Sleep and pain

The effects of sleep restriction on pain and evoked potentials

by Leif Andre Viken

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Department of Human Movement Science

Faculty of Social Science and Technology Management

Norwegian University of Science and Technology

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Abstract

Objective: This study investigates the 1) effect of sleep restriction on a) neurophysiological and b) psychophysiological pain responses. We also investigated the 2) effect of sleep on habituation by introducing stimulus repetition as a factor.

Methods: Twenty-two healthy volunteers were engaged in a within-subject cross-over design comparing two nights of 50% sleep restriction with habitual sleep. For activation of the nociceptive pathway, three blocks á thirty (total of 90) electrical stimulations of different intensity were directed to the forearm. Subjective pain responses were measured with numerical rating scale (NRS). Event related brain oscillations in somatosensory cortex (C3/C4) were recorded using 32 channel electroencephalography (EEG). Time-frequency presentation and point-by-point statistical analyses revealed stimulus induced changes in event related potentials (ERP), event related desyncronization (ERD) and gamma-band-oscillations.

Results: Two nights of 50% sleep restriction increased subjective pain scores (NRS) and event related potentials (ERP) to electrical stimulation. These results were not followed by changes in event related desynchronization (ERD) or gamma band oscillations (GBO). Habituation was unaffected by sleep restriction.

Preface

This master's thesis is a part of a larger research project on shift-work and pain at the National Institute for Occupational Health (NIOH), Department of Work Psychology and Physiology, Oslo. The research program will investigate the possible effects of working shifts on pain and pain sensitivity. Project methods are divided in to an experimental and a epidemiological approaches, with different intermediate aims. This paper is limited to a pilot study investigating whether experimental sleep restriction affects the responses to standardized laboratory tests of pain. The research group consists of two research scientist, two technicians and three master students. Data collection started in March 2012 and ended in December 2012. All laboratory tests were performed at NIOH, Gydas vei 8, Oslo.

Contens

Abbreviations

EEG	Electroencephalography
ERD	Event related desynchronization
ERP	Event related potentials
ERS	Event related synchronization
EP	Evoked potentials
EES	Epworth Sleepiness Scale
ISI	Inter stimulus interval
LEP	Laser evoked potentials
N1	Evoked potential. “N” reflects polarity (negative) and “1” reflects typical latency (100ms post-stimulus).
N2	Evoked potential, “N” reflects polarity (negative) and “2” reflects typical latency (200ms post-stimulus).
P2	Evoked potential, “P” reflects polarity (positive) and “2” reflects typical latency (200ms post-stimulus).
P300	Evoked potential, “P” reflects polarity (positive) and “300” reflects typical latency (300ms post-stimulus).
NRS	Numerical Rating Scale
PSQI	Pittsburg sleep Quality Index
PT	Pain threshold
PVT	Psychomotor Vigilance Test
RT	Reaction time
ST	Sensory threshold

1.0 Introduction

Shift work is common in the Norwegian labor force. Work outside regular work hours has increased since 2006 and data from statistics Norway (SSB) states that 23.7 % of all employees in Norway work in shifts [1]. Despite the fact that shift work is common and increasing, we do not have enough knowledge about the consequences and how it affects the health.

One of the characteristics of shift work is night work and repeatedly alternations of circadian rhythm. Shift work related to alternations of circadian rhythms has been linked to development of sleep disturbance and insomnia [2, 3]. Furthermore, studies indicate a relationship between shift work and musculoskeletal pain. In a Norwegian study investigating factors of low back pain related sick leave among 4266 nurses, night shift workers had a higher risk of absence from work due to low back pain than nurses not working night shifts [4]. Although the association between shift work and pain can be caused by other work factors related to night shifts, it is reasonable to presume that reduced sleep may contribute to an adverse health effect.

Adequate quantity and quality of sleep is essential to maintain health and daytime functioning. Poor sleep has been shown to have a number of negative physical and mental consequences, including alterations in the regulation of the neural and endocrine systems. This may in turn results in impaired perception, weakened concentration, impaired memory, and emotional disorders [5]. Sleep problems are also a strong risk factor for future development of chronic musculoskeletal pain [6]. Chronic pain of moderate to severe intensity is estimated to affect 19% of the adult European population [7]. The high prevalence of chronic pain is responsible for causing disability in a substantial number of people, and is therefore a considerable burden for the health- and social care systems [7]. Reduced sleep has also been shown to influence acute pain perception [8-13]. Increased spontaneous pain after a previous night of reduced sleep was found by Edwards and co-workers, investigating 971 randomly selected subjects in a telephone study [14].

Potential mechanisms by which sleep restriction cause both chronic musculoskeletal pain, increase acute pain perception and change of sensitivity to experimental pain is not well understood. However, abnormality in the pain modulation mechanisms has been explored in respect to sleep disturbance [9, 12, 15]. Moreover, studies indicate that sleep loss impairs how the brain responds to painful stimulations [10, 16]. Proposed as a protective mechanism,

habitual brain responses will gradual decrease (habituate) in response to repeated delivery of stimulations. Whereas repetitive painful stimulations leads to decrease in cortical responses in healthy subjects, migraine patients show increased or unchanged cortical responses [17]. Interestingly, specificity of the dis-habituation phenomenon in migraine patients has been questioned and is hypothesized to be relevant for other unspecific pain processes such as e.g. fibromyalgia [18]. One may therefore speculate if alternations in habituation may occur in response to reduced sleep.

1.1 Background

1.1.1 Pain response recording

It is important to note that pain is a central interpretation of the nociceptive signal and includes affective components such as physical, cognitive, and emotional factors [19]. Even more complex is the fact that nociceptive information will be experienced differently between individuals, as well as vary within the same individual over time [20]. According to Tracey and coworkers, objective pain measures such as brain imaging may be useful determining how human brain handle the nociceptive input and how these processes shape the actual perception of pain [19]. Electroencephalography (EEG) can detect fast changes in the electrical fields occurring in cortical areas in response to sensory stimulations, also known as evoked potentials (EP). These potentials can be generated by visual, auditory or somatosensory stimulations. In example, electric or radiant heat activation of selective of Aδ and C-fibers can be measured as somatosensory EPs by EEG electrodes over the cortex 150-380ms subsequent to the stimulus [21]. Latency of the response depends primarily on the propagation velocity of the neurons which are activated, as well as the distance to cortex. Brief electrical pulses of 0.1–0.2 ms and stimulus intensity 2-3 times sensory threshold is a prerequisite to evoke EPs [21]. Because these signals are time-locked to the pain stimulus, they are commonly referred to as event related potentials (ERPs).

The most commonly studied ERP complex is a vertex wave called ‘N2-P2’, referring to a negative-positive biphasic waveform and with mean latency peaking around 200ms post-stimulus. Gracia-Larrea and coworkers (2003) reviewed literature of cortical areas responsible for generating ERPs due to laser stimulations, and suggested that these arise from several somatosensory areas (Primary somatosensory cortex, secondary somatosensory cortex, anterior cingulate cortex and insula), areas sometimes referred to as the ‘pain-matrix’ [22]. Moreover, studies have found that the magnitude of ERP correlates to the subjective sensation

of pain [23, 24]. Interestingly, although some studies endorse ERPs as an objective correlate of pain, there are studies reporting deviation between ERP and perceived pain [25, 26].

1.1.2 EEG analytical considerations.

Evaluation of the ERP requires an extraction of this component from the other continuous EEG signal. Retrieving the information in the time-domain is solved by averaging many stimulus-relevant EEG trails, leading to improvement of the signal-to-noise ratio. However, because the ERP waveform is time locked to stimuli, the averaging method is criticized for lacking information about the fact that each stimuli occur with small differences in latency [25, 26]. This problem is accompanied by the notion that painful stimulations induce transient changes in ongoing EEG oscillations not time-locked to stimulus, and thereby being difficult to evaluate in time-domain [26]. It has therefore been suggested that stimulus relevant modulations of ongoing EEG activity also should be evaluated with time-frequency (TF) analysis [25-29]. In contrast to the time-domain, TF decomposition of the signal provides two dimensional information of how the signal changes both in time and frequency. Post-stimulus changes in different frequency bands appear either as increased or decreased EEG band power, named event related synchronization (ERS) or event related desynchronization (ERD), respectively.

1.1.3 Aim

The aims of the present study was to use TF analyses of EEG signals to investigate 1) how sleep restriction affect pain scores and neurophysiological responses to electrical stimulation, 2) investigate habituation as potential mechanism between sleep restriction and experimental pain 3) and review possible neurophysiological correlates of pain.

2.0 Methods

2.1 Subjects

Twenty-two healthy subjects (8 men and 14 women) aged 18-31yr (mean 23 ± 4) were recruited to participate in three laboratory experiments at the National Institute of Occupational Health. Participants did not have shift work, reported good sleep quality as assessed with Pittsburg sleep quality index (PSQI, Appendix 1) and Epworth sleepiness scale (ESS, Appendix 2). PSQI is a validated instrument used to distinguish between good and poor sleepers, while ESS measures general level of daytime sleepiness [30, 31]. A global PSQI index below seven (scale 0-21) and ESS score below eleven (scale 0-24) was required for participation in this study. Other exclusion criteria were: no current or prior history of chronic pain (> 3 months over the last 2 years) with intensity ≥ 3 (scale 0-10), frequent headaches (mild headache < 2 days per month allowed), psychiatric, cardiovascular, neurological disorders, pregnancy or breastfeeding (Appendix 3). The experiment was carried out in the period between the fourth and fourteenth day of a menstrual cycle for the female participants. Participants were recruited by posters at colleges and universities in Oslo, advertisements in newspapers and at the website of the National Institute for Occupational Health. All participants gave a written informed consent (Appendix 4) and the experimental protocol was approved by the Regional Committee for Medical and Research Ethics.

2.2 Experimental design and protocol

Subjects participated in three laboratory experiments at the National Institute for Occupational health, Oslo. The first experiment lasted for approximately one hour. The purpose was to inform about the nature of the experiments and let the subjects familiarize with the Numerical Rating Scale (NRS) for pain assessment and determining painful thresholds for electrical stimulations.

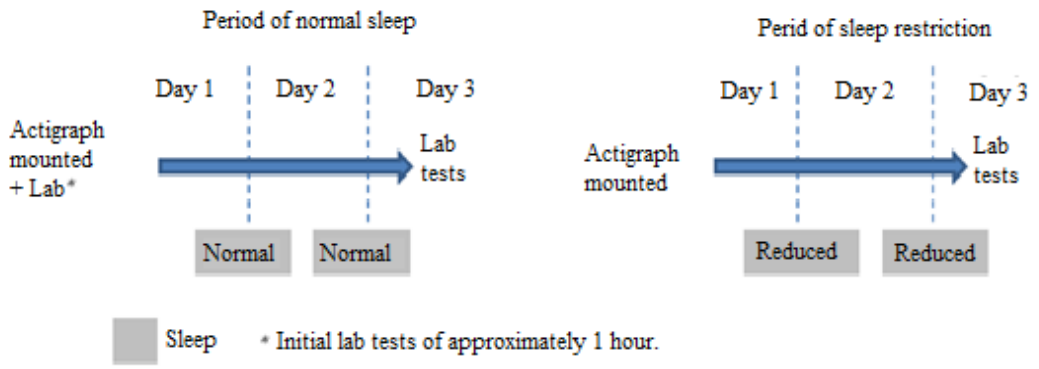

Figure 1. Within-subject cross-over design in counterbalanced order. One lab test following two nights of normal sleep, second experiment after two nights of reduced sleep. Pain threshold was defined in a separate initial lab session.

For the two other experiments a within-subject cross-over design was employed (figure 1). Each subject underwent an experimental session after two different sleep conditions in counterbalanced order in. One session following two consecutive nights of habitual sleep, and another session after two nights of 50% sleep time reduction. Time between each session was approximately one month. Duration of sleep reduction was calculated from self-reported habitual sleep (from Appendix 1). Subjects stayed at home in both experimental conditions and sleep was deprived during the first part of the night. Time of experiments was set to 09.00 am for both sleep conditions, and subjects were instructed to get up at 07.00 am. They were required to abstain from nicotine and caffeine in the morning and from alcohol 24 hours prior to the sessions.

In addition to the instructions, participants were asked to fill in a sleep log (Appendix 5) with time when turning of the lights and wake up time next day. Wake periods during the night were noted with approximate duration and timing the morning after. Motor activity was measured with an actigraph (ActiSleep+ by ActiGraph, US) worn on the left wrist. Low activity was considered as periods in sleep. Coarse differences between sleep log and actigraph data were manually reviewed. The experiment was carried out by a senior engineer, EEG preprocessing and TF analyses done by supervisor in collaboration with student. Final analyses in SPSS were conducted by student.

2.3 Physiological recordings/ Experimental protocol

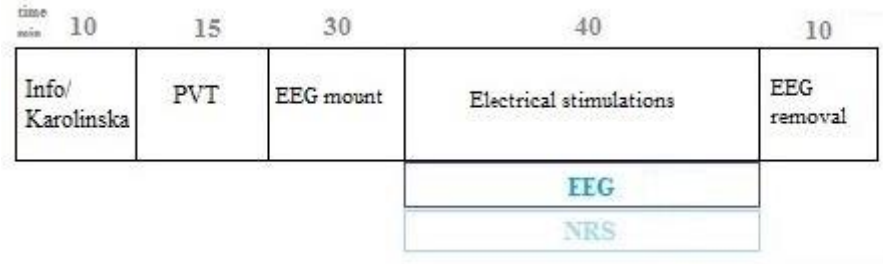

Figure 2. Time line presenting order and the duration of each tests in this study.

Subjects were seated in a comfortable chair and given brief verbal introduction of the experiment. Sleep log was collected and they were asked to complete Karolinska sleepiness scale short version (Appendix 6). Figure 1 shows the experimental time line for the two experimental sessions.

2.3.1 Control of sleep restriction.

Karolinska sleepiness scale (KSS) measures subjective sleepiness at a given time during the day [32]. It is a one dimensional scale ranging from 1 (extremely alert) to 9 (very sleepy, fighting against sleep).

A computer based version of the 10 minutes Psychomotor Vigilance Test (PVT) was used for repeated measures of selected parameters of cognitive factors reported to be sensitive to sleep loss [33]. Subjects were instructed to focus at a red computer screen and press the response button as soon as a white colored number appeared in a rectangular box. The test lasted for 10 minutes. Interval between each laps varied between 2-10 seconds after response button were pressed. Mean reaction time (RT), mean 10% fastest RT, mean 10% slowest RT in milliseconds, and their associated inverse measures (Mean 1/RT) were computed.

2.3.2 Electrical stimulations.

For electrical stimulations, the cathode was a platinum pin electrode with a diameter of 0.2 mm that protruded 0.4 mm from the surface of a polyoxymethylen frame, designed to give currents of very high density. It was placed in the center between cubital foassa and the wrist, one centimeter medial to the center line. The anode was electrode band placed around the upper arm just above the elbow (National institute of occupational Health, Oslo). Brief electrical pulses were generated by a constant current stimulator, including a trigger

generator (Digitimer, Great Britain). The high frequency stimulations were made up of two unipolar pulses with duration of 0.5 ms and a constant inter-pulse interval of 10 ms. Intensity of each pulse was encoded by a custom made encoder (by National institute of occupational Health, Oslo) that sent a trigger to the EEG software (Vision Recorder 1.20 version 005 software , Brain products, Germany).

Pain threshold for the electric stimulations was defined the 1st experimental day by gradual increasing intensity with 0,1mA until sensory threshold (ST). ST refer to the lowest level at which a stimulus can be detected. Subjects were informed before each stimulus and asked to indicate ST. From ST we continued incrementing intensity by 0,2mA until pain threshold was detected (PT). PT is defined as the intensity at which a stimuli starts to evoke pain. The procedure was repeated two times, starting from ST increasing by 0.2 mA. Average stimulus intensity of the two last measurements was defined as PT.

Three series of 30 repeated noxious electric stimulations (equally divided between intensity A, B and C) were applied to the volar forearm. The interval between repeated series was 2 minutes. Stimulations of three different intensities (A=2 times, B=3 times and C=4 times pain threshold) were presented in pseudo-randomized order (figure 3). Within each series, the inter-stimulus interval (ISI) varied between 10 and 15 seconds. Subject perceived stimuli with open eyes, focusing on an item placed 3 meters in front of them. They were instructed to verbally rate the intensity of each painful stimulus on a numerical rating scale between 0 (no pain) and 10 (most intense pain imaginable) 3 to 4 seconds after the stimulus.

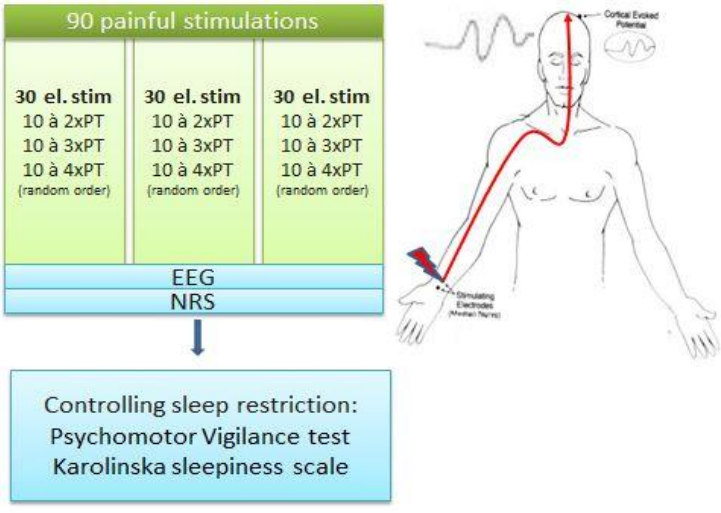

Figure 3. Three series of thirty repeated painful electric stimulations of three different intensities were presented in pseudo-randomized order to the fore arm. Pain response vas measured with EEG recording and numerical rating score. We used psychomotor Vigilance test and Karolinska sleepiness scale to measure seepiness.

2.3.3 EEG recording.

EEG was recorded using a 32 channel actiCAP electrode system (Brain Products, Germany). Electrodes were placed on the head according to the International 10-20 system using a soft electrode cap (actiCAP by Brain Products, Germany) with a cap size matching the subjects head size. The EEG signals were sampled from electrode contralateral to stimulus site (C3/C4), referenced to electrodes behind the ears (A1/A2), grounded at Fz, sampled at 2 kHz with high and low pass filters at 0,53 Hz and 100 Hz respectively. Impedance was kept below 20 kΩ and visually controlled immediately before the experiment using actiCAP Control version 1.2.4.0 software (Brain Products, Germany). Ocular movements and eye blinks were registered by two surface electrodes placed at the upper left (VEOG) and lower right (HEOG) side of the eye. The continuous EEG signal was amplified with QuickAmp 40-channel system (Brain Products, Germany) and recorded by Vision Recorder software.

2.3.4 EEG preprocessing.

Raw EEG was preprocessed using Brain Vision Analyzer 2.0 software (Brain Products, Germany). The EEG signals were downsampled to 512 Hz and notch filtered at 50 Hz using an infinite impulse response filter (IIR). The signal was corrected for eye movements with a semiautomatic independent component analysis (ICA). Automatic marked components were manually evaluated before original data were corrected. Next, we subdivided the signal into blocks corresponding to the three different stimulus intensities (A=2xPT, B=3xPT, C=4xPT). The three different blocks, each containing responses from the three series (S1, S2, S3) were exported to Matlab (R2012 The Mathworks, Massachusetts, US) in which epoching and artifact correction was performed in EEG-lab (http://sccn.ucsd.edu/eeglab/ Version 10.2.2.4b). The response from each individual pain stimulus for each series (S1, S2, S3) and intensity (A, B, C) were extracted using a time window from 1000ms pre-stimulus to 2000ms post-stimulus. Epochs with amplitude exceeding ±200 µV were considered artefactual and rejected. Remaining epochs were further processed using time-frequency analyses.

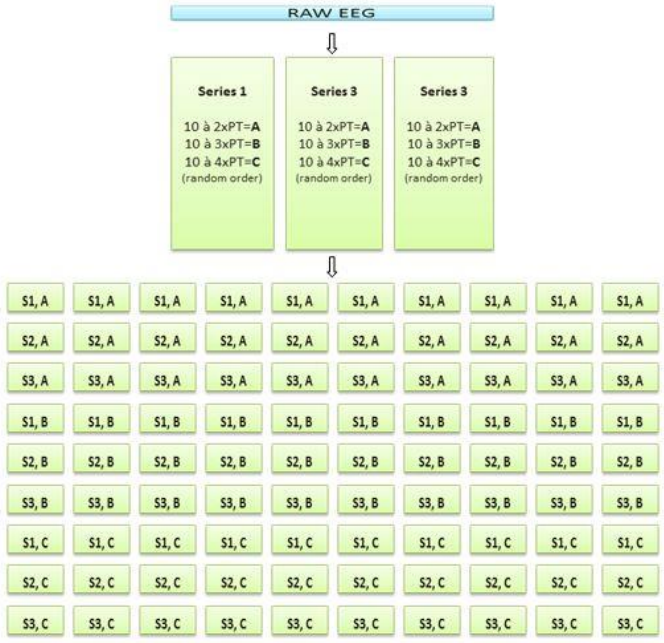

Figure 4. EEG raw data was epoched and artifact corrected using Brain Viasion Analyzer and Mathlab.

2.3.5 Time-frequency-analyses:

a) Time/frequency (TF) analyses were performed for each epoch using a custom written Matlab program according to the method described by Zhang and coworkers (2012) [28]. For the time interval between -1000ms pre stimulus to 2000ms post stimulus, the power spectral density for each time point was calculated using Windowed Fourier transform (WFT) with a fixed 200ms Hanning window. This analyses returned one TF plot for each stimulus with x-axis consisting of 1536 data points (sampling rate x time interval) and frequency distribution (y-axis) ranging from 0-100 Hz (figure 5). To express the size of stimulus-induced changes in activity, a percentage change in power for each TF-point after stimulus was calculated from a pre stimulus reference interval from - 900ms to -100ms. Output data consisted of 18 TF-maps for each person (3 series x 3 intensities x 2 sleep) with stimulus induced change of power expressed in percentage.

b) Next, we sought to let statistics determine which time/frequency areas that were significantly changed by pain stimulus. Using Bootstrapping and a paired t-test, we determined which TF-points post-stimulus (0 - 800ms after stimulus) that was different from the reference period (- 900ms -100ms before stimulus). The T-test compared each TF-point to baseline, and provided statistical p-values of whom TF-points with $p < 0.01$ were retained.

Three collections of significant p-values were obtained, and named “regions of interest” (ROI), 1, 2 and 3.

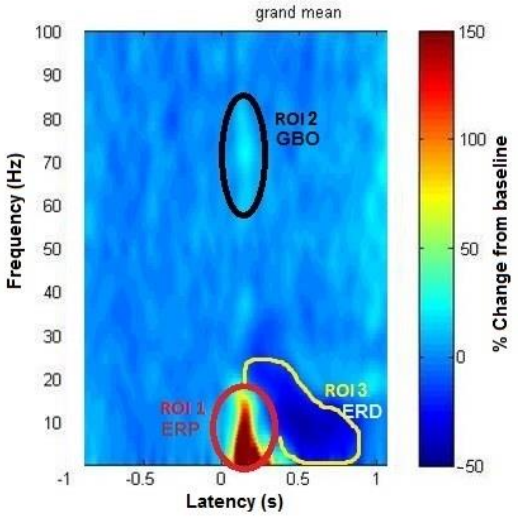

Figure 5. Grand mean Time-frequency distribution (% change) of EEG responses elicited by 90 stimulations of three different intensities (2xPT, 3xPT, 4xPT) devided in three different series (S1, S2, S3). x-axis, time (s); y-axis, frequency (Hz). Displayed signals were recorded at C3/C4. Color scale represents the average increase (ERS%) and decrease (ERD%) of oscillation relative to baseline (-0,9s to -0,1s), before stimulus (0s).

ROI 1 revealed a clear response of stimulus-induced increased power of the frequency area ranging from 0.5-20Hz (0- 200 ms after stimulus). Although ROI 1 contains information of both phase-locked and not-phase locked activity, Zhang and coworkers found that this component mainly includes information comparable to phase-locked ERP [28]. In this study frequency changes in ROI 1 will be referred to as ERPs. ERP was followed by ROI 3 showing mainly desynchronization of alpha and lower beta oscillations (8-20 Hz, 300-700 ms after stimulus), referred to as event-related desynchronization (ERD) in the following. ROI 2 (60-90 Hz, 0-200 ms after stimulus) represents neural oscillations of high frequencies. Frequencies between 25 and 100 Hz are in general reported as gamma band oscillations (GBO), a term used from this time forth.

c) Ultimately, three binary masks were created identifying ERP, GBO and ERD globally. Each binary mask was multiplied with each of the 18 TF-maps (per subject) to isolate the %-change for each subject and condition (sleep, series and intensity). Average %-change within each region (ERP, GBO and ERD) for each subject and condition was calculated and saved in a SPSS readable tab-delimited text file.

2.3.6 Statistical analyses.

Further analyses were performed in IBM statistics SPSS, version 20. For the main analyses a repeated measures mixed-model with **a)** sleep **b)** series and **c)** intensity as independent variables, and average power in **1)** ERP, **2)** GBO and **3)** ERD as dependent variables was used. The dependent variables were analyzed separately. Dependent variables significantly responding to series were included in further analyses of possible interaction effects between sleep and series. Identical procedure was performed for psychophysiological scores, using NRS as the dependent variable. Measures of sleepiness were analyzed with Wilcoxon signed rank test. For all final analyses, p-values < 0.05 were considered significant, and p-values $0.05 – 0.1$ were considered trends.

3.0 Results

3.1 Sleepiness

Increase sleepiness after sleep restriction was confirmed both objectively and subjectively. Wilcoxon Signed Rank Test show a significant difference between self-reported sleep duration between normal and reduced sleep condition ($Z = -4.107$, $p<0.001$). Averaged self-reported sleep duration was 7.36 ±0.72 h following habitual sleep condition, whereas average sleeping hours in the reduced sleep period was 3.77 ±0.53 h.

Wilcoxon Signed Rank Test show significant decreased in mean inverse RT ($Z = -2.520$, $p=0.012$), indicating increase in response time measured with PVT. Averaged mean inverse RT was 3.08 ±0.28 (s^-1) for normal sleep and 2.93 ±0.22 (s^-1) for 50 % sleep restriction.

Karolinska sleepiness scale show increased subjective sleepiness 09.00 am following two nights of reduced sleep (6.75 ± 1.29) compared to two nights of habitual sleep (4.00 ±1.41) ($Z= -38.83$, $p<0.001$).

3.2 Psychophysiological results

Table 1. Mean and SD for NRS scores by sleep, stimulus repetition and stimulus intensity

NRS	Normal sleep, Mean (SD)	Sleep restriction, Mean (SD)
Intensity 2xPT		
Series 1	2.77 (1.20)	2.92 (1.62)
Series 2	2.55 (1.31)	2.61 (1.53)
Series 3	2.52 (1.31)	2.56 (1.59)
Intensity 3xPT		
Series 1	3.64 (1.28)	3.81 (1.66)
Series 2	3.47 (1.37)	3.66 (1.54)
Series 3	3.27 (1.20)	3.40 (1.69)
Intensity 4xPT		
Series 1	4.58 (1.42)	4.74 (1.77)
Series 2	4.29 (1.43)	4.87 (1.71)
Series 3	4.24 (1.49)	4.55 (1.84)

3.2.1 Effects of sleep, repetition and intensity on NRS

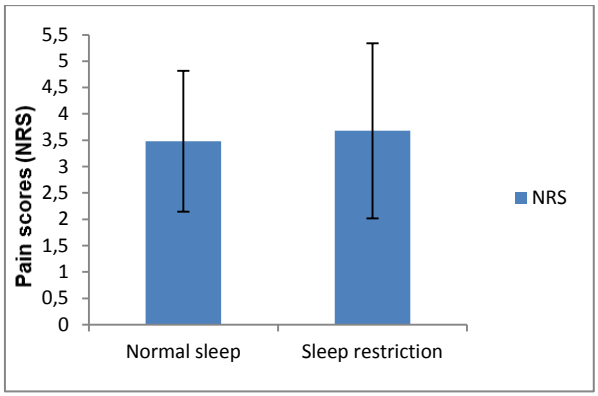

Figure 6. Effects of sleep restriction on pain perception (NRS) to electrical stimulations. The pain scores increased after sleep restriction $p<0.05$.

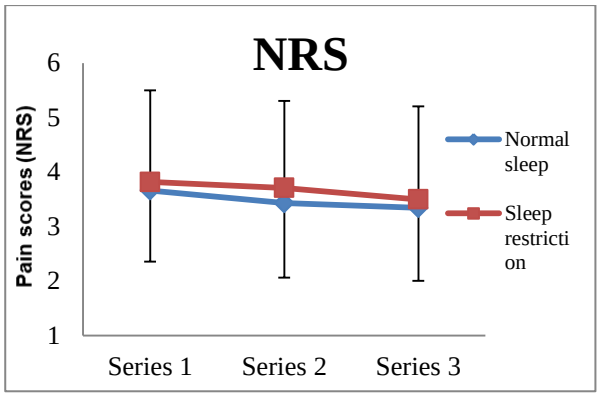

Figure 7. Effects of stimulus repetition (series 1- series 3) and sleep on the pain perception (NRS). Stimulus repetition significantly reduced pain scores $p<0.05$. There was no interaction between the two factors.

We found 5.4% increased pain perception to the stimulations after two nights of reduced sleep (Table 1) compared to normal sleep ($F(1, 374) = 5.6$, $p=0.019$)). We also found an effect of stimulus repetition ($F(2, 374) = 4.9$, $p=0.008$)), with subjective pain rating across series decreasing progressively (habituation). NRS significantly increased in proportion to increased stimulus intensity ($F(2, 374) = 170.3$, $p<0.001$)).

Habituation of pain perception was not affected by sleep, sleep x series; ($F(2, 374) = 0.24$, $p=0.788$)).

3.3 Neurophysiological results

Table 2. Means and SD for ERD, gamma activity and ERD by sleep, stimulus repetition and stimulus intensity

	Normal sleep, Mean (SD)	Sleep restriction, Mean (SD)
ERP		
Intensity 2xPT		
Series 1	93.40 (80.33)	140.80 (107.94)
Series 2	77.39 (58.90)	96.10 (96.22)
Series 3	53.25 (38.77)	72.26 (72.44)
Intensity 3xPT		
Series 1	129.46 (87.61)	115.28 (99.06)
Series 2	77.79 (58.40)	97.66 (92.58)
Series 3	59.88 (50.22)	87.99 (88.09)
Intensity 4xPT		
Series 1	118.10 (66.66)	126.51 (101.53)
Series 2	100.51 (84.15)	94.10 (94.72)
Series 3	68.13 (64.05)	84.68 (86.48)
GBO		
Intensity 2xPT		
Series 1	24.27 (30.39)	24.50 (38.38)
Series 2	14.55 (25.16)	18.22 (40.88)
Series 3	4.56 (26.60)	6.40 (34.08)
Intensity 3xPT		
Series 1	19.30 (43.57)	6.86 (32.92)
Series 2	11.92 (35.47)	18.00 (36.61)
Series 3	12.23 (39.47)	26.61 (40.41)
Intensity 4xPT		
Series 1	14.47 (33.71)	12.95 (57.87)
Series 2	24.29 (30.96)	14.83 (30.11)
Series 3	16.55 (29.03)	18.43 (53.82)
ERD		
Intensity A		
Series 1	-17.77 (21.76)	-15.85 (22.80)
Series 2	-19.96 (25.36)	-15.17 (31.34)
Series 3	-7.12 (33.60)	-12.77 (26.82)
Intensity B		
Series 1	-20.25 (19.21)	-24.15 (25.18)
Series 2	-18.87 (15.95)	-16.53 (33.48)
Series 3	-19.52 (21.71)	-15.39 (34.70)
Intensity C		
Series 1	-27.43 (20.46)	-28.67 (20.98)
Series 2	-24.49 (20.99)	-27.61 (28.51)
Series 3	-25.81 (21.66)	-21.41 (23.88)

3.3.1 Effects of sleep, repetition and intensity on ERP¨

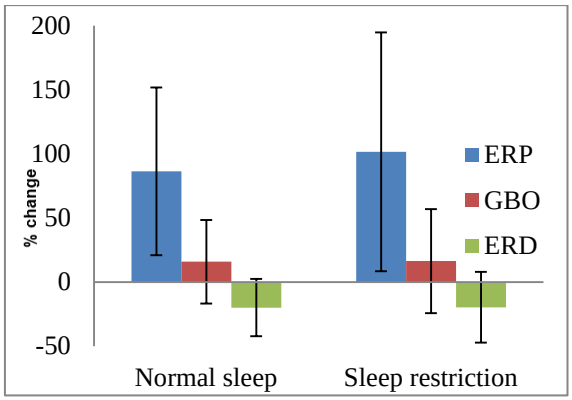

Figure 8. Effects of sleep restriction on the time frequency distribution (% change) to electrical stimulations. Time frequency distribution of ERP (blue) significantly increased after sleep restriction p<0.05.

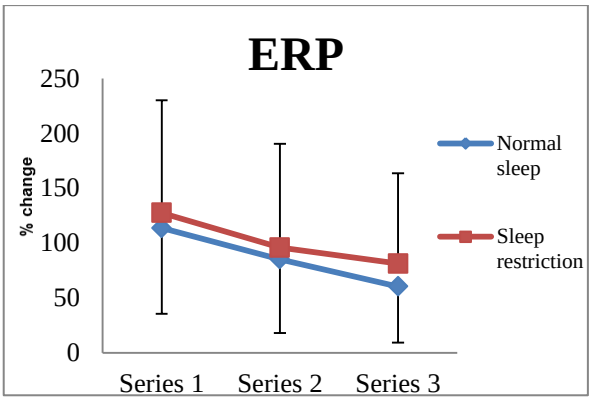

Figure 9. Effects of stimulus repetition and sleep on the time frequency distribution (%change) of ERP. Time frequency distribution of ERP significantly decreased from series 1 to series 3 p<0.05. There was no interaction between the two factors (sleep x series).

For the ERP's a significant effect of sleep was found (F (1, 357) = 5.9, p=0.016)). Moreover, a significant effect of stimulus repetition (habituation) was found (main effect of series; (F (2, 357) = 21.3, p<0,001)). No effect of stimulus intensity was found (F (2, 357) = 0.82, p=0.441)). Stimulus repetition was followed by attenuation of power (Table 2). Furthermore, no interaction between sleep and habituation was found (F (2, 357) = 0.23, p=0.795)), i.e. habituation did not differ between normal and reduced sleep.

3.3.2 Effects of sleep, repetition and intensity on GBO and ERD

No effects of sleep was found on neither GBO nor ERD (p>0.88). For ERD, an effect of stimulus intensity was found (F (2,357) = 12.4, p<0.001)), and a trend towards an effect of stimulus repetition, i.e. habituation, was found (F (2,357) = 2.8, p=0.064)). However, no effects of stimulus intensity or stimulus repetition (p=0.741) was found for GBO. No interaction between sleep and repetition was found for neither stimulus repetition nor stimulus intensity (p>0.47).

4.0 Discussion

4.1 Sleep restriction and pain responses.

In this study we investigate how sleep reduction affects pain perception and electrophysiological potentials, suggested to be neurophysiological correlate for subjective pain. Furthermore, we examine if alternations in response habituation can explain a possible increase in pain due to reduced sleep.

We found that two nights of 50% sleep restriction increased subjective pain scores with 5.4% and event related potentials (ERPs) with 15.2% to electrical stimulation. This indicates that sleep reduction leads to increased activation in the spinothalamic pathway. Second, the observed connection between sleep, pain and ERPs, is not followed by increased event related desynchronization (ERD) or gamma band oscillations (GBO) in somatosensory cortex. Thirdly, increased pain following sleep reduction is not followed by abnormal habituation.

Previous research has found increased pain experience related to reduced sleep in healthy subjects [8, 11-13]. Enhanced pain response is also found in subjects with insomnia compared to healthy controls [9]. However, many studies have evaluated pain thresholds (PT) for different stimulation modalities. There are considerable variations in the use of sleep restriction regimes which make studies difficult to compare.

Nevertheless, Tiede and coworkers (2010) performed a highly comparative study in which they evaluated the effect of max 4 hours of sleep on laser evoked potentials (LEPs) and pain perception. They found that laser stimulations directed to the hand were scored 30% more painful after sleep restriction compared to one night of habitual sleep [10]. In contrast to our findings, the ERP amplitudes, quantified in time domain, were significantly reduced after one night of 50% sleep restriction [10]. Interestingly, sleep induced reduced activity in the spinothalamic pathway was also proposed by Azevedo and coworkers (2011), showing that two night of total sleep deprivation caused elevation of ERP thresholds and concomitant increased pain experience [16].

Discrepancy between the evoked potentials in studies may be due to different way of quantifying post-stimulus ERP changes. Whereas ERP amplitudes in the time domain may be affected by latency variations between averaged potentials, ERP power would not be affected by such limitations quantified in the time-frequency (TF) domain [25, 26]. It may be

speculated whether sleep restriction increase ERP latency variations between stimulus repetitions and thereby cause the attenuated amplitude of average ERPs after sleep deprivation, as observed by Tiede and coworkers [10].

However, it is important to consider that ERP power in the current study is limited by not differentiating between phase-locked and not-phase locked power. Although some of the increased ERP power after sleep deprivation in present study may include increased not-phase brain activity (ERS), Zhang and coworkers (2012) found that similar components mainly contains information comparable to phase-locked ERP [28]. Furthermore, a significant difference between ERP in time-domain and TF analyses is that energy in the latter contains more information for a longer period of time. ERPs in TF domain do not distinguish between early (e.g. N1) and later pain processing phase-locked potentials (e.g. N2, P2, P300). This makes comparisons between different quantification methods somewhat complicated.

Furthermore, ERP data in these two studies are sampled from different EEG electrode positions. In the present study signals located above the somatosensory cortex (C3/C4) were sampled, whereas Tiede measured averaged time-domain ERP over the midline (Cz). We intended to detect not-phase locked EEG changes in response to painful stimulations. Some of these oscillations have shown to be more localization specific, and C3/C4 is most commonly used in studies that analyze painful stimulations in TF domain [27-29, 34]. However, ERP's are reported to exhibit greatest amplitude over vertex [35]. Consequently, the observed disparity between the two studies may be even greater than reported here.

One might hypothesize that different results between sleep studies and discrepancy between subjective and objective pain could arise from later post-stimulus or internal cognitive processing. Our study found significant ERD in the 8-20 Hz frequency region following presentation of painful stimulations. Nevertheless, we observed that event related desynchronization (ERD) did not change with sleep reduction.

In all simplicity, low frequency ERD may be interpreted as cortical areas that are active. In previous research, increased low frequency ERD is found in subjects performing tasks that demand enhanced perceptual, judgmental and memory skills [34, 36]. Accordingly, widespread cortical ERD are evident over cortical areas both during sensory information processing, movements and cognitive tasks. In terms of sensory information processing, ERD is suggested to reflect an integration and modulation of interneurons on the ascending

sensory pathways (ERPs) [34].

Knowing that ERD may influence ERPs for information processing of external stimulations, one can speculate if somnolent subjects would execute increased perceptual effort to evaluate the sensory information expressed as increased ERD in somatosensory cortex. In this study we failed to detect any sleep effect on post-stimuli ERD. However, we do not know if sleep has led to increased ERD in other brain areas.

The influence and the origin of stimulus induced ERD oscillations are debated [29]. Some studies claim that low frequency ERD mainly arise from information processing generated by the primary sensory cortex, whereas other studies show that ERD are related to internal cognitive processes measureable over the occipital cortex [29]. Peng and coworkers (2012) conducted a source analyses study in which they compared late ERPs (P300) and ERD for the four different stimulus modalities (visual, auditory, somatosensory and pain). They showed that ERD was most present in occipital brain areas for all stimulation modalities, indicating that these oscillations are most sensitive for modulation by internal mental events. Moreover, they confirmed that stimulus induced occipital ERD sends information to subsequent late ERPs (P300) and thereby may reflect integration of high cognitive information communication [29].

The suggested link between occipital ERD and sensory processing points out the relevance of measuring occipital ERD changes following the painful stimulations in present study. Although we found no ERD changes in somatosensory cortex, the increased pain experience and ERP's after sleep may still have been modulated by a corresponding increase ERD in occipital region.

In addition to the above-mentioned ERD oscillations, recent studies have called attention to higher frequency bands, especially GBO's [20, 27, 28]. Besides being related to cortical integration of pain perception, GBO has proven to explain the short-term differences in pain within the same individuals [20]. Moreover, Zhang and coworkers revealed that GBO's do not reflect attentional encoding (saliency) [28].

The presence of post-stimulus GBOs in this study verifies that these oscillations may be involved in sensory processing. However, as high frequency bands did not change in respect to sleep restriction, stimulus intensity or stimulus repetition, this study did not confirm a possible relation between GBOs and pain experience.

4.2 Sleep restriction and habituation.

Both pain scores and ERP's habituated in the present study. To the extent of our knowledge, the effect of sleep restriction on habituation is not investigated earlier. However, dis-habituation is found in more chronic pain syndromes such as fibromyalgia [18], low back pain and migraine (reviewed in [17]), and may be a relevant mechanism for the relation between increased pain sensitivity and sleep deprivation.

This study investigated cortical responses resulting from ninety stimulus repetition across three different series of painful electrical stimulations (10-15 second inter-stimulus interval and 2 minutes inter-series interval). We found steady habituation of subjective and ERP responses, however, we found that habituation is unaffected by 50% sleep restriction.

One might argue that pain modulation assessed with habituation may be exclusively relevant for chronic conditions. This is a potentially interesting objective for future research.

Additionally, if dis-habituation is predominant in chronic states, one can also assume that habituation display higher sleep exposure threshold. For example, subjects exposed to total sleep deprivation for two consecutive nights have increased thresholds for detection of evoked potentials. In contrast, selective REM sleep deprivation failed to cause the same effect [16]. The fact that various sleep paradigms display mixed impact on experimental pain and pain modulations is confirmed by other studies [12, 13, 37]. Furthermore, experimental studies report that recovery sleep after sleep restriction contains increased amount slow wave sleep, suggested to have an analgesic effect [13, 38]. These findings indicate that periods of undisturbed sleep in present study may have equalized some the negative effect on the pain physiology.

Nevertheless, it should be noted that two consecutive nights of 50% sleep restriction as interpreted in the current study are probably more clinical relevant compared to one or more night of total sleep deprivation.

4.3 Neurophysiological correlates of pain perception.

Painful electrical stimulations in this study induced ERPs followed by prolonged ERD and GBO over the somatosensory cortex. Therefore, it is likely that all these frequency bands may contribute in early sensory processing, either directly or indirectly.

As expected, the subjective pain scores increased proportional to stimulus intensity. Surprisingly, ERPs did not significantly change with stimulus intensity. This indicates that ERPs do not reflect the neural coding of subjective pain intensity alone. That ERP's do not reflect nociception is also reported by others [25, 26].

Interestingly, we observed that ERD power increased proportional to stimulus intensity and thereby shows a similar pattern as the subjective scores. Stancak and coworkers (2003) conducted a study evaluating the ERD effect of stimulus intensity for electrical stimulations [39]. As in the current study, ERD increased with stimulus intensity. However, there was no significant correlation between ERD and the subjective scores, suggesting that ERD reflect an orienting response rather than pain processing [39]. As mentioned, ERD responses are also explored in motor and cognitive tasks, as well as sensory information processing [34, 36]. Further correlation analyses are needed to verify a possible relationship between ERD and pain. Moreover, this study is not designed to assess ERD in other stimulus or task-related factors.

Although high-frequency GBOs are suggested to reflect pain [20, 27, 28], we found no concomitant change in GBO and stimulus intensity. In studies providing evidence for a relationship between GBO and pain experience, GBO changes are analyzed relative to perceived pain intensity [28]. In contrast, GBO do not correlate significantly with the actual stimulus intensity [28]. In the present study, we analyzed the GBO change in response to actual stimulus energy which may explain the results. However, since NRS (perceived intensity) significantly increased in proportion to increased stimulus intensity (applied intensity) in this study, correlating GBO with NRS may not affect the main results. Unfortunately, there was not enough time to analyze neurophysiological measurements whit respect of perceived pain in this study. Nor investigate possible gender differences.

In summary, potential neurophysiological correlates of pain arise in response to painful stimulation. Nevertheless, the principal question remains unanswered: Where is the pain? Obviously, no current research methods can determine the whole truth of the central pain processing per se. Pain is a complex experience which includes the nociceptive input

influenced by many context-sensitive and subjective factors [19]. Different brain regions will continuously change activity level depending upon factors that are involved. The complex features complicates assessment of relevant neural elements [19]. However, research of EEG oscillations has become a growing field the last decades. EEG is now considered to play an important role for future understanding of how the brain process information [40]. Moreover, new methods of analyzing EEG signals are considered an important and useful tool for future pain research [25].

4.4 Discussion of methods.

Within-subject design reduces the variance associated with individual differences in present study. Compared to between-subject designs, inter-individual differences in pain perception become less significant when subjects are their own controls. Moreover, randomized order of sleep conditions prevents order effects (e.g. participation in normal sleep condition affects the performance in reduced sleep condition). Within-subject designs are also less resource-demanding because fewer participants are required. Additionally, we performed repeated measure mixed-model statistical analyses in the present study. Mixed models are preferred over more traditional designs for repeated measures because the model regards that measurement arises from the same subjects and may be correlated. Furthermore, the model does not delete experimental subjects with missing data.

Besides design and analysis method, several other factors strengthen the internal validity in the present study. Initial questionnaires was use to ensure a homogeneous group and control for possible confounding factors. Second, all subjects were tested by the same test leader and received identical information each session. However, the nature of the experiment complicated both single and double blinding. Knowing that individual expectations may be relevant for pain perception [41], it is possible that subjects who are not blinded would expect increased pain after reduced sleep compared to habitual sleep condition.

It is important to utilize reliable instruments that measure what is supposed to be assessed. Here, evoked potentials and pain was induced by electrical stimulations shown to mainly activate Aδ afferents [42]. In addition, we used active EEG electrodes which improves the signal quality compared to passive electrodes, and performed semiautomatic and manual removal of artifacts. NRS is considered to be applicable for pain intensity measurements [43].

Although electrophysiological EEG studies of painful stimulations is useful for evaluating temporal changes in pain processing, these studies are criticized for not measuring later pain responses more clinical relevant for long term pain conditions [35]. To generalize

the results, the sample should also reflect the general population. The external validity in this may therefore be influenced by only including self-selected healthy subjects. Nevertheless, the purpose here was to investigate normal pain mechanisms and how they are affected by sleep. Consequently, there is a trade-off between internal and external validity many experimental studies. However, most of the subjects are recruited from universities and colleges and the average age is relatively low.

5.0 Conclusion

The present study shows that partial sleep restriction cause hyperalgesia to experimental pain in healthy subjects. This acute effect is followed by increased excitation of phase-locked brain activity (ERP). Furthermore, painful electrical stimulations induce changes in not-phase locked ERD and GBO. ERP's, GBO's and ERD have been suggested as neurophysiological correlates for subjective pain experience. However, it still remains to determine the exact origin and functional properties of these cortical changes.

Temporary sleep restrictions do not affect habituation of painful electrical stimulations in healthy subjects. Nevertheless, future studies should investigate whether chronic sleep restriction or chronic sleep problems affect habituation of painful stimuli.

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Appendix 1

Pittsburg Sleep Quality Index

PSQI

Instruksjoner: Følgende spørsmål har med ditt vanlige søvnmønster *den siste måneden* å gjøre. Du skal svare på hva som er mest riktig for *de fleste* dager og netter den siste måneden. Vennligst svar på alle spørsmål.

1. I løpet av den siste måneden, når har du vanligvis lagt deg om kvelden?
   VANLIG LEGGETID_____

2. I løpet av den siste måneden, hvor lang tid (i minutter) har det vanligvis tatt deg å sovne om kvelden?
   ANTALL MINUTTER_____

3. I løpet av den siste måneden, når har du vanligvis stått opp om morgenen?
   VANLIGVIS STÅTT OPP KL_____

4. I løpet av den siste måneden, hvor mange timer søvn har du *faktisk* fått om natten? (Dette kan være forskjellig fra hvor mange timer du oppholdt deg i sengen.)
   ANTALL TIMER SØVN HVER NATT _____

For hvert av de følgende spørsmål, kryss av for det beste svar. Vennligst svar på *alle* spørsmålene.

5. I løpet av den siste måneden, hvor ofte har du hatt problemer med søvnen fordi du…

(a) Ikke klarer å sovne i løpet av 30 minutter

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(b) Våkner opp midt på natten eller tidlig om morgenen

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(c) Må opp for å gå på toalettet

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(d) Ikke klarer å puste ordentlig

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(e) Hoster eller snorker høyt

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(f) Føler deg for kald

Ikke i løpet av den s iste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(g) Føler deg for varm

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(h) Har vonde drømmer

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(i) Har smerter

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(j) Andre grunner, vennligst beskriv_____

_____

Hvor ofte, løpet av den siste måneden, har du hatt problemer med søvnen på grunn av dette

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

6. I løpet av den siste måneden, hvordan vil du bedømme søvnkvaliteten din totalt sett?
   - Veldig bra _____
   - Ganske bra _____
   - Ganske dårlig _____
   - Veldig dårlig _____

7. I løpet av den siste måneden, hvor ofte har du tatt medisin (med eller uten resept) som hjelp til å sove?

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

8. I løpet av den siste måneden, hvor ofte har du hatt problemer med å holde deg våken under bilkjøring, måltider eller når du holder på med sosiale aktiviteter?

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

9. I løpet av den siste måneden, hvor stort problem har det vært for deg å ha overskudd nok til å få ting gjort?
   - Ikke noe problem i det hele tatt _____
   - Bare et lite problem _____
   - Et visst problem _____
   - Et stort problem _____

10. Deler du seng eller rom med noen?
    - Deler ikke seng eller rom med noen _____
    - Partner/romkamerat i annet rom _____
    - Partner i samme rom, men ikke i samme seng _____
    - Partner i samme seng _____

Hvis du har en partner eller romkamerat, spør han/henne hvor ofte i løpet av den siste måneden du har hatt…

(a) høy snorking

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(b) lange pustestopp under søvnen

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(c) rykninger eller sammentrekninger i beina under søvnen

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(d) episoder med desorientering eller forvirring under søvnen

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(e) annen type uro under søvnen; vennligst beskriv_____

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

Pittsburgh Sleep Quality Index
(Buysse, Reynolds III, Monk, Berman & Kupfer, 1989)
Til norsk ved Petter Franer, Inger Hilde Nordhus, Ståle Pallesen og Simen Øverland

Appendix 2

Epworth sleepiness scale

ID-nr:……...

Dato for utfyllt skjema:……

Hvor sannsynlig er det at du sovner (eller dupper av) i følgende situasjoner, i motsetning til kun å føle deg trett? Dette gjelder hvordan du *vanligvis* opplever disse situasjonene. Hvis du ikke har vært i slike situasjoner i det siste, prøv å svare slik du tror du ville ha opplevd situasjonene.

Sett kryss i én av rutene på hver linje.

Situasjon	**Ville aldri sovne**	**En viss sjanse for å sovne**	**Middels sjanse for å sovne**	**Stor sjanse for å sovne**
Sitter og leser				
Ser på TV				
Sitter, inaktiv, på et offentlig sted (f.eks. på teater/kino eller møte)				
Som passasjer på en én-timers				

biltur uten pause				
Legger deg ned for å hvile om ettermiddagen				
Sitter og snakker med noen				
Sitter stille etter lunsj (uten alkoholinntak)				
I en bil som har stoppet opp i trafikken i noen minutter				

Takk for at du besvarte spørreskjemaet!

Appendix 3

STAMI 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?		
6. Har du hatt, eller har, en sykdom i en av følgende kategorier:		
a. Psykiatrisk sykdom (angst, depresjon inkludert)		
b. Nevrologisk sykdom		
c. Hjertesykdom		
d. Lungesykdom (velregulert astma er lov)		
7. Har du hodepine 2 dager eller mer pr. måned (i gjennomsnitt)		
8. Hvis du av og til har hodepine, hvor sterk er hodepinen du vanligvis har:		
a. Mild		

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

Appendix 4

Informed consent

Skiftarbeid og helseplager – Hoveddel 1 – rev. 19.4.12

Forespørsel om deltakelse i forskningsprosjektet

"Skiftarbeid og smertefølsomhet"

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 utstyr som registrerer bevegelser og/eller søvnmønster. Man sover hjemme som normalt. Montering av utstyret skjer ved STAMI eller ved Oslo universitetssykehus 2 døgn for 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 B.

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.

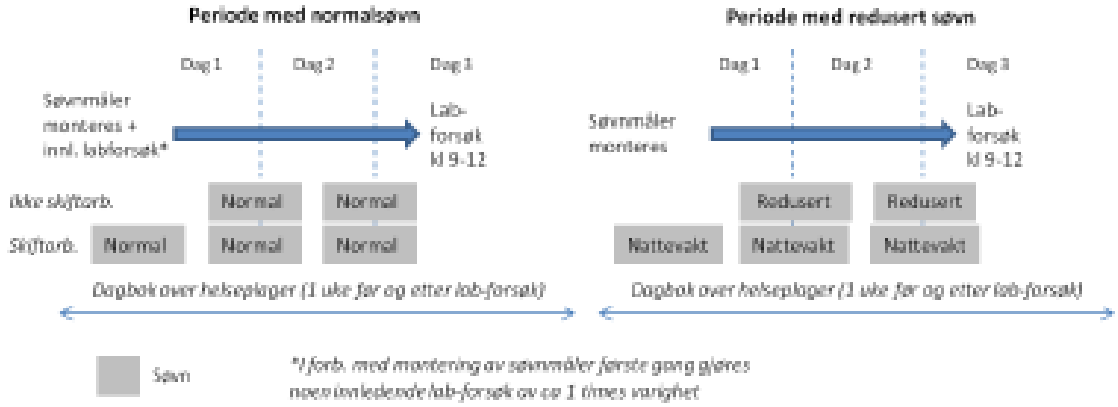
Del	Test[1]	Beskrivelse
1	**Smerteterskler** • Trykk • Varme • Kulde • Elektrisk	Smerteterskler bestemmes ved at ved at intensiteten på stimuleringen gradvis økes inntil moderat smerte kjennes og testen avbrytes. Gjentas 2-3 ganger for hver type stimulering.
	EEG monteres	En hette med 32 elektroder plasseres 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 3 timer hver gang. I tillegg dekkes reisekostnader med offentlig transport til/fra STAMI t.o.m. Ruters sone 4 (ruter.no). Godtgjørelsen blir utbetalt 2-3 uker etter siste forsøksdag.

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)

Appendix 5

Sleep log

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.

Se baksiden

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)

Appendix 6

Karolinska Sleepiness Scale

ID: _____ Dato: _____

Hvor søvnig føler du deg nå?

Besvar spørsmålene ved å angi et tall Anvend gjerne mellomnivåene 2,4,6,8 også

1 veldig opplagt
2
3 opplagt
4
5 verken opplagt eller søvnig
6
7 søvnig, men ikke anstrengende å være våken
8
9 veldig søvnig, kamp mot søvnen, anstrengende å være våken