased and pain ratings decreased following the 25 % MVC until task failure
(Umeda et al., 2009)	23 healthy subjects (23/0) 18-30 years of age	Isometric muscle contraction with hand dynamometer 1: 25 % MVC for 1 min 2: 25 % MVC for 3 min	Within-subject rest control	Pressure pain threshold and pain rating to right forefinger	No EIH effects compared with rest
(Bement et al., 2009)	20 healthy subjects (20/0) 21 (1.0)	Isometric muscle contraction with elbow flexor muscles 25 % MVC Until task failure	Two different menstrual cycle phases	Pressure pain threshold and pain ratings on the right index finger	Pain threshold increased and pain ratings decreased following exercise in both menstrual phases
(Umeda et al., 2010)	50 healthy subjects (25/25) 18-40 years	Isometric muscle contraction with hand dynamometer 25 % MVC 1: 1 min 2: 3 min 3: 5 min	Within subject different durations as control	Pressure pain threshold and pain intensity to the forefinger of the dominant hand	Pain threshold increased and pain ratings decreased following all 3 exercise durations. No dose response pattern
(Koltyn et al., 2013)	88 healthy subjects (divided into two experiments) (44/44) 18-20 years of age	Isometric muscle contraction with hand dynamometer 1: 40 % MVC until exhaustion 2: 25 % MVC for 3 min	None	Pain ratings during increasing heat stimuli delivered to the thenar eminence of the dominant hand (temporal summation)	Reduction in temporal summation after both exercise conditions

(Paris et al., 2013)	38 healthy subjects (19/19) 18-43 years of age	Isometric muscle contraction with pinch grip by index finger and thumb on the right hand 25 % MVC 15 s	Within subject working memory task	Heat pain and heat non-pain ratings applied to both hands	Heat non-pain ratings decreased during exercise
(Naugle et al., 2014)	27 healthy young subjects (15/12) Unknown	Isometric muscle contraction with hand dynamometer 25 % MVC 3 min	Within subject rest condition	Pressure pain threshold Suprathreshold pressure pain intensity Heat pain intensity Temporal summation to heat pain Applied to both forearms	Pressure pain thresholds increased after exercise Heat pain intensity was reduced after exercise in women only Reduced temporal summation after exercise
(Misra et al., 2014)	42 healthy subjects (21/21) 18-45 years of age	Isometric muscle contraction with pinch grip by index finger and thumb on the right hand. 1: 5 % MVC 2: 25 % MVC 3: 50 % MVC 15 s	Within subject different exercise conditions	Heat pain ratings applied to both hands	Dose-response effect with larger EIH with more intense contractions
(Bement et al., 2014)	26 healthy subjects (13/13) 20.3 (0.8)	Isometric muscle contraction with elbow flexor muscles 25 % MVC Until fatigue	Within-subject rest condition	Pressure pain threshold and pain rating on the right index finger after exercise	Pressure pain threshold increased after exercise in men and women Pain rating decreased after exercise in men
(Lemley et al., 2014a)	24 healthy subjects (12/12) 72.2 (6.3)	Isometric muscle contraction with elbow flexor muscles 1: 3 maximal contractions 2: 25 % MVC for 2 min 3: 25 % MVC until fatigue	Within subject different exercise protocols and quiet rest control condition	Pressure pain threshold and pain rating on the right index finger after exercise	Pressure pain threshold increased after all exercise conditions in older men and women Pain rating decreased after exercise in women
(Lemley et al., 2014b)	20 healthy young subjects (10/10) Unknown  19 healthy old subjects (9/10) Unknown	Isometric muscle contraction with elbow flexor muscles 25 % MVC Until fatigue	Exercise and CPM protocol (control vs ice water)	Pressure pain intensity at the right index finger (Lucite edge). Assessed before and after exercise	Pain intensity decreased after exercise in older and younger men and women Arm pain during exercise was not associated with EIH No relation between EIH and physical activity level/fear of pain/catastrophizing or pain attitude
(Koltyn et al., 2014)	58 healthy subjects (29/29) 21 (3)	Isometric muscle contraction with hand dynamometer 25 % MVC 3 min	Within subject naltrexone and placebo conditions	Pressure pain threshold and pain rating applied to the dominant forefinger and heat pain ratings during repetitive stimulations (temporal summation) at the thenar eminence of the dominant hand	Temporal summation to heat pain and pressure pain ratings decreased following exercise. Pressure pain thresholds increased with no difference between men and women Naltrexone did not alter the EIH response. The decrease in temporal summation to heat pain was significantly correlated with the increase in endocannabinoid

<b>Reference</b>	<b>Subjects Total number Gender (F/M) Age (SD) or age range</b>	<b>Exercise protocol 'resistance' Intensity Duration</b>	<b>Control condition</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Koltyn and Arbogast, 1998)	13 healthy subjects (6/7) 23 (5)	Resistance exercise 4 different exercises with 3 sets of 10 repetitions at 75 % MVC 45 min	Within-subject rest condition	Pressure pain thresholds and pain ratings at the left middle finger	Pain threshold increased and pain ratings decreased 5 min following exercise, but not 15 min after
(Weissman-Fogel et al., 2008)	48 healthy subjects (29/19) 24.3 (20-30)	Resistance exercise with hand dynamometer 25 % MVC 3 min	None	Heat pain rating at the non-dominant thenar eminence after exercise	Exercise reduced heat pain ratings in both men and women A significant correlation was found between pain catastrophizing and EIH
(Focht and Koltyn, 2009)	21 healthy subjects (0/21) 21.4 (2.5)	Resistance exercise 4 different exercises with 3 sets of 10 repetitions at 75 % MVC 45 min	Within subject condition with testing either in the morning or in the evening	Pressure pain threshold and pain rating	Pain threshold increased and pain ratings decreased 1 min after but not 15 min after exercise both in the morning and evening
<b>Reference</b>	<b>Subjects Total number Gender (F/M) Age (SD) or age range</b>	<b>Exercise protocol 'mixed' Intensity Duration</b>	<b>Control condition</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Bartholomew et al., 1996)	17 healthy subjects (0/17) Unknown	Mixed Moderate 20 min	Within-subject rest condition	Pressure pain threshold and tolerance at the tibial muscle	Pain tolerance increased following the exercise session
<b>Reference</b>	<b>Subjects Total number Gender (F/M) Age (SD) or age range</b>	<b>Exercise protocol 'passive' Intensity Duration</b>	<b>Control condition</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Nielsen et al., 2009)	17 healthy subjects (11/6) 23.9 (2.5)	Passive physiological movements of the knee joint performed by electric bicycle ? 30 min	Within-subject rest condition	Pressure pain thresholds and pain intensity after hypertonic saline injection in tibialis anterior	Pain threshold increased and pain ratings decreased during passive physiological movements

**Appendix 4:** A summary of clinical studies examining exercise-induced hypoalgesia in human adults, primarily organized according to exercise modality in the following order: ‘aerobic’, ‘isometric’ and secondly after year of publication.

Reference	Subjects Total number Gender (F/M) Age (SD) or range	Healthy controls or within-subjects control condition	Exercise protocol ‘aerobic’ Intensity Duration	Pain sensitivity parameters	Main findings
(Droste et al., 1988)	8 subjects with symptomatic myocardial ischemia (0/8) 54 (7)	9 subjects with asymptomatic myocardial ischemia (0/9) 54 (7)	Aerobic bicycling Increasing workload from 50-125 watt 8-10 min	Electrical pain threshold at the non-dominant middle finger Pain thresholds and pain ratings during ischemic arm pain test	<b>Symptomatic myocardial ischemia:</b> No significant EIH response <b>Asymptomatic myocardial ischemia:</b> No significant EIH response
(Kemppainen et al., 1998)	8 pilots with previous neck pain (0/8) 22-35 years of age	8 pilots without neck pain (0/8) 22-35 years of age	Aerobic bicycling Increasing workload from 50-200 watt 25 min	Pain threshold during cold pressor test and pain intensity during cold pressor test with right hand	<b>Previous neck pain group:</b> Pain threshold increased and pain rating decreased after exercise <b>Healthy controls:</b> Pain rating decreased after exercise
(Vierck et al., 2001)	10 subjects with fibromyalgia (10/0) 46.41 (?)	20 healthy controls (10/10) 46.25 (?)	Aerobic treadmill According to protocol by Bruce et al., 1973 Until exhaustion	Temporal summation to heat pain on both hands	<b>Fibromyalgia patients:</b> Temporal summation was increased after exercise <b>Healthy controls:</b> Temporal summation was reduced after exercise
(Whiteside et al., 2004)	5 subjects with chronic fatigue syndrome (1/4) 28-49 years of age	5 healthy controls (1/4) 30-54 years of age	Aerobic treadmill 5 km/h 3 x 5 min	Pressure pain thresholds on both hands	<b>Chronic fatigue syndrome:</b> Pain thresholds decreased after exercise <b>Healthy controls:</b> Pain thresholds increased after exercise
(Hoffman et al., 2005)	8 subjects with chronic low back pain (4/4) 40 (10)	10 healthy controls (only rest condition) (3/7) 34 (8)  Within subjects rest condition	Aerobic bicycling 70 % VO <sub>2peak</sub> 20 min	Pressure pain rating at the non-dominant index finger	<b>Chronic low back pain:</b> Pain ratings were decreased after exercise
(Cook et al., 2010)	11 Gulf war veterans with chronic widespread pain (0/11) 39.4 (7.4)	16 Gulf war veterans without pain (0/16) 40.9 (7.9)	Aerobic bicycling 70 % VO <sub>2peak</sub> 30 min	Heat pain threshold and pain ratings at the thenar eminence of the non-dominant hand Pressure pain threshold at the non-dominant forefinger	<b>Veterans with chronic widespread pain:</b> Pain ratings increased after exercise <b>Veterans without pain:</b> No change in pain thresholds or ratings following exercise
(Meeus et al., 2010)	26 subjects with chronic fatigue syndrome (21/5) 41.52 (11.38)  21 chronic low back pain patients (11/10) 41.55 (12.4)	31 healthy sedentary subjects (21/10) 39.88 (12.63)	Aerobic bicycling Increasing workload from 20-130 watt 37 min	Pressure pain thresholds bilaterally at the hand, the lower back, the deltoid muscle and the calf muscle	<b>Chronic fatigue syndrome:</b> Pain thresholds decreased after exercise <b>Low back pain subjects:</b> Pain thresholds increased after exercise <b>Healthy subjects:</b> Pain thresholds increased after exercise

(Van Oosterwijck et al., 2010)	22 subjects with chronic fatigue syndrome (22/0) 34.3 (8.8)	22 healthy controls (22/0) 38.9 (15)	Aerobic bicycling 1: 75 % of age-predicted heart rate (APHR) 2: Self-paced ? (duration)	Pressure pain threshold at the hand, the lower back and the calf	<b>Chronic fatigue syndrome:</b> -Pain thresholds decreased at the back and calf after the 75% APHR condition -Pain thresholds decreased at the calf and hand after the self-paced condition -Pain threshold increased at the back after the self-paced exercise condition <b>Healthy controls:</b> Pain thresholds increased after both exercise conditions
(Newcomb et al., 2011)	21 subjects with fibromyalgia (21/0) 18-59 years of age	Within subjects control Different exercise protocols	Aerobic bicycling 1: Self-selected intensity 2: 62 % of HR max 20 min	Pressure pain threshold, pain ratings and tolerance applied to the right forefinger	<b>Fibromyalgia:</b> Pain threshold and tolerance increased after both exercise conditions Pain threshold increased more after the self-selected intensity Pain ratings decreased after both exercise conditions
(Van Oosterwijck et al., 2012)	22 subjects with whiplash associated disorder (22/0) 38.4 (9.2)	22 healthy controls (22/0) 37.1 (14.6)	Aerobic bicycling 1: 75 % of APHR 2: Self-paced ? (duration)	Pressure pain threshold at the hand, the lower back and the calf	<b>Whiplash patients:</b> Pain thresholds decreased at the back and calf after the 75% APHR condition Pain thresholds decreased at the calf and hand after the self-paced condition Pain thresholds increased at the back after the self-paced exercise condition <b>Healthy controls:</b> Pain thresholds increased after both exercise conditions
(Meeus et al., 2014)	16 subjects with rheumatoid arthritis (16/0) 54.3 (8.4)  19 subjects with chronic fatigue syndrome and fibromyalgia (19/0) 44.6 (7.3)	18 healthy controls (18/0) 41.1 (14.5)  Within-subject paracetamol and placebo conditions	Aerobic bicycling Increasing workload 25 watt/min from 0 watt until 75 % of APHR is achieved. Less than 15 min	Pressure pain ratings and temporal summation at the middle finger	<b>Rheumatoid arthritis:</b> Decrease in temporal summation after exercise. <b>Chronic fatigue syndrome and fibromyalgia:</b> No EIH response <b>Healthy controls:</b> Decrease (non-significant) in temporal summation after exercise
<b>Reference</b>	<b>Subjects Total number Gender (F/M) Age (SD) or range</b>	<b>Healthy controls or within-subjects control condition</b>	<b>Exercise protocol 'isometric' Intensity Duration</b>	<b>Pain sensitivity parameters</b>	<b>Main findings</b>
(Kosek et al., 1996)	14 subjects with fibromyalgia (14/0) 29-59 years of age	14 healthy controls (14/0) 20-54 years of age	Isometric muscle contraction with knee extensors 20-25 % MVC Until exhaustion (max 5 min)	Pressure pain thresholds at the quadriceps femoris muscle	<b>Fibromyalgia patients:</b> Pain thresholds decreased during exercise <b>Healthy controls:</b> Pain thresholds increased during exercise
(Staud et al., 2005)	12 subjects with fibromyalgia (12/0) 48.4 (7.1)	11 healthy controls (11/0) 45.7 (10.2)	Isometric muscle contraction with hand dynamometer 30 % MVC 90 s	Heat pain and pressure pain at both forearms	<b>Fibromyalgia patients:</b> Heat pain ratings increased in both arms during exercise Pressure pain thresholds decreased in both arms during exercise <b>Healthy controls:</b> Heat pain ratings decreased in both arms during exercise Pressure pain thresholds increased in both arms during exercise

(Kadetoff and Kosek, 2007)	17 subjects with fibromyalgia (17/0) 22-56 years of age	17 healthy controls (17/0) 22-53 years of age	Isometric muscle contraction with knee extensors 10-15 % MVC Until exhaustion (max 8-10 min)	Pressure pain thresholds at the exercising quadriceps and the opposite deltoid muscle	<b>Fibromyalgia patients</b> Pain threshold at the deltoid increased during exercise <b>Healthy controls:</b> Pain threshold at the deltoid increased during exercise
(Lannersten and Kosek, 2010)	20 subjects with shoulder myalgia (20/0) 28-57 years of age 20 subjects with fibromyalgia (20/0) 24-47 years of age	21 healthy controls (21/0) 19-49 years of age	Isometric muscle contraction with knee extensors and shoulder external rotators 20-25 % MVC Until exhaustion (max 5 min)	Pressure pain thresholds at the infraspinatus and quadriceps femoris muscles	<b>Myalgia patients:</b> Pain thresholds increased during quadriceps contractions <b>Fibromyalgia patients:</b> Pain thresholds did not change after any of the exercise conditions <b>Healthy controls:</b> Pain thresholds increased after both exercise conditions
(Bement et al., 2011)	15 subjects with fibromyalgia (15/0) 19-64 years of age	Within subjects rest condition	Isometric muscle contraction with elbow flexors 1: 25 % MVC Until exhaustion (max 5 min) 2: 25 % MVC held for 2 min 3: 3x 100 % MVC	Pressure pain threshold and pain ratings at the right index finger	<b>Fibromyalgia patients:</b> No change in pressure pain threshold or pain ratings after any of the exercise conditions Subgroup analysis showed increase in pressure pain threshold in younger patients, and those with high pain sensitivity
(Ge et al., 2012)	22 subjects with fibromyalgia (22/0) 53.6 (2.5)	22 healthy controls (22/0) 52.4 (2.4)	Isometric muscle contraction with shoulder abductors Hold arms horizontally Until exhaustion	Pressure pain thresholds in the trapezius and tibialis anterior muscles	<b>Fibromyalgia patients:</b> Pain thresholds in the tibialis anterior decreased after exercise <b>Healthy controls:</b> Pain thresholds increased in the trapezius after exercise
(Kosek et al., 2013)	66 subjects with knee osteoarthritis (OA) (39/27) 68 (4.3)  47 subjects with hip OA (26/21) 67.1 (4.0)	43 healthy controls (23/20) 68.9 (4.6)	Isometric muscle contraction with knee extensors 50 % MVC Until exhaustion (max 5 min)	Pressure pain thresholds at the exercising quadriceps and the opposite deltoid muscle	<b>Knee OA:</b> Pain threshold increased during exercise <b>Hip OA:</b> Pain threshold increased during exercise <b>Healthy controls:</b> Pain threshold increased during exercise
(Burrows et al., 2014)	11 subjects with knee OA (6/5) 65.9 (10.4)	11 old healthy subjects (6/5) 61.3 (8.2)  11 young healthy subjects (7/4) 25 (4.9)	Isometric muscle contractions arm and leg with 3 sets of 10 repetitions at 60 % MVC 1: 3 upper body exercises 2: 3 lower body exercises	Pressure pain threshold and pain ratings applied to the arms and legs	<b>Knee OA:</b> Pain thresholds increased after upper body exercise condition <b>Old healthy subjects:</b> Pain thresholds increased after both exercise conditions <b>Young healthy subjects:</b> Pain thresholds increased after both exercise conditions No difference between older and younger healthy groups
(Knauf and Koltyn, 2014)	9 subjects with diabetes mellitus and painful diabetic neuropathy (??) 53 (7)	9 subjects with diabetes mellitus and no pain (??) 46(13)	Isometric muscle contraction with hand dynamometer 25 % MVC 180 s	Heat pain rating and temporal summation at the dominant hand and arm	<b>Painful diabetic neuropathy:</b> No significant EIH response <b>Diabetes mellitus and no pain:</b> Decrease in pain ratings and temporal summation after exercise