# Pain modulation and gender differences

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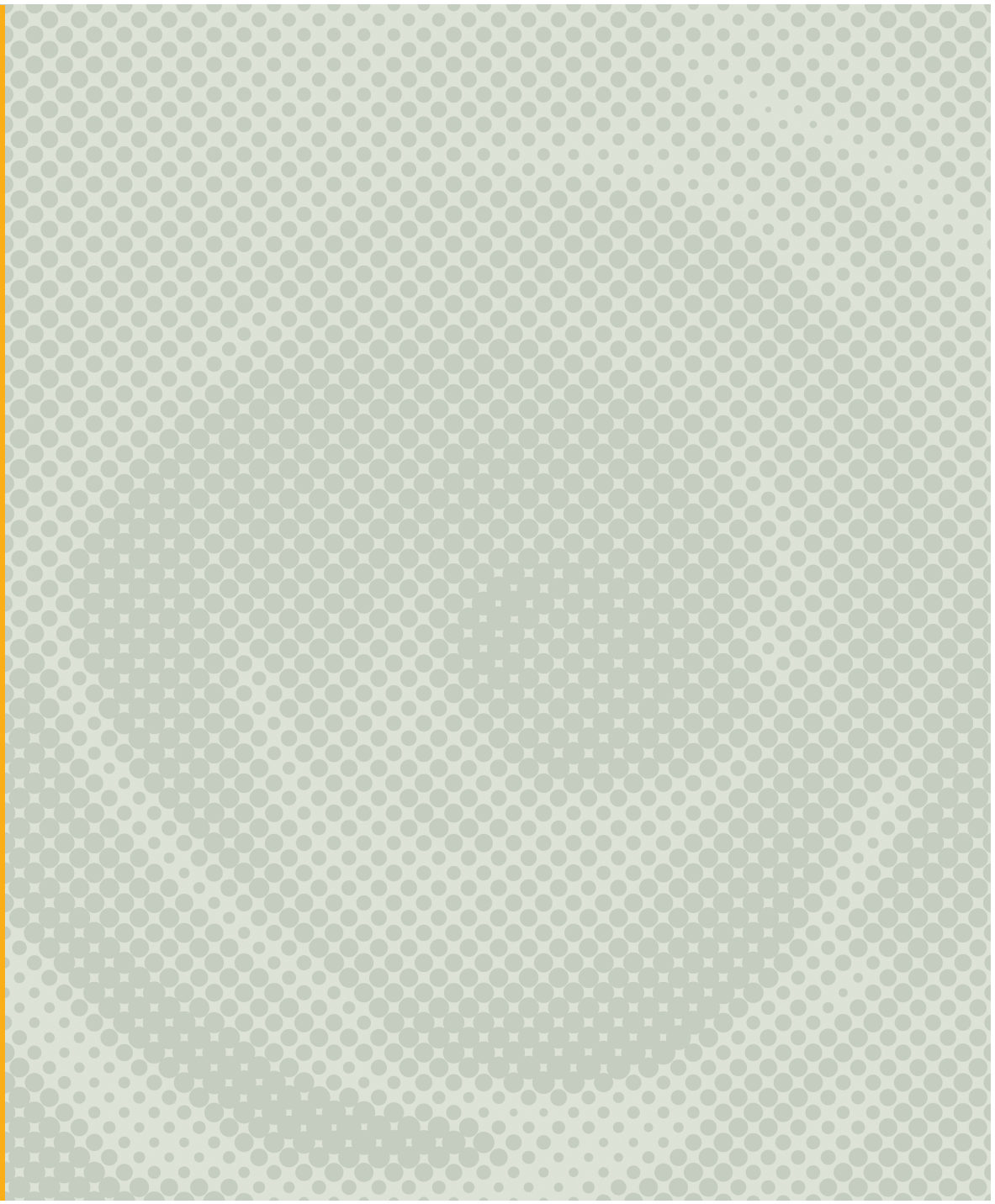

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Master of Public Health 2010
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## Summary

The thesis *Pain modulation and gender differences* consist of two parts; first, an introduction to the study which provides detailed theoretical information on the topic in a larger context, and second, the article *Inhibition of electrically induced Tibialis anterior pain is inhibited by painful and non painful conditioning* which give an thorough presentation of methodology and results.

The thesis describes an experimental pain study, conducted at the National institute of Occupational health in Oslo. The experiment was designed to test the pain inhibitory system in men and women, focusing on the following questions:

- Is electrically induced muscle pain inhibited by a conditioning heat pain stimulus?
- Do women show signs of reduced inhibition compared to men?

A conditioned pain modulation (CPM) model was used in the experiment, where the experimental setup included both a painful and a non painful session. A total of 40 healthy volunteers (50% women) participated. Electrical muscle pain was induced in Tibialis anterior and heat pain was induced on the opposite forearm. The inhibitory effect was measured from the participants' subjective responses using a visual analogue scale (VAS).

Statistical analyses were performed in SPSS by the use of independent samples t-test and RM ANOVA respectively.

The analyses showed no CPM effect, but revealed that painful and non-painful conditioning reduced the pain experience among both women and men. The thesis discusses several methodological concerns related to the results and what consequences this might have had for gender differences in previous CPM studies. Finally, the conclusion emphasize the importance of attention in CPM studies and the significance of considering sex hormones when studying gender differences in pain.

# Resume

Specialet *Smertemodulation og kønsforskelle* består af to dele. Først, en introduktion til forsøget med information om emnet i en større sammenhæng samt en teoretisk fremstilling. Dernæst, artiklen *Inhibition of electrically induced Tibialis anterior pain is inhibited by painful and non painful conditioning* som indeholder en detaljeret præsentation af metode og resultater.

Artiklen omhandler et smertefysiologisk eksperiment, udført ved Statens arbeidsmiljøinstitutt i Oslo. Eksperimentets formål var at teste det smertehæmmende system hos mænd og kvinder med fokus på følgende problemstillinger:

- Hæmmes elektrisk induceret smerte af varmesmerte som konditionering?
- Viser kvinder tegn til reduceret smertehæmmende effekt sammenlignet med mænd?

Til udførelse af eksperimentet blev en Conditioned pain modulation (CPM) model benyttet. Det eksperimentelle opsæt indeholdte både en smertefuld- og en ikke smertefuld del som begge var inkluderet i den efterfølgende analyse. I alt deltog 40 frivillige, raske, personer (50 % kvinder). Elektrisk muskelsmerte blev påført i Tibialis anterior og varmesmerte blev påført på modsatte sides underarm. Den smertehæmmende effekt blev målt ud fra deltagernes subjektive oplevelse ved brug af en visuel analog skala (VAS).

Alle statistiske analyser blev foretaget i SPSS ved brug af t-test og RM-ANOVA.

Resultatet viste ingen CPM effekt, men viste at både smertefuld- og ikke smertefuld konditionering reducerede smerteoplevelsen for både kvinder og mænd. I specialet diskuteres CPM metoden i forhold til resultaterne og hvilke konsekvenser metoden kan have medført for kønsforskelle i tidligere CPM studier. Afslutningsvis vægtlægger konklusionen betydningen af opmærksomhed i CPM studier, og peger derudover på vigtigheden af at tage kønshormoner i betragtning når man ønsker at studere kønsforskelle og smerte.

## Acknowledgement

This assignment which in the past summer seemed far away has now turned into a finished thesis. My time at The National Institute of Occupational Health has been exciting and very educational throughout the process, this I have enjoyed daily. Therefore, I want to thank my main supervisor PhD Dagfinn Matre who has contributed with detailed guidance, inspiring discussions and good advice when my mind stood still. I would also like to thank my co-supervisor from the Norwegian University of Life Science PhD Camilla Ihlebæk who gave good guidance and positive inputs.

I am outmost thankful for all my participants who made this assignment possible by allowing me to cause them discomfort. Thank you for letting me poke needles with electricity into your leg muscle and adding red marks onto your forearms. I have great respect for you and I am very grateful because you joined voluntarily, many thanks for your help. Also thanks to everyone in the Department of Work-related Musculoskeletal Disorders and to the girls on the 5$^{th}$ floor. The cozy lunch breaks, always happy smiles and encouraging comments gave the everyday a fresh breath.

My dearest parents' home in Copenhagen must be thanked for the positive support that despite of the distance has been felt all the way to Oslo. It has been enormously appreciated, I hope you know.

Finally, I want to thank Trond. The whole way through you have had the most significant role. Smile, calm and motivation are probably the golden words behind the support and presence you have given me along the way. You have been an indispensable support.

Maria Gullander

Oslo, maj 2010

# Forord

Den opgave som i sommer så ud til at være langt ude i fremtiden er nu blevet til et færdigskrevet speciale. Min tid ved Statens Arbeidsmiljøinstitutt har igennem hele specialeprocessen været spændende og lærerig, dette har jeg sat stor pris på. I den forbindelse ønsker jeg, at rette en stor tak til min hovedvejleder PhD Dagfinn Matre for have bidraget med grundig vejledning, inspirerende diskussioner og gode råd, når tankerne stod stille. Min bivejleder fra Universitetet for Miljø og Biovitenskab PhD Camilla Ihlebæk vil jeg også sige tak til for god vejledning og positive indspil.

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Maria Gullander

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# Contents

## List of figures and tables

## Abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| CNS | Central nervous system |
| CPM | Conditioned pain modulation |
| CS | Conditioning stimuli |
| Hz | Hertz |
| Min | Minutes |
| Mm | Millimeter |
| Ms | Milliseconds |
| PAG | Periaqueductal gray |
| PT | Pain threshold |
| PPT | Pressure pain threshold |
| Sec | Seconds |
| SEM | Standard error of the mean |
| TS | Test stimuli |
| VAS | Visual analogue scale |

# 1.0 Introduction

## 1.1 Pain in a public health perspective

Pain, commonly expressed as musculoskeletal pain, is a major public health challenge and is one of the major reasons for considerable suffering, reduced life-quality, utilization of the health care system and long-term sick leave in Norway (Ihlebæk and Lærum 2004). In addition, there are indications that musculoskeletal pain has a gendered feature with more suffering among women compared to men (Greenspan et al. 2007). The term musculoskeletal pain includes a diversity of pain and discomfort, originated or localized in joints, bones, cartilage, ligaments, tendons, tendon sheaths, muscle or skeleton (Kamaleri 2009). Pain is a complex phenomenon and can only be defined by the individual himself. Most of the natural history of pain conditions is still poorly understood and is often a part of the subjective conditions with diffuse and comorbid symptoms such as wide spread pain, tiredness, sleep difficulties, depression etc., rather than objective findings (Ihlebæk and Lærum 2004;Eriksen and Ursin 2004;Ursin and Eriksen 2007;Kamaleri et al. 2008a;Frølich 2009).

Today, most individuals with musculoskeletal pain are assessed by physicians to reduce their problems (Rainville et al. 2005). However, many are failing in the present treatment regime due to the commonly diffuse symptoms or missing explanations for their pain condition. This is a major challenge for the treatment system. The physicians' experiences that they do not have adequate treatment or knowledge may result in the consequence that responsibility for solving the problem is left to the patient (Frølich 2009). In addition, misunderstandings of causes and consequences of pain can lead to chronification and disability (Staff 2009). Therefore, a broader view should be developed in the treatment regime where pain is considered as an integrated package where both sensory- and emotional discomforts are represented (Brodal 2007). Cognitive behavioral treatment where the aim is to identify and change negative thoughts and ways of living can be used as an example (Staff 2009;Mogensen 2009).

### 1.1.1 Prevalence

Several studies show the same pattern with high prevalence of musculoskeletal pain. For example: according to Eriksen and Ursin (2004) approximately 80 % of the Norwegian population have reported the experiencing of musculoskeletal complaints during the last month; and in a study of Kamaleri et al. (2008a) 91.5 % reported the experiencing of musculoskeletal pain in one or more body sites during the past year. Furthermore, more women (94 %) than men (87 %) reported this, and 46 % of the women experienced pain in five or more body sites, whereas only 29.5 % of the men had the same experience (Kamaleri et al. 2008a). The five most

common experiences among the women were; neck pain (43 %), shoulder pain (39.5 %), headache (39.3 %) and low back pain (38.6 %), whereas among the men the five most common were; low back pain (29.3 %), shoulder pain (27.4 %), neck pain (26.9 %) and headache (21.3 %) (Kamaleri et al. 2008b). The current study follows a general pattern from most epidemiological studies which show that women reports more levels of pain, more frequent pain, pain in more areas, and pain of longer duration than men. In addition, it can be noted that the numbers of pain sites increased by age, peaking around 55 years old (Kamaleri et al. 2008a).

The high prevalence of musculoskeletal pain among Norwegians can, among other things, be recognized in high sick leave rates and widespread request for rehabilitation related to musculoskeletal problems. For example 40 % of all absences from work in 2008 were related to musculoskeletal pain (NAV 2009). The cost of these pain conditions has been estimated to be somewhere around 30 billion Norwegian kroner per year and this represents a huge burden on both private and public expenses (Ihlebæk and Lærum 2004;Arbeidstilsynet 2007;Staff 2009). Even though these costs seem high they are considered to be underestimated since patients in hospitals and nursing homes are excluded from these estimates (Nielsen 2007). In addition to the socio-economic consequences, it is of great importance for the individual to stay active in the labor market considering the effects on one's personal health, well-being and identity (Hauge and Thune 2008). The potential future negative outcome of musculoskeletal pain can be demonstrated by the fact that a third of those who have been on continuous sick leave for 8 weeks never return to working life (Hauge and Thune 2008). Hence, it is therefore crucial to reduce and avoid significant reasons for sick leave, such as musculoskeletal pain. However, it should be noted that sick leave is not a single question about musculoskeletal pain, and most studies also conclude that reasons for sick leave are multi-factorial. Social society system, attitudes towards sick leave, individual physical and psychological differences as well as gender[1], age, social background, type of job, education and health conditions are some of the components which should be linked to the complexity of pain conditions and sick leave (Andersen et al. 2009).

### 1.1.2 Causal explanations

Many epidemiological studies point out several possible explanations or at least factors that seem to be associated with musculoskeletal pain. For example a study by Kamaleri et al (2008a)

[1] This thesis considers sex differences. However, the term gender will be used in the text because men and women are seen as living individuals in the science of public health in accordance with the definition of gender: "*a person's self representation as male or female, or how that person is responded to by social institutions on basis of the individual's gender presentation"* (Holdcroft and Berkley 2005).

revealed that the number of pain sites experienced can be associated with a reduction in overall health, quality of sleep and psychological health. Furthermore, the study also indicated that individuals who report multi-site pain continued to report multi-site pain over a period of 14 years. Hence, multisite pain at an early age is a strong predictor for future multi-site pain in adults (Kamaleri et al. 2009). This can be supported by a study of Brage et al. (2007) which showed that persons only reporting localized low back pain differed from individuals reporting low back pain in combination with pain occurring in other sites. The study revealed an increased risk of long term disability with the latter since a high level of emotional distress predicted increased risk of low back disability, but only when they had a history of low back pain. It has also been uncovered that low socioeconomic status is associated with a higher risk of experience of musculoskeletal pain (Kristenson et al. 2004). And equally, several studies have shown that women with a low level of education and low self-assessed health in general turn out to be at a higher risk of sick leave and musculoskeletal pain (Andersen et al. 2009) in accordance with the previous mentioned pattern with higher prevalence among women. Furthermore, studies have uncovered that men and women differ in their perception of pain and in their response to pain (van Wijk and Veldhuijzen 2010). It has also been revealed that gender differences occur in virtually every sensory system, with women appearing to be more sensitive than men (Fillingim et al. 2009).

These differences between men and women can be explained by different approaches. Following Andersen et al. (2009), gender differences in the experience of pain may be due to factors such as different professions, different expectations, or exposure to different work demands. In addition, also differential vulnerability of the same strain can be a reason. Another approach has been to look at hormonal and reproductive factors that underlie what appears to be a general lifelong vulnerability for female's pain perception which may contribute to individual variations in pain (Berkley 2000). Other studies have focused on specific women's issues such as gynecological or obstetric conditions, or specific male disorders such as prostate cancer (Holdcroft and Berkley 2005). It can also be noted that gender differences in pain are observed in relation to age, test paradigm, type and location of pain, symptomatology, subjects' demographics, reproductive status, genetic profile, behavior and response to treatment (Berkley 2000). In addition, confounding factors including psychological and socio-cultural issues should be noticed. For example are women more willing to seek healthcare and are also more willing to report pain compared to men (Holdcroft and Berkley 2005). To summarize, the variability between men and women depends on complex interactions among multiple endogenous and exogenous variables that may contribute to an explanation of these differences. Hence, it is therefore difficult but important to consider all aspects of gender differences when investigating musculoskeletal pain and gender.

## 1.2. The Pain System

The following paragraphs contain a description of the pain modulatory system followed by a description of nociception, A- and C nociceptors and how they contribute to the pain experience. Thereafter will the difference between acute and chronic pain be presented with a short introduction to sensitization. The menstrual cycle and the importance of sex hormones related to pain are then briefly described. The discussion ends with a presentation of some psychological elements which can be related to the pain complex.

The human pain system is part of the body's sensory system. Sensory signals indicate many conditions in the body which are evident on several levels in the nervous system. In accordance with this, pain is defined as *An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage* (Loeser and Treede 2008, p. 475). The pain perception and the experience of pain are also influenced by psychological factors. For example, the pain perception is important for human survival. Because pain signals danger or injury, an individual will be able to avoid unwanted situations and prevent further injury. Hence, one can consequently conclude that the experience of pain includes: perception, assessment, activation and behavior, which all are influenced by psychological factors.

### 1.2.1 The pain modulation system

The pain modulatory system is located in the pain system as a pathway from the higher cortical structures. For example, such a pathway goes from the prefrontal cortex to periaqueductal gray (PAG) in the brain stem and further to the dorsal horn in the spinal cord (Figure 3A). The modulatory system is dynamic and is able to both strengthen and reduce nociceptive signals. The brain uses the pain modulatory system to continuously inhibit nociceptive signals which are of less importance and strengthen signals which are of importance. An example of pain modulation can be an individual's expectation of pain reduction (e.g. after receiving an analgesic drug) where a combination of a pharmacological effects and a placebo (expectancy) effect will take place through the pain modulatory system by an increase in pain inhibition (Jensen et al. 2004;Gebhart 2004;Colloca and Benedetti 2005;Pertovaara and Almeida 2006).

In the pain modulation system are descending inhibitory pathways (Figure 3B) playing an important role in the negative response of nocieptive signals at the spinal cord level (Pertovaara and Almeida 2006). This is termed top down activation and includes cortical structures (e.g. prefrontal cortex) that sends signals to PAG in the brain stem and further on to the dorsal horn in the spinal cord. PAG is important for the pain modulation and have an essential effect (Tracey and Mantyh 2007). From here run connections to the spinal cord and back to the brain

stem, which creates a kind of a feed-back pathway which is able to control and regulate nociceptive signals.

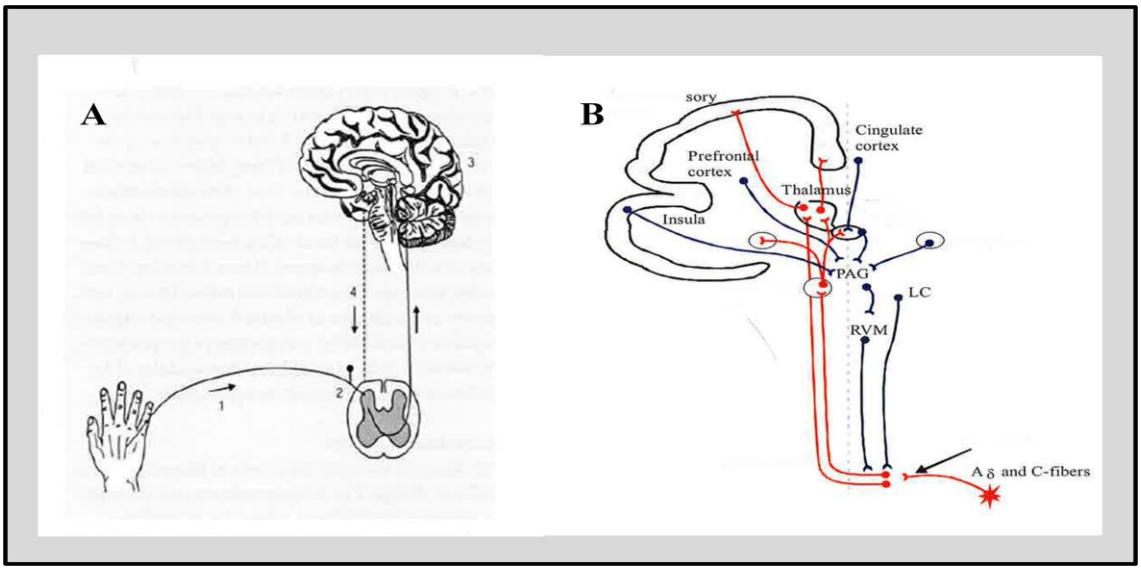



**Figure 3A**: Basic illustration of the pain modulation pathway based on (Drewes 2006). 1) Activation of Aδ- and C fibers 2) The pain pathway transmitting a stimuli from the dorsal horn to the brain 4) The descending pathway from higher cortical structures (e.g. the frontal lobe) to PAG and the dorsal horn. **Figure 3B**) Shows the ascending pathways (red line) and the descending pathways (black line) (Gjerstad 2007).

During the bottom up activation is the ascending pathway (which runs from the dorsal horn to PAG in the brain stem and further on to areas in the brain) activated. The thalamus coordinates and transmits pain signals to higher structures such as insula and gyrus cinguli which is of importance to affective and emotional aspects of pain. These areas are in connection with, among other things, the amygdala and the hypothalamus. The amygdala is responsible for the interpretation of the meaning of the stimuli, whereas the hypothalamus is responsible for the autoimmune[2] and the endocrine[3] response. This involves changes in heart rate, respiration and the release of stress hormones. The motor cortex is involved in reactions of avoiding and behavioral changes. Furthermore, the prefrontal cortex is involved in cognitive functions. Thethalamus, motor cortex and prefrontal cortex are all areas closely connected and involved in communication of the complexity of pain that involves the coding of intensity, localization, and cognitive components (Brodal 2007).

[2] Autoimmune responses refer to attacks and destroying of normal cells in the body. These responses occur in the autoimmune system when it cannot distinguish itself from foreign structures (Tabers 1993).
[3] Endocrine system refer to the system that uses hormones to regulate several functions including mood, development tissue function etc. (Tabers 1993).

### 1.2.2Nociception vs. pain perception

Because pain is a subjective experience is it relevant to distinguish between nociception and pain perception. Nociception is defined as *The neural processes of encoding and processing noxious stimuli* (Loeser and Treede 2008, p. 475) and can only lead to pain by transmission of nociceptive information in form of intensity which is sufficient to induce a conscious experience of pain (Friederich et al. 2001;Benedetti et al. 2005). This refers to signals in the central nervous system (CNS) which are evoked by activation of specialized sensory receptors (called nociceptors) which provide information about tissue damage (Kandel et al. 1991). Nociceptors are to be found under layers of the skin, at the wall of blood vessels and on the periosteum of bone and joint capsules and will under normal circumstances only be activated by tissue destructive stimulus (Waldman 2008). Nociception can be seen as an element in sensory physiology, but is not a sufficient condition for pain. The nociceptors are only activated by tissue damaged stimulation and to get the nociceptive signals to lead to pain the transmission of nociceptive input have to be at an intensity level that is sufficient to elicit a conscious experience (Fields et al. 2005). Pain perception is the conscious experience of pain as a result of a complex perceptual process in the brain where sensory information is combined with cognitive and emotionally processes.

Attentions to other stimuli than the pain causing effect reduce the awareness of the pain. Conversely, high awareness will normally imply high pain perception. The explanation for this is that high awareness will enhance the anxiety level which subsequently will increase the sensitivity so that the influence of nociceptive stimulation is higher (Jones and Zachariae 2004). Studies which have manipulated the expectation of pain supports the hypotheses of expectations as a major component in pain perception (Wager et al. 2006). In other words, only a higher-order interpretation of nociceptive signals will lead to pain. In this process the activation of the nociceptive system will trigger autonome, motor functions and other behavioral patterns which are designed to avoid damage, and nociceptive signals that will be transmitted through the nociceptors, such as myelinated Aδ or unmyelinated C-fibers (Jensen et al. 2004).

The thick myelinated Aβ-nociceptors have low activation threshold receptors which are responsible for the communication of sensory information such as touch and stroking. The C- and Aδ-nociceptors conduct potentials at different velocities with Aδ-nociceptor as the fastest (approx. 10 m/s) and the C-nociceptor as the slowest (approx. 1 m/s). Both Aδ- and C-nociceptors are referred to as polymodal which means that if a fiber responds to heat and mechanical stimuli, the fiber might also respond to chemical stimuli (Meyer et al. 2005). Most of the C-fibers respond to different types of stimuli (mechanical, heat, chemical) and have characteristic responses to activation (Meyer et al. 2005). They can both adapt (which means to decrease by repeated stimulation) and sum (which means to increase by repeated stimulus). The

activation of C-fibers leads to sensation of slow, burning and aching pain. The Aδ-fiber-nociceptorers respond to both heat and mechanical stimuli (Fields et al. 2005) . Aδ-nociceptorer has an extreme high threshold during regular conditions and is in particular to be found in smooth skin. Activation of Aδ-fibers leads to sensation of fast, sharp and pricking pain.

### 1.2.3 Acute vs. chronic pain

The nociceptive system has an integrated plasticity[4] that ensures that the pain system may change the characteristic of the response depending on the level of the stimulus, and also on what kind of tissue that is activated (Brodal 2007). Therefore, it is important to distinguish between acute pain and chronic pain. Acute pain can be caused by direct activation of high threshold nociceptors in the skin, viscera, joints, tendons or muscles (Jensen et al. 2004). Acute pain warns about impending tissue damage and is crucial for human survival since it can be recalled so that future danger can be avoided. The nociceptive activity is short and self limiting, but in the case of pain lasting more than a few seconds may neuro plastic changes in the cell membrane be seen. This may be an indicator of the wind-up which is a repeated stimulation of nociceptiv input from Aδ- or C nociceptors. A continuing of nociceptiv stimulation may also contribute to noticeable changes in cells and membranes which may lead to a more chronic phase.

Chronic pain is commonly defined as pain persisting for more than three months (Tracey and Mantyh 2007). The causes for why the pain gets chronical are often unknown. Chronic pain is characterized by a general plasticity in the nociceptive system which means that the nerve system has changed response properties and elicited an excessive reaction to a stimulus (Brodal 2007). Cell biological changes can take place and are probably the explanation for the spread of pain into healthy areas where pain provoked by a normally non-painful stimuli will result in a painful experience (Jensen et al. 2004). An example can be a long lasting nociceptive input, e.g. surgery. This can have different consequences such as plastic changes in the nervous system, high degree of hyperexcitability[5], somatic input, and possibly chronic pain.

An important component in musculoskeletal pain is central sensitization which may explain conditions that increase the sensitivity of neurons in the spinal cord (Meyer et al. 2005). Consequences can be that neurons in the spinal cord receive signals from a larger area of the body than before, the threshold for activation decreases (a lower intensity of stimulus is needed before the neurons transmit impulses), reactivity increases (neurons transmit more impulses at the same stimulation level), and sensory neurons which normally do not signalize pain, will

[4] Plasticity: the ability to be molded
[5] Hyperexcitability: an excessive reaction to stimuli

activate the pain systems (Meyer et al. 2005). All these components will normally be related to musculoskeletal pain. Hence, it has been concluded that the pain modulating system contributes to central sensitization through increased gain or reduced inhibitory function of sensory neurons (Ursin 2005).

### 1.2.4 Menstrual cycle

When studying pain it is necessary to include sex hormones (estrogen, progesterone and testosterone) which seem to have a considerable influence on pain perception (Tousignant-Laflamme and Marchand 2009;Teepker et al. 2010). Sex hormones produce effects throughout the peripheral and CNS and concentrations differ on a regular basis among both men and women. Most women experience changes in their hormone level both after menopause, throughout the menstrual cycle and during pregnancy, and there are strong indications that these differences have major consequences for the perception of pain (Fillingim et al. 2009). For example studies have shown that there is a correlation between the perception of heat pain and estrogen levels, where higher levels of estrogen were associated with a lower heat pain and heat tolerance threshold (Fillingim et al. 1997). Other studies have revealed that the pain modulatory system varies throughout the menstrual cycle with less effect in menstrual phase (day 1-3) and luteal phase (day 19-23) compared to the ovulatory phase (day 12-14) (Tousignant-Laflamme 2009, Teepker et al. 2010). Men, on the other hand are, in general, less vulnerable to changes in their hormone level during the lifespan, even if there is a significant reduction in their testosterone level with increasing age (Fillingim et al. 2009).

### 1.2.5 Psychology and pain

Psychological and physiological mechanisms also affect pain sensitivity and, according to Price (1999), pain can be seen as a conscious experience. This experience of pain is a result of several elements which includes cognition (memory, problem solution, learning, perception), context (social and cultural aspects), mood (psychological), genetics, chemical and structural processes (biological), injury and nociception (Figure 4) (Tracey 2008).

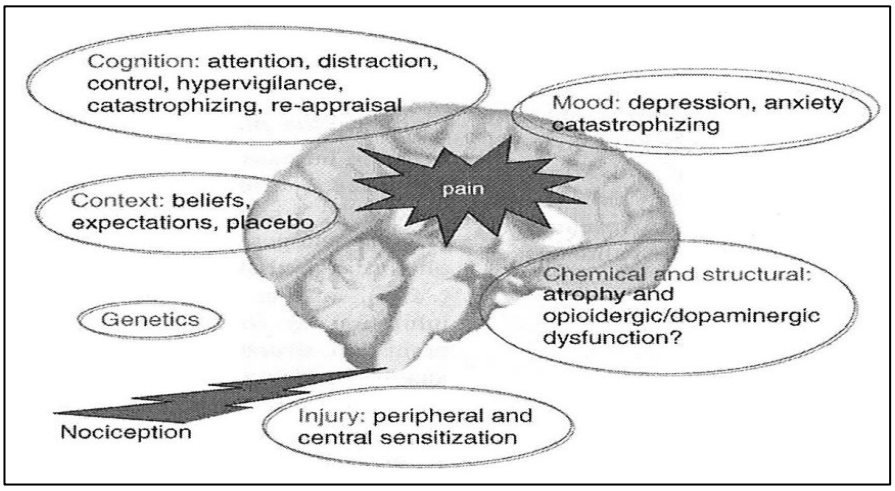



**Figure 4:** Inputs that affect pain perception (Tracey 2008).

Pain perception is an outcome from a complex interaction of learning and interpretation. In addition to basic assumptions, attitudes and understanding of pain that all may contribute to how individuals interpret and process pain (Knardahl 1998). Pain has also a sensory, an affective motivational, and a cognitive motivation extent (Price 1999). The sensory pain component refers to the individual's capacity to identify "where does it hurt?", "how long does it last?" and "how intense is it?" and the affective motivational component is an essential part of the sensation. These two aspects impart avoiding elements and emotional reactions to noxious stimuli such as "I don't like it", whereas the cognitive-motivational aspect is characterized by the evaluation of pain in terms of past experience, environmental context, expectation and its significance for daily life (Melzack and Casey 1968).

**Summary**

The pain system includes a multiplicity of factors in the sensory system where information about tissue damage is communicated to the brain in which many areas are involved and activated. This activation is responsible for the complex and nuanced experience of pain. The pain system is dynamic and is able to change character with the presence of inhibitory and facilitatory mechanisms. These systems are essential to pain because the experience of pain can be interrupted when tissue damage is stopped and they are also of importance for the persistent pain in chronic pain conditions.

## 1.3 Experimental pain studies

The accomplishment of pain studies is a complex field; especially due to the subjective aspect in individuals' perception of pain. Various approaches exist, one is psychophysics where pain is measured by subjective ratings which among other things include pain threshold and tolerance threshold (Gracely 2005). Hence, this exposition introduces experimental pain studies in psychophysics and how to measure pain despite of the subjective element in pain. This is followed by a description of a commonly used model in psychophysics; the conditioned pain modulation (CPM) model. Finally, a reflection on gender differences in the CPM model will be presented.

An experimental pain study design is commonly used method in psychophysics when the pain system is investigated. This method involves testing of volunteers in a laboratory with various painful procedures such as heat, cold, pressure, electrical and chemical (Arendt-Nielsen 2004). It is well-reputed for investigating pain because it involves the individual's active participation and thereby effects such as motivation, attention and other psychological effects (Arendt-Nielsen 2004). Another advantage of the experimental pain study is that the researcher has full control over the applied stimulus intensity and can easily assess the pain intensity. On the other hand experimental studies have been criticized for not being relevant for clinical situations, and it has been argued that the lab administration of experimentally painful stimuli cannot duplicate the physiological trait of either acute or chronic pain conditions or produce psychological elements such as anxiety and suffering (Gracely 2005).

### 1.3.1 Pain measurement

An objective measurement of pain does not exist due to the subjective and personal trait of pain experience (Arendt-Nielsen 2004). In experimental pain studies the pain system is therefore activated by a standardized and reproducible method where the subjective pain experience is measured in the form of intensity and unpleasantness (Gracely 2005). The participant reports his/her pain by means of a standardized measurement tool, which can be regarded as an objective phenomenon. To objectively measure the subjective intensity of pain the Visual Analogue Scale (VAS) is often used (Gracely 2005). VAS consists of a 10 cm line with labels at the anchor points with "no pain" and "worst possible pain". The individuals indicate their rating by marking the line at the appropriate point. An alternative measurement method is the McGill Pain questionnaire which was developed to describe the quality and the intensity of pain (Arendt-Nielsen 2004). This questionnaire contains four parts; 1) drawing of pain, 2) description of different kinds of pain, 3) pain pattern and 4) intensity of pain). The advantage of

the McGill Pain questionnaire is that it is able to determine affective elements and can evaluate elements such as intensity. In addition, the questionnaire can also be used as a tool for diagnosis. A drawback with the questionnaire is that it is a lot of work to fill out and some of the descriptive variables overlap in some categories. A third method for measuring pain is to identify objective neural correlates of subjective differences in the use of SPECT (topography), PET (positron emission tomography) and fMRI (functional magnetic resonance imaging) (Gracely 2005;Tracey and Mantyh 2007). These findings validate the utility of the observation and subjective reporting as a mean of communication a narrative experience.

### 1.3.2 Conditioned Pain Modulation

In the 1970s the pain-inhibits pain phenomena was discovered and termed diffuse noxious inhibitory system (DNIC) (LeBars et al. 1979a;LeBars et al. 1979b). DNIC demonstrates modulation of noxious information at the spinal level and has been used in several human studies to test the pain inhibitory system (Le Bars 2002;Weissman-Fogel et al. 2008;Arendt-Nielsen et al. 2008;Pud et al. 2009). In 2009 DNIC was replaced by the new term Conditioned Pain Modulation (CPM) where the purpose was to better reflect experiments in humans (Yarnitsky et al. 2010). The CPM method is based on the Gate Control theory, developed by Melzack and Wall in the 1960s. The theory introduced the importance of balance between nociceptive and non-nociceptive afferent fibers (Melzack and Wall 1965) and illustrated that perception of pain depends on the level of activity in both nociceptive and non-nociceptive afferent fibers, which either can be inhibited or improved before reaching the brain (Kandel et al. 1991). In other words, pain can be modulated by both psychological and physiological mechanisms. A common psychological model is to manipulate the subject's expectations by giving inert (non-active) treatments, whereas a common physiological model is to give two painful stimuli simultaneously (Pud et al. 2009). The stronger, longer-lasting, pain will then inhibit a briefer shorter-lasting test stimulus.

However, to capture both the psychological and the physiological aspects of pain it is appropriate and common to use the CPM method when investigating the pain modulatory system in an experimental study setup. This approach tests the pain modulatory system in a before-during-after paradigm (Figure 1, Article p. 34). The application of painful test stimulation (TS) is first done during a control condition (before), followed by simultaneous application of the test stimulus and another noxious conditioning stimulus (CS) (during). The test stimulus may also be repeated after the conditioning stimulus (after) in order to see whether the inhibitory effect outlasts the CS. The CPM-effect, a reduced pain response, is expected when another painful stimulation is applied simultaneously. The main outcome measure in CPM studies in humans is the reported pain intensity of the test pain whereas reduced test pain

intensity is a measure of the efficacy of the pain modulatory system (Pud et al. 2009). In CPM studies attention is an important factor because CS necessarily takes some attention when it is given at the same time as TS (Fillingim et al. 2009). Consequently, the CPM method will activate the pain modulatory system by both the bottom up and the top down activation. Hence, it should be noted that attention may contribute to a pain causing effect which is able to reduce the awareness of the pain.

### 1.3.3 Previous CPM studies

Studies have shown that ongoing musculoskeletal pain disturbs the balance between descending inhibition and facilitation which may be particularly important in women (Arendt-Nielsen et al. 2008). The descending sensitivity to pain seems to last longer in men compared to women which could indicate that men are more able to activate CPM pathways and that a CPM effect might last longer in men (Arendt-Nielsen et al. 2008). Some of these different components might underlie some of the preponderant pain conditions. As earlier described, for women it seems that the menstrual cycle plays an important role due to the variation of pain perception throughout the menstrual cycle (Tousignant-Laflamme and Marchand 2009; Teepker et al. 2010). In table 2 and 3 (p. 20 and 21) CPM studies which have assessed gender differences are presented. For example did Arendt-Nielsen et al. (2008) show that women had less efficient CPM compared to men by using cold pressor test during and after experimental muscle pain and a study by Ge et al (2005) showed that repeated bilateral injection of hypertonic saline into the trapezius muscle resulted in a higher pressure pain threshold in men than in women. Furthermore, a study by Granot et al. (2008) showed a greater CPM effect in men and only a tendency to CPM effect in women and Serrao et al.(2004) observed differences in modulation mechanisms between men and women. On the other hand Lautenbacher et al. (2008) did not observe any gender difference in CPM effect, but observed a lower PT in women compared to men. And Pud et al. (2005) showed a CPM effect with both painful and non-painful CS in both men and women. Hence, the many different results contribute to disputing whether there are gender differences in CPM or not. However, differences between men and women could be explained by chronic pain that seems to be over-represented in women (Greenspan et al. 2007).

## 1.4 Research objectives

The understanding of pain mechanisms is of great importance, and is relevant for both the individual and the society. However, explanations for many pain conditions are still missing or are poorly understood. A highly relevant example is the prevalence of pain conditions between men and women, respectively. The research field of pain has moved from whether sex differences exist to recognizing the importance of these differences (Greenspan et al. 2007) and several human studies indicate that women have a greater pain sensitivity than men (Fillingim et al. 2009). Pain sensitivity has been assessed by a number of different measures such as: behavioral indices of threshold, tolerance and self reported measures of pain intensity, and unpleasantness (Fillingim et al. 2009). Fillingim et al. (2009) suggest being aware of stimuli duration, stimulation site, and the possible role of hormonal conditions and psychological effects when assessing sex-related differences in CPM. Greenspan et al. (2007) point out the importance of including both men and women in research, whereas Mogil and Chanda (2005) in addition emphasize the importance of not just including but also studying gender differences. The lack of knowledge in relation to pain conditions and gender differences can be illustrated by an investigation of the 540 journal articles of basic pain research published during the period 1995-2005 (Mogil and Chanda 2005). In 79 % of the articles only male subjects were included, whereas 8% had only female subjects. Only 5% of the journal articles included both male and female subjects. This investigation uncovers the need for both including and studying both men and women in pain research.

Hence, based on the considerations in the introduction, the aim of this study is to investigate pain inhibition in both men and women. The study will use a CPM method that requires test stimulation and conditioning stimulation which leads to the following research questions:

1) *Is electrically induced muscle pain inhibited by a conditioning heat pain stimulus?*

2) *Do women show signs of reduced inhibition compared to men?*

# 2.0 Methodology

## 2.1 Summary of method

The method is described in the article (p. 32) and will only be briefly summarized and illustrated with figures that are not presented in the article.

Forty healthy volunteers (50% women) participated in this experiment. Recruiting took place by advertising at universities and colleges in Oslo and on the homepage of STAMI (Advertisement, Appendix III). All participants were paid 150 NOK/hour, and the whole session took about two and a half hours. All participants were self reported healthy and aged between 18 and 45 years (mean age: 24.4 years). All women self reported their menstrual cycle and participated during the ovulatory phase (day 12 – 14).

This study used a cross-over design with painful (45 – 49˚C) and non painful (35˚C) conditioning heat stimuli to the contralateral forearm (Figure 1, Article p. 34). Electrical stimulation was used as test stimuli and was applied in the Tibialis Anterior muscle.

Before the experiment information was given and during sessions all participants received instruction according to the laboratory logbook (Appendix I). Individual pain threshold (PT) was tested by a ladder regime consisting of five ascending series of stimuli (Laursen 1997) (Figure 5). The participants needed 20 to 30 stimulations in the electric calibration process and the mean of the five ascending thresholds were used as the pain threshold for each participant.

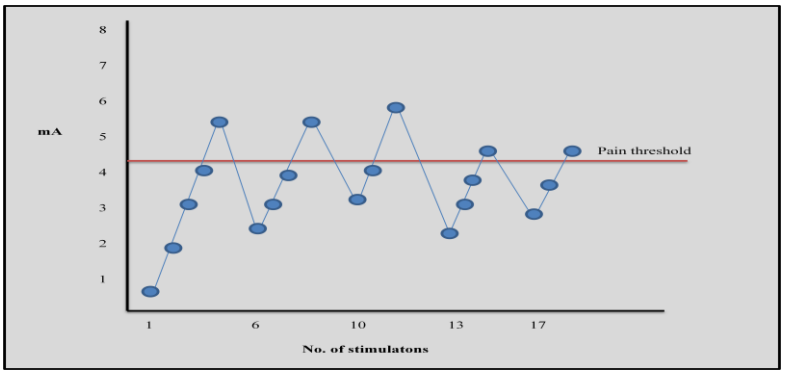



**Figure 5.** Ladder regime for calibration of pain threshold. Based on Laursen (1997).

In the pilot study the Pain-6 model was used to determine the temperature of the heat stimulation (Granot et al. 2008) (Figure 6). Because pilots responded that Pain-6 was too warm for the painful session the Pain-6 model was reduced to Pain-5. Based on stimuli at 45˚C, 46˚C and 47˚C, each of 10 seconds duration, determination of temperature was assessed according the model Pain-5 based on Granot et al. (2008). The Visual Analogue Scale (VAS) was used as pain measurement (Gracely 2005).

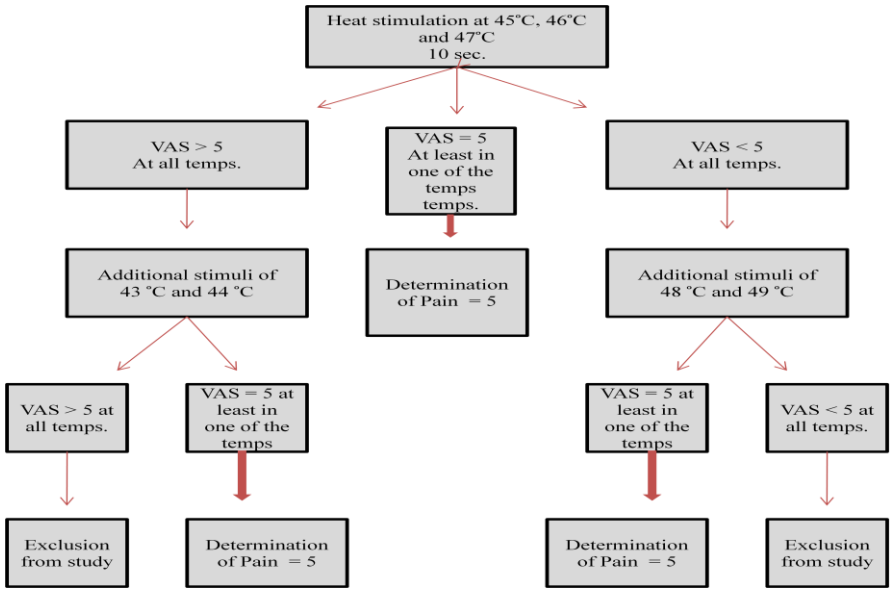
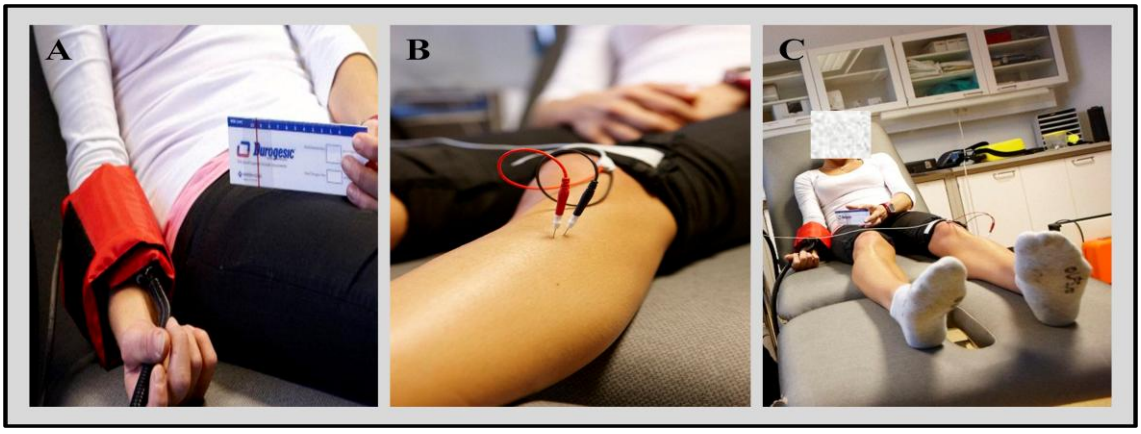



**Figure 6.** Calibration model for Pain-5. Based on Granot et al. (2008).

The experiment was conducted through two sessions where each session consisted of three trials (Figure 1, Article p. 34). In the painful session the participants were first exposed to an electrical stimulation. Next they received an electrical stimulation and a conditioning. Third, they received only an electrical stimulation without conditioning. In the non-painful session the participants were exposed to an electrical stimulation and non-painful heat at baseline level (35˚ C) in all three trials. After a break of 30 min the session was repeated on the opposite side of the body.

During the experiment reported all individuals their pain intensity by the use of a VAS scale after each electrical stimulus. All ratings were noted in the laboratory logbook and used for the statistical analysis




**Picture 1: A**) Heat termode on forearm. **B**) Needle electrodes in Tibialis Anterior. **C**) Experimental setup.

### 2.1.1 Methodological considerations

The methodology for the present study was chosen for several reasons. Electrically induced pain has rarely been used, and only a few studies (Svensson et al. 1999) have used the same type of TS as in the present studies. Nevertheless, electrically induced muscle pain was chosen because it together with heat stimuli could contribute to activating the CPM effect in a new combination. Cold pressor, which is more common as CS, was excluded due to the risk of an analgesic effect caused by increasing blood pressure. In addition, the timeline for the data gathering played a role in selection of CS. Cold pressor would have a much longer effect compared to heat stimuli on the vital sensitivity in the area exposed to CS. Hence, cold pressor as CS would have implied longer breaks between the sessions and all participants would have had to come to the laboratory on two different days.

Other arguments for the chosen method are that both electrical and heat stimulation are easy to use, and intensities are easily adjusted and adapted to the participant. Furthermore, both stimulation types are easily stopped if the participant wishes to end the experiment.

### 2.1.2 Ethic

The experimental protocol was approved by Regional Ethical Committee in Oslo (REK) (Appendix IV) and was performed according to the Declaration of Helsinki ethical principles for medical research involving human subjects (WMA 2008).

All participants were volunteers that had responded to the advertisement. They were guaranteed anonymity. Information that could identify the subjects was locked in and kept separate from ID numbers, logbooks and results. The participants received a payment of 150 NOK per hour.

All participants signed a consent form and were informed that they at any time could withdraw from the experiment.

Other ethical issues exist were primary related to the painful stimulation. The intensity of the electric and heat stimuli were based on the subjective ratings. Thus, participants were exposed to pain that they accepted. During the experiments medical assistance was available at STAMI.

# 3.0 Results

### 3.1 Summary of main results

The results are described in the article (p. 36) and only the main results will be briefly summarized here.

The main effect of conditioning was observed in reduced VAS scores (87% ± 27%) during the painful session with respect to before conditioning ($p = 0.02$). The reduction in VAS scores during the painful session (87% ± 27 %) was not different from the reduction in VAS scores during the non-painful session (92 % ± 21 %) ($p = 0.31$) (Figure 2, Article p. 37). These results indicated an effect of TS, but not a CPM effect.

No difference was observed between men and women ($p = 0.28$); mean VAS scores in men were 91 % ± 21 % whereas mean VAS scores in females were 89 % ± 27 % during (vs. before) conditioning (Figure 2, Article p. 37).

# 4.0 Discussion

This section is an elaboration of the discussion in the article. First, some methodological considerations will be introduced. This will be followed by a discussion on gender differences in CPM studies. As a final point, reflections on validity, reliability and representativeness of the present study will be presented.

### 4.1 Methodological considerations

A CPM effect may depend on several factors such as the duration of stimulations, the body region stimulated, the strength of the stimulations, etc. (Holdcroft and Berkley 2005;Pud et al. 2009). The missing CPM effect in our study may be explained by several factors such as habituation, attention, calibration methods, and intensity of test stimuli during the sessions. Previous studies have showed that these are all components which can lead to a decrease in reported pain from baseline level (Treister et al. 2009;van Wijk and Veldhuijzen 2010). As discussed in the article there is no reason to believe that habituation had any effect in electrical stimulation, whereas there are indications to that attention may have contributed to the observed reduction in muscle pain during CS.

Furthermore, the use of heat termode as CS may be discussed. Even if this is a frequently used method in CPM studies, the use of Pain-5 to calibrate heat pain in the present study may be

criticized. This is based on the limited time used in the calibration for Pain-5 (10 seconds) compared to the time of a painful session (ca. 3 minutes). This can contribute to a level of painful conditioning that is too low even if heat may be felt as painful at the end of a session (Lautenbacher et al. 2002). In addition, the short calibration time in Pain-5 may also cause a habituation effect. A study of Tousignat-Laflamme and Marchand (2008) illustrates this where the peak in pain intensity was reached five seconds after the termode reached the fixed temperature. However, for the next 15 seconds a reduction in pain intensity was observed, followed by a period of ± 50 seconds with a constant intensity level. In other words, a person who jumps into a hot bathtub will in the beginning feel uncomfortable, but will soon adjust to the temperature. The present study may indicate that the calibration model Pain-5 use was too short of a calibration phase. Hence, it may be discussed whether other calibration methods could have been used.

Also the use of the ladder regime in electric calibration to determine the participants PT should be discussed (Figure 5, p.15). During the calibration process some of the participants reported that it was difficult to distinguish between stimulations. Therefore, we looked at the individual VAS plots (data not presented) and observed that 50 % of the participants (no gender differences) were not able to distinguish between low and high intensity, when 0.5 cm was defined as minimum difference. This is illustrated by figure 7A and 7B, where figure 7A shows an individual who is able to report a difference between stimulation intensities and figure 7B shows an individual who is not. Consequently, participants who lack this ability may also have difficulties to distinguish between TS before and during CS. Hence, when studying a CPM effect it should be considered whether an inclusion criterion should be that all participants have to be able to distinguish between high and low intensities before an experiment. Alternatively could a detections scale (finding sensory threshold) or a dose response curve (participants all receive same stimulations to observe if one group differ from another) been used for electric calibration (Arendt-Nielsen 2004).

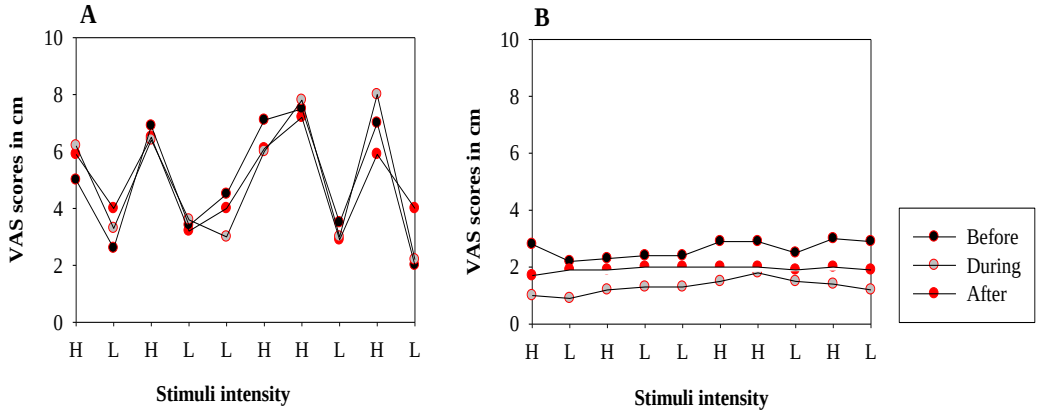



**Figure 7:** Response on stimulations measured in VAS. **A**) Reported difference between 1.1 x PT (L) and 1.6 x PT (H). **B**) No Reported difference between 1.1 x PT (L) and 1.6 x PT (H).

## 4.2 Gender differences in CPM studies

In the present study no differences were observed either in pain threshold to heat and electric stimulations or in reduced pain during painful and non-painful sessions. Several studies have indicated that women provide higher pain intensity ratings to experimental noxious stimulus compared to men (Ge et al. 2004;Arendt-Nielsen et al. 2008) and most studies (Table 2 and 3) indicate that men have a higher PT than women. Although most studies indicate this tendency can it be noted that the scientific literature emphasize that only minor changes in test stimulation, protocol, participants' expectation, etc. may have an influence on the results in experimental studies (Berkley 2000). It is therefore important to take into consideration these factors when investigating gender differences. Our results diverged from the general tendency, which is probably due to the woman participants' menstrual phase. It has been documented that women's pain perception varies throughout the menstrual cycle (Tousignant-Laflamme and Marchand 2009) and it should therefore be questioned why only two of the studies in table 2 and 3 controlled for women's menstrual cycle. To the contrary, in the present study we controlled for women's menstrual cycle by testing all women in the ovulatory phase (day 12 - 14) given that women's pain modulation system is most effective during these days (Tousignant-Laflamme and Marchand 2009;Teepker et al. 2010). With this approach we then obtained a group of woman participants who were more equal to the men, which our results also indicate. Hence, it can be argued that the menstrual cycle is a key factor in pain studies and by including this variable our study can contribute to a better understanding of gender differences in pain experience. However, we relied on the women's self report and did not take any blood test to ensure the levels of sex hormones, which may be criticized. The menstrual cycle varies between and within women, and also the hormone level varies from day to day in some phases of the cycle. According to Greenspan et al. (2007) should therefore hormonal status be directly measured rather than self reported. This is also due to that some women describe their cycle as regular although it in fact is irregular. Future research should therefore collect blood samples to ensure that the menstrual phase is determined more accurate.

The disparity in activation of the pain inhibitory system between men and women has been more and more discussed during the last decade, and Greenspan et al. (2007) recommended that future research should include both men and women in pain studies. However, studies on gender differences in pain still differ substantially. This is illustrated in a review article by van Wijk and Veldhuijzen (2010) which revealed that seven studies from 2004 to 2009 showed a more efficient CPM effect in men than women (Table 2), whereas six other studies from 1999 to 2008 showed no gender difference in CPM effect (Table 3). Pud et al. (2009) states that methodological variations used in CPM studies makes it difficult to generalize findings. This can be observed in both tables. The seven studies with gender difference (Table 2) used four

different kinds of TS (Hypertonic saline, pressure pain, heat pain and electrically pain) and four different kinds of CS used (Isotonic saline, cold pressor, warmth water bath, hand grip devise), whereas the six studies with no gender difference (Table 3) used six different methods to induce pain (Capsaicin, electrically pain, glutamate inj., pressure pain, heat pain, cold pressor) and five different methods for CS (Ischemic pain, glutamate inj., cold pressor, punctuate, warm water bath). In addition, several methods were used in the experimental setups for recalling a CPM effect. Consequently, it is difficult to draw any clear conclusion on gender differences due to the different methodological characteristics in these studies (Fillingim et al 2009). Instead, the variation in use of TS and CS may in itself explain the different results. Furthermore, the methodological differences could also be considered as an advantage because it is relevant to combine methods to capture different elements of pain (Arendt-Nielsen 2004). Different methods activate different mechanisms in the pain system, which is important for experimental studies. It can also be argued that variation in activation of mechanisms may contribute to a better understanding of the situation regarding how a painful disorder may influence an individual in general (Berkley 2000).

**Table 2.** Studies indicating a better CPM effect in men.

| Author | 1. Participants[1]<br>2. Test stimuli<br>3. Conditioning stimuli | Results | Comments on menstrual cycle |
|---|---|---|---|
| **Arendt-Nielsen et al (2008)** | 1. 10 men, 10 women<br>2. Hypertonic saline<br>3. Cold pressor | Men had higher PT vs. women<br><br>Women were less able to maintain CPM vs. men | No comments |
| **Ge et al. (2004)** | 1. 11 men, 10 women<br>2. Hypertonic saline<br>3. Isotonic saline | Men had higher PT vs. women<br><br>Women were less able to maintain CPM vs. men | Self reported regular phases. Women were not tested in any specific phase |
| **Goodin et al. (2009)** | 1. 14 men, 21 women<br>2. Pressure pain<br>3. Cold pressor | Men had higher PT vs. women<br><br>Greater CPM effect in men vs. women | No comments |
| **Granot et al. (2008)** | 1. 21 men, 10 women<br>2. Heat<br>3. Cold pressor and warth water bath | Women were less able to maintain CPM vs. men<br><br>Greater CPM effect in men vs. women | No comments |
| **Serrao et al. (2004)** | 1. 16 men, 20 women<br>2. Electric<br>3. Cold pressor and warmth water bath | Women were less able to maintain CPM vs. men<br><br>Greater CPM effect in men vs. women | All women participated in follicular phase (day 8-10) |
| **Staud et al. (2003)** | 1. 11 men, 22 women, 11 women with fibromyalgi<br>2. Heat<br>3. Warmth water bath | Women with fibromyalgia were less able to maintain CPM vs. healthy men and women<br><br>Greater CPM effect in men vs. women | No comments |
| **Weissman-Fogel et al. (2008)** | 1. 19 men, 29 women<br>2. Heat<br>3. Muscle pain (hand grip devise) | Catastrophizing level seems to be a larger indicater than gender in the relation between gender and pain modulation | No comments |

[1] If nothing else is added are participants self reported healthy

**Table 3.** Studies indicating no difference between men and women in CPM effect.

| Author | 1. Participants[1]<br>2. Test stimuli<br>3. Conditioning stimuli | Results | Comments on menstrual cycle |
|---|---|---|---|
| **Baad-Hansen et al. (2005)** | 1. 20 men, 34 women<br>2. capsaicin<br>3. Warmth water bath | No gender differences in CPM | All women participated in the follicular phase (day 3 – 9) |
| **France & Suchowiecki et al. (1999)** | 1. 39 men, 44 women<br>2. electric<br>3. Ischemic pain | Men had higher PT vs. women<br><br>No gender difference in CPM<br><br>Higher anxiety ratings in women vs. men | No comments |
| **Ge et al. (2005)** | 1. 14 men, 14 women<br>2. Glutamate inj.<br>3. Glutamate inj. | Men had higher PT vs. women<br><br>No gender difference in reported pain | Self reported regular phases. Women were not tested in any specific phase |
| **Lautenbacher et al. (2008)** | 1. 20 men, 20 women<br>2. Pressure pain<br>3. Warmth water bath | Men had higher PT vs. women<br><br>No gender difference in CPM<br><br>CPM effect observed in painful and non-painful session | No comments |
| **Pud et al. (2005)** | 1. 23 men, 17 women<br>2. Cold pressor<br>3. Punctuate | Men had higher PT vs. women<br><br>No gender difference in CPM<br><br>CPM effect observed in painful and non-painful session | No comments |
| **Tousignant-Laflamme et al. (2008)** | 1. 42 men, 41 women<br>2. Heat pain<br>3. Cold pressor | Men had higher PT vs. women<br><br>No gender difference in CPM | No comments |

## 4.3 Validity, reliability and representativeness

The understanding of both strengths and limitations of the present study is of importance. This is grounded in principal questions related to validity, reliability and the representativeness.

Validity refers to *the soundness of the interpretation of a test* and indicates to which degree a test measures what is supposed to be measured (Thomas and Nelson 1996, p. 214). The present study was based on a solid design with a before, during and after paradigm which was done in both a painful and a non-painful control session. This design is a frequently used method and has been demonstrated by several studies (Fillingim et al. 2009;van Wijk and Veldhuijzen 2010). The validity of the VAS in experimental research has also been demonstrated by several studies (Serrao et al. 2004; Baad-Hansen et al. 2005; Pud et al. 2005), and the scale was considered relevant due to the validity of pain measurement (Gracely 2005). Hence, the validity of the VAS scale in the present study should be regarded respectable.

Reliability refers to the *consistency of a measure* that has led to the results, and the degree of exactness in this process, determines the reliability of a study (Thomas and Nelson 1996, p. 220). As already mentioned, our results differ compared to several other studies, which initially indicate low reliability. However, it can be argued that this is caused by the lack of controlling

[1] If nothing else is added are participants self reported healthy

for women's menstrual phase in those studies. Moreover, throughout the last decade the CPM method has been established as an accepted tool for studying pain and pain experience (Greenspan et al. 2007). It can also be noted that in the present study there was no difference in calibration of electrically intensity between legs, which can indicate that the needle electrodes have been placed properly during both calibration and experiment. Hence, the reliability of the CPM method used in this study should be regarded as sufficient. An important element in the present study was to compare groups. The VAS scale was therefore regarded as a reliable instrument because VAS provides data which gives a good presentation and description of a sample (Dionne et al. 2005). The reliability is confirmed by the concentrated VAS scores at the baseline level, although the VAS scale was difficult to handle in the heat calibration. In addition, the VAS scale was also a helpful instrument to control for habituation during the experiment.

To ensure reliability it is important that the recording and processing of the data is accurate. For this experiment a logbook was therefore developed which contained instructions, information and space for registration of intensities and VAS during the sessions. All data were registered in a mutual database which was used for the final analysis and with the logbook it was possible to verify the database to ensure that occasional errors did not occur. Hence, because the database has been controlled for biases it is reasonable to believe that the reliability of this work is adequate.

Representativeness refers to what degree the results of the present study can be generalized into a larger perspective (Skovlund and Vatn 2004). In other words, do the results of our sample reflect what is typical of the whole population?

First, it is worth questioning whether pain conditions should be measured in a laboratory setting. Experimental studies have been criticized for not being relevant for the clinical situation because experimental pain studies usually are testing a model of a pain condition (e.g. by the use of short stimulations such as electrical or pressure pain), whereas clinical pain in general is associated with long term pain conditions such as neck, shoulder and low back pain (Kamaleri et al. 2008). However, according to Arendt-Nielsen (2004) is a quantitative description of pain of major importance for development and optimization of future treatment regimes.

Another relevant element is that the participants in our study needed to be healthy, whereas individuals with prior pain history were excluded. This is a common inclusion criterion in experimental studies, because it is common to study healthy individuals as a model for a healthy pain system. Furthermore, an important aspect is the age of the participants. The mean age in our study was 24.4 years, whereas musculoskeletal pain conditions in general peak at around 55 years in a population (Kamaleri et al. 2008a). This disparity in age may represent a limitation

since the sample is not representative for those who are largely exposed to musculoskeletal pain. Hence, both the exclusion of individuals with prior pain history and the disparity in age can make it difficult to generalized findings in the present study.

# 5.0 Conclusion and implications

This study included forty healthy participants in an experimental cross-over study which used a conditioned pain modulation method (CPM). Among the participants pain was reported to be reduced with both painful and non-painful conditioning stimulation. However, there was not found any CPM effect. We did neither identify any difference between men and women in calibration of pain threshold nor in the pain threshold in electric- or heat pain.
Based on the identical information given in both the painful and the non painful session an attentional factor is considered to play an important role. This was not included in the research questions but was brought up as an explanation based on the observed results in the pain experiment.

## 5.1 Implications

First, according to the *article* was attention of importance for our results. Future studies related to CPM and pain in a public health perspective should therefore consider including psychological variables. This is based on the belief that psychological traits are considered to play an important role in the complexity of pain conditions and disorders (Tracey 2008). In addition, long lasting pain conditions cause strong emotions such as anxiety, hopelessness and depression and are often related to a negative circle which may contribute to changes in relation to surrounding environment and the individual's coping and behavior in the daily life (Ursin and Eriksen 2007).

Second, as mentioned in the paragraph *Methodological considerations*, it could be considered whether a future inclusion criterion should be that participants have to be able to distinguish between high and low intensities in beforehand of an experiment.

Third, as mentioned in *Gender differences in CPM studies* blood tests should be included in future studies of pain. Women's menstrual cycles need to be ensured by blood tests, which also can give other relevant information on sex hormones.

Fourth, in future studies it could be of importance to consider how gender differences are studied. It is worth to question whether it is possible or even interesting to compare men and women when they at the basic level are different. This is relevant for epidemiological studies, which usually only include gender as a control variable. Hence, it can be argued that it is an advantage to separate gender in research related to pain.

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**Article:** Inhibition of electrically induced Tibialis anterior pain is inhibited by painful and non painful conditioning

# Inhibition of electrically induced Tibialis anterior pain is inhibited by painful and non painful conditioning

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## Abstract

**Objectives:** Women report more musculoskeletal pain than men. A dysfunctional pain inhibitory system has been launched as a contributing factor for these gender differences. This study used a conditioned pain modulation paradigm and asked the following questions: (1) Is electrically induced muscle pain inhibited by a painful heat stimulus to the forearm, and (2) Do women show signs of reduced inhibition compared to men? **Methods:** Forty healthy individuals (50 % women; 18 - 45 years) participated in a cross-over design with painful (45 – 49 °C) and non-painful (35 °C) conditioning heat stimuli (in balanced order) to the contralateral forearm. The subjects received 10 painful electrical stimuli in the Tibialis anterior muscle before, during and after conditioning and rated each electrical stimulus on a 0 - 10 cm visual analogue scale. There were 30 min between experiments. All women participated during the ovulatory phase (day 12 to 14). **Statistics:** All VAS scores were normalized to scores before conditioning (100 %) and analyzed by RM-ANOVA. **Results:** There was a main effect of conditioning. VAS scores during conditioning were reduced to 87% ± 27% with respect to before conditioning ($p = 0.02$). There was no difference between painful and non-painful session ($p = 0.31$). Neither was there any difference between men and women ($p = 0.28$); mean VAS in men were reduced to 91% ± 21% and mean VAS in women were reduced to 89% ± 27% during (vs. before) conditioning. **Conclusion:** Electrically induced muscle pain was inhibited by both painful CS and by non-painful CS. The inhibition by painful CS was most likely due to both pain and attention, whereas the inhibition by non painful CS may be explained by attention alone. We did not identify any differences between men and women.

## Introduction

Musculoskeletal pain is a major public health challenge and is one of the major reasons for considerable suffering and reduced life-quality, utilization of the health care system and long term sick leave in the western world (Ihlebæk and Lærum 2004). Several studies show significant gender differences in musculoskeletal pain, with an overrepresentation of women in most pain disorders (HUSK 2000;Ihlebaek et al. 2007;Kamaleri et al. 2008). Some studies point

to biological reasons for these differences (Greenspan et al. 2007) and that they may be related to the pain modulatory system (Ge et al. 2004). Hence, the present study investigated whether the pain modulatory system affects muscle pain differently in men and women.

The pain system is dynamic and is able to strengthen or reduce nociceptive signals (Gebhart 2004;Jensen et al. 2004;Pertovaara and Almeida 2006). Pain modulation can be triggered by either psychological or physiological mechanisms. A common psychological modulation is to manipulate the subject's expectations by giving an inert (non-active) treatment (Colloca and Benedetti 2006). In the present study we used two painful stimuli simultaneously which is a common physiological model of pain modulation (Granot et al. 2008;Pud et al. 2009). The stronger, longer-lasting, pain (conditioning stimulus (CS)) will then inhibit a briefer shorter-lasting test stimulus (TS). This was termed diffuse noxious inhibitory control (DNIC) and the mechanism is believed to be inhibition of nociceptive signals at the level of the spinal cord (LeBars et al. 1979a;LeBars et al. 1979b). Today, the term Conditioned Pain Modulation (CPM) is used when a DNIC effect is studied in humans (Yarnitsky et al. 2010). The main outcome measure in CPM studies in humans is reported pain intensity of the test pain. Reduced test pain intensity during conditioning is a measure of the efficacy of the pain modulatory system (Pud et al. 2009).

***Hypothesis***

The aim of this study was to determine whether the pain inhibitory system was more effective in men than in women. We were asking the following questions:

(1) *Is electrically induced muscle pain inhibited by a painful heat stimulus to the forearm?*
(2) *Do women show signs of reduced inhibition compared to men?*

## Method

### Participants

Forty (50 % women) individuals participated in the study (mean age: 24.4 years). All participants responded to an announcement on the homepage of STAMI[1] or flyers posted at the university and colleges in Oslo. All participants were paid 150 NOK/hour. Inclusion criteria for all individuals were an age of 18 to 45 years and to be self-reported healthy. Exclusion criteria were somatic or psychiatric diseases such as diabetes, fibromyalgia, depression, anxiety, metabolic- or heart diseases. Furthermore, individuals that used prescription imposed medicine, (such as for: blood pressure, sedative antidepressants, or allergy medication), smokers, individuals with pain more than a few days during the last month and individuals who knew the

[1] National Institute of Occupational health, Oslo, Norway

experimenter were also excluded. In addition, use of alcohol during the last 24 hours before the experiment was not allowed.

An informed consent was obtained from each individual. The experimental protocol was approved by the local ethical committee and conducted according to the Helsinki Declaration.

### Menstrual cycle

Sex hormones are of importance to gender differences in pain (Fillingim et al. 2009;Teepker et al. 2010). Women's pain perception varies throughout the menstrual cycle and according to Tousignant-Laflamme & Marchand (2009) women have the best CPM effect during the ovulatory phase (day 12 - 14). We therefore decided to test all women during the day 12 to 14, in reference to the first menstrual day. All women self reported their menstrual cycle. Hence, we were then able to compare men and women when they are most equal.

### Test and conditioning stimuli

Several combinations of test stimuli and conditioning stimuli exist, each with advantages and disadvantages (for a review, see Pud et al 2009). Two studies (Arendt-Nielsen et al. 2008;Weissman-Fogel et al. 2008) investigating sex differences in CPM used a muscular TS (pressure pain threshold). In the present study, we chose intramuscular electrical stimulation as TS, similar to Svensson et al. (1999), which could easily be administered at different intensities. For CS we chose heat pain which is easy to assess. The cold pressor test is a common condoning stimulus used in pain studies (Arendt-Nielsen et al. 2008;Goodin et al. 2009), but was not selected. A disadvantage with this CS is that the corresponding increase in blood pressure itself can have an analgesic effect.

### Pain measurement

Participants reported their pain intensity by the use of a visual analogue scale (VAS) (Gracely 2005). The method is based on a 10 cm straight line containing a 0 – 10 scale. Number 0 indicates no pain whereas number 10 indicates the worst pain imaginable. In this experiment, the participants reported VAS after each electrical stimulus. The result was noted in the laboratory logbook and was used for the statistical analysis.

### Experiment

The experiment was a single-blind cross-over design. Each participants participated in one non-painful session and one painful session on the same day (Figure 1), conducted on opposite sides of the body. The order of non-painful and painful was balanced across individuals.

At the start of each session, the pain threshold to electrical stimuli was determined. Heat pain was determined at the beginning of the first session. Each session consisted of three trials. The first trial consisted of electrical stimuli, the second consisted of electrical stimuli and conditioning, and the third trial consisted of electrical stimuli. Each trial consisted of 10 stimuli with 6.5 - 10 seconds interval. Two stimulus intensities were used; both were higher than the individual's pain threshold (PT). The low intensity was 1.1 x PT; the high intensity was 1.6 x PT. The 10 stimuli were given in a randomized sequence, with five low- and five high intensities. VAS was registered after each electrical stimulus. Between each trial there was a three minute interval and between the sessions there was a 30 minute break.

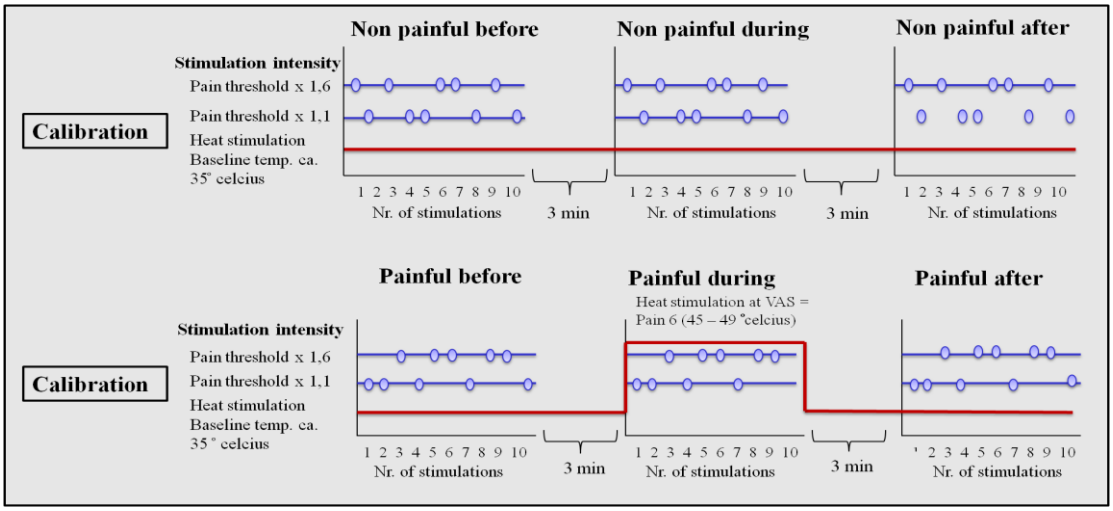


**Figure 1**: Experimental setup.

### Stimulations

Electrical stimuli were applied to the Tibialis anterior muscle as TS. Electrical stimulation of the muscle was conducted by inserting two needle electrodes (9013R0271, Alpine BioMed, Skovlunde, Denmark) 10-15 mm into the muscle, 10 cm under the edge of Patella with approximately one cm in between. The needle electrodes were connected to an electrical stimulator which was approved for human use (Noxitest, Aalborg, Denmark) and controlled by a computer (Labview, National Instruments, Texas, USA). Each stimulus consisted of a brief train of five 1-ms square pulses at 200 Hz.

CS was given in the form of a 25 x 50mm Peltier Thermode in a 3-minute heat stimulation to the skin of the volar forearm on the opposite side of the electrical stimuli (MSA-II, Somedic AB, Solna, Sweden). The temperature was calibrated to be moderately painful for each participant before the experiment began by the use of the Pain-5 calibration method as described below. The heated element was maintained by a cuff and had a constant temperature of 35˚C during the experiment, except for the second session in the painful session.

**Calibration**

Before each session, the participant was tested to find the individual pain threshold by reporting "pain" or "no pain" verbally. The PT was determined by a ladder regime consisting of five ascending series of stimulus (Laursen 1997). The mean of the five ascending thresholds were used as the pain threshold, which was multiplied by 1.1 and 1.6 to determine the test intensities used in the experiment. The number of stimuli used to determine the PT was 20 – 30.

To determine a moderately painful temperature, a calibration model called Pain-6 was used (Granot et al. 2008). Based on pilot trials we modified the model to Pain-5 due to the responses from the pilot participants who had difficulties in tolerating the heat based on Pain-6 for the duration of ten electric stimulations during the painful session. In the Pain-5 calibration each individual received stimulus at 45˚C, 46˚C and 47˚C, each with 10 seconds duration. After each temperature application the individual reported pain intensity by using VAS. If the individual reported VAS = 5 in at least one of the given temperatures, that temperature was determined as Pain-5.

- If the individual reported all three stimuli higher than VAS = 5, they received stimuli at 43 ˚C and 44˚C. If they reported VAS = 5 in at least one of these temperatures, this was determined as Pain-5. If VAS was reported higher than 5 in 43˚C and 44˚C the individual was excluded.
- If the individual reported all three stimuli (45˚C, 46˚C and 47˚C) smaller than VAS = 5 they received stimuli at 48˚C and 49˚C. If they reported VAS = 5 in at least one of these temperatures this was determined as Pain-5. If VAS was reported smaller than 5 in 48˚C and 49˚C the individual was excluded.

**Instructions to participants**

All participants received information before the experiment. During the experiment all participants were given identical instructions in both sessions. They were told that the sessions consisted of three series with 10 stimuli in each, the first without CS, the second with heat pain as CS and the third without CS.

### Statistics

SPSS version 17.0 was used for all statistical analysis. Data in text, figures and tables are presented as mean ± SEM (standard error of the mean). All VAS data were normalized to scores before conditioning (100 %). The effect of painful vs. non-painful conditioning was analyzed with these data by repeated measures ANOVA (RM-ANOVA) with two within-group factors: before, during and after conditioning; and painful vs. non-painful conditioning. Gender was taken as a between group factor. Comparisons of pain threshold between men and women and between sessions were calculated by independent samples t–tests and Pearson's correlation. $P < 0.05$ was considered significant.

## Results

### *Calibration of TS and CS*

The pain threshold for the first calibration (5.43 ± 0.98 mA) vs. the second calibration (5.83 ± 1.24 mA) was not different ($p = 0.61$). This indicated no habituation between sessions and indicated that the electrodes in the tibialis anterior were placed in the same type of tissue. Bivariate correlations analysis was used for test-retest reliability across the first and second calibration (Pearsons $r = 0.68$). This indicated rather good correlation across calibrations.

An independent samples t-test was used for testing potential gender differences in the pain threshold (average of the two calibrations) and pain sensitivity to heat. No significant difference in pain threshold between men and women was observed (6.55 ± 1.59 mA vs. 4.71 ± 1.06 mA, respectively) ($p = 0.67$). The temperature equal to Pain-5 was for men 47.75˚ C ± 0.14˚ C and for women 46.9˚ C ± 0.18˚ C, ($p = 0.92$).

### *Effect of painful and non-painful conditioning*

For each experiment, the five individual pain intensity ratings were averaged for each stimulus intensity (1.1 x PT and 1.6 x PT). Pain intensity ratings to 1.1 x PT and 1.6 x PT were, however, not different (3.03 ± 1.88 vs. 2.87 ± 1.74 cm; paired t-test; $p = 0.44$), so data from both stimulus intensities were pooled in the remaining analyses.

There was a main effect of conditioning. VAS scores during conditioning were reduced to 87 % ± 27 % with respect to before conditioning ($p = 0.02$). VAS scores after conditioning were 95 % ± 34 % with respect to before ($p = 0.34$). The reduction in VAS during painful conditioning (87 % ± 27 %) was not different from the reduction in VAS during non-painful conditioning (92 % ± 21 %) ($p = 0.31$) (Figure 2). Neither was there any difference between men and women ($p = 0.28$); mean VAS scores in men were 91 % ± 21 % whereas mean VAS scores in females were 89 % ± 27 % during (vs. before) conditioning (Figure 2).

**Table 1:** VAS Scores (measured in cm) presented in mean and SEM for both painful and non-painful sessions.

| | | **Painful** *before* | **Painful** *during* | **Painful** *after* | **Non-painful** *before* | **Non-painful** *during* | **Non-painful** *after* |
|---|---|---|---|---|---|---|---|
| **Male** | ***Mean*** | 2.60 | 2.33 | 2.48 | 2.82 | 2.60 | 2.53 |
| | ***SEM*** | 0.37 | 0.35 | 0.39 | 0.42 | 0.42 | 0.36 |
| **Female** | ***Mean*** | 3.45 | 3.01 | 3.20 | 2.93 | 2.67 | 2.51 |
| | ***SEM*** | 0.45 | 0.46 | 0.53 | 0.36 | 0.37 | 0.35 |

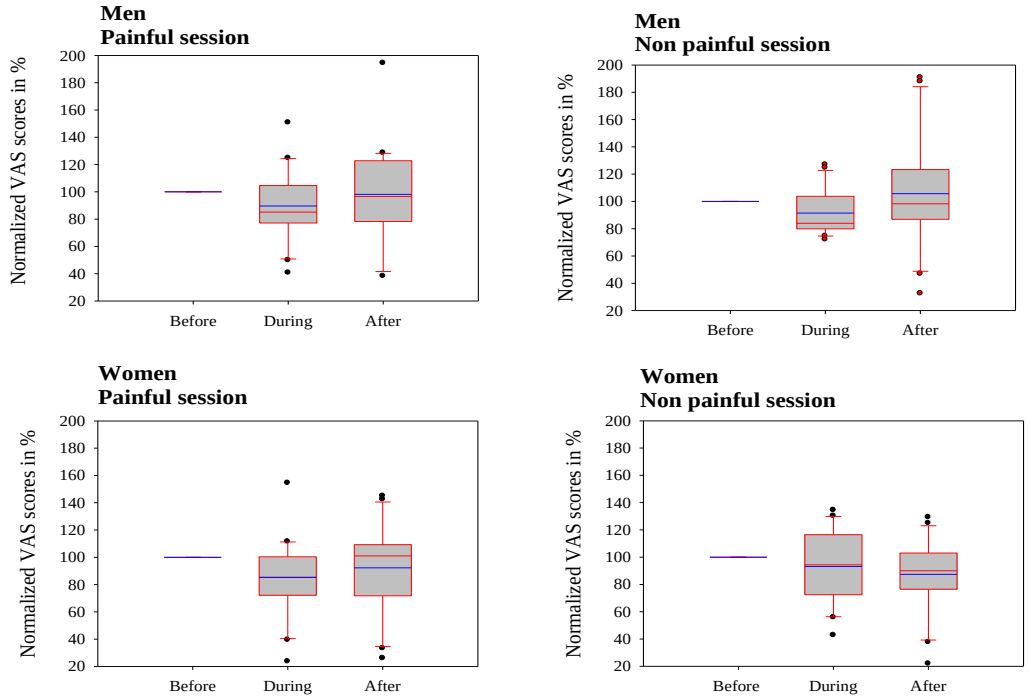


**Figure 2:** VAS ratings in % of before conditioning. Data are displayed as the mean (blue colored line), median, inter-quartile range (box), 5–95% confidence intervals (leaf), and outliers (dots).

## Discussion

The aim of this study was to answer the following questions; (1) is electrically induced muscle pain inhibited by a painful heat stimulus to the forearm?, and (2) do women show signs of reduced inhibition compared to men? The results showed that electrically induced muscle pain was reduced with both painful and non-painful CS. In addition, no differences between men and women were observed.

### Effect of painful and non-painful conditioning

In studies like ours with repeated stimulations and an effect during both painful and non-painful CS, controlling for habituation is important (Treister et al. 2009). In this study habituation was controlled by reported pain during all electrically induced stimulations: before, during and after in both painful and non painful session. These results are presented as averages (Table 1 and figure 2) and do not indicate a habituation component since VAS scores after conditioning are higher than scores during conditioning.

According to Heymen et al. (2010) is attention included in nonspecific effects which are known to have influence on CPM effects. Nonspecific effects describe a reduction in reported pain during non-painful CS. The participants received specific instructions during the experiment where it was emphasized that they would be exposed to a painful conditioning in both sessions. Hence, the participants' expectancy of receiving a painful stimulation without receiving it may have contributed to confounding the results. If the participants had been told that the non-painful session was a control condition without any painful CS, it is likely that it would have resulted in larger differences between the non-painful and the painful session. A participant would not draw the attention towards the heat CS, since they would know they would not be exposed to it. Hence, attention is an important factor which indicates that the reduced muscle pain during the non-painful session is due to the attention component. In addition, few studies have found a significant CPM effect when using non- painful CS (Treister et al. 2009;Heymen et al. 2010), which may support the impression that attention has an effect on the reduction in reported pain in non-painful sessions. On the other hand, it is unlikely that reduction in VAS scores during the non-painful session may be influenced by a CPM effect because a painful CS is needed to activate the inhibitory system.

The reduction in VAS scores during the painful session is probably caused by a combination of a CPM effect and unspecific effects. Therefore, it can be argued that reduced muscle pain during both the painful and the non-painful session have an attentional component. According to Valet et al. (2004) will an attentional distraction occur when a similar stimuli in perceptual quality between TS and CS is used. This is due to the difficulty of drawing attention towards two painful stimuli at the same time (Roelofs et al. 2003). The potential problem of scoring TS and CS at the same time, however, can be circumvented by measuring TS after CS is finished. One must then assume that the inhibitory effect caused by CS outlasts the CS stimulus.

### Gender differences in CPM

Differential activation of the pain inhibitory system in men and women has during the last decade been more commonly discussed. The consensus report by Greenspan et al. (2007) recommended that future research should include both men and women in pain studies.

However, whether there are gender differences in pain or not is still disputed. According to a review conducted by van Wijk and Veldhuijzen (2010) did seven studies from 2004 to 2009 demonstrate a more efficient CPM effect in men than in women (Staud et al. 2003;Ge et al. 2004;Serrao et al. 2004;Arendt-Nielsen et al. 2008;Granot et al. 2008;Weissman-Fogel et al. 2008;Goodin et al. 2009). On the other hand six other studies from 1999 to 2008 showed no gender differences in CPM effect (France and Suchowiecki 1999;Baad-Hansen et al. 2005;Ge et al. 2005;Pud et al. 2005;Tousignant-Laflamme et al. 2008;Lautenbacher et al. 2008).

Pud et al. (2009) argue that methodological variations used in CPM studies make it difficult to generalize across findings. Many different methods have been used in experimental setups for recalling a CPM effect in humans. In addition, a CPM effect may depend on several factors such as duration of stimulations, body region stimulated, strength of stimulations, etc. (Holdcroft and Berkley 2005;Pud et al. 2009). A closer look at the seven studies indicating gender differences in CPM show that four different kinds of TS (Hypertonic saline, pressure pain, heat pain, electrically pain) and four different CS (Isotonic saline, cold pressor, warmth water bath, hand grip devise) were used. Furthermore, different body sites were used (hands, forearm, tiabialis anterior- and trapezius muscle). Only one of the seven studies tested women in a specific menstrual phase (follicular phase). The six studies which revealed no gender differences in CPM effect, used six different methods to induce pain (Capsaicin, electrically pain, glutamate inj., pressure pain, cold pressor, heat pain) and four different methods for CS (ischemic pain, glutamate inj., cold pressor, warmth water bath, punctuate). Only in one of these studies were women tested in a specific phase (follicular phase, day 3 - 9), whereas the other five were neither controlled for sex hormones nor menstrual cycle. In our experiment we controlled for women's menstrual cycle by testing all women in the ovulatory phase. We relied on women's self-reporting and did not take any blood tests to ensure the levels of sex hormones. This can be criticized. For future research collecting blood samples would be a possible way to control menstrual phases in a more objective way. Following Greenspan et al. (2007) hormonal status should be directly measured rather than self reported. This is because some women describe their cycle as regular although they are in fact is irregular.

In most previous studies women have rated pain higher than men have, which indicates that men have a higher pain threshold than women. In addition, men often need a higher temperature than women in calibrating PT to heat (Greenspan et al. 2007). In contrast, no significant differences were revealed between men and women in the present study. There was no difference in Pain-5, the electric calibration indicated no overall PT difference, and there was no observed difference in VAS scores during the sessions. Furthermore, there was not any difference between men and women during either painful or non-painful conditioning. Since we could not isolate a CPM effect it was not possible to conclude on a gender effect on CPM.

However, the strength of this experiment is the balanced design where both a painful and a non-painful session were implemented in the study. Other studies (France and Suchowiecki 1999;Pud et al. 2005) who found a CPM effect and no gender differences did not include control sessions in their studies, which may be a limitation of their observations. In addition, it should be noted that the CPM method has been criticized in studies of the inhibitory system in humans, since mechanisms at the spinal cord level is not taken into account. Hence, it is difficult to ensure whether descending pathways or psychological mechanisms may have influenced the results of the present study.

In sum, electrically induced muscle pain was inhibited by painful heat stimulus and by a non-painful warmth stimulus. During both the painful and the non-painful sessions a reduction in muscle pain was observed where attention is a possible explanation. We did not observe any difference between men and women which indicate that the menstrual cycle as an important factor in investigating the inhibitory system in gender.

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**Appendix I:** Laboratory logbook

ID # _____ Dato og kl. ved opstart _____
Smerte / ikke smerte _____
El. Stimulation side: H / V
Konditionering side: H / V

| | |
|---|---|
| **Rød tekst** | – udføres af Maria |
| **Blå tekst** | – læses af Maria |

**→ FP ønskes velkommen i receptionen og følges til venteværelset.**

**Indledning i venteværelset**

**Ankomst og information**

**Først vil jeg sige at stort set al information som du modtager i løbet af dette forsøg bliver læst op fra en færdigskrevet instruks. Det medfører at noget af det jeg siger, vil blive gentaget. I et forsøg som dette kræver det at alle FP udsættes for de samme betingelser, inkluderet instruktioner og information undervejs. Vi har arbejdet meget med at gøre informationen som du vil modtage let at forstå. Hvis der alligevel er noget som du ikke forstår og som er vigtig for gennemføringen af forsøget så vil du få anledning til at spørge undervejs. Andre spørgsmål og kommentarer kan vi tage efter at forsøget er færdigt. Lyder det i orden?**

**Skemaer**

**Først vil jeg bede dig om at udfylde nogen skemaer.**

**→ Uddel og forklar.**

| Skema | Forklaring til FP |
|---|---|
| Information om forsøget og samtykkeerklæring | **Dette skema beder jeg dig læse igennem og signerer på side 2. Du signerer på at du deltager frivilligt. Jeg minder dig om at du når som helst kan trække dig fra forsøget undervejs.** |

**→ FP udfylder skemaerne alene.**

**→ Kom tilbage efter 15 min.**

**Opsummering af dagens program**

**Det som skal ske i dag er først en kort test af din følsomhed ved varme stimulering. Herefter vil jeg foretage en test af din følsomhed ved elektrisk stimulering i din skinnebensmuskel, dvs. foran på skinnebenet. Disse to tests vil være udgangspunktet for din smertetærskel og vil dermed danne grundlag for de stimuleringerne du vil modtage i forsøget. Det endelige forsøg vil være opdelt i tre blokke, hver blok tager ca. 3 min med 3 minutters pause mellem hver blok. Herefter vil der være 30 minutters pause, hvorefter test og forsøg vil gentage sig.**

**Jeg vil nu følge dig ind i laboratoriet.**

**→ Følg FP til laboratoriet → Bede FP om at sætte sig i stolen**

**I laboratoriet (varme kalibrering)**

**FP skal blive kendt med varme stimulering**

**Jeg vil nu teste dig for at finde dit personlige niveau ved varme stimulering. Til at begynde med skal du blive lidt kendt med varmestimulering. Første skal vi gøre dig lidt kendt med hvor intens varmen kan blive igennem forsøget. Jeg vil nu bruge fire forskellige temperaturer. Temperaturen vil stige fra 35 grader til en temperatur som er lidt højere for hver gang. Den højeste temperatur vare hver gang i 5 sek.**

**→ Giv FP varmeelementet og forklar kort herom: er du klar?**

**→ Udfør 44-45-47-49˚C graders stimulering på underarm.**

| Arm hø/ve? | 44˚C | 45˚C | 47˚ C | 49˚C |
|---|---|---|---|---|
| | | | | |

**Nu skal vi gøre det samme igen. Denne gang skal du angive smerten under hver stimulering. Det betyder at du skal rapportere smerten på en skala fra 0 til 10, hvor 0 er ingen smerte og 10 er det værste du kan tænke dig. → Giv FP en VAS skala. Her er en skala som du skal bruge. Den kaldes en visuel analog skala, eller VAS. Efter hver stimulering skal du angive hvor smertefuld stimuleringen var. Du kan markere det som du oplever og vise det til mig, herefter vil læse det af og notere dit svar.**

**→ Sæt varmeelementet fast: er du klar?**

**→ Udfør 44-45-47-49˚C graders stimulering på underarm.**

| Arm hø/ve? | 44˚C | 45˚C | 47˚ C | 49˚C |
|---|---|---|---|---|
| VAS | | | | |

**Kalibrering Pain-5**

**Det næste jeg skal er at finde ud af hvilken temperatur som vi skal bruge i forsøget. Den tempereratur som vi finder frem til tilsvare din personlige smertetærskel. Varmen vil nu stige til en forhåndsbestemt temperatur hvor den blive i 10 sek. Du skal bestemme hvor intens du synes varmen er. Når den er smertefuld indikerer du det på VAS-skalaen.**

**Er du klar?**

| Varme stimulering (10 sek.) | VAS |
|---|---|
| 45° C | |
| | 1 min. pause |
| 46° C | |
| | 1 min. pause |
| 47° C | |

- Ved VAS = 5 bestemmes denne temp. som Pain-5
- **Pain-5 =**
- Hvis ikke Pain-5 bestemmes ud fra dette fortsættes i en af de to næste tabeller.

| | Varme stimulering (10 sek.) | VAS |
|---|---|---|
| **VAS = større end 5 ved alle temp.** | 43° C | |
| | | 1 min. pause |
| | 44° C | |

- VAS større end 5 ved begge = eksklusion
- VAS = 5 ved af temp. = pain-5
- **Pain-5 =**

**ELLER**

| | Varme stimulering (10 sek.) | VAS |
|---|---|---|
| **VAS = mindre end 5 ved alle temp.** | 48° C | |
| | | 1 min. Pause |
| | 49° C | |

- VAS mindre end 5 ved begge = eksklusion
- VAS = 5 ved af temp. = pain-5
- **Pain-5 =**

Evt.

## I laboratoriet (elektrisk kalibrering)

**Forklaring om elektrisk muskelstimulering**

**Jeg vil nu teste din personlige smertetærskel ved elektrisk muskelstimulering, som skal danne grundlag for stimuleringsniveauet under forsøget. Til at starte med sætter jeg to tynde elektroder ind i muskelen på dit skinneben.**

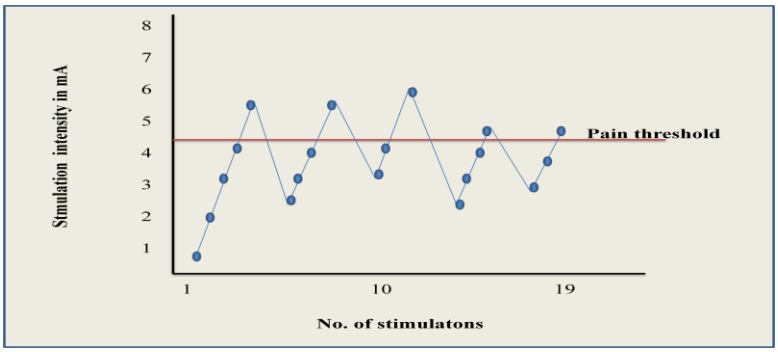
**→ Mål ud fra underkanten af knæskallen og 10 cm ned. Herefter et 2 cm ned på siden af muskelen. Sæt nålene på plads med ca. 1 cm mellem hver.**

**(→ (Spørg først!) Vis nålen frem)**

**Jeg kommer til at styre stimuleringerne manuelt og jeg beder dig fortælle mig, for hver gang du mærker noget, om stimuleringen er smertefuld eller ej. Før vi starter vil**

jeg gøre dig opmærksom på at smerteoplevelsen er subjektiv. Der findes derfor ikke et rigtigt eller forkert svar når du fortæller mig om oplevelsen er smertefuld eller ej.

→ **Fremvis den visuelle fremstilling af kalibrering.**




Det kan tage lidt tid i begyndelsen før vi kommer op i niveau, men prøv at koncentrerer dig frem til vi har fundet dit niveau. Du vil nok opleve at muskelen kontrahere sig og at elektroderne rykker sig når der kommer en stimulering. Det er helt normalt.

→ **Når elektroden er på plads og udstyret klar:** Er du klar til at begynde?

| De 5 ascenderende pain thresshold | | | | | |
|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** |
| **"Smertefuldt"** | | | | | |
| **eller** | | | | | |
| **"ikke smertefuldt"** | | | | | |
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- **Beregn gennemsnit af de 5 PT topværdier = stimulus intensiteten under forsøget**

= _____ + _____ + _____ + _____ + _____= _____/5

=_____ gennemsnit for den enkelte

- **Beregn lav og høj intensitet hos FP.**

Gennemsnit _____ x 1,1 = _____ lav tærskel

Gennemsnit _____ x 1,6 = _____ høj tærskel

## CPM forsøg

**Forsættelse med forsøget**

**Nu har vi fundet dit personlige niveau for forsøget. Jeg vil nu starte forsøget som kommer til at foregå over tre serier. Du vil modtage 10 stimuleringer i hver serie. For hver stimulering skal du rapportere din smerteoplevelse på VAS skalaen fra 0 = ingen smerte til 10 = den værst tænkelige smerte. I første serie får du kun elektriske stimuleringer. I anden serie får du elektriske stimuleringer og varme stimulering og tredje serie får du kun elektriske stimuleringer.**

**→ Når intensitet lav / høj er udfyldt: Er du klar?**

| | 1. Serie | | | 2. Serie | | | 3. Serie | |
|---|---|---|---|---|---|---|---|---|
| | TS | | | TS & kond. | | | TS | |
| Intensitet Lav / Høj | Antal stim. | VAS | 3 Min. pause | Antal stim. | VAS | 3 Min. pause | Antal stim. | VAS |
| | 1 | | | 1 | | | 1 | |
| | 2 | | | 2 | | | 2 | |
| | 3 | | | 3 | | | 3 | |
| | 4 | | | 4 | | | 4 | |
| | 5 | | | 5 | | | 5 | |
| | 6 | | | 6 | | | 6 | |
| | 7 | | | 7 | | | 7 | |
| | 8 | | | 8 | | | 8 | |
| | 9 | | | 9 | | | 9 | |
| | 10 | | | 10 | | | 10 | |

**Tak skal du have. Nu er den første del overstået.**

**→ Demonter og 30 minutters pause**

## Efter 30 minutters pause

ID # _____ Dato og kl. ved opstart _____
Smerte / ikke smerte _____ (Modsat af 1. forsøg)
El. Stimulation side: H / V (Modsat af 1. forsøg)
Konditionering side: H / V (Modsat af 1. forsøg)

**→ FP kommer tilbage fra pause og følges til laboratoriet → Bede FP om at sætte sig i stolen**

## I laboratoriet (elektrisk kalibrering)

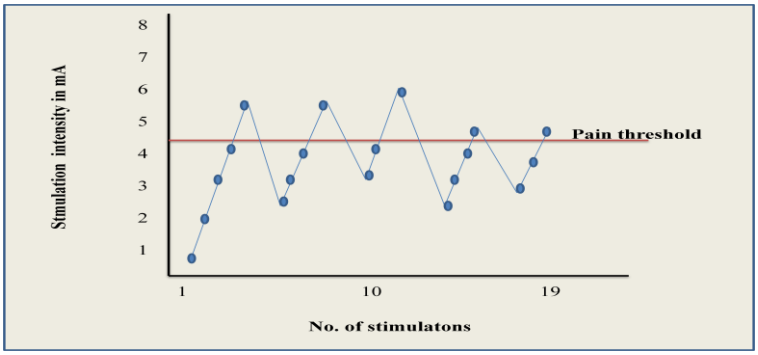
**Forklaring om elektrisk muskelstimulering**
**Jeg vil nu teste din personlige smertetærskel ved elektrisk muskelstimulering, som skal danne grundlag for stimuleringsniveauet under forsøget. Til at starte med sætter jeg to tynde elektroder ind i muskelen på dit skinneben.**

**→ Mål ud fra underkanten af knæskallen og 10 cm ned. Herefter 2 par cm ned på siden af muskelen. Sæt nålene på plads med ca. 1 cm mellem hver.**

**(→ (Spørg først!) Vis nålen frem)**

**Jeg kommer til at styre stimuleringerne manuelt og jeg beder dig fortælle mig, for hver gang du mærker noget, om stimuleringen er smertefuld eller ej. Før vi starter vil jeg gøre dig opmærksom på at smerteoplevelsen er subjektiv. Der findes derfor ikke et rigtigt eller forkert svar når du fortæller mig om oplevelsen er smertefuld eller ej.**

**→ Fremvis den visuelle fremstilling af kalibrering.**




**Det kan tage lidt tid i begyndelsen før vi kommer op i niveau, men prøv at koncentrerer dig frem til vi har fundet dit niveau. Du vil nok opleve at muskelen kontrahere sig og at elektroderne rykker sig når der kommer en stimulering. Det er helt normalt.**

Når elektroden er på plads og udstyret klar: **Er du klar til at begynde?**

| De 5 ascenderende pain thresshold | | | | | |
|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** |
| **"Smertefuldt"** | | | | | |
| **eller** | | | | | |
| **"ikke smertefuldt"** | | | | | |
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| | | | | | |
| | | | | | |

- **Gennemsnit af de 5 PT topværdier = stimulus intensiteten under forsøget**

= _____ + _____ +_____ + _____ +_____ = _____/5

= _____ gennemsnit for den enkelte

- **Beregning af lav og høj intensitet hos FP.**

Gennemsnit _____ x 1,1 = _____ lav tærskel

Gennemsnit _____ x 1,6 = _____ høj tærskel

## CPM forsøg

**Forsættelse med forsøget**

**Nu har vi fundet dit personlige niveau for forsøget. Jeg vil nu starte forsøget som kommer til at foregå over tre serier. Du vil modtage 10 stimuleringer i hver serie. For hver stimulering skal du rapportere din smerteoplevelse på VAS skalaen fra 0 = ingen smerte til 10 = de værst tænkelige smerte. I første serie får du kun elektriske stimuleringer. I anden serie får du elektriske stimuleringer og varme stimulering og tredje serie får du kun elektriske stimuleringer.**

**→ Når intensitet lav / høj er udfyldt: Er du klar?**

| | 1. Serie | | 3 Min. pause | 2. Serie | | 3 Min. pause | 3. Serie | |
|---|---|---|---|---|---|---|---|---|
| | TS | | | TS + kond. | | | TS | |
| Intensitet Lav / Høj | Antal stim. | VAS | | Antal stim. | VAS | | Antal stim. | VAS |
| | 1 | | | | | | | |
| | 2 | | | | | | | |
| | 3 | | | | | | | |
| | 4 | | | | | | | |
| | 5 | | | | | | | |
| | 6 | | | | | | | |
| | 7 | | | | | | | |
| | 8 | | | | | | | |
| | 9 | | | | | | | |
| | 10 | | | | | | | |

**Tak skal du have. Nu er det overstået.**

**→ Demonter og afslut**

Evt.

**Appendix II:** Informed consent

Statens arbeidsmiljøinstitutt

Forespørsel om deltakelse i forskningsprosjektet:

# Smertemodulasjon

Du har sagt deg interessert i å delta i et forsøk som er en del av forskningen ved Avdeling for arbeidsrelaterte muskelskjelettplager ved Statens arbeidsmiljøinstitutt.

**Bakgrunn og formål**

Smerte i huden kan oppleves svakere eller sterkere når andre smerter er tilstede samtidig. Formålet med forsøket er å undersøke hvordan elektriske stimuleringer oppleves når smerte gis stamtidig et annet sted på kroppen.

**Krav til deltakelse**

For å delta i forsøket må du være frisk og ikke være plaget av smerter til daglig. Ved tidspunkt for deltakelse må behandling med reseptbelagte og ikke reseptbelagte smertestillende medisiner være avsluttet minst 24 t i forveien. Videre må du være mellom 18 og 45 år, ikke ha noen kjente somatiske eller psykiatriske sykdommer, ha blodtrykk under 165/100. Du må ikke bruke blodtrykkssenkende eller reseptbelagte beroligende, antidepressive eller allergimedisiner fast. Du må være ikke-røyker og vi ber deg avstå fra å drikke alkohol de siste 24 timer før forsøket.

**Metoder**

To metoder benyttes i prosjektet. Begge metodene er alminnelig brukt innen forskning.

*Elektrisk stimulering av muskel*

To nålelektroder settes inn i en muskel på leggen. Elektriske stimuleringer gis som ved muskelstimuleringer. I alt vil du motta ca 60 elektriske stimuleringer av muskelen.

*Varmestimulering*

Et 43-50°C varmelegeme legges inntil huden i 3 min. Prosedyren vil være forbundet med noe smerte.

**Opplegg**

Deltakelsen strekker seg over 1 gang á ca 2,5 time.

**Bivirkninger**

Når muskelen stimuleres elektrisk kan det medføre noe stølhet/tretthet i den aktuelle muskelen resten av dagen. Ellers er det ikke rapportert noen kjente bivirkninger. Dersom du likevel opplever plager kan du ta kontakt med prosjektlederne ved STAMI (se nedenfor). Som forsøksperson er du dekket av en skadeforsikring tegnet for dette prosjektet.

Prosjektet er initiert av Avdeling for arbeidsrelaterte muskelskjelettplager, Statens arbeidsmiljøinstitutt, Oslo. Prosjektleder er Dagfinn Matre (Dagfinn@stami.no). Kontaktpersoner er prosjektleder (tlf. 23 19 52 15) eller forskningssjef Stein Knardahl.

**Honorering**
Deltakerne honoreres med 150 kr time for tapt arbeidsfortjeneste.

**Dataregistrering**
Innsamlede data blir anonymisert og lagret elektronisk. Anonymiseringsnøkkelen blir lagret manuelt i låsbart arkiv og destrueres når resultatene fra undersøkelsen er publisert.

# Samtykkeerklæring

Jeg har lest informasjonen om prosjektet *Smertemodulasjon* og samtykker i å være med i forsøket. Jeg erkjenner at jeg oppfyller kriteriene for deltakelse. Jeg er klar over at mitt samtykke ikke hindrer meg i når som helst å trekke meg fra forsøket uten å oppgi grunn.

| | |
|---|---|
| Dato | Navn med blokkbokstaver |
| | Underskrift |

**Appendix III:** Advertisement

Statens
arbeidsmiljøinstitutt

## Forsøkspersoner søkes til forskning

Friske personer mellom 18 og 45 år søkes til å delta i en undersøkelse.

Deltakerne vil motta to ulike typer moderate smertefulle stimuli: Varmestimulering på underarmen og elektrisk stimulering av en leggmuskel. Begge metodene er alminnelig brukt i forskning.

Undersøkelsen strekker seg over ca 2,5 timer og deltakelse honoreres med 150 kr/time (skattefritt).

Forsøket gjennomføres i regi av Statens arbeidsmiljøinstitutt på Majorstua (Gydas vei 8) i Oslo fra begynnelsen av januar 2010.

Kontakt Maria Gullander for mer informasjon på telefon 95 21 85 64  eller epost mariagullander@gmail.com

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**Appendix IV:** Approveal from Regional Committees for Medical and Health Research Ethics (REK)

# UNIVERSITETET I OSLO

DET MEDISINSKE FAKULTET

KOPI



Forsker Dagfinn Matre
Statens arbeidsmiljøinstitutt
Postboks 8149 Dep
0033 Oslo

**Regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst C (REK Sør-Øst C)**
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 22 84 46 67
Telefaks: 22 85 05 90
E-post: t.e.svanes@medisin.uio.no
Nettadresse: www.etikkom.no

**Dato: 29.04.09**
**Deres ref.:**
**Vår ref.: S-09278c 2009/6214** (oppgis ved henvendelse)

**Kroppens smertemodulerende system, sentral sensitivisering og smerte fra hud og muskel**

Komiteen behandlet søknaden 22.04.09. Prosjektet er vurdert etter lov om behandling av etikk og redelighet i forskning av 30. juni 2006, jfr. Kunnskapsdepartementets forskrift av 8. juni 2007 og retningslinjer av 27. juni 2007 for de regionale komiteer for medisinsk og helsefaglig forskningsetikk.

*Prosjektet er en videreføring av nylig avsluttet studie av hvordan sentral sensitivisering påvirkes av klinisk nakke/skuldersmerte, hvor man ønsker å belyse hvordan sentral sensitivisering påvirkes når et annet smertefullt sensorisk stimulus gis samtidig i friske forsøkspersoner. Videre søkes det å belyse hvilken rolle forventning til den andre smertefulle stimuleringen har å si på sensitivisering. Det skal også undersøkes om det smertemodulerende system virker ulikt på hud eller muskel, og om kjønn spiller noen rolle.*

Komiteen har ingen innvendinger mot studien, men bemerker at det er uklarhet med henhold til bruken av begrepene avidentifisert og anonymt i informasjonsskrivet til deltakerne.

Med avidentifiserte opplysninger menes opplysninger der navn, fødselsnummer og andre personlige kjennetegn er fjernet. Man kan imidlertid finne tilbake til hvem opplysningene gjelder ved hjelp av en nøkkel eller kode. Dersom opplysningene er anonymisert finnes det ingen nøkkel eller kode som gjør det mulig å koble opplysningene sammen igjen.

Anonymiseringsnøkkel er således ikke et begrep man benytter. Komiteen ber om at informasjonen korrigeres i informasjonsskriv til deltakerne.

**Vedtak:**
Prosjektet godkjennes under forutsetning av at ovennevnte merknad følges opp før igangsetting.

Komiteens avgjørelse var enstemmig.

Komiteenes vedtak etter forskningsetikklovens § 4 kan påklages (jfr. forvaltningsloven § 28) til Den nasjonale forskningsetiske komité for medisin og helsefag. Klagen skal sendes