The effect of experimental sleep restriction on pain inhibition is sex dependent

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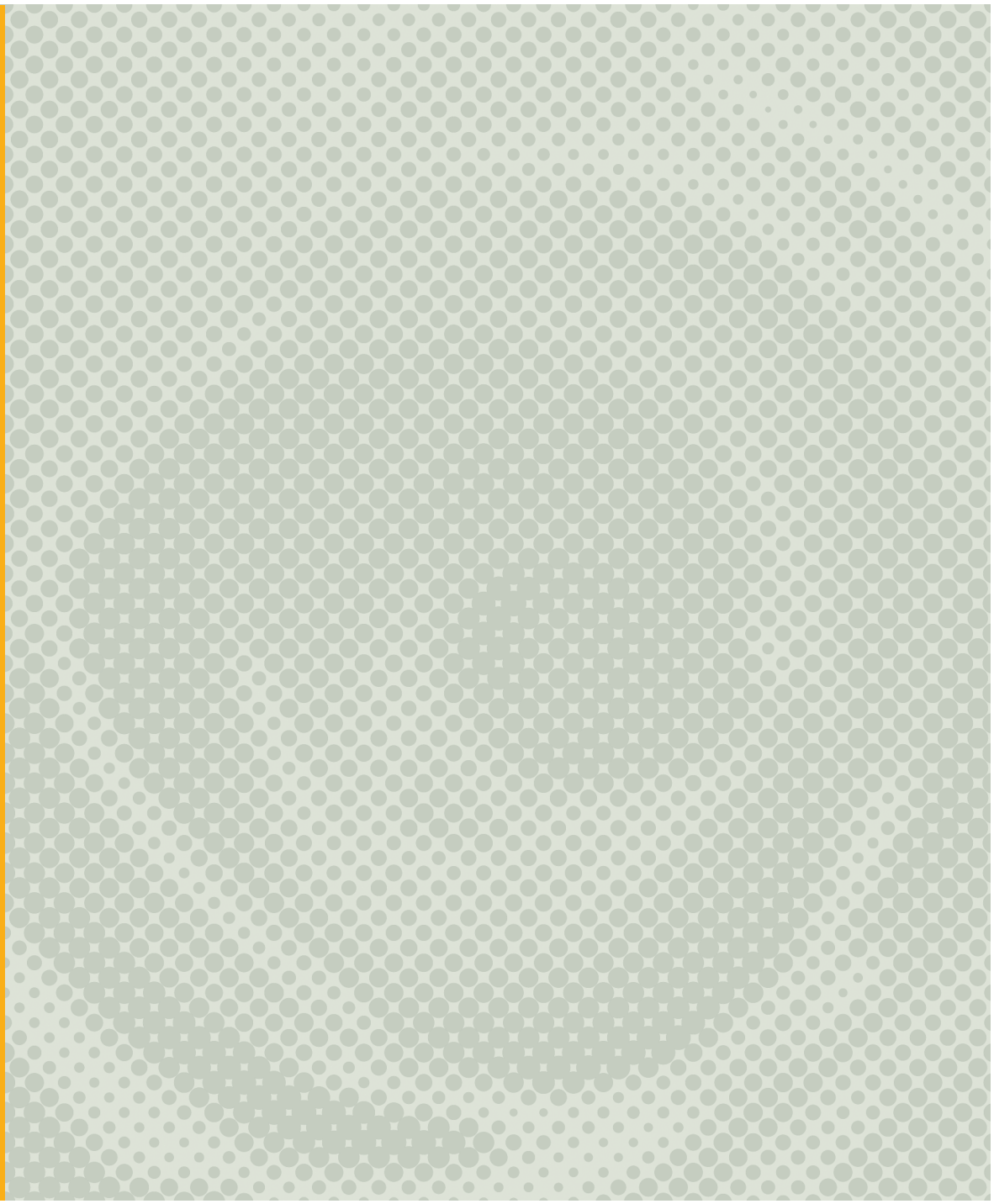

I Forord

Statens arbeidsmiljøinstitutt (STAMI) gav mig mulighed for at skrive min masteropgave som en del af forskningsprojektet ”Skiftarbeide, søvn og smerte”. Smerte er udbredt i befolkningen og udgør derfor et vigtigt folkesundhedsproblem. Med min baggrund som fysioterapeut har jeg mødt mange af disse patienter med smerter og set hvordan deres livskvalitet er påvirket. Søvn og effekten af mangel på søvn er noget jeg, som de fleste andre, har mærket på egen krop. Derfor var jeg nysgerrig efter at lære om hvordan mangel på søvn påvirker smerte.

At skrive masteropgave har været inspirerende, spændende og lærerigt, men til tider også ret krævende. Denne proces ville have været væsentlig mere krævende og ikke nær så lærerigt uden hjælp fra mine to vejledere. Derfor vil jeg takke Dagfinn Matre, forsker ved STAMI, for uundværlig vejledning, spændende og inspirerende faglige diskussioner og god støtte undervejs i skriveprocessen. Camilla Martha Ihlebæk, professor i folkehelsevitenskap ved UMB (ILP) vil jeg takke for mange gode råd og opmuntring og vigtige indspil til opgaven. Videre vil jeg takke Kristian Bernhard Nilsen, overlege ved OUS og STAMI, for gennemlæsning af opgaven og rigtig nyttige faglige kommentarer.

Data fra smerte fysiologiske tests på STAMI er grundlaget for denne masteropgave. Der er mange, der har bidraget til gennemførelsen af disse forsøg. Jeg ønsker at takke forsøgspersonerne for deres bidrag. Jeg har stor respekt for at I frivilligt har accepteret at få påført smertesmertestimuli og undvære søvn. Jorid Thrane Stuenæs, overingeniør ved STAMI, vil jeg takke for at have gennemført alle forsøgene og for at have taget godt hånd om forsøgspersonerne. Rune A. Madsen, overingeniør ved STAMI, skal have tak for at have bidraget med alle former for teknisk assistance.

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Maria Raae Andersen, Oslo 15.11.2013

II Sammendrag

Baggrund: I den norske befolkning er prævalensen af kronisk smerte på 30 %. For personer med kronisk smerte påvirker smerterne i høj grad både det sociale liv og arbejdslivet. Søvnkvalitet og -længde har vist sig at påvirke smerteopfattelse i en negativ retning. Det er derfor foreslået at søvnproblemer kan føre til ændringer i det smertemodulerende system. Eksperimentelle fund indikerer at søvnrestriktion fører til nedsat smertehæmning. Prævalensen af både søvnproblemer og smertetilstande er højere blandt kvinder end blandt mænd. Blodtryk og smerte interagerer og søvnrestriktion kan påvirke blodtrykket.

Formål: Målet med dette studie var 1) at undersøge om eksperimentel påført søvnrestriktion medfører ændring i smertehæmning og 2) at afgøre om der er forskel i denne ændring mellem kvinder og mænd og 3) at undersøge om blodtryksændringer under "smertefuld betinget stimulering" (Eng. CPM) påvirkes af søvnrestriktion eller varierer mellem kønnene.

Metode: Det smertehæmmende system blev testet på 22 friske forsøgspersoner (14 kvinder, 8 mænd) i et overkrydsningsstudie med to betingelser (to nætter med normal søvn vs. to nætter med søvnrestriktion). Smertehæmning blev undersøgt med CPM paradigmet. Test stimuleringen (TS) bestod af to min varmestimulering (47 °C ± 1,3) påført med en termode mod volar siden af underarmen. TS blev givet før og samtidig med en 7 °C kuldepresser-test (CS) på den modsatte hånd. Subjektiv smerte opfattelse af TS blev scoret kontinuerlig på en 0-10 visuel analog skala. Under CPM testen blev blodtrykket målt kontinuerligt.

Resultater: Hos kvinder øgede smerte angivelser af TS før CS efter søvnrestriktion sammenlignet med efter normal søvn ($p = 0{,}001$). Hos mænd var der ingen forskel i smerteangivelser af TS før CS mellem de to søvn betingelser ($p = 0{,}42$). En kraftigere smertehæmning var fundet efter søvnrestriktion vs. efter normal søvn ($p < 0{,}001$). Denne forskel i smerteinhibering var drevet af resultaterne fra kvinderne i studiet, som havde en signifikant øgning i smertehæmning efter søvnrestriktion ($p < 0{,}001$). Blandt mændene i studiet viste resultaterne et svagt fald i smertehæmning efter søvnrestriktion ($p < 0{,}001$). Blodtryksændringer under CPM testen var ikke påvirket af søvnrestriktion og varierede ikke mellem kønnene ($p \geq 0{,}88$).

Konklusion: Disse resultater indikerede at kvinder havde en højere smerteopfattelse efter søvnrestriktion sammenlignet med normal søvn, hvorimod mænds smerteopfattelse var upåvirket af søvnrestriktion. Videre viste resultaterne at søvnrestriktion førte til kraftigere smertehæmning hos kvinder, hvorimod smertehæmningen faldt svagt hos mænd.

III Abstract

Background: The prevalence of chronic pain in the Norwegian population is 30 %. Chronic pain strongly affects the quality of social and working life for the population affected. Sleep quality and quantity has been shown to influence pain perception in a negative direction. Due to that it has been proposed that sleep problems leads to alteration in the function of the pain modulatory system. Some experimental findings indicate that sleep restriction leads to decreased pain inhibition. The prevalence of both sleep problems and pain conditions is higher among women than men and pain perception and modulation differs between sexes. Blood pressure and pain interacts and sleep restriction affects blood pressure.

Aims: The aims of this study were 1) to investigate if experimental induced sleep restriction led to altered pain inhibition and 2) to determine if this alteration had a different pattern in females than in males, and 3) to investigate if blood pressure changes during the conditioned pain modulation (CPM) test were affected by sleep restriction or varied between genders.

Method: In a paired measure cross-over design with two conditions (2 nights normal sleep vs. 2 nights 50 % sleep restriction) the pain inhibitory system was tested in 22 healthy individuals (14 female, 8 males). Pain inhibition was tested with the CPM paradigm. Test stimulus (TS) was induced with a 2-min contact heat test stimulus (47°C ± 1.3) to the volar forearm. TS was delivered before and during a 7° C cold pressor test (CS) to the contralateral hand. Subjective pain ratings of TS were given continuously on a 0-10 visual analogue scale. During the CPM test the blood pressure was obtained continuously.

Results: Among the females pain ratings of TS before CS increased after sleep restriction compared normal sleep ($p = 0.001$). Among the males there were no difference in pain ratings of TS before CS between the two sleep conditions ($p = 0.42$). A stronger pain inhibition was found after sleep deprivation vs. after normal sleep ($p < 0.001$). This difference in pain inhibition was driven by the females, who had a significant increase in pain inhibition after sleep restriction ($p < 0.001$). Among the males a small decrease in pain inhibition was found ($p < 0.001$). Blood pressure changes during the CPM test was not affected by sleep restriction and did not vary between sexes ($p \geq 0.88$).

Conclusion: These results indicated that females had a higher pain perception after sleep restriction compared to after normal sleep, whereas pain perception among males were unaffected by sleep restriction. Furthermore the results indicated that sleep restriction led to an enhanced pain inhibition among females, whereas sleep restriction led to reduced pain inhibition among males.

IV Innhold

V Overview of abbreviations

BP	Blood pressure
CPM	Conditioned Pain Modulation
CS	Conditioning Stimulus
DNIC	Diffuse Noxious Inhibitory Control
IASP	International Association for the Study of Pain
KSS	Karolinska Sleepiness Scale
NRS	Numerical rating scale
PAG	Periaqueductal gray
PPT	Pressure pain threshold
PVT	Psychomotor vigilance test
REK	Regionale komiteer for medisinsk og helse faglig forskningsetikk (Regional commitees for medical and health research)
RVM	Rostral ventromedial medulla
STAMI	Statens arbeidsmiljøinstitutt (National Institute of Occupational Health)
TS	Test stimulus alone
TS + CS	Test stimulus during conditioning stimulus
VAS	Visual analogue scale

VI Overview of figures and tables

VII Overview of appendices

1 Introduction

1.1 Pain and sleep in a public health perspective

Pain conditions are a common health problem in Norway. Around 30 % of the Norwegian population report that they suffer from chronic pain (Breivik et al. 2006; Landmark et al. 2013; Nielsen 2013). This is the highest prevalence of chronic pain found among 15 European countries (Breivik et al. 2006).

Pain is the most common reason for seeking medical assistance in Norway (Den norske legeforening 2009). Many people living with chronic pain experience that they are less able or unable to work (Breivik et al. 2006). Around 50 % of the disability cases in Norway are related to chronic pain (Landmark et al. 2013; Nasjonalt Folkehelseinstitutt 2010). As chronic pain leads to large health care expenses, loss in workforce and expenses related to social compensations and sickness-retirement, it has serious implications on the economy of the society (Nielsen 2013). For musculoskeletal pain alone it is estimated that these expenses amount to between NOK 69-73 billion annually in Norway (Lærum 2013).

For individuals suffering from chronic pain, it has significant impact on life quality by seriously affecting daily activities, social and working life (Breivik et al. 2006) and individuals with many pain symptoms also have a lower self-reported health (Kamaleri et al. 2008; Kjeldsberg et al. 2013).

Pain is often caused by chronic somatic disease and injuries. Psychological illness and chronic pain, too often appears together. However, around 2/3 of the population suffering from chronic pain does not indicate a specific disease to attribute their pain (Rustoen et al. 2004).

Sleep problems are often linked to pain conditions (Morin et al. 1998; Sivertsen et al. 2009). The association between pain and insomnia is perceived as bidirectional (Smith & Haythornthwaite 2004). Sleep problems are a well-documented consequence of chronic pain (Morin et al. 1998).

On the other hand prospective studies show that sleep problems increase the likelihood of developing chronic pain (Canivet et al. 2008; Gupta et al. 2007; Mork & Nilsen 2012). That sleep problems can lead to pain is a relatively new hypothesis (Kaila-Kangas et al. 2006; Smith &

Haythornthwaite 2004). Experimentally induced sleep restriction has been shown to increase pain perception (Kundermann et al. 2004a; Lautenbacher et al. 2006; Schuh-Hofer et al. 2013) and a few studies indicate that this could to be due to alteration in pain modulation caused by sleep restriction (Smith et al. 2007; Tiede et al. 2010). Still, the underlying mechanisms are not clear and more research in this area is needed (Caruso & Waters 2008; Kaila-Kangas et al. 2006; Kundermann et al. 2004a).

Pain and insomnia are not equally distributed in the population. Females and individuals with lower socioeconomic status are more likely to have pain and insomnia symptoms (Kjeldsberg et al. 2013; Landmark et al. 2013; Rustoen et al. 2004; Sivertsen et al. 2009).

Chronic pain affects a large part of the population and there is a social gradient and sex difference in the occurrence of the symptoms. This contributes to social inequities in health. Chronic pain has large consequences for the economy of the society and for the individual it strongly impacts the quality of life. Therefore, chronic pain represents a large public health challenge.

More knowledge about the link between sleep and pain can potentially contribute to better prevention of pain conditions provoked by sleeping problems. Thus the primary aim of this experimental study is to investigate the effect of sleep restriction on pain mechanisms. A second aim is to investigate if there is a sex difference on this effect.

Acute pain leads to increase in blood pressure (BP) (Sacco et al. 2013). Sleep loss either due to sleep problems or experimental sleep restriction has also been found to increase BP (Palagini et al. 2013). Increased BP is associated with decreased pain perception (Sacco et al. 2013). Because of this association between BP, sleep and pain, a third aim is to investigate the effect of sleep restriction and pain on BP.

2 Theory

2.1 Pain and nociception

When describing pain it is important to distinguish between the terms “pain” and “nociception”. The terms are mutually dependent, but describe two different phenomena.
When the body is affected by a potential tissue damaging stimulus, nerve cells called **nociceptiors** are activated. Thus, nociception is the neurological process in the nervous system activated by a stimulus causing, or potentially causing tissue damage (Brodal 2007).
The term **pain** is defined by the International Association for the Study of Pain (IASP) as: “… An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” (Merskey & Bogduk 1994).

Thus, normally pain is a subjective interpretation of a nociceptive signal.
The nociceptive signal in the human body starts in the free nerve endings of the nociceptor, which are found in skin, muscle, periost and other tissue. These terminals can be activated by mechanical, thermal or chemical stimuli. Activation of nociceptors normally requires a stimulus which is so intense that it potentially can lead to tissue damage (Brodal 2007).

The nociceptive signal is transmitted via ascending nociceptors, Aδ-fibers or C-fibers. Aδ-fibres are covered in a myelin sheath which serves as electrical insulation and increases the velocity of the nerve signal (Brodal 2007). Therefore the Aδ-fibers leads the signal faster than the C-fibers which are unmyelinated. Aδ-fibers evoke the first sharp pricking pain, whereas C-fibers are responsible for the burning pain with a slower onset (Ringcamp et al. 2006). Both Aδ-fibers and C-fibers are polymodal, i.e. react on different stimulus modalities. When it comes to thermal stimuli, C-fibers are activated by heat stimuli and Aδ-fibers are activated both by heat and cold stimuli (Ringcamp et al. 2006).

Through the nociceptors the signal is led to the dorsal horn in the spinal cord. In the dorsal horn the signal is passed on through a synapse to a projection neuron. The projection neuron ascends though the spinothalamic tract in spinal cord to the thalamus and the periaqueductal gray (PAG) in the brainstem. From the thalamus the signal is passed on to the insular cortex, somatosensory cortex and cingulate cortex. In these brain areas the nociceptive signal is processed and perceived as pain (Brodal 2007).

The pain perception of a nociceptive signal widely varies dependent on context, attention, genetics, emotional state and simultaneous sensory stimulation (Tracey & Mantyh 2007).

Under normal conditions pain can occur as a result of a potential tissue damaging stimulus or from an inflammatory process in the tissue, but pain can also be caused by damage or dysfunction of the central nervous system (Woolf et al. 2004). In this case pain occurs without any incoming nociceptive signals from the tissue (Woolf et al. 2004). Pain arising from lesions of the peripheral or central nervous system is called neuropathic pain. Functional pain describes a dysfunction in the nervous system where the response to and processing of the nociceptive signal are altered, leading to increased pain sensitivity. Several chronic pain conditions can be categorized as functional pain (Woolf et al. 2004). These examples illustrate how pain can occur without a nociceptive signal.

2.2 Mechanisms of pain modulation

In 1965 the gate control theory was introduced (Melzack & Wall 1965). This theory revolutionized the understanding of pain mechanisms. Before this, pain was thought to be a result of an uninterrupted signal from the tissue to the brain. The gate control theory proposed that the ascending nociceptive signal was modulated in the dorsal horn by descending signals from the brain and by ascending activity in large myelinated nerve fibers (Dickenson 2002). Since the introduction of the gate control theory the understanding of the pain modulation has developed a lot. Today the pain modulating system is seen as a complex and dynamic system (Heinricher & Fields 2006).

Pain modulation involves both excitation and inhibition of the nociceptive signal and finds place in all the synapses from the peripheral tissue to the brain (Nilsen et al. 2010).

Excitatory processes will lead to increased pain perception. An example of an excitatory process is wind-up. Wind-up is induced by temporal summation of excitatory signals in the C-fiber due to repeated activation of the fiber (Sandkühler 2006). Injury of tissue can also lead to lowered pain threshold and higher pain sensitivity in the areas surrounding the injury. This phenomenon is called hyperalgesia and is induced by increased facilitation of nerve signals in the periphery and in the dorsal horn (Ringcamp et al. 2006; Sandkühler 2006).

Repeated painful stimulus can lead to a decrease in pain sensation. This can be due to fatique of the C-fibers (Ringcamp et al. 2006). It can also be due to habituation, which is a process where a sensory response to identical repeated stimuli decreases due to reduction of attention towards the stimulus (Prescott 1998).

At higher levels of the central nervous system the periapueductal grey area (PAG) plays a central role in pain modulation (Heinricher & Fields 2006). PAG receives ascending nociceptive signals from the dorsal horn and descending signals from the limbic system and from the frontal lobe via hypothalamus. The frontal lobe and the limbic system are important for regulating psychological and cognitive mechanisms like fear and attention, which affect pain modulation (Heinricher & Fields 2006). The incoming signals are processed in PAG. PAG is in close and reciprocal connection with the rostral ventromedial medulla (RVM). Via RVM, PAG projects decending signals to the dorsal horn. From the RVM the signal is passed on by either "on-cells" which have an excitatory effect on the ascending nociceptor or by "off-cells" which have an inhibitory effect on the ascending nociceptor (Heinricher & Fields 2006).

Since the PAG-RVM system receives both ascending and descending signals it integrates both bottom-up and top-down processes of pain modulation (Heinricher & Fields 2006). Top-down processes are activated by cognitive and psychological mechanisms in the brain which either leads to inhibition or facilitation of the nociceptive signal. When pain is modulated by attention or mood PAG has been found to be involved in the process (Valet et al. 2004; Villemure & Bushnell 2002). Placebo and nocebo effect is another example of how psychological processes affect pain modulation through the PAG-RVM system (Wager & Howard 2006). Placebo is the pain inhibitory effect which occurs with the expectation of pain relief. Nocebo is the opposite phenomenon, where an expectation of increased pain leads to increased pain in itself (Nilsen et al. 2010).

Diffuse noxious inhibitory control (DNIC) describes the phenomen where the nociceptive signal are inhibited by another noxious stimulus applied in a distant part of the body (Yarnitsky et al. 2010). This is example of a bottom-up process where an ascending signal inhibits another ascending signal. This process also involves the PAG-RVM system (Wilder-Smith et al. 2004).

2.3 Pain modulating in acute and chronic pain

The descending pain modulation is tonically active and there is a dynamic balance between inhibitory and facilitory processes (Heinricher et al. 2009). Thus, the pain modulating system makes the individual capable of acting appropriately on acute pain dependent on the situation. In a situation with threat of further danger the pain modulating system will inhibit the pain signal so escape is possible and in a situation with possibility to rest the pain modulating system will facilitate pain to decrease activity and thereby promote healing (Sacco, 2013).

Several explanations exist for pain states that transit from an acute to a chronic state. One is that the balance shifts towards more facilitory processes (Heinricher et al. 2009). Another is linked to alterations in pain modulation (Staud 2012), such as increased facilitation (Maixner et al. 1998; Staud et al. 2001) and decreased pain inhibition (Lewis et al. 2012b).

There are individual variations in endogenous pain inhibition (Edwards 2005). One study indicate that individuals with less pain inhibitory capacity are in higher risk of developing chronic pain after surgery (Yarnitsky et al. 2008), it is therefore suggested that individuals with reduced inhibitory capacity are more vulnerable to developing chronic pain (Edwards 2005; Yarnitsky et al. 2008). For example the ability to inhibit pain decreases with age and this may partly explain the higher prevalence of pain in elderly (Edwards et al. 2003b).

2.4 Sex differences in pain perception and modulation

Sex differences in pain modulation are found in several pain studies (Fillingim et al. 2009). Females are more sensitive to experimental pain than males and express a higher degree of temporal summation (Fillingim et al. 2009). For pain inhibition the findings are inconsistent, but most studies indicate that females have decreased ability to inhibit pain compared to males (Popescu et al. 2010).

The prevalence of chronic pain conditions is higher among females than among males (Fillingim et al. 2009; Rustoen et al. 2004). Differences in pain modulation between sexes could be one explanation of the higher prevalence of chronic pain among females compared to males (Popescu et al. 2010). Cultural, psychosocial, psychological and hormonal factors can contribute to these differences in pain perception and modulation between sexes (Fillingim et al. 2009).

In females, pain sensitivity changes during the menstrual cycle, due to hormonal fluctuations. This is important to consider in human studies (Greenspan et al. 2007).

2.5 Pain and sleep

Chronic sleep restriction occurs frequently due to shift work (Åkerstedt 2003), social and domestic responsibilities or life style (Banks & Dinges 2007).

Epidemiological studies show strong associations between sleep problems and pain (Morin et al. 1998; Sivertsen et al. 2009). The relationship between sleep and pain is bidirectional (Lautenbacher et al. 2006). Sleep disturbance is a common complaint in chronic pain patients (Morin et al. 1998; Smith & Haythornthwaite 2004), but sleep problems have been identified as a risk factor for developing pain conditions as fibromyalgia, chronic widespread pain and musculoskeletal pain (Canivet et al. 2008; Gupta et al. 2007; Mork & Nilsen 2012).

In healthy human populations sleep also seems to affect pain. Edwards et al. (2008) finds that even one night of too little (<6 hours) or too much (>9 hours) sleep leads to more pain, and experimental studies indicate that sleep deprivation causes decreased pain threshold in healthy subjects (Lautenbacher et al. 2006).

Increase in pain sensitivity due to sleep loss could possibly be explained by the alterations in the pain modulating system (Smith et al. 2007). This is supported by findings from Haack et al. (2012) who found less pain inhibition in insomnia subjects and Paul-Savoie et al. (2012) who found that lower sleep quality is associated with decreased pain inhibition in fibromyalgia patients.

Yet only a few studies have investigated the effect of experimentally induced sleep restriction on pain modulation. Smith et al found that sleep continuity disturbance impaired the ability to inhibit pain, but that simple 50 % sleep restriction did not affect pain inhibition (Smith et al. 2007). Tiede et al. found that attentional modulation of pain was reduced after 50 % sleep restriction and suggests that this reduction could be due to lack of descending pain inhibition (Tiede et al. 2010).

Sleep restriction can cause neurobehavioral deficits such as lapses of attention and depressed mood (Banks & Dinges 2007) which, as mentioned earlier, are factors that affect pain perception. Measures of such effects has, however, not been included in the present project.

2.6 Blood pressure, pain and sleep

Blood pressure and pain interacts (Sacco et al. 2013). High blood pressure can lead to increased pain threshold and reduced pain sensitivity to experimental pain stimuli (Ring et al. 2008) and epidemiologic data shows that the prevalence of chronic musculoskeletal pain is reduced in populations with elevated blood pressure (Hagen et al. 2005). This effect of blood pressure on pain sensitivity is called blood pressure-related hypoalgesia. A study by Olsen et al. (2013) indicates that females have a greater blood pressure-related hypoalgesia than men.

There is a functional interaction between cardiovascular reactions and the pain modulation systems. Acute pain leads to an increased sympathetic nervous activity and this increase in sympathetic nervous activity is associated with an increase in blood pressure (Sacco et al. 2013). Thus, acute pain leads to an increase in blood pressure.

Sleep loss either due to sleep problems or experimental sleep restriction, has in most studies been found to increase blood pressure. The increase in blood pressure due to reduced sleep has been suggested to be caused by increased activation of the sympathetic nervous system (Palagini et al. 2013). However, a study by Pagani et al. (2009) finds that one night of experimentally induced sleep restriction does not increase blood pressure.

3 Experimental pain studies

Experimental studies of pain mechanisms in healthy individuals are important to improve the understanding of physiological and psychological processes that modulate pain (Gracely 2006).

3.1 Diffuse noxious inhibitory controls (DNIC) and conditioned pain modulation (CPM)

The DNIC/CPM paradigm is the most direct way to assess the endogenous pain inhibitory processes in humans (Edwards 2005) and it is therefore commonly used in pain research (Staud 2012). The CPM/DNIC test is performed by inducing a painful test stimulus (TS) twice. The first time the TS is applied alone and the second time it is applied concurrent with (or after) a painful conditioning stimulus (CS). To find the inhibitory effect, the change in pain perception from the first to the second test stimulus is measured (Yarnitsky et al. 2010).

Originally, DNIC described a bottom-up process where a nociceptive signal was inhibited by another noxious stimulus in animals (Pud et al. 2009). This model was adapted to human research and in 2010 Yarnitsky et al. introduced the term “conditioned pain modulation” (CPM) for testing DNIC in humans. CPM is dependent on several excitatory and inhibitory pain processing mechanisms (Yarnitsky et al. 2010). Moont et al. found that the CPM effect in humans was partly due to cognitive distraction, but that there was an additional effect of CPM not explained by cognitive distraction (Moont et al. 2010). Thus, the CPM effect is partly due to bottom-up processes activated by a conditioning noxious stimulus, but also partly dependent on top-down processes activated by e.g. attention.

Even though the CPM model is widely used, the method is not standardized and there is a large methodological diversity (Matre 2013). Different pain modalities (thermal, mechanical, chemical, electrical and ischemic) are used for both TS and CS (Pud et al. 2009). The timing of the CS also varies. In some studies the CS is given concurrent with the TS (parallel testing) and in some studies it is given between the two TS (sequence testing) (Pud et al. 2009).

3.2 Methods for experimental pain stimulation

To study pain an external stimulus must be applied. Thermal, electrical, ischemic, chemical and mechanical stimuli can be used to evoke pain (Gracely 2006)

3.2.1 Heat pain stimulation

Heat is the most commonly used method of pain stimulation in research studies. The heat can be applied either by contact with warm water or a heated object or by radiation (Gracely 2006). Heat stimulation represents a natural stimulation which excites a restricted and well-known group of nociceptors, C-fibers and Aδ-fibers (Gracely 2006; Tousignant-Laflamme et al. 2008). Contact heat stimulation has been used frequently as TS in the CPM paradigm (Chalaye et al. 2013; Granot et al. 2008; Moont et al. 2010; Tousignant-Laflamme et al. 2008). In the present study we have used contact heat stimulation applied with a thermode for TS.

3.2.2 Cold pressor test

Cold stimulus is commonly induced by immersion of a limb in cold water. This procedure is called the cold pressor test. It produces a severe pain which increases rapidly. The fibers activated by cold stimulus is mainly Aδ-fibers (Gracely 2006). When used as CS in the CPM model, the cold pressor test evokes the smallest inter-individual variation compared to ischemic and mechanical pressure pain and is therefore seen as the most efficient conditioning stimuli to induce CPM (Lewis et al. 2012a; Oono et al. 2011). Therefore the cold pressor test was used as conditioning stimulus in the present study.

The cold pressor test triggers a vascular sympathetic activation which leads to increase in BP (Mourot et al. 2009). The increase in BP evoked by the cold pressor test has been found to be related to the magnitude of the CPM effect (Chalaye et al. 2013).

3.3 Subjective pain assessment

Pain is a subjective experience. Subjective pain can be evaluated with qualitative descriptions of the sensation, location and temporal profile. The intensity of the pain is often assessed either with a visual or verbal scale (Arendt-Nielsen & Mogensen 2009).

The visual analog scale (VAS) and numerical rating scale (NRS) scales are found to be valid and reliable and appropriate for pain assessment (Williamson & Hoggart 2005). However, when pain of very high or low intensity is measured with the VAS, ceiling or floor effect can occur (Paul-Dauphin et al. 1999).

Both of these scales provide interval data which can be analyzed with parametric test and they are therefore useful in experimental studies (Williamson & Hoggart 2005).

3.4 Experimental setting

Psychological and cognitive factors like motivation, attention and emotional state influence the results of pain studies. Therefore acclimatization, instruction and information in the experimental setting is important (Arendt-Nielsen & Mogensen 2009). Which time of the day the experiment is performed can as well influence the results of a pain study (Arendt-Nielsen & Mogensen 2009). Another factor found to influence the pain ratings in pain studies is the sex of the experimenter versus sex of the participant (Riley et al. 1998).

4 Main aims and hypotheses

Strong association is found between sleep problems and pain conditions (Morin et al. 1998; Sivertsen et al. 2009). Sleep restriction and sleep problems have been shown to increase pain sensitivity in epidemiological and experimental studies (Edwards et al. 2008; Kundermann et al. 2004b; Schuh-Hofer et al. 2013). It has been suggested that this increase in pain sensitivity could be due to a decreased pain inhibition after sleep restriction (Smith et al. 2007). This has been confirmed by two experimental that indicate that pain inhibition is increased after sleep restriction (Smith et al. 2007; Tiede et al. 2010). Still, the underlying mechanisms are not clear and more research on this area is needed (Caruso & Waters 2008; Kaila-Kangas et al. 2006; Kundermann et al. 2004a)

Therefore the main aim of this study was to investigate if sleep restriction affected pain inhibition. Based on this aim the first null hypothesis of this study was:

H_0: Pain inhibition is equal after sleep restriction vs. after normal sleep.

Insomnia and chronic pain is more prevalent among females than among males (Rustoen et al. 2004; Sivertsen et al. 2009) and females have been shown to have higher pain sensitivity and decreased pain inhibition compared to males (Fillingim et al. 2009).

Therefore, the second aim of this study was to investigate if there is a sex difference in sleep restrictions effect on pain inhibition. Based on this aim following null hypothesis was formed:

H_0: The effect of sleep restriction on pain inhibition is equal for males and females.

There is an interaction between pain modulation and cardiovascular responses (Sacco et al. 2013). Restricted sleep can increase blood pressure (Palagini et al. 2013). Blood pressure could therefore mediate the effect of sleep restriction on pain. Because of this interaction between blood pressure, sleep and pain, the third aim of this study was to investigate if sleep restriction and pain had an effect of blood pressure. Therefore, the last null hypothesis of this study was:

H_0: Blood pressure responses to painful stimulus was equal for both sleep conditions

5 Material and method

5.1 Participants

The participants in the study were recruited from universities and university colleges in Oslo where they all responded to posters placed on central places at the different campuses (Appendix 1). Most of the participants were students. 23 volunteers contacted National Institute of Occupational Health (STAMI) and were included in the study. One person decided to withdraw from the experiment. The remaining group of participant consisted of 14 women and 8 men. The participants were between 18 to 29 years old, with a mean age of 23.2 (SD ± 3.8) years.

Participants had to be between 18-60 years old, be able to understand written and spoken Norwegian and have good self-reported health. The exclusion criteria were a period of chronic pain (pain > 3 VAS, lasting more than 3 months) in the past two years, high degree of sleepiness (see below), poor sleep quality (see below), drug abuse, hypertension (>160/110), pregnancy, breast feeding, cancer, sick leave, psychiatric disease, neurological disease (mild headache for 1-2 days a month was permitted) or regular medication for epilepsy, depression, pain or other medication with neurological effects.

To ensure that the participants fulfilled the inclusion criteria, they were asked to fill out a questionnaire with questions concerning their health (Appendix 2). In addition daytime sleepiness, sleep quality and quantity were assessed with the Epworth sleepiness scale (<11) and the Pittsburg sleep quality index (<7) (Buysse et al. 1989; Johns 1991).

Naturally, hormonal fluctuations in the menstrual cycle affect pain perception in females (Fillingim & Ness 2000). When testing female subjects it is therefore recommended to test all female in the same period of the cycle and avoid the ovulation period because of rapid changes in hormonal levels (Greenspan et al. 2007). The females in this study were tested on the 4-10th day of the menstrual cycle.

Baseline brachial resting blood pressure was examined before the experiment was started. All participants were found to be normotensive.

The participants were offered compensation for travel expenses in addition to NOK 150 per testing hour to compensate for lost work earnings.

5.2 Power analysis

To determine the number of participants needed for the study, a power analysis was performed. Based on the results of a study by Nielsen et al. (submitted), we expected 0.74 cm VAS difference in CPM effect between the two sleep conditions with a standard division (SD) of 1.1. 19 people were needed to be able to reject the null hypothesis with power 0.8 and confidence interval of 95%.

5.3 Design

This study had an experimental, paired measures cross-over design. The CPM test was repeated twice on the same study population under two different conditions (normal sleep vs. sleep deprivation). Thus, the participants were their own controls. An advantage with this design vs. a design with a separate control group is reduced inter-subject variance and therefore fewer subjects needed (Field 2009). The order of the sleep condition was counterbalanced.

The experiments were performed under standardized conditions. Light and room temperature were kept stable. During both sleep conditions the participant received the heat stimulus and cold stimulus on the same arm, but between participants the side for heat and cold stimulus was counterbalanced. Before the study started, a standardized research protocol was developed. The research protocol contained instructions and information to the participants and the manual for the performance of the experiment (Appendix 3). All experiments were carried out by the same female experimenter, who was blinded for the sleeping condition at the time of the experiment.

5.4 Experiment setup

The experiment took place on the STAMI. The experiment was carried out over three days. On the first day a pretest was performed and on the second and third days the actual experiment was carried out. The pretest day took place two days before the first test day and there was at least one week between the first and second test days (Figure 1).

5.4.1 Pretest

The pretest took place 2 days before the first test day. On this day the preparations for the CPM test days were carried out (see section “Preparation for the heat stimulus”) and the order of the sleep condition (normal sleep vs. sleep restriction) for each participant was randomly determined.

5.4.2 Test days

The first and the second test days were similar. Participants went through the experiment after two days of normal sleep and after two days of 50 % sleep restriction (see description below). The second test day found place approximately one month and at least one week after the first test day (Figure 1).

5.4.3 Sleep restriction

During the two days of sleep restriction the participants were instructed to restrict their sleep to 50 % of their normal sleeping time by going to bed later and to wake up at 07:00 (Appendix 4). The participants registered the time they went to bed and the time they got up in a sleep diary (Appendix 5).

To validate the effect of the sleep restriction, three tests were performed to investigate if the participant felt tired. With the psychomotor vigilance test (PVT) the behavioral alertness was tested. The test is carried out by instructing the participants to press a button as soon as they see a figure on a computer screen. The time from the figure appears to the button is pressed is used to indicate the behavioral alertness. Behavioral alertness has been show to be decreasing with increased sleepiness and this test is sensitive to detecting this effect (Basner & Dinges 2011). In addition to PVT, the Karolinska Sleepiness Scale (KSS) were used for detect subjective sleepiness. KSS relies on self report. The score is rated on a scale from very alert to very sleepy (Kaida et al. 2006)

At the end of the test days the participants were placed in a dark quiet room in a lying position with a blanket. They were told to lie down for 20 min and try to fall asleep. Their sleep latency was examined by monitoring their brain activity with electroencephalogram equipment on the scalp.

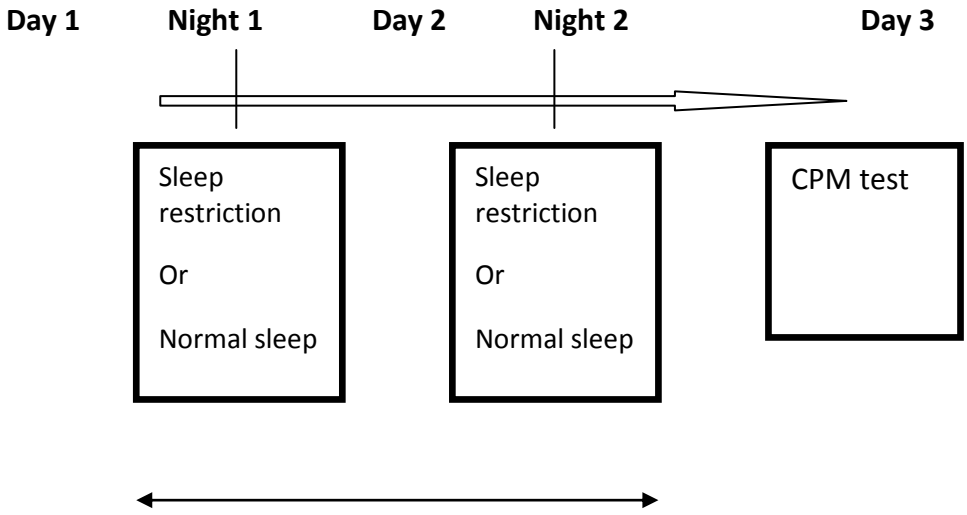

Figure 1. Overview of the implementation of the two sleep conditions (sleep restriction and normal sleep) before the conditioned pain modulation (CPM) test.

5.5 Experimental method

5.5.1 Conditioned pain modulation

To evaluate the participants' ability to inhibit pain, the conditioned pain modulation paradigm was used. The CPM test was performed by inducing a painful heat stimulus (test stimulus) twice for 2 min. The first time the heat stimulus was applied alone. After a 5 min break the heat stimulus was given again concurrently with the cold pressor test (conditioning stimulus). The CPM effect was assessed by calculating the reduction in the pain rating of the TS with the introduction of the CS (Figure 2).

TS	Break	TS + CS
2 min TS	5 min	2 min TS + CS

Figure 2. Timeline of the conditioned pain modulation test. Test stimulus (TS) and test stimulus given concurrently with conditioning stimulus (TS + CS)

5.5.2 Test stimuli

The TS consisted of a nociceptive heat stimulation applied with a 12.5 cm^2 thermode attached to the volar side of the forearm (MSA-II, Somedic AB, Solna, Sweden). The thermode was attached with a blood pressure cuff with a pressure of 20mmHg to ensure that the pressure toward the skin was the same in every test. The stimulation started at 32°c and increased to pain6 (described below), where the temperature was kept stable for 120sek. Before the test began, the participant was informed that the temperature would increase from 32°c and persist for 2 minutes. They were instructed to continuously score the pain that they experienced on the VAS.

5.5.3 Preparations for the heat stimulus

5.5.3.1 Warmth insensitive areas

The innervations of warmth sensitive neurons on human skin are sparse. In some individuals areas as big at a couple of square cm lack sensitivity to warmth stimulation of up to 41°C. These areas also show a significantly higher heat pain threshold (Green & Cruz 1998). As a preparation for the following heat stimulation the participants were tested for warmth insensitive areas. If warmth insensitive areas were found, these areas avoided for the heat stimulation.

5.5.3.2 Determining individual temperature on test stimulus

The temperature for the TS was set to be the temperature which the participant rated as 6 on the NRS scale (pain6). The method used for determination of pain6 was equivalent to the one described by Granot et al. (2008). If the participant did not score NRS 6 at temperatures from 43°C to 49°C, the participant was excluded (figure 3). All of the participants rated NRS 6 at a temperature between 43°C and 49°C.

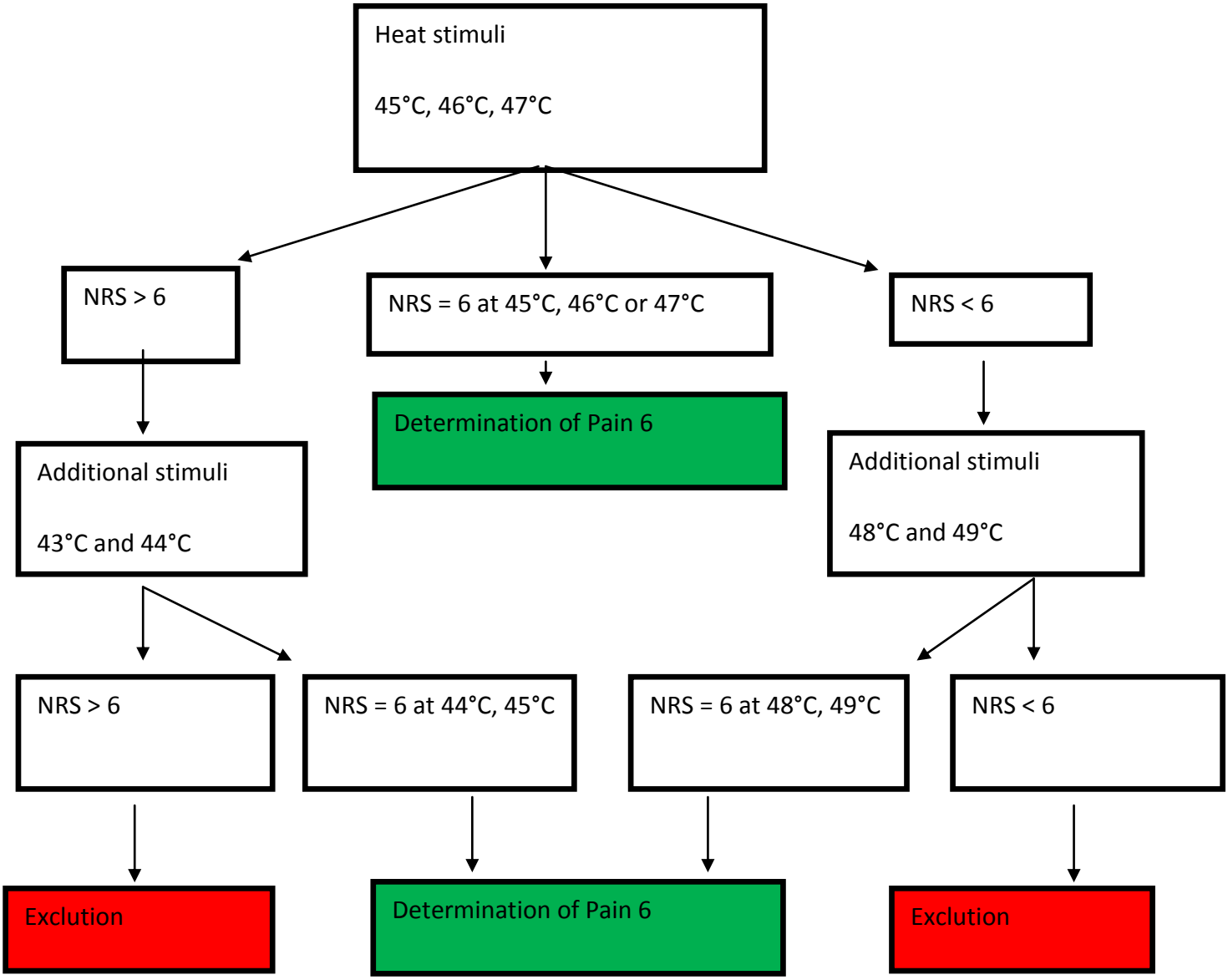

Figure 3. After Granot et al. (2008). Determination of Pain6. Subjective pain ratings (NRS 0-10)

5.5.4 Conditioning stimulus

The cold stimulus was given with a DT hetotherm (type 03 DT 622-1/1) which is a cold bath with 7° C circulating water. The participant was told to keep the hand steady in the bath with water up to the wrist and fingers spread for 120 sec while receiving the heat stimuli simultaneous. Every 30. sec the participant was asked to rate their pain intensity on the NRS.

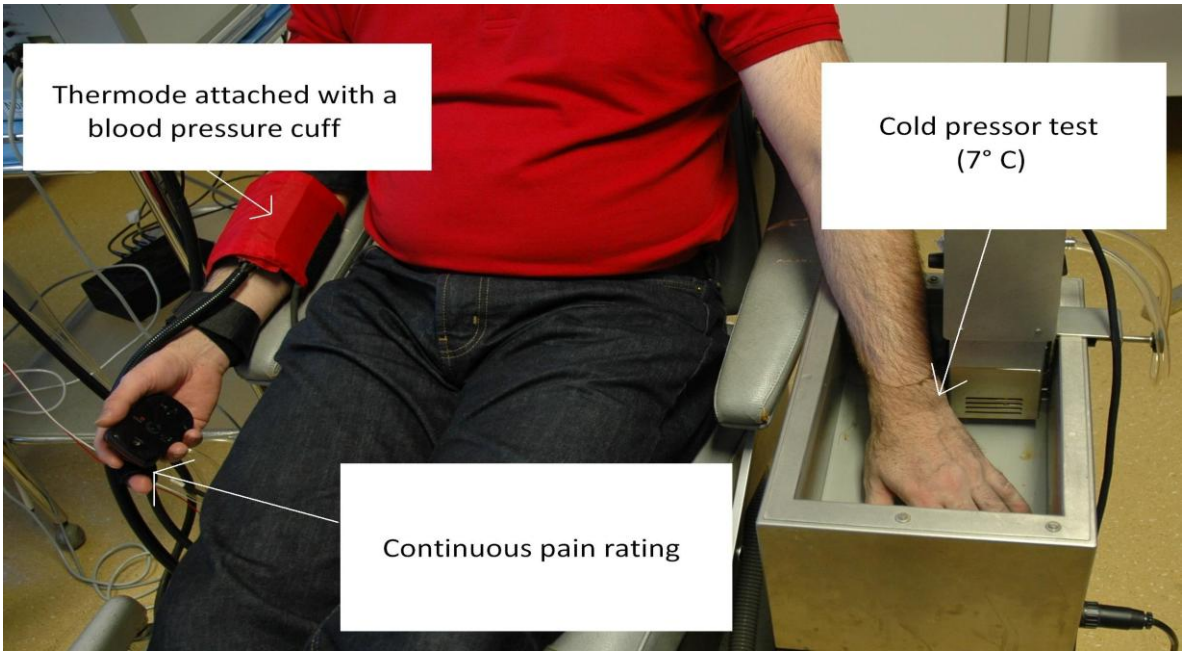

Figure 4. Picture of the conditioned pain modulation (CPM) test setting.

5.6 The outcome measures

The aim of this study is to investigate how sleep restriction affects pain modulation. Therefore, the main outcome measures were subjective pain scores. In addition blood pressure was obtained. The following section describes these two outcome measures.

5.6.1 Pain assessment

To rate the pain from the heat stimulation, the participants used a custom-made computer program (Paindicator, STAMI) which allowed them to rate their pain on a VAS scale by scrolling on a computer mouse. The participants were able to follow their score on the computer screen where a marker was moved in a horizontal direction between the left-end “no pain” to the right-end “worst imaginable pain” on a 10 cm line. The pain score was given continuously and the score was sampled (1 Hz) and saved on a computer file.

For pain assessment of the CS and determination of pain6 the NRS was used. The participants were asked to rate their pain verbally from 0 representing “no pain” to 10 representing “worst imaginable pain” every 30th second. They were allowed to use one decimal.

5.6.2 Blood pressure measurement

Finger BP was measured continuous by (Finometer Model-1, Finapres Medical Systems, Amsterdam, Nederland) during TS and TS + CS.

6 Analyses

6.1 Data processing

Systolic and diastolic finger BP and temperature on the thermode were sampled by a computer (2 kHz; AcqKnowlegde 4.2, BIOPAC Systems, Inc). Two-min. mean values for systolic, diastolic and mean finger BP during TS and during TS + CS were calculated in AcqKnowlegde. BP data from 4 CPM tests were excluded because of technical problems, yielding some of the BP data from 4 patients.

From the continuous (1 Hz) VAS scores 120 data points was stored for each 2-min period. The mean value for every 5 sec was calculated and the corresponding 24 mean VAS scores values (one for each 5 sec in 120 sec) were used in the statistical analysis.

By subtracting the pain ratings from TS + CS from the pain rating from TS, the values for CPM effect were calculated.

6.2 Statistical analyses

SPSS Statistics v.20 (IBM Corporation, USA) was used for the statistics. Descriptive statistics are presented as mean values ± standard error.

The statistical analysis was carried out to compare the results from the CPM tests on the two different test days (after normal sleep vs. after sleep restriction). Furthermore, it was evaluated if there were sex differences in the response to sleep restriction. Finally it was investigated if BP changes were affected by sleep restriction or if there were differences in BP changes between sexes.

A multilevel linear mixed model was used for the statistical analysis. This model takes into account that the independent variables can have a hieratical structure. In this study there were three levels: sleep condition (normal sleep and sleep restriction), testing condition (TS and TS + CS), and time (24 time units).

The residuals of the dependent variables were tested for normality. The assertion was based on evaluation of the histogram of the residual and the Kolmogorov-Smirnov test. In the case of extreme values, the corresponding outcome variables were excluded. One participant had some extremely low VAS values; these values were excluded from the data set, while the rest of

the data from this participant still were included in the data set. Very low VAS ratings could have been a true observation, but in this case it was most likely due to errors in the data processing (see methodological limitations in Discussion), therefore these data was excluded. One participant had extreme systolic blood pressure values, therefore these data were also excluded from the data set.

Data from PVT, KSS, sleep latency and self reported sleeping time were tested for normal distribution. Since data were found not to be normally distributed, a non-parametric test was chosen for the analysis of these data. To investigate if there were any significant differences in scores between the two sleep conditions a Wilcoxons Signed Rank test was performed.

Before analyses were performed, a plot with one slope for every participant was made. On the y-axis the VAS rating was given and on the x-axis the test condition and sleep condition were given respectively. Assessment of this plot indicated that slope and intercept for the VAS ratings for both sleep condition and test condition. Therefore the model included random intercept and slope for both test condition and sleep condition. By including random intercept and slope, the BIC value of the model increased, which indicated that this model fitted the data better.

6.3 Statistical models

The aim of the first analysis was to see if there was a significant change in VAS ratings of TS between the test conditions and the sleep conditions. This model had VAS ratings as the dependent variable. Sleep condition and test condition were set to be independent factors, and testing time was set to be a covariant. Furthermore, to explore if the sleep restriction affected the CPM effect, an interaction between these two conditions were included in the analyses.

To control for sex and age, these variables were included in the model as independent variables. A test was performed to explore if there were sex differences in the effect of sleep condition and test condition on VAS ratings. A 3-way interaction between sex, test condition and sleep condition was tested.

Due to statistical limitation in the analysis of a 3-way interaction, it was not possible to explore if the CPM effect increased or decreased significantly between sleep conditions for males and females. Therefore the CPM effect was included as the dependent variable in a new model.

Thereby the interaction was restricted to a 2-way interaction between sleep condition and sex on the CPM effect.

Blood pressure was treated as the dependent variable to investigate if the sleep condition, sex and test condition affected the blood pressure.

6.4 Ethics

The Helsinki declaration is a statement of ethical principles developed to protect participants in human medical research (WMA Declaration of Helsinki 2008). This study is prepared according to these ethical principles. Some of ethical principles in the Helsinki declaration with great importance for this study are voluntary participation, informed consensus, confidentiality of personal information and that the ricks are accessed and found acceptable compared to the benefits of the study (WMA Declaration of Helsinki 2008). These issues are taken into account by only including volunteer participants, and by taking into consideration that the amount of money paid for participation only covered expenses and lost work earnings, so that the money was not an incitement for participating. All participants gave informed consensus and it was made sure that everyone understood the consent.

The participants were informed that the test would be painful and that the heat stimulus could leave over-sensible and red marks on the skin which would disappear within 24 hours. None of the tests could lead to permanent damage. All participants were informed that they, without any consequences, could withdraw from the study at any time (Appendix 6). Personal information was protected by giving all participants a number code and thereby anonymizing all data. In this study there was no conflict of interests.

This study is a part of at bigger project on STAMI called “Shift work, sleep and pain”. The protocol for this project is approved by the regional committees for medical and health research ethics REK (Appendix 7). All medical and health research on Norwegian territory has to be approved by REK. REK approves medical research according to Norwegian law and ethical guidelines, including the Helsinki declaration (Forskningsetikkloven 2007).

7 Results

7.1 Sleep latency and sleepiness

During the two nights with normal sleep the participant slept on average 7.36 ± 0.72 (mean ± SD) hours. This was significantly more than the average sleeping time of 3.77 ± 0.53 hours during the two nights of sleep deprivation ($Z = -5.8$, $p < 0.001$).

Mean inverse reaction time decreased significantly from 3.01 ± 0.30 s^{-1} after normal sleep to 2.89 ± 0.27 s^{-1} after sleep restriction ($Z=-2.5$, $p = 0.012$). This means that the actual reaction time increased after sleep restriction. The mean score on Karolinska sleepiness scale increased significantly from 4 ± 1.41 after normal sleep to 6.75 ± 1.29 after sleep deprivation ($Z=-3.9$, $p < 0.001$). Sleep latency showed a decreasing trend from 8.82 min after normal sleep to 6.32 min after sleep restriction, but this effect was non-significant ($Z=-1.6$, $p = 0.116$).

A higher reaction time and increased subjective sleepiness and tendency toward lower sleep latency strongly indicate that the participants felt more tired after sleep restriction.

7.2 The effect of sleep condition and test condition on pain ratings

The mean temperature of the test stimulus was 47°C (SD ±1.3).

The first analysis tested if sleep condition affected the TS pain ratings. The main effects of sleep condition and test condition as well as the interaction between these were analyzed. Mean VAS scores are shown in table 1.

A significant main effect of test condition was found. It showed that the participants generally rated the TS pain higher when it was given alone compared to when it was given concurrent with CS ($F(1,1820) = 952.3$, $p < 0.001$). Thus, a significant CPM effect was shown.

The result also showed a significant main effect of sleep condition. Pain ratings increased after sleep restriction vs. after normal sleep ($F(1,1820) = 23.8$, $p < 0.001$).

Most importantly, there was a significant interaction between test condition and sleep condition ($F(1,1820) = 34.1$, $p < 0,001$), showing that the CPM effect was increased after sleep restriction compared to after normal sleep (table 1).

Table 1. Descriptive statistics. Mean subjective pain ratings (VAS) (± SE) of test stimulus given alone (TS) and during conditioning stimulus (TS + CS) and the two different sleep conditions.

	TS	TS + CS	Change (%)
Normal sleep	4.8 ± 0.1	3.3 ± 0.1	-32.6
Sleep restriction	5.5 ± 0.1	3.2 ± 0.1	-41.9

7.3 The effect of sex on the interaction between test condition and sleep condition

In the second analysis, sex was added to the model. It was tested if the interaction between CPM effect and sleep condition differed between males and females.

A significant 3-way interaction was found between test condition, sleep condition and sex ($F(4,794) = 11.7$, $p < 0.001$). This indicates that sleep restriction affected the CPM effect differently between males and females (Figure 5 and table 2).

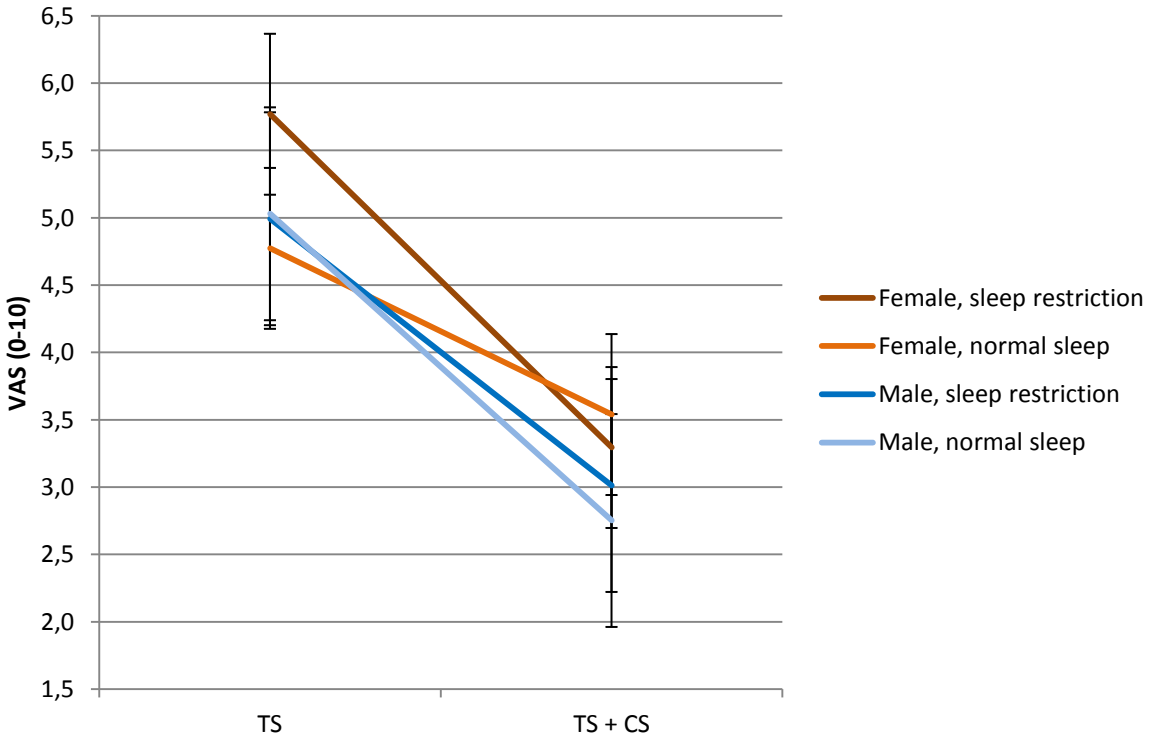

Figure 5. Mean subjective pain ratings (VAS) (± SE) of test stimulus given alone (TS) and during conditioning stimulus (TS + CS) for males and females after normal sleep and after sleep restriction.

Table 2. Descriptive statistics. Mean subjective pain ratings (VAS) (± SE) of test stimulus given alone (TS) and during conditioning stimulus (TS + CS) after normal sleep and after sleep restriction. Split on sex.

		TS	TS + CS	Change (%)
Female	Normal sleep	4.8 ± 0.6	3.5 ± 0.6	25.8
	Sleep restriction	5.8 ± 0.6	3.3 ± 0.6	43.0
Male	Normal sleep	5.0 ± 0.8	2.8 ± 0.8	45.3
	Sleep restriction	5.0 ± 0.8	3.0 ± 0.8	39.7

To get a statistical comparison of the CPM effects between sexes, an analysis with CPM effect as the dependent variable was carried out. This model showed that sleep restriction affected the CPM effect differently in females than in males. The females exhibit a 1.26 cm larger CPM effect after sleep restriction compared to after normal sleep ($F(1,558) = 135.8$, $p < 0.001$). In the males the CPM effect decreased by 0.27 cm following sleep restriction compared with normal sleep ($F(1,301) = 15.1$, $p < 0.001$). Figure 6 shows the difference in CPM effect between males and females dependent on sleep condition.

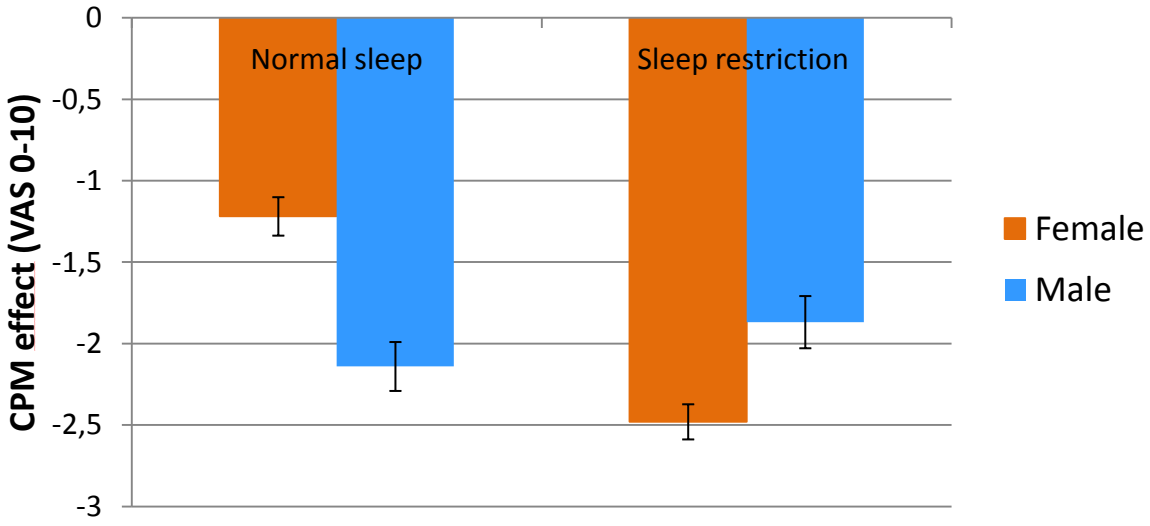

Figure 6. Mean CPM effect (± SE) for males and females after normal sleep and after sleep restriction. Negative values represents a decrease in subjective pain ratings (VAS) of TS with the introduction of the conditioning stimulus.

These results indicate that most of the interaction between test condition and sleep condition was driven by the females, who's pain ratings of TS increased by 20.83 % after sleep restriction compared with after normal sleep ($F(1,574) = 158.3$ $p = 0.001$). For males there were no significant difference in pain ratings of TS between normal sleep and sleep restriction ($F(1,328) = 0.65$, $p = 0.42$) (Figure 5). This indicates that there is a sex difference in effect of sleep restriction on pain perception of TS.

In females pain ratings for TS + CS decrease by 0.2 cm after sleep restriction compared to normal sleep ($F(1,568) = 4.8$, $p = 0.029$). For men the pain ratings for TS + CS increased by 0.2 cm ($F(1,328) = 5.73$, $p = 0.017$) after sleep restriction compared with normal sleep (figure 5).

When age was controlled for in the analysis it showed no effect on the VAS ratings ($F(22) = 0.07$, $p = 0{,}797$) and there was no significant interaction between age and test condition on VAS ratings ($F(1,1820) = 1{,}65$, $p = 0{,}199$) or age and sleep condition on VAS ratings ($F(1,1820) = 1{,}86$, $p = 0{,}172$). Nor was there any 3-ways interaction between sleep condition, test condition and age on VAS ratings ($F(1,1820) = 1{,}56$, $p = 0{,}212$)

7.4 Blood pressure

The last analysis investigated if the conditioning stimulus led to a BP change and if sleep restriction and sex affected this change. In this analysis, systolic, diastolic and mean BP was the dependent variables.

Systolic BP ($F(1,56.7) = 40.2$ $p < 0{,}001$), diastolic BP ($F(1,59.4) = 51.7$, $p < 0{,}001$) and mean BP ($F(1,59.5) = 59.5$, $p < 0{,}001$) increased from TS to TS + CS. Mean values are shown in table 3.

Table 3. Descriptive statistics. Mean blood pressure (BP) (±SE) during test stimulus given alone (TS) and during conditioning stimulus (TS + CS) and BP changes from TS to TS + CS.

	TS	TS + CS	Change (%)
Sys BP (mmHg)	132.6 ± 2.9	146.6 ± 2.9	10.6
Dia BP (mmHg)	75.3 ± 1.8	86.9 ± 1.8	15.4
Mean BP(mmHg)	98.4 ± 2.3	112.5 ± 2.3	14.3

Mean BP (mmHg) (±SE)

An analysis was performed to investigate if change in BP from TS to TS + CS was different after sleep restriction compared to after normal sleep and if a there was a difference between sexes. The results of this analysis showed no significant interaction between test condition, sleep condition and sexes on neither systolic BP ($F(3,57.1) = 0.18$ $p = 0.911$) diastolic BP ($F(3,60.0) = 0.36$ $p = 0.785$) or mean BP ($F(3, 60.1) = 0.22$ $p = 0.88$).

This shows that the BP change from TS to TS + CS did not vary with sleep condition or between sexes. Therefore BP was not integrated in the model as a covariate.

8 Discussion

8.1 Summary of main results

The aim of this study was to investigate the effect of sleep restriction on the CPM effect. Furthermore, it was investigated if this effect was different between sexes. Finally it was investigated if BP changes were affected by sleep restriction or if there were differences in BP changes between sexes.

A prerequisite for investigating the effect of sleep restriction was that the sleep restriction has had the expected impact on the participants. Results from the psychomotor vigilance test and karolinska sleepiness scale showed a significant effect of the sleep restriction, whereas for sleep latency only a trend towards change was found.

A stronger pain inhibition was found after sleep deprivation vs. after normal sleep. This difference was driven by the females, who had a significant increase in pain inhibition after sleep restriction. Among the males a small decrease in pain inhibition was found.

In females the pain ratings of TS increased after sleep restriction compared to after normal sleep. In males the pain ratings of TS was unaffected by sleep restriction.

BP was significantly higher during the TS + CS compared to when TS was given alone. There was no effect of sleep restriction on BP change during the CPM test and no differences in BP response between sexes.

8.2 Discussion of method

8.2.1 Choice of CPM model

The CPM model is seen as the most direct way to assess the endogenous pain inhibitory processes in humans (Edwards 2005) and is therefore commonly used in pain research (Staud 2012).

The CS can be induced by either parallel or sequential stimulation. The parallel model induces a higher CPM effect (Pud et al. 2009) and was therefore chosen for this study.

Many different pain modalities (thermal, chemical, electrical and mechanical) are used for TS and CS (Pud et al. 2009). Heat pain is commonly used as the TS in the CPM paradigm (Chalaye

et al. 2013; Granot et al. 2008; Moont et al. 2010). The advantages of heat stimulation is that it is a natural stimulation which excites a restricted and well-known group of nociceptors (Gracely 2006). Tonic heat stimulation also has good test-retest reliability (Naert et al. 2008). This is important in a paired measure design, where the differences between two identical tests are compared.

Heat pain tolerance varies between subjects. It is therefore difficult to assess individual differences with a fixed temperature, since a certain temperature can be perceived as non-painful in one individual and painful in another (Nielsen et al. 2005). In this study the heat stimulus was therefore individually adjusted to pain6. Pain6 has been shown to reveal a small range of pain score during TS and to be less prone to floor and ceiling effects (Granot et al. 2006).

The temperature for the TS was supposed to evoke a pain sensation with intensity 6 cm on the VAS, but was rated just below 5 cm. When determining pain6, a heat stimulus of 7 sec. was given, while the TS was lasting for 120 sec. The heat pain peaks after 4-15 sec of heat stimulation, mainly due to Aδ-fiber activity (Tousignant-Laflamme et al. 2008). Since pain6 was determined during the peak period, this could explain why the mean score of the TS is below pain6.

The heat stimulus was applied to the same place both during TS and TS + CS. Hyperalgesia can be induced by 46° C for 5 min (Matre et al. 2006). A mean temperature of 47° C in 120 sec could potentially have led to heat induced hyperalgesia. In hyperalgesia to a heat stimulus, the heat pain threshold is lowered (Ringcamp et al. 2006). Thus, hyperalgesia could have led to higher pain ratings of TS during TS + CS, and thereby reduced the CPM effect. Fatigue of the C-fibers can have had the opposite effect and have led to a decrease in pain ratings (Ringcamp et al. 2006). Since these factors had the same influence on the CPM effect during both sleep conditions, it is assumed not to affect the comparison of the sleep conditions.

The cold pressor test induces a natural, strong pain sensation by activation of Aδ-fibers (Arendt-Nielsen & Mogensen 2009; Gracely 2006). In the CPM paradigm the cold presser test has proved to be the most efficient CS to induce CPM effect (Nielsen et al. submitted). It is also found to be reliable between sessions and between individuals (Lewis et al. 2012a; Oono et al.

2011). A temperature of 7° C was chosen because it has been shown to evoke a strong CPM effect (Tousignant-Laflamme et al. 2008) and it was expected to be tolerable for two minutes (Mourot et al. 2009).

8.2.2 Method for sleep restriction

Experimental studies investigating the relation between sleep restriction and pain have used many different methods. The sleep restriction is performed as partial sleep restriction, total sleep deprivation (Schuh-Hofer et al. 2013; Smith et al. 2007; Tiede et al. 2010) or restriction of specific sleep stages (Onen et al. 2001). Partial sleep restriction is more relevant to a clinical setting than total sleep restriction (Banks & Dinges 2007), therefore two days of partial sleep restriction was chosen in this study.

Some authors have the participants sleeping in the laboratory, where sleep quality and duration can be controlled and measured in a more precise manner (Edwards et al. 2009; Haack & Mullington 2005; Smith et al. 2007), while others, like in this study, give the participants sleep instructions and let them sleep in their home environment and then rely on self- reported sleep duration (Goodin et al. 2012; Tiede et al. 2010).

By letting the participants sleep at home we were less able to control the sleep duration and not able to assess the sleep quality. On the other hand the participants slept in a more natural setting, which could be more relevant for a clinical situation (i.e. higher external validity). With the psychomotor vigilance test, karolinska sleepiness scale and sleep latency it was examined if the sleep restriction had the expected effect. The results from these tests confirmed that the sleep restriction had an effect.

8.2.3 Study design

In a paired measures design the individual differences are controlled for by measuring the same participant twice and therefore the effect of the experimental condition is more likely to show up in a smaller group of participants and fewer participants are needed (Field 2009).

When the participants go through the same test twice, the response to the test can be affected by the order of the conditions, and that may have cause a systematic variation. This can be controlled for by randomizing the order of the condition (Field 2009). In our study we could for example expect that the participants would have different expectations and levels of fear from

the first to the second test. Therefore, the order of the sleep condition (sleep restriction vs. normal sleep) was counterbalanced.

8.2.4 Choice of statistical model

The residuals of the data from this study were normally distributed and the dependent variables were continues data. Therefore a parametric test was chosen. The statistical model had to be suitable for repeated measure data. The linear mixed model was chosen above the paired sample t-test, mainly because the aim of this study was to compare the effect of several conditions on VAS ratings. When comparing more than two conditions the t-test cannot be used. Whereas the linear mixed model can compare several condition and covariates can be integrated in the model (Field 2009).

8.2.5 Validity and reliability

Internal validity describes if the observed effect of an independent variable on the dependent variable is a real effect and can be trusted. Therefore the internal validity has to be high to draw a causal conclusion. In order to achieve a high internal validity it is necessary to avoid systematic errors (Benestad & Laake 2008).

Several factors are known to affect pain perception and sleep. To avoid systematic errors these factors were taken into consideration in the inclusion criteria. This led to a relatively homogenous group of subjects with good sleep habits, good health and without any clinical diseases.

Sex differences are found in pain perception and modulation therefore it is important to investigate this differences (Greenspan et al. 2007). Both males and females were therefore included in the study and the differences between sexes were analyzed. To minimize the effect of changes in hormonal level (during the menstrual cycle) all females were tested in the same period of the menstrual cycle under both sleep conditions. By testing the females on day 4-10 of their cycle, we avoided the ovulation, where rapid changes in hormone levels occurs and the pre-menstrual phase where mood changes can occur (Greenspan et al. 2007). This makes us able to conclude that the differences found between the sexes were not due to random hormonal fluctuations or hormonally induced mood changes.

A decrease in CPM effect with age has been shown (Edwards, 2003), and therefore age was controlled for in the analyses.

High BP can reduce pain sensitivity (Sacco et al. 2013). In this study the baseline blood pressure was measured to ensure that all participants had blood pressure values within the normal range (< 160/110 mmHg).

Blinding is important for the internal validity (Skovlund & Vatn 2008). This study is single blinded since the experimenter was blinded for the sleep condition, but blinding of the participants was impossible. The fact that the participants were not blinded can have impact on the results because expectations to the effect of sleep restriction can have affected the pain evaluation. However, the participants were blinded from the hypothesis of the study and from the aim of the CPM test, which can have protected the validity of the tests.

Instructions and information in the experimental setting is important aspects for the validity of experimental pain studies (Arendt-Nielsen & Mogensen 2009). Ahead of the experiment all participants received written information about the pain testing. All instructions and information given during the experiment were read aloud from a written manuscript to ensure that all participants received the same information and instructions. The same female experimenter was performing all the experiments.

Another important aspect of validity is whether the instrument used in the experiment is measuring what it is supposed to measure. In addition to being valid, the instrument also has to be reliable, which means that the instrument has to produce the same results under the same conditions (Fields et al. 2006).

The main outcome of this study was subjective pain ratings assessed with the VAS. The VAS is perceived to be a valid and reliable pain rating tool (Gracely 2006; Williamson & Hoggart 2005). Though, floor and ceiling effect can occur when using the VAS (Paul-Dauphin et al. 1999), but in this study most pain ratings were on the middle of the VAS and therefore it is not likely that this effect will interfere with the results. The orientation of the scale is also important for the validity of the tool, it is recommended that the scale is oriented in the same direction as the reading direction (Williamson & Hoggart 2005). In accordance with the recommendations a horizontal VAS scale was used in this study.

To measure changes in BP during the CPM test the finger cuff method was used. This method gives the opportunity to measure the BP continuously and gives an accurate estimate of BP changes over time (Pickering et al. 2005). The validity of this method is good (Pickering et al. 2005)

As discussed in the section “Choice of CPM model”, the validity and reliability of the thermal stimulation is also perceived as good.

8.2.6 Clinical relevance and external validity

The external validity describes if the results of at study can be generalized to the general population. Experimental studies typically have a low degree of external validity because the study population are not representative for the general population (Skovlund & Vatn 2008), this is also true for this study.

In the general population there is a large prevalence of sleep problems and pain conditions (Breivik et al. 2006; Sivertsen et al. 2009). The prevalence of chronic pain in the population increases with age and is higher among people with lower socioeconomic status (Breivik et al. 2006). Everyone in this study population was pain-free, healthy, young and slept well and were about to get a higher education (i.e. high socioeconomic status). Therefore the study population of this study is not representative for the general population and the results cannot be uncritical generalized.

In experimental pain studies the responses to an acute pain stimulation is often investigated in pain-free, healthy subjects (Gracely 2006). The mechanisms behind chronic pain differ from those of acute pain in many aspects. Chronic pain patients are found to have impaired pain inhibition and increased pain sensitivity (Staud 2012). Therefore the participants in this study it can be expected to have different pain modulating reactions to experimentally induced pain than chronic pain patients would have had.

People suffering from chronic pain conditions often experience that their daily activities, social- and working life are affected by their pain (Breivik et al. 2006). The experimental setting will not imitate the negative psychosocial consequences of chronic pain conditions.

The sleep restriction in this study had a short time perspective. People with sleep problems will often experience sleep loss over long time periods. In general, the negative effects of sleep

restriction accumulate over time (Banks & Dinges 2007). Therefore, this study will not directly be related to clinical sleep problems, where the negative consequences can build up over time.

The advantages of experimental pain studies are that they can provide information about physiological mechanisms that modulates pain (Gracely 2006). Pain conditions and sleep problems are prevalent, and sex differences are observed in both conditions. Knowledge about the mechanisms behind this association will be useful in the prevention and treatment of pain conditions. Therefore the findings of this study can be beneficial for both pain patients and the general population.

8.2.7 Methodological limitations

The heat stimulus started at 32°C and increased by 1°C/sec until the pain6 temperature was reached. Thereafter it was maintained for 2 minutes before it again ramped down to 32 °c. The exact starting point for the 2 minute plateau was not marked in the VAS rating file; therefore it was set to be the first VAS rating > 0. Since the heat rose from 32° C to pain6, the first VAS rating can have been before the 2 minute heat stimulation started and this part of the data processing can have led to a wrong onset of TS alone and during TS + CS. Therefore, the analysis was carried out without the first 15 VAS ratings of each TS in the CPM tests.

8.3 Discussion of results

8.3.1 After normal sleep

8.3.1.1 Pain perception

Both males and females rated the pain from the TS just around 5 cm on the VAS after normal sleep.

8.3.1.2 Pain inhibition

A prerequisite for evaluating the effect of sleep restriction on the CPM effect is that the CPM test actually evokes a CPM effect in the participants.

After normal sleep the mean CPM effect was 32.6 %. There are no standardized CPM paradigm and large methodological diversity between studies and therefore it is difficult to make comparisons between studies (Matre 2013). So whether this CPM effect is small or large is difficult to decide.

In this study we investigate a pain-free self-reported healthy population. Edwards finds that in a healthy population, greater DNIC effect is related to less pain and better self-reported general health (Edwards et al. 2003b). Therefore, we can assume that this population will have a relative strong CPM effect.

The results of this study showed that males had greater CPM effect than females. This effect was driven by a higher CPM effect in males than in females after normal sleep. Previous studies also find greater CPM effect in males than females (Ge et al. 2004; Ge et al. 2005; Serrao et al. 2004; Staud et al. 2003) Less efficient pain inhibitory effect in females could be a contributing factor to the higher prevalence of pain conditions in females (Ge et al. 2005).

8.3.2 After sleep restriction

8.3.2.1 Pain perception

Sleep restriction affected pain perception different in females than in males.

In females the pain ratings of TS alone increased by 20.8 % after sleep restriction. This result indicates that the pain perception increases after sleep restriction. This finding is consistent with findings from several studies which indicate that less sleep increases pain perception (Kundermann et al. 2004b; Lautenbacher et al. 2006; Schuh-Hofer et al. 2013).

Pain ratings will increase during tonic heat stimulation. This may be due to temporal summation and/or a local build up of heat in the tissue (Granot et al. 2006; Tousignant-Laflamme et al. 2008). Therefore, the increase in pain ratings of TS after sleep restriction could also be due to increased temporal summation in females after sleep restriction.

In general, females exhibit more temporal summation than men do (Fillingim et al. 2009). Increase in temporal summation after sleep restriction would be in opposition to the findings from Schuh-Hofer et al. (2013), who find that sleep deprivation does not affect wind-up, but they do not look at sex differences.

In males the pain ratings of TS were not affected by sleep restriction. Thus, the males' pain perception seems to be unaffected by the sleep restriction. This is not consistent with findings of increased pain perception after sleep restriction form studies by e.g. Kundermann et al. (2004b) and Schuh-Hofer et al. (2013), but these studies included both males and females. A study by Onen et al. (2001) only included male subjects and they found no effect of sleep

interruption or deprivation on thermal pain tolerance tests which supports the findings of this study.

8.3.2.2 Pain inhibition

Decreased CPM effect is found in insomnia patients (Haack et al. 2012), and poor sleep is associated with lower CPM effect in pain patients (Edwards et al. 2009). To understand the mechanisms behind this association between sleep and pain inhibition, and to find out whether the association is causal, experimental studies are needed (Smith & Haythornthwaite 2004). Today only a few experimental studies have investigated the effect of sleep restriction on pain inhibition (Smith et al. 2007; Tiede et al. 2010).

Smith et al. (2007) found that simple 50 % sleep restriction over three days did not affect the CPM effect in females, whereas 50 % partial sleep restriction induced by waking up 8 times during the night led to a decrease in CPM effect. Tiede et al. (2010) found that attentional modulation of pain was reduced following one night of 50 % sleep restriction and suggest that this reduction can be due to reduced decending pain inhibition (Tiede et al. 2010).

Based on these findings, it was expected to find a neutral or negative effect of sleep restriction on the CPM effect.

In the male subjects a 0.3 cm decrease in CPM effect was found after sleep restriction, which corresponded with these earlier findings from Tiede et al. (2010) and (Smith et al. 2007).

In females the CPM effect increased by 1.3 cm. Even though the pain rating of TS was higher after sleep restriction compared to after normal sleep, the pain ratings of TS during TS + CS was inhibited to a even lower level after sleep restriction compared to after normal sleep.

This finding is not supported by the findings from Smith et al. (2007) who included only females in the same age group and used the same kind of sleep restriction (50 % simple sleep restriction). The most significant difference between the present study and the study by Smith et al. (2007) is the pain modality of the TS. Smith used pressure pain threshold (PPT) as TS. PPT was measured before and during the cold pressor test. PPT represented a short phasic stimulus and could therefore not lead to a temporal summation. If sleep restriction affects temporal summation this would not have affected the results from the study by Smith et al. (2007).

In females the results of this study could indicate an increased facilitory effect, and at the same time an increased pain inhibitory effect of sleep restriction. One hypothesis could be that sleep restriction leads to alterations in the pain modulating systems by up-regulating both the inhibitory and facilitory mechanisms in females.

A central part of the endogenous pain modulating system (PAG-RVM) integrates bottom-up and top-down processes and provides a dynamic balance between pain inhibitory and facilitory activity (Heinricher et al. 2009). It may be speculated that up-regulating of the bottom-up facilitory mechanisms lead to an increased top-down regulation pain inhibitory mechanisms.

PAG is known to be involved in both sleep mechanisms and pain modulation (Smith & Haythornthwaite 2004), this could explain the interaction between sleep and pain modulation.

Sleep problems and chronic pain conditions are more prevalent among females than among males (Rustoen et al. 2004; Sivertsen et al. 2009). In general, females have higher pain sensitivity, stronger pain facilitation and less pain inhibition (Fillingim et al. 2009). Maybe inter-relating mechanisms between sleep and pain affects females differently than males.

No articles investigating sex differences in pain as an effect of sleep restriction were found. A review article of the consequences of sleep deprivation by Orzel-Gryglewska (2010) found that most studies in this field do not take sex differences into consideration.

The findings of this study could also have been affected by methodological issues. Earlier results from studies performed in at the pain laboratory on STAMI show that pain ratings of TS around 6 cm on VAS lead to higher CPM effect than lower pain ratings of TS (unpublished). From this perspective, the increase in CPM effect could simply be due to pain ratings are closer to VAS 6 cm after sleep restriction compared to after normal sleep.

The pain perception from the cold pressor could also have increased. Increase in the intensity of the conditioning stimuli has been shown to increase the CPM effect (Tousignant-Laflamme et al. 2008). This could also have affected the results of this study. Still it is unlikely that this effect is only due to these methodological issues, since ratings of TS + CS is inhibited to a even lower level after sleep restriction compared to normal sleep.

8.3.3 Blood pressure

Activation of the sympathetic nervous system and increase in BP are known effects of the cold pressor test (Mourot et al. 2009). The CPM effect could partly be due to activation of the sympathetic nervous system an rise in BP, which in itself has an analgesic effect (Chalaye et al. 2013).

In the present study BP increased during the cold presser test, as expected. However, it did not vary with sleep condition.

Partial or total sleep deprivation has been shown to lead to increased BP (Palagini et al. 2013). Rise in BP during the cold pressure test is related to the magnitude of the CPM effect according to Chalaye et al. (2013). If sleep restriction in this study led to BP changes this could possible interfere with the CPM effect. Sex differences have been found in BP-related hypoalgesia (Olsen et al. 2013). Therefore, it was also investigated if there were sex differences in BP changes during CS.

The relative BP response did not vary with sleep condition or between sexes. Therefore, it is not likely that the sex difference in the effect of sleep restriction on the CPM effect is explained by differences in the BP response to the CS.

Pagani et al. (2009) found no effect of one night of total sleep restriction an suggest that this could be because one single night of sleep restriction was not enough to cause an effect on BP in healthy individuals. It is likely that two nights of 50 % sleep restriction not is enough to cause an effect on BP.

8.3.4 Age

The CPM effect was not dependent on the age of the participants in this study. This is not surprising since the age range in this study population were only 11 years, while a study which found an effect of age on CPM effect compared two groups with 40 years in mean difference (Edwards et al. 2003a). There were no interaction between age, test condition and sleep condition on pain ratings. The effect of sleep restriction on the CPM effect could therefore not be explained by age.

8.3.5 Cognitive and psychological processes

Sleep problems is often associated with mental conditions such as anxiety and depression (Sivertsen et al. 2009). Experimental sleep restriction has also been found to affect mood (Pilcher & Huffcutt 1996). Negative emotions affects pain perception (Rainville et al. 2005) and sex differences in pain perception and modulation have been suggested to be partly due to psychological mechanisms (Fillingim et al. 2009). Different psychological reactions to sleep restriction between sexes could maybe be part of the explanation why sleep restriction affect pain perception and modulation different between sexes.

However, (Haack & Mullington 2005) showed that sleep deprivation compromised optimistic outlook and psychosocial functioning, but that these factors could not explain the increase in pain reporting (Haack & Mullington 2005).

Several cognitive functions like attention, memory and behavioral alertness are affected by sleep restriction (Banks & Dinges 2007). Participants in this study showed decreased behavioral alertness. Other cognitive functions could also have been affected by the sleep restriction. Since cognitive and psychological processes affect top-down pain modulation, it would have been relevant to examine the cognitive and psychological state of the participants.

9 Conclusion

The results of this study indicate that there are sex differences in the effect of sleep restriction on pain inhibition and pain perception.

Sleep restriction led to increased pain inhibition in females, whereas in males sleep restriction led to slightly reduced pain inhibition.

Furthermore the results indicate that pain perception increases in females after sleep restriction, whereas pain perception in males are unaffected by sleep restriction.

Changes in BP during the CPM test did not vary between sexes and were not associated with sleep restriction. It is therefore not likely that differences in BP changes can explain the findings of this study.

The finding of increased pain inhibition after sleep restriction in females is not supported by earlier findings. The foundation for this finding is unclear and more research is therefore needed to verify the results of this study. Focus on sex differences in the interaction between sleep restriction and pain modulation is required.

Experimental pain research is needed to identify and understand the link between sleep and pain mechanisms. More knowledge in this field could contribute to better prevention and treatments of pain conditions provoked by sleep problems and thereby improve the public health and benefit both individuals and society.

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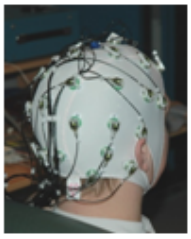
11 Appendices

11.1 Appendix 1. Recruitment poster

Statens arbeidsmiljøinstitutt



Forsøkspersoner søkes til forskning

Friske personer mellom 18 - 60 år søkes til å delta i en undersøkelse av fysiologiske effekter av lite søvn. Deltakerne vil motta moderat smertefulle stimuleringer på huden. Denne type stimulering er alminnelig brukt i forskning. Elektrisk aktivitet fra hjernen (EEG) vil registreres samtidig.

Undersøkelsen strekker seg over i alt ca 7 timer fordelt på 3 ulike dager høsten 2012. To netter vil deltakeren sove mindre enn vanlig.

Deltakelse honoreres.

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

Kontakt Statens arbeidsmiljøinstitutt for mer informasjon på telefon 40 72 17 88 eller e-post forsok@stami.no.

Godtgjørelse: 150 kr/time (ca. 1.000 kr). + 500 kr som kompensasjon for søvnreduksjon. Godtgjørelsen er skattefri t.o.m 1.000 kr. Reiseutgifter med offentlig transport dekkes i stor-Oslo t.o.m Ruters sone 4.

rev. 13.09.12 lav

40 72 17 88 forsok@stami.no

11.2 Appendix 2. Health questionnaire

Kjære forsøksdeltaker

Vi søker i dette prosjektet etter friske forsøkspersoner mellom 18 og 45 år. Hensikten med dette skjemaet er å kartlegge helsesituasjonen til forsøksdeltakerne. I tillegg ønsker vi å kartlegge noen andre faktorer som har betydning for smertefysiologiske forsøk. Vi ber deg om å svare på alle spørsmålene og returnere skjemaet ved å poste det i utlevert konvolutt.

1. Hvor gammel er du?		
2. Kjønn	Kvinne	Mann
Sett et kryss i kolonnene til høyre for hvert spørsmål	**Ja**	**Nei**
3. Er du frisk?		
4. Har du hatt vedvarende (mer enn 3 mnd) smerter i noen del av kroppen de siste 2 årene?		
5. Hvis du svarte ja på spørsmålet over, hvor sterke var disse smertene på en skala fra 0 til 10, hvor 0 er ingen smerte og 10 er verst tenkelig smerte?	Mindre enn 3 er ok, 3 eller mer betyr ut	
6. Har du hatt, eller har, en sykdom i en av følgende kategorier:		
a. Psykiatrisk sykdom (angst, depresjon inkludert)	Ut	
b. Nevrologisk sykdom	ut	
c. Hjertesykdom	Ut	
d. Lungesykdom (velregulert astma er lov)	Ut	
7. Har du hodepine 2 dager eller mer pr. måned (i gjennomsnitt)	Ut	
8. Hvis du av og til har hodepine, hvor sterk er hodepinen du vanligvis har:		

a. Mild	Ok	
b. Moderat	Ut	
c. Kraftig	Ut	
9. Bruker du noen form for medisiner fast (inkludert håndkjøpsanalgetika som paracet/ibux)?	Ut	
Hvis ja, hvilken type:		
10. Har du høyt blodtrykk (mer enn 140/90 mmHg)?	UT	
Vet ikke		
11. Er du gravid?	UT	
12. Ammer du?	UT	
13. Har du reagert med overfølsomhet for elektrodepasta eller saltholdige kremer tidligere?	UT	
14. Jobber du skiftarbeid med nattevakter? Spesifiser på neste side		
15. Har du en diagnostisert søvnlidelse (eks. obstruktiv søvnapne, insomni, essensiell hypersomni, narkolepsi)	UT	
Hvis ja, hvilken:		
16. For kvinner: Dato for siste menstruasjons første dag		

*Vi gjør oppmerksom på at du ikke må være **alkoholpåvirket** de siste 24 t før hver forsøksdag. Vi ber deg også om å avstå fra **kaffe, te og røyk/snus** siste time før du møter til undersøkelsen.*

Skiftarbeid

Jobber du aldri nattevakter? _____

Jobber du faste nattevakter? _____

Jobber du av og til nattevakter (ekstravakter)? _____ Hvis du svarte ja på en av de to siste spørsmålene, vennligst skisser vaktplanen for de siste to måneder nedenfor.

11.3 Appendix 3. Research protocol

ID Filnr		Dato og klokkeslett	

Slå på utstyr og PC-er	
• To skilletrafoer	
• **Mini-PC** og **PC2** (brukernavn: forsok / passord: abc123)	
• **SENSELab** thermotester, trykk *Reset* etter oppstart	
• Elektrisk stimulator **DS7A** og kontrollenhet **DG2A**	
• Legg jordelektroder i kar med saltvann	
Klargjøring av PC-er	
PC2. Start ***Exposure*** (varmestimulatorprogram)	

Mini-PC. Logg inn som bruker forsok (ingen passord) og start **Paindicator**. Sjekk at PC-mus er slått på	

Forsøkspersonen ankommer og føres til venterommet.

Blå tekst i ” ” leses i størst mulig grad.

Utfylling av skjemaer
Gjennomgang av forsøket

Kort gjennomgang av forsøket. Bruk arket som viser oversikt over opplegget. Del ut ”Forespørsel om deltakelse”-dokument. Dette har de fått tilsendt på forhånd og lest, men noen vil kanskje lese deg igjen. Minn FP på å svare om han/hun kan tenke seg å bli kontaktet igjen (siste side).

”Forsøksdag 1, som er i dag, skal brukes til å gjøre deg kjent med testene som skal foregå de to andre dagene.

Du skal først lese gjennom ”Forespørsel om deltakelse”-dokumentet og signere denne. Det gjøres her på venterommet. Deretter går vi inn i laben og starter med å måle blodtrykket ditt etter at du har hvilt i 5 min. Etterpå skal vi gjøre noen varmestimuleringer på underarmen, noen trykkstimuleringer på ryggen og noen elektriske stimuleringer på underarmen. Til slutt monteres aktivitetsmåleren som du skal ha på deg fram til du kommer tilbake om 2 dager.”

Godtgjørelsen på 150 kr per time beregnes ut fra tiden du er på STAMI, avrundet opp til nærmeste halvtime. Pengene utbetales 2-3 uker du har vært her siste gang. **NY**

Forsøkspersonen føres til laben.

Måling av blodtrykk

Blodtrykksmansjett (Dinamap) festes rundt venstre overarm og FP blir bedt om å slappe av i 5 min.

Etter 5 min: Stolen legges tilbake til liggende posisjon.

Tre blodtrykksmålinger gjøres mens FP ligger.

Blodtrykk baseline	
Måling 1	/ mmHg
Måling 2	/ mmHg
Måling 3	/ mmHg

Reis opp stolen til en komfortabel stilling.

Trekk arm som skal motta varme

Arm som skal motta varmestimulering *("VARMEARM")*	V / H
Arm som skal motta elektrisk stimulering *("ELEKTRISK ARM")*	V / H

Testing av WIFs

"Jeg skal nå teste varmefølsomheten på underarmen. Jeg vil plassere varmeelementet i noen sekunder på ulike steder på innsiden av underarmen. Du skal svare JA eller NEI ettersom du kjenner varme eller ikke. De områdene du eventuelt ikke føler varme, vil jeg merke av med tusj."

Gjøres på innsiden av testarm i områdene som er aktuelle for plassering av termoden.

Test for WIFs (temperatur 41 °C). Bruk kortsiden av termoden, gå systematisk fram. Marker med tusj områder som ikke er varmesensitive. Hold varmeelementet mot huden i 3 sek om gangen.

Innstillinger Somedic, WIFs:

Exposure30:

a) Start: 32
b) Stop: 41
c) Slope: 1
d) Time: 120
e) Mode: Single Pulse

Sjekk COM1-innstilling (NY) hvis Exposure ikke viser temperaturen i MSA-vinduet.

Om angivelse av smerte

I de ulike prosedyrene du skal gjennom vil vi be deg angi graden av smerte. Til å angi smerten brukes en skala fra 0 til 10.

To varianter av skalaen brukes (VIS FIGUR)**. Den ene varianten er en kontinuerlig skala, den andre varianten er en numerisk skala med tallene fra 0 til 10 som gjerne brukes muntlig.**

Helt til venstre på skalaen indikerer at du absolutt ikke føler noen smerte. Mild smerte ligger i den venstre delen av skalaen, moderat smerte ligger i midten mens kraftig smerte ligger i den høyre delen av skalaen. Helt til høyre på skalaen indikerer at smerten er uutholdelig. Det er det nivået hvor du ikke tåler at stimuleringen fortsetter.

Før vi starter vil jeg gjøre oppmerksom på at opplevelsen av smerte er subjektiv. Det er derfor ikke slik at det finnes et riktig eller galt svar når du bruker denne skalaen. Din smerteopplevelse kommer ikke til å bli sammenliknet med noen andres. Din

eneste oppgave er å vise smerten så presist som mulig. Et tips er at du hele tiden konsentrerer deg om hva du kjenner, og at du angir dette så presist og konsistent som mulig.

Har du noen spørsmål til det å angi smerte?

Bestemmelse av pain-6

Side: VARMEARM

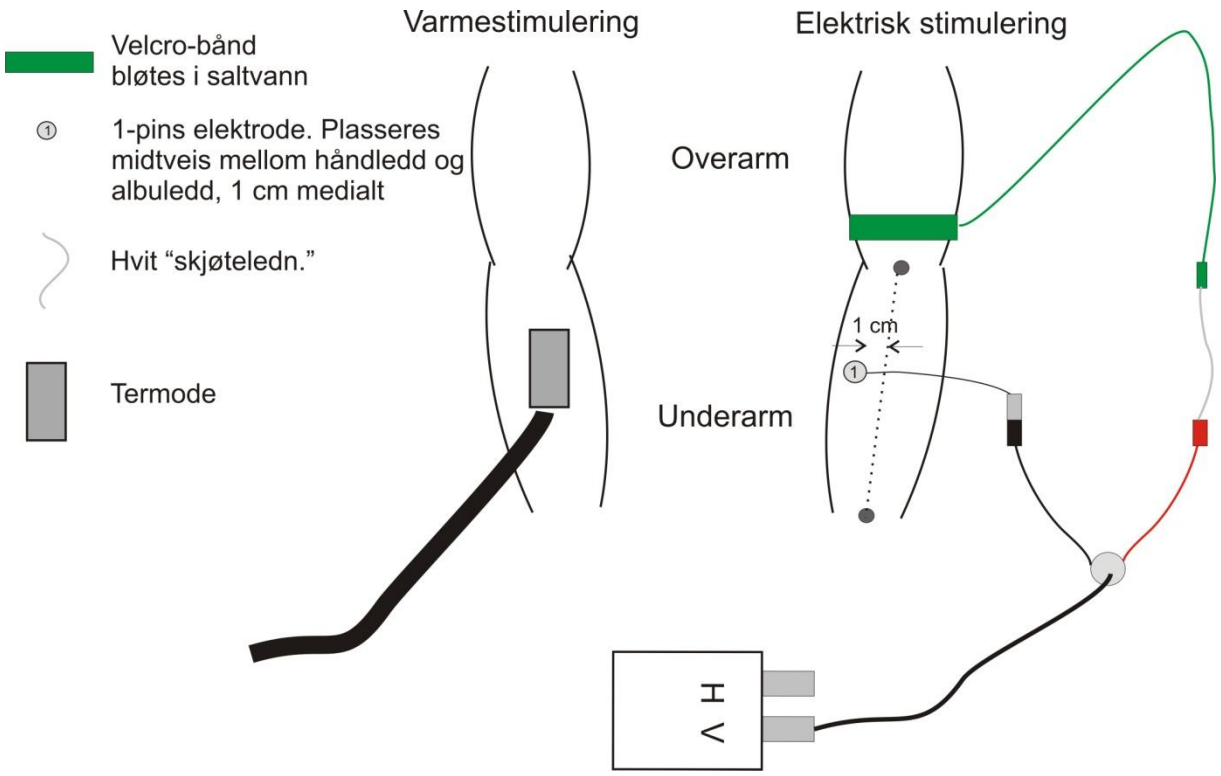
For at du skal bli kjent med varmestimuleringene vil du nå motta ulike temperaturer med varmeelementet. Du skal selv holde varmeelementet på innsiden av underarmen, ned mot håndleddet. Temperaturen på varmeelementet vil stige fra 32 grader til ulike forhåndsbestemte temperaturer. Hver temperatur vil vare i 7 sekunder. Det vil være et opphold på 1 minutt mellom hver av temperaturene. I dette oppholdet vil jeg at du skal angi muntlig hvor intens du synes varmen var på det varmeste ved å bruke skalaen fra 0 til 10. Du kan bruke desimaler f. eks angi 2,5.

Du gir FP termoden og viser hvordan han skal holde den mot underarmen. **"Er du klar? Da setter jeg i gang varmestimuleringen. "**

Innstillinger Somedic, pre-test:

Exposure30:

a) Start: 32
b) Stop: 45
c) Slope: 1
d) Time: 7
e) Mode: Single Pulse



Utfør 45- 46 - 47 °C stimulering mens FP selv holder termoden mot underarmen. I hver pause (1 min,- sett på klokke for tid):

"Da kan du fjerne varmeelementet fra huden din. Du skal nå angi den maksimale smerten du følte under varmestimuleringen, fra 0 til 10. "

Etter 1 min pause: **"Jeg setter nå på varmen igjen. Er du klar? "**

Kalibrering Pain-6

Varmestimulering (7 sek)	**NRS (verbal)**
45 °C	
	1 min. pause
46 °C	
	1 min. pause
47 °C	

Om ikke Pain- 6 er satt ut ifra disse tre temperaturene, fortsetter pre-testen med tabell l) eller ll):

l) NRS/VAS > 6 ved 45, 46, 47 °C:

Varmestimulering (7 sek)	NRS/VAS (verbal)	
43 °C		
	1 min. pause	
44 °C		

NRS/VAS > 6 ved 43°C og 44°C = eksklusjon

ll) NRS/VAS < 6 ved 45, 46, 47 °C:

Varmestimulering (7 sek)	NRS/VAS (verbal)	
48 °C		
	1 min. pause	
49 °C		

NRS/VAS < 6 ved 48 og 49 °C = eksklusjon

Beregnet pain-6 (vha Excel-ark)	°C

Markering på plastfolie

Marker dette på plastfolie som merkes med FPs ID og dato:

- Plassering av termode for pain-6
- Plassering av termode for varmestimulering forsøksdag 3
- Marker anatomiske merker (albuledd, håndledd, sener, føflekker, etc)

Trykkstimulering på ryggen

Side: IKKE-DOMINERENDE SIDE V / H

"Du vil nå motta tre trykkstimuleringer på den øverste delen av ryggen."

Be FP løsne klærne rundt halsen, slik at du kommer til. Mål ut avstanden mellom overgangen

mellom C7 og bakre kant av akromion: _____ cm. Merk av 1/3 av avstanden fra C7.

Klargjør mini-PC med programmet Paindex.

- Slå på Wagner trykkalgometer og klikk **Send** på algometeret, påse at symboler blinker
- Klikk **Search sensors** i Paindex programmet på PC-en
- Når programmet er klart, klikk **Start**

"Nå skal du angi smerten på den kontinuerlige skalaen. I stedet for å angi et tall mellom 0 og 10 skal du markere smerten ved å skyve på en markør."

Gi VAS til forsøkspersonen og forklar/demonstrer.

"Akkurat idet du synes trykkstimuleringen blir smertefull begynner du å flytte markøren mot høyre. Etter hvert som smerten øker fortsetter du å flytte markøren. Du skal si stopp idet du flytter markøren forbi midten av skalaen. Da stopper jeg å trykke.

Har du noen spørsmål?"

Lagre filen ved å klikke Save. Filnavn: **fp201-dag1-1**.

Gjenta to ganger til med ca 1 min mellom hver test. (filnavn: **fp201-dag1-2, fp201-dag1-3)**

Sensorisk terskel og smerteterskel

Monter elektroder ihht figuren. **Side: ELEKTRISK ARM.**

"Nå vil du motta noen elektriske stimuleringer. Jeg sier fra før hver stimulering. Det er ikke sikkert du kjenner de svakeste stimuleringene. Så snart du kjenner stimuleringen sier du fra". Start med 0,1 mA og øk med 0,1 mA inntil sensorisk terskel (ST). Marker i tabellen nedenfor hvor mange mA som tilsvarer ST.

"Styrken vil nå fortsette å øke for hver stimulering og jeg vil nå at du skal si fra så snart du synes de er smertefulle. Vi skal nå fortsette og som sagt vil jeg ikke nå si fra før hver stimulering. Du sier fra så snart den elektriske stimuleringen er smertefull"

Fortsett med økning på 0,2 mA inntil smerteterskel (PT). Marker i Måling 1-kolonnen i tabellen nedenfor hvor mange mA som tilsvarer PT.

"Det samme skjer nå en gang til. Jeg øker stimuleringene mellom hver gang inntil du sier fra at den er smertefull"

Reduser mA-verdien noe og beregn PT to ganger til (måling 2 og måling 3).

	Måling 1	Måling 2	Måling 3
	mA	mA	mA
Noter ned mA-verdien som svarer til ST og PT i første kolonne. Noter kun PT i andre og tredje kolonne.			

Beregning av gj.snittlig PT av de to siste:

_____ + _____ / 2 = _____ mA

Øving på smerteskåring

Gi denne instruksen om skåring av VAS:

"Nå har du blitt litt kjent med de elektriske stimuleringene. Vi skal nå fortsette med noen flere elektriske stimuleringer av ulik styrke. Etter hver stimulering vil jeg at du skal angi hvor smertefull du syntes stimuleringen var på den muntlige skalaen fra 0 til 10.

Du skal bruke denne skalaen til å angi intensiteten til de elektriske stimuleringene muntlig. Etter hver elektriske stimulering vil du få noen sekunder til å bestemme deg på. Hvis du ikke har sagt noe i løpet av 4-5 sekunder vil jeg spørre deg om skåringen din. Da starter jeg om noen få sekunder."

Gi 6 stimuli som skåres muntlig. La det gå minst 10 sek mellom hver stimulering.

Vi ønsker ikke å måtte bruke x10-bryteren for å regulere strømstyrke. Dersom PT > 2,5 mA (4xPT > 10 mA) settes 4xPT til 10 mA. Gjør en merknad om dette til dag 3. NY

	PT overført		mA	VAS (cm)
2x		=		
4x		=		
3x		=		
4x		=		
2x		=		
3x		=		

Trekk lapp om søvn

Nå skal du trekke en lapp som bestemmer om de neste to nettene skal være med normal søvn eller med redusert søvn.

Normal søvn / søvndeprivert (sett ring). Fra tabellen blir filnr neste gang _____ (overføres kjøreplan for forsøksdag 3)

Montering av aktivitetfsmåler

"Det siste som skal skje i dag er montering av aktivitetsmåleren som skal sitte på til du kommer tilbake om 2 dager. Den skal sitte på hele tiden, også om natten, bortsett fra når du dusjer."

Gi FP søvnlogg og monter aktivitetsmåler på samme siden som klokka. V / H

Aktivitetsmåler nr 26 / 27 ble utlevert (sett ring)

Mobil til registrering av plager

Spør om FP kan tenke seg å delta i uttesting av mobil til å registrere helseplager. Registrering skjer vha lånetelefon fra STAMI. Del ut forhåndsfrankert foret konvolutt med ekstra bobleplast. Gi instruks for bruk av appen **Mail2**.

Utlånt telefon

_____ nr 1 / 2

Påminnelse

_____ forsøkspersonen ønsker ikke påminnelse per SMS

_____ forsøkspersonen ønsker påminnelse per SMS kl _____ til ___ lånetelefon

eller til ____ annen telefon med nummer _____

Minn på om frammøte om 2 dager kl 9.

Beregning av timer

Klokkelslett for avslutning	
- Klokkeslett for oppstart (fra side 1)	
Tidsforbruk i dag (avrundet til ½ timer) som det skal betales for, overføres skjema for timer totalt	

11.4 Appendix 4. Sleep instruction

Statens arbeidsmiljøinstitutt

Instruks om soving

Om to dager, _____kl 9 skal du delta i det ene av to laboratorieforsøk. På baksiden av arket finner du en søvnlogg som vi ber deg fylle ut fram til lab.forsøket. De to nettene før lab-forsøket skal du

___ sove like lenge som du oppga som din vanlige søvnlengde i spørreskjemaet som du sendte inn til STAMI, altså _____ timer. Vi ønsker at du stå opp kl 7 i morgen og den dagen du skal delta i laboratorieforsøket. Du skal derfor legge deg til å sove kl ____ både i kveld og i morgen kveld.

___ sove halvparten av din normale søvnlengde, dvs ____ timer. Vi ønsker at du stå opp kl 7 i morgen og den dagen du skal delta i laboratorieforsøket. Du skal derfor legge deg til å sove kl ____ både i kveld og i morgen kveld. Vi ber deg om ikke å sove på andre tidspunkter .

Husk: aktivitetsmåleren skal sitte på hele tiden fram til du kommer tilbake, også om natten. Ta den kun av dersom du dusjer.

Alkohol, medisiner, kaffe/te, tobakk

Vi ber deg om ikke å drikke alkohol, bruke andre rusmidler eller ta smertestillende medisiner de siste 24 timer før lab.forsøket. Dersom du pleier å drikke kaffe/te om morgenen kan du gjøre dette også morgenen før lab.forsøket. Unngå snus og røyk den siste timen før forsøket.

11.5 Appendix 5. Sleep diary.

Søvnlogg

Fylles ut av forsøksleder		
Utlevert	Dato og klokkeslett	
Innlevert	Dato og klokkeslett	
Aktigraf nr	26 / 27	
ID-nr		

Fylles ut av forsøksdeltaker		
Første natt		
Soving om natten		
Tid for når du legger deg ned for å sove (f.eks når du slukker lyset)	Klokkeslett	
Tid når du våkner	Klokkeslett	
Oppvåkninger om natten		
Hvis du våkner opp om natten skriver du dette opp nedenfor. Vent til neste dag med å notere dette og angi kun omtrentlig klokkslett.		
Klokkeslett	Hvor lenge	Eventuell beskrivelse av aktivitet (f.eks. for å drikke, toalettbesøk)
Andre natt		
Soving om natten		
Tid for når du legger deg ned for å sove (f.eks når du slukker lyset)	Klokkeslett	
Tid når du våkner	Klokkeslett	
Oppvåkninger om natten		
Hvis du våkner opp om natten skriver du dette opp nedenfor. Vent til neste dag med å notere dette og angi kun omtrentlig klokkslett.		
Klokkeslett	Hvor lenge	Eventuell beskrivelse av aktivitet (f.eks. for å drikke, toalettbesøk)

11.6 Appendix 6. Written information and consent form

Forespørsel om deltakelse i forskningsprosjektet

"Skiftarbeid og smerteføIsomhet"

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie hvor formålet er å bestemme om skiftarbeid fører til ulike helseplager. Personer som ikke jobber skift [ ] og personer som jobber varierende dag- og nattskift [ ] blir spurt om å delta.

Skiftarbeid kan være ugunstig for helsa. Vi vet i dag for lite om eventuelle mekanismer for dette og det er bakgrunnen for at Statens arbeidsmiljøinstitutt (STAMI) har planlagt denne studien.

Hva innebærer studien?

Studien innebærer deltakelse i tre laboratorieforsøk ved STAMI, samt registrering av søvn to døgn i forkant av hvert disse forsøkene. Det første laboratorieforsøket foregår i forbindelse med montering av søvnmålerutstyret og varer i ca 1 time. De to andre laboratorieforsøkene foregår morgenen etter siste søvnregistrering og varer i ca 2,5 timer. Personer som ikke jobber skift vil bli bedt om å redusere sin normale søvnlengde i en eller begge nettene forut for et av forsøkene. Personer som jobber skift deltar i de samme laboratorieforsøkene etter siste nattevakt i en serie av påfølgende nattevakter og etter minst 3 påfølgende dagvakter. Registrering av søvn skjer ved ustyr som registrerer bevegelser og/eller søvnmønster. Man sover hjemme som normalt. Montering av utstyret skjer ved STAMI eller ved Oslo universitetssykehus 2 døgn før hvert laboratorieforsøk.

Under laboratorieforsøkene vil det gjennomføres flere nevrofysiologiske tester. Et eksempel på en slik test er trykk mot huden. Noen stimuleringer kan være smertefulle. De nevrofysiologiske testene vil utføres flere steder på kroppen. De fleste testene er av kort varighet (få sekunder), mens noen varer i 5-6 minutter. De korteste testene gjentas evt. flere

ganger. En deltaker kan når som helst be om at testene avbrytes. Under testene er det innlagt flere pauser. Testene er beskrevet i vedlegg A. Som deltaker vil du bli bedt om å vurdere intensiteten til stimuleringene vha. en skala. Under enkelte av testene vil hjerteaktivitet (EKG), blodtrykk, svetterespons og den elektriske aktiviteten fra hjernen (EEG) registreres.

Mulige fordeler og ulemper

Deltakelse i studien vil ikke gi noen personlige fordeler. Erfaringene fra studien vil imidlertid kunne bidra til bedre kartlegging av risikofaktorer for å utvikle kroniske smerter og kunnskap om planlegging av skiftordninger som er mindre helseskadelige. Andre fordeler kan være redusert sykefravær. Deltakelse i studien vil ikke medføre andre ulemper enn at de deltakerne som ikke jobber skift får mindre søvn forut for en av undersøkelsene.

Hva skjer med informasjonen om deg?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få noen konsekvenser. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte forsker, ph.d. Dagfinn Matre, tlf 23 19 51 00.

Ytterligere informasjon om studien finnes i kapittel *A* – *utdypende forklaring av hva studien innebærer.*

Ytterligere informasjon om biobank, personvern og forsikring finnes i kapittel B – *Personvern, biobank, økonomi og forsikring.*

Samtykkeerklæring følger etter kapittel

Kapittel A- utdypende forklaring av hva studien innebærer

Kriterier for deltakelse

For å delta i studien må du være mellom 18 og 60 år og forstå norsk muntlig og skriftlig. Du kan ikke delta dersom du har kroniske smerter (mer enn 3 måneder i løpet av siste 2 år), er avhengig av narkotika, er gravid, har psykiatrisk sykdom, har nevrologisk sykdom (mild hodepine 1 - 2 dager per måned er tillatt), har høyt blodtrykk, har kreft, eller bruker medikamenter mot epilepsi, depresjon eller nevrologiske lidelser funksjon.

Laboratorieforsøk

Nevrofysiologiske tester

Laboratorietestene ved STAMI vil bestå av følgende tester. I de fleste testene blir du bedt om å bestemme intensiteten til hver enkelt stimulering.

Del	Test[1]	Beskrivelse
1	**Smerteterskler** • Trykk • Varme • Kulde • Elektrisk	Smerteterskler bestemmes ved at ved at intensiteten på stimuleringen gradvis økes inntil moderat smerte kjennes og testen avbrytes. Gjentas 2-3 ganger for hver type stimulering.
	EEG monteres	En hette med 32 elektroder plasseres på hodet. Litt gele sprøytes i hver elektrode slik at vi kan registrere den elektriske aktiviteten fra hjernen.

2	**Elektrisk stimulering** • 3 x 30 elektriske stimuleringer.	Gjennom to elektroder klistret på armen sendes elektrisk strøm (1-5 mA). Hver elektrisk stimulering er veldig kort (noen millisekunder) og oppleves som et lite nålestikk mot huden.
3	**Spørreskjema**	Hver forsøksdag vil du bli bedt om å svare på et spørreskjema om helseplager.
4	**Varmestimulering + smerte på motsatt arm** • Varmestim • Varmestim + smerte på motsatt arm	Et varmelegeme legges inntil huden på armen og varmes opp til du kjenner moderat smerte. Dette gjentas 3-5 ganger. Varmelegemet ligger inntil huden i 2 min. Disse varmetestene gjentas etter smertefull stimulering på motsatt arm.
	EEG avmonteres	EEG-hetten tas av og du får mulighet til å vaske håret med sjampo.

[1]Nøyaktig rekkefølge og antall tester kan avvike noe fra det som er beskrevet her. EEG = elektroencephalografi (registrering av hjernens elektriske aktivitet).

Søvnmåling

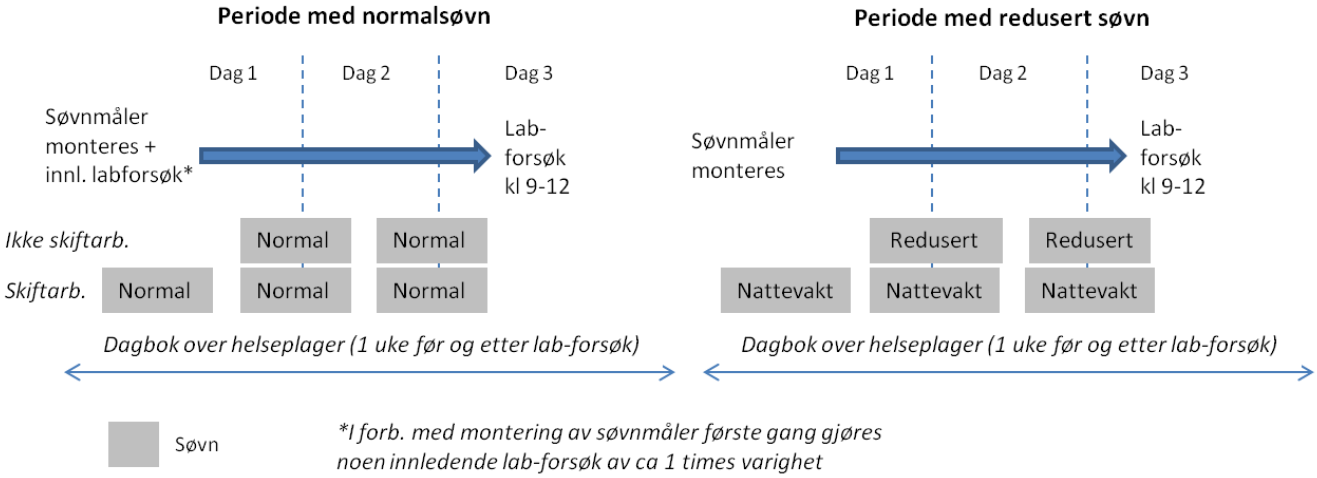
Søvn registreres i 2 døgn før hver laboratorietest og montering av søvnmåler gjøres ved STAMI eller OUS om morgenen 2 dager før. Søvnmåleren består av registreringsenhet som festes med en reim til bryst/arm og evt. med tillegg av elektroder som festes på hodet. Søvnmåleren tas av før lab-forsøket dag 3.

Dagbok

Mellom dag 1 og i en uke etter dag 3 vil du bli bedt om å fylle ut et skjema over hvilke helseplager du har hatt den dagen. Skjemaet vil fylles ut på papir, via internett eller via mobiltelefon.

Tidsskjema

Deltakelse i studien går over to perioder, en periode med normal søvn og en med redusert søvn. For deltakere som ikke jobber skift innebærer perioden med redusert søvn f.eks at du blir bedt om å sove halvparten av din normale nattesøvn de siste to nettene før et av lab-forsøkene. Noen deltakere vil bli bedt om å avstå fra søvn en natt. For deltakere som jobber skift vil perioden med redusert søvn være perioden med tre påfølgende nattevakter.



Mulige bivirkninger

Ved elektrisk- og varmestimulering som beskrevet i dette prosjektet blir huden av og til rød som ved solbrenthet. Dette vil være over i løpet av noen døgn og vil ikke gi noen varige skader. Huden i dette området kan også bli noe overfølsom for berøring, noe som varer maksimalt i noen timer. Det er lite sannsynlig at du vil hemmes av denne overfølsomheten. Ellers er det ikke rapportert noen kjente bivirkninger.

Fordeler og ulemper ved deltakelse

Studien innebærer ingen personlige fordeler ut over en økonomisk kompensasjon for å dekke tapt arbeidsfortjeneste og utgifter til transport. Ulempene ved å delta er knyttet til følgene av redusert søvn, samt laboratorietestene som innebærer noe smerte. Denne smerten er av en slik art at den ikke skader kroppen, men kun gir et relativt kortvarig ubehag.

Eventuell kompensasjon til og dekning av utgifter for deltakere

Det gis en kompensasjon på 150 kr/time til deltakerne for ulempe og tidsbruk. Tidsbruk ved labforsøket dag 1 (første gang) anslås til ca 1 time. Tidsbruk ved labforsøket dag 3 anslås til ca 2,5 timer hver gang. I tillegg dekkes reisekostnader med offentlig transport til/fra STAMI t.o.m. Ruters sone 4 (ruter.no).

Kapittel B - Personvern, biobank, økonomi og forsikring

Personvern

Opplysninger som registreres om deg er fødselsdato, kjønn, samt informasjon fra ulike spørreskjema og undersøkelsene som blir utført. Det er kun prosjektleder og tilknyttede prosjektmedarbeidere som har tilgang til datamaterialet. Statens arbeidsmiljøinstitutt ved administrerende direktør er databehandlingsansvarlig. Vi ber også om samtykke til at du kan kontaktes for eventuell deltagelse i senere studier med lignende problemstillinger.

Utlevering av materiale og opplysninger til andre

Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger utleveres til samarbeidspartnere. Dette kan være land med lover som ikke tilfredsstiller europeisk personvernlovgivning.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver

Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi

Studien er finansiert gjennom interne forskningsmidler fra Statens arbeidsmiljøinstitutt og/eller ved midler fra Norges forskningsråd. Det er ingen interessekonflikter knyttet til studiens finansiering.

Forsikring

Deltakerne er dekket av en skadeforsikring tegnet for dette prosjektet.

Informasjon om utfallet av studien

Som deltaker i prosjektet har du rett til å informeres om resultatet i studien. Dette fås ved henvendelse til Dagfinn Matre.

Samtykke til deltakelse i studien

Jeg er villig til eventuelt å bli innbudt til en ekstra forsøksdag Ja / Nei

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

11.7 Appendix 7. REK approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Harsha Gajjar Mikkelsen	22845513	02.04.2012	2012/199 REK sør-øst B
			Deres dato:	Deres referanse:
			16.03.2012	

Vår referanse må oppgis ved alle henvendelser

Dagfinn Matre
Statens arbeidsmiljøinstitutt

2012/199b Skiftarbeid og smerte.

Prosjektleder: Dagfinn Matre
Forskningsansvarlig: Statens arbeidsmiljøinstitutt

Vi viser til innsendt brev med svar på merknader av ovennevnte prosjektet datert 13.03.12. Det informeres om følgende endringer i studien:

1. Informasjonsskriv for studien er revidert slik at informasjon om tidsbruken, hvordan ytterligere informasjonsinnhenting skal foregå, og informasjon en ytterligere oppfølgingsstudie er nå inkludert.
2. Det informeres om en mindre endring med antall forsøksdager. Både informasjonsskriv og tidsskjema er oppdatert.

Forskningsetisk vurdering
Komiteens leder Stein Opjordsmoen Ilner har på delegert fullmakt vurdert endringssøknaden. REK sør-øst B har ingen forskningsetiske innvendinger til prosjektet slik det nå foreligger.

Vedtak
Komiteen har vurdert endringsmeldingen og godkjenner prosjektet slik det nå foreligger med hjemmel i helseforskningsloven § 11. Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og de bestemmelser som følger av helseforskningsloven med forskrifter.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «*Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren*».

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til post@helseforskning.etikkom.no. Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen,

Stein Opjordsmoen Ilner
Professor dr. med.
Komiteleder

Harsha Gajjar Mikkelsen
førstekonsulent

Kopi til: Direktør Pål Molander, Statens arbeidsmiljøinstitutt

Besøksadresse: Gullhaug torg 4A, Nydalen, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff