

Morten Engstrøm

The headache-sleep study: Sleep and pain thresholds in healthy controls and patients with migraine and tension type headache

Thesis for the degree philosophiae doctor

Trondheim, December 2013

Norwegian University of Science and Technology

Faculty of medicine

Department of Clinical Neurosciences



Table of Contents

Preface and acknowledgement.....	6
List of abbreviations.....	8
Summary in English.....	10
Summary in Norwegian.....	12
List of papers.....	14
Introduction.....	15
1. Headache.....	15
1.1 <i>Migraine and tension type headache.....</i>	<i>15</i>
1.2 <i>Diagnostic criteria, Table 1.....</i>	<i>16</i>
2. Pain.....	18
2.1 <i>Pain in general.....</i>	<i>18</i>
2.2 <i>Head and neck pain.....</i>	<i>19</i>
2.3 <i>Pain in migraine and tension type headache.....</i>	<i>19</i>
3. Sleep.....	22
3.1 <i>Sleep.....</i>	<i>22</i>
3.2 <i>Arousals.....</i>	<i>24</i>
3.3 <i>Insomnia.....</i>	<i>25</i>
3.4 <i>Sleep apnea.....</i>	<i>26</i>
3.5 <i>Restless legs and periodic limb movement.....</i>	<i>27</i>
4. Sleep, pain thresholds and headache.....	28
5. Main objectives.....	32

Methods and materials.....	33
6. Design.....	33
7. Participants.....	34
8. Procedure.....	37
9. Statistics.....	39
Summary of main results.....	40
10 Questionnaire and diary.....	40
11 Measurements.....	40
11.1 Fast arousals, SWS and PT.....	40
11.2 Slow arousals, light sleep and awakenings.....	40
11.3 NSM versus SM.....	41
11.4 Preictal versus interictal migraineurs.....	41
11.5 Post hoc TTH.....	41
Discussion.....	44
12 Methods.....	44
12.1 Design.....	44
12.2 Diagnosis and misclassification.....	45
12.3 Controls.....	46
12.4 Bias.....	46
12.5 Measurements.....	47
12.6 The role of chance.....	51
12.7 Confounding.....	51
13 Main results.....	53
13.1 Subjective and objective sleep quality.....	53
13.2 Sleep, arousability and pain.....	57

14 Etiology and pathophysiology	58
14.1 <i>How is a headache attack initiated?</i>	58
14.2 <i>Possible pathophysiological explanations</i>	60
14.3 <i>Possible clinical implications</i>	63
15 What is achieved and where to go	65
15.1 <i>What this thesis adds</i>	65
15.2 <i>Future perspectives</i>	66
15.3 <i>Conclusions</i>	67
Reference list	68
Appendix	75
Articles	77

Preface and acknowledgement

The present work was conducted at Norwegian University of Science and Technology (NTNU), Faculty of medicine, Department of Neurosciences. The data collection was done 2005-2007. Analysis of data was performed in 2009-2013. The study was supported by grants from Department of Clinical Neurosciences; NTNU, and Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (NTNU). I participated in the planning of the study realization and the data collection while working at St. Olavs Hospital and thereafter worked fulltime as a PhD-student from august 2009-2011 and 50% from august 2011-2013.

My main supervisor in this project has been Trond Sand. I thank him for introducing me to this field, his enormous work capacity and knowledge, and for being supportive during ups and downs in this period of time. Lars Jacob Stovner and Knut Hagen have been co-supervisors in this project and I thank them for the clinical evaluation of the headache patients and their quick responses during the writing process, and also Knut Hagen for providing my scholarship. I am also thankful to co-author Marte Bjørk who so enthusiastically corrected my drafts. I thank Gøril Bruvik Gravdahl and Grethe Helde for administering the participants in the study and Gøril Bruvik Gravdahl also plotted all questionnaire and diary data. I am very thankful to Marit Stjern who mounted the polysomnography equipment and performed the pain threshold (PT) tests on most participants. Kari Todnem continued to work part-time at St. Olavs Hospital after retiring to compensate for my PhD-leave period. Both I and the colleagues appreciate her contribution very much. I thank my supportive colleagues and not to mention the 126 persons who voluntarily participated in the present study and made this project achievable. Cooperation with parallel PhD students: Siv Steinsmo Ødegaard, Petter Moe Omland and Martin Uglem, has also been a pleasant experience.

Finally I thank my wife for her daily runs from work in the evenings in order to pick up our youngest children and subsequent conjuring lovely dinners from nothing during no time. I also thank our lovely children: Vegard, Helene and Magnus who fill my heart with joy and hope.

List of abbreviations

AASM - American Academy of Sleep
medicine

AHI – Apnoea-hypopnea-index

ATP – Adenosine triphosphate

BMI – Body mass index

CAP – Cyclic alternating pattern

CTTH – Chronic tension type headache

COX-2 – Cyclooxygenase 2 (enzyme)

CPT – Cold pain thresholds

CRGP – Calcitonin gene related peptide

CRP – C-reactive protein

CSD – Cortical spreading depression

DSM – Diagnostic and Statistical Manual of
Mental Disorders

EEG – Electroencephalography

EMG – Electromyography

ETTH – Episodic tension type headache

fMRI – Functional Magnetic Resonance
Imaging

HADS – Hospital Anxiety and Depression
Scale

HPT – Heat pain thresholds

IL-6 – Interleukin 6

ICD – International classification of diseases

KSQ – Karolinska sleep questionnaire

LDT- Lateral dorsal tegmentum

MA – Migraine with aura

Mg⁺⁺ - Magnesium (ion)

MwoA – Migraine without aura

NMDA – N-methyl-D-aspartate

NO – Nitric oxide

NREM – Non-rapid eye movement (sleep)

NSM – Non-sleep related migraine

NSTTH – Non-sleep-related tension type
headache

NTS – Nucleus tractus solitarius

NTNU - Norwegian University of Science
and Technology

OR – Odds ratio

OSA – Obstructive sleep apnea

PAG – Periaqueductal grey matter

PBN – Parabrachial nucleus

PET – Positron emission tomography

PGE2 – Prostaglandin E2

PLMD – Periodic limb movement disorder

PLMS – Periodic limb movement during
sleep

PLMs – Periodic limb movements

PLMW – Periodic limb movement during
wakefulness

PPT – Pressure pain threshold

PPT- Pedunculopontine tegmentum

PSG – Polysomnography

PSQI - Pittsburgh sleep quality index

PT – Pain thresholds

REM – Rapid eye movement (sleep)

RLS – Restless legs syndrome

RVM – Rostroventral medulla

SM – Sleep (related) migraine

STTH – Sleep (related) tension type
headache

TNC – Trigeminal nucleus caudalis

TNF- α – Tumor necrosis factor alpha

TPT – Thermal pain threshold

TTH – Tension type headache

vIPAG – Ventrolateral periaqueductal
grey matter

VLPO – Ventrolateral preoptic nucleus

Summary in English

Background

Headache can be relieved or released during sleep, but there are few polysomnographic (PSG) studies on headache patients. Our aim was to evaluate subjective and objective sleep, affective symptoms and pain thresholds (PT) in patients with tension type headache (TTH) and migraine and healthy controls.

Methods

All results are based on a blinded study comparing data in headache patients and controls regarding polysomnography, measurements of PT, data from headache and sleep diaries and questionnaires. We included 20 patients with TTH, 50 migraineurs and 34 healthy controls. Migraineurs who had their sleep recording more than two days from an attack were classified as interictal (n=33) while those registered 2 days or less from an attack were classified as either preictal (n=9) or postictal (n=8). Migraineurs with attack onset mainly during night or by awakenings was classified as sleep related migraine (SM) and compared to migraineurs without a preference for nightly attacks (non-sleep related migraine (NSM)). TTH patients were classified either as episodic TTH (ETTH) or chronic (CTTH) if headache days per month respectively were <15 or ≥ 15 .

Results

All headache groups had more anxiety symptoms, more subjective sleep disturbances than controls, but sleep diaries revealed no sleep time differences. Migraineurs recorded in the preictal phase had shorter latency to sleep onset than migraineurs registered in the

interictal phase. Both TTH and NSM patients had findings consistent with foregoing sleep deprivation i.e. more slow wave sleep in PSG, more frequent subjective daytime tiredness and a tendency to lower PT than healthy controls. SM patients had findings consistent with slightly reduced sleep quality in PSG, but not increased frequency of daytime tiredness or reduced PT.

Conclusions

Based on data in this thesis headache patients with attack onset during daytime may need more sleep than healthy controls. Subjects with SM had findings indicating slightly disturbed sleep. However, since no specific clinically relevant disturbing factor was detected, an increased sensitivity to slight subclinical sleep disturbances might be characteristic for patients with headache onset during sleep.

Summary in Norwegian

Bakgrunn

Hodepine kan lindres og utløses under søvn, men få har undersøkt hodepinepasienter med polysomnografi. Vårt mål var å evaluere subjektiv og objektiv søvnkvalitet, affektive symptomer og smerteterskler hos pasienter med tensjonshodepine og migrene og friske kontroller.

Metode

Alle resultater i denne avhandlingen bygger på data fra en blindet studie der informasjon fra polysomnografi (PSG), smerteterskelmålinger, hodepine- og søvndagbøker samt spørreskjema sammenlignes mellom hodepinegrupper og kontroller. Vi inkluderte 20 TTH- og 50 migrene pasienter samt 34 friske kontroller. Migrenepasienter som hadde søvnregistreringen mer enn 2 døgn fra et anfall (n=33) ble klassifisert som interiktale mens de som fikk søvnregistreringen mindre enn 2 døgn fra anfall ble klassifisert som enten pre- (n=9) eller post ictale (n=8). Migrenepasienter som i hovedsak fikk anfall under søvn eller ved oppvåkning (søvn-relatert-migrene, SM), ble også sammenliknet med migrenepasienter som ikke vanligvis fikk hodepineanfall ved søvn eller oppvåkning (ikke-søvn-relatert-migrene, NSM). Pasienter med tensjonshodepine (TTH) ble delt inn i episodisk (<15 dager per måned)(n=12) og kronisk type (≥15 dager per måned)(n=8).

Resultater

Alle hodepinepasientene hadde mer angstsymptomer og mer subjektive søvnplager enn de friske kontrollene, men søvndagbøkene avslørte ingen forskjeller i søvntid.

Migrenepasienter i preiktalfasen hadde kortere innsovningslatens enn i interiktalfasen.

Både TTH og NSM pasienter hadde funn forenlig med økt søvnkvalitet som etter foregående søvndeprivasjon: Økt mengde dyp søvn vurdert med PSG, økt frekvens av subjektiv dagtrettthet og tendens til lavere smerteterskler sammenliknet med de friske kontrollene. Interiktale SM pasienter hadde funn som passet med lett redusert søvnkvalitet vurdert med PSG. De hadde verken økt frekvens av dagtrettthet eller reduserte smerteterskler.

Konklusjon

Data i denne avhandlingen kan tyde på at personer med hodepinestart om dagen trenger mer søvn enn friske kontroller. Personer med migrenestart under søvn hadde lett forstyrret søvn, men ingen klinisk betydningsfulle søvnforstyrrende faktor ble påvist. Økt sensitivitet for små «subkliniske» søvnforstyrrelser kan derfor være et mulig kjennetegn for pasienter med hodepinestart under søvn.

List of papers

Paper I:

Morten Engstrøm, Knut Hagen, Marte Helene Bjørk, Lars Jacob Stovner, Gøril Bruvik Gravdahl, Marit Stjern, Trond Sand.

Sleep quality, arousal and pain thresholds in migraineurs.

A blinded controlled polysomnographic study.

The Journal of Headache and Pain 2013, 14:12

Paper II

Morten Engstrøm, Knut Hagen, Marte Bjørk, Gøril Bruvik Gravdahl, Trond Sand.

Sleep-related and non-sleep-related migraine:

Interictal sleep quality, arousals and pain thresholds.

The Journal of Headache and Pain 2013, 14:68

Paper III

Morten Engstrøm; Knut Hagen; Marte Bjørk; Lars Jacob Stovner; Marit Stjern;

Trond Sand

Sleep quality, arousal and pain thresholds in tension-type headache.

A blinded controlled polysomnographic study.

Cephalalgia, In press

General introduction

1 Headache

1.1 Migraine and Tension Type Headache

Headache is one of the most common disorders of the nervous system, and globally the percentages of the adult population with an active headache disorder are 46% for headache in general, 42% for tension-type headache (TTH) and 11% for migraine (Stovner et al., 2007). Headache is associated with affective symptoms (Zwart et al., 2003) and sleep disturbances (Odegard et al., 2010). The relation between insomnia and headache seems to be bidirectional (Odegard et al., 2011, Odegard et al., 2013). Furthermore, compared to men the women have higher prevalence of headache (Stovner et al., 2007), insomnia (Zhang and Wing, 2006) and affective symptoms (Monti and Monti, 2000, Faravelli et al., 2013). Migraine and TTH have several triggers in common (Giffin et al., 2003, Karli et al., 2005). Headaches are classified as primary as long as they not are attributed to another disorder (Olesen J, 2004). Groups of symptoms are listed as diagnostic criteria to describe and classify the two most prevalent primary headache entities (Table 1).

1.2 Diagnostic criteria, Table 1

International Classification of Headache Disorders, Second Edition (ICHD-II) criteria for migraine and tension type headache diagnosis are listed below:

1.1 Migraine without aura:

A. At least five attacks fulfilling criteria B-D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

D. During headache at least one of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia

E. Not attributed to another disorder

1.2 Migraine with aura:

A. At least two attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following, but no motor weakness:

- 1 fully reversible visual symptoms including positive features (e.g. flickering lights, spots, or lines) and/or negative features (i.e. loss of vision)
- 2 fully reversible sensory symptoms including positive features (pins and needles) and/or negative features (i.e. numbness)
- 3 fully reversible dysphasic speech disturbance

C. At least two of the following:

1. homonymous visual symptoms and/or unilateral sensory symptoms
2. at least one aura symptom develops gradually during ≥ 5 minutes and/or different aura symptoms occur in succession over 5 minutes
3. each symptom lasts between 5 and 60 minutes

D. Headache fulfilling criteria B-D for migraine without aura begins during the aura or follows aura within 60 minutes

E. Not attributed to another disorder

2.1. Infrequent episodic TTH

A. At least 10 episodes occurring on < day/month on average (<12 days/year) and fulfilling criteria B-D

B. Headache lasting from 30 minutes to 7 days

C. Headache has at least two of the following characteristics:

- 1 bilateral location,
- 2 pressing/tightening (non-pulsatile quality)
- 3 mild to moderate intensity
- 4 not aggravated by routine physical activity such as walking or climbing stairs

D. Both of the following:

- 1 no nausea or vomiting (anorexia may occur)
- 2 no more than one of the photophobia or phonophobia

E. Not attributed to another disorder

2.2. Frequent episodic TTH

A. At least 10 episodes occurring on ≥ 1 but <15 days per month for at least 3 months (≥ 12 and <180 days/year) and fulfilling criteria B-D)

2.3 Chronic TTH

A. Headache happens on ≥ 15 days/month on average >3 months (≥ 180 days/year and fulfilling criteria B-D)

B. Headache lasts an hour or may be continuous

C. Headache has at least two of the following characteristics:

- 1 bilateral location,
- 2 pressing/tightening (nonpulsating) quality
- 3 mild or moderate intensity,
- 4 not aggravated by routine physical activity such as walking or climbing in stairs

D. Both of the following:

- 1 no more than one of photophobia, phonophobia, or mild nausea
- 2 neither moderate nor severe nausea or vomiting

E. Not attributed to another disorder

2 Pain

2.1 Pain in general

Free nerve endings acting as high-threshold mechanoreceptors, polymodal nociceptors or silent nociceptors register painful stimuli. Thin myelinated A-delta and unmyelinated and C nerve fibers respectively transmit the signals and have synapses posteriorly (especially lamina II) in the spinal gray matter. The signals are further transmitted obliquely to the opposite side and ascend in the contralateral white matter column as the lateral spinothalamic tract (Snell, 2001, Brodal, 2007).

Repeated input from unmyelinated fibers gradually increases the excitability in spinal dorsal horn: first probably by removal of magnesium (Mg^{2+}) blockage in the N-methyl-D-Aspartat (NMDA) receptor. Increased number of synaptic connections between first and second order neurons (homosynaptic facilitation) may occur after a while and reduce pain thresholds (PT). Nociceptive terminals probably also modulate the synapse - by recruiting first order mechanosensitive neurons to participate in central pain pathway activation (heterosynaptic facilitation). Furthermore the release of Prostaglandin E2 (PGE2) in the dorsal horn has also been associated with the development of hyperalgesia and allodynia (Chen, 2009).

The second synapse is in the thalamus where the third order neurons transmit the signals partly to the postcentral gyrus and mainly to other sensory areas of the cerebral cortex: insula, secondary sensory area and anterior parts of cingulate gyrus.

Periaqueductal gray matter (PAG) in mesencephalon, raphe nuclei and rostroventral medulla (part of the reticular substance) are known pain modulating areas regulating the incoming stimuli by inhibiting signal transmission in the posterior gray column and probably in thalamus (Snell, 2001, Brodal, 2007).

2.2 Pain in head and neck

The trigeminal nerve supplemented by n. glossopharyngeus, n. vagus and cervical roots C1-C3 constitute the sensory innervation of the head (Brennan and Charles, 2009). All afferents converge to trigeminal nucleus caudalis (TNC). Brain parenchyma does not feel pain, maybe apart from PAG and insula. The cerebral arteries and dural sinuses are heavily innervated with pain-transmitting A-delta and C-fibers. TNC has close connections with hypothalamus, the solitary tract and parabrachial nucleus and has thereby contact with all components of the central autonomic control system. It is likely that these networks are responsible for the clinical connection between sleep and headache (Brennan and Charles, 2009).

Trigeminal stimulation causes antidromic release of substance P, neurokinin and CGRP from afferent nerve terminals. Then dilatation and leakage from dural and superficial cortical vessels take place causing further nerve depolarization in a feedback loop. Activation of parasympathetic efferents may amplify this feedback and is referred to as the trigemino-autonomic reflex (Brennan and Charles, 2009).

2.3 Pain in migraine and tension type headache

Migraine is hypothetically related to chronic low serotonin (5-HT) disposition while sudden 5-HT release possibly contributes to trigger a migraine attacks (Hamel, 2007). 5-HT agonists have well known therapeutic effects in migraine and rather unknown effect in TTH (Cologno et al., 2012).

Experimentally, glyceryl trinitrate has been shown to induce headache in healthy controls, but the headache was more intense and long-lasting in migraineurs than controls

with TTH patients in between (Olesen et al., 1993, Olesen et al., 1994). Glyceryl trinitrate may be regarded as a pro-drug for nitric oxide (NO) since its biological effects are due to the formation of NO (Rand, 1992).

CGRP and substance P are transmitters released from presynaptic terminals during migraine and cluster headache attacks. A similar increase has not been found in cerebrospinal fluid or blood plasma in TTH (Chen, 2009).

In chronic TTH homosynaptic and heterosynaptic facilitation is hypothesized to explain reduced PT in the pericranial muscles and at other body sites (Chen, 2009) while thalamic sensitization is suggested when changes in pain apprehension are generalized during a migraine attack (Burstein et al., 2010). Reduced activity in descending inhibitors as rostroventral medulla (RVM) and possibly dorsal raphe nuclei has also been suggested to occur in TTH (Chen, 2009).

PAG seems to be central in headache and pain control (Brennan and Charles 2006). Both stimulation and lesions in the periaqueductal gray matter (PAG) can induce migraine-like headache (Raskin et al., 1987, Haas et al., 1993, Veloso et al., 1998, Gee et al., 2005). Increased activity in mencephalic structures as PAG and dorsal pons, has been shown in positron emission tomography (PET) studies (Weiller et al., 1995, Bahra et al., 2001, Afridi et al., 2005) and functional magnetic resonance imaging (fMRI) during migraine attacks (Cao et al., 2002). Multiple sclerosis (MS) patients with plaques in the midbrain/PAG had 3.9 fold (odds ratio (OR)) increase for migraine-like headache, 2.5 fold (OR) increase for TTH like headache and 2.7 fold (OR) increase for having both migraine and TTH like headache (Gee 2004). Also altered functional Magnetic Resonance Imaging resting-state connectivity in PAG networks has been found in

migraine (Mainero et al., 2011). However, PAG activation has been found in many different conditions (Linnman et al., 2012) and it seems not to be specific for headache.

Cortical spreading depression (CSD) is a wave of increased cerebral activity spreading 2-6 mm per minute followed by relatively long lasting reduced neural activity. CSD seems related to aura and probably to headache (Lauritzen et al., 2011, Burstein et al., 2012, Levy et al., 2012).

3 Sleep

3.1 Sleep

“Sleep is not simply an absence of wakefulness and perception, nor is it just a suspension of sensorial processes; rather, it is a result of a combination of passive withdrawal of afferent stimuli to the brain and functional activation of certain neurons in selective brain areas” (Chokroverty, 2009a). However, sleep is defined by both behavioral and physiological aspects (Table 2).

Table 2. Different variables evaluated to confirm sleep
(Chokroverty, 2009a)

<u>Behavioral aspects:</u>	Reduced: mobility, -response to external stimulation -and cognitive function Increased reaction time and elevated arousal threshold Closed eyes, species-specific sleeping posture, quiescence and reversible unconscious state. Based on behavioral criteria most animal probably do sleep.
<u>Physiologic aspects:</u>	Electroencephalography (EEG), electro-oculography (EOG) and electromyography (EMG) as well as other physiologic changes in ventilation and circulation

Based on three physiologic measurements (EEG, EOG and EMG), sleep is divided into two states: rapid eye movement (REM)- and non-REM (NREM) sleep (Chokroverty, 2009a). The first consensus based guideline for sleep scoring was published by Rechtschaffen and Kales in 1968 and sleep scoring was based on one electrode placed centrally (Rechtschaffen and Kales, 1968). American Academy of Sleep Medicine (AASM) published a new manual for sleep scoring in 2007 where a minimum of three electrodes were recommended (frontal, central and occipital) (Iber et al., 2007).

Sleep onset is normally NREM (except for in newborn children), deepening increases gradually and after about 70 minutes the first REM sleep period

(active/paradoxical sleep or “sommeil paradoxal”) starts. This NREM-REM-cycle repeats about every 90 minutes (McCarley, 2007). The REM percentage of total sleep time gradually reduces to about 20 by the age of 10 years, where it remains in most people (adult level). REM sleep is probably important to support growth and development of the central nervous system (CNS) (McCarley, 2009b). REM sleep is also related to lifelike dreaming and it is postulated that approximately 80% of dreams occur during REM- and 20% occur during NREM sleep (Chokroverty, 2009a). NREM sleep is in “the restorative theory” ascribed to body tissue restoration while REM sleep is ascribed to brain tissue restoration (Chokroverty, 2009a).

Both a sleep-dependent process (Process S) and a sleep-independent circadian process (Process C) are important in sleep regulation (Borbely, 1982).

The duration of prior wakefulness has major effects on sleep propensity (homeostatic factor/Process S) (Chokroverty, 2009b). Adenosine is a probable sleep-promoting factor since it accumulates in the basal forebrain and the ventrolateral preoptic area of hypothalamus (VLPO) during the day (McCarley, 2007). Adenosine also inhibits basal forebrain (important for arousal) and exogenously administered adenosine can set on slow wave sleep (SWS) (McCarley, 2007). PGE2 and NO increase along with adenosine and are necessary for recovery sleep (Kalinchuk et al., 2006). Caffeine and theophylline are on the other hand adenosine receptor antagonists which probably explains the universal use of coffee and tea to increase alertness (McCarley, 2007)

Most human physiological processes have a cyclic rhythmicity and are under influence of time (Process C). A cycle could be characterized as either circadian (about one day), infradian (longer than a day) or ultradian (shorter than a day) (Chokroverty,

2009a). The suprachiasmatic nucleus (SCN) has pacemaker cells with a cycle of about 24 hours adjusted by exposure for darkness (through melatonin from corpus pineale) and light (Brennan and Charles, 2009). However, the existence of multiple circadian oscillators in the human body functioning independently from the SCN has been shown (Chokroverty, 2009a).

Brainstem nuclei utilizing monoamine transmitters as serotonin (raphe nuclei) and norepinephrine (locus coeruleus) reduce their activity with increasing sleep-depth. These nuclei have almost no activity during REM-sleep before activity temporarily increase at the end of the REM period (REM-off cells)(McCarley, 2007). Cerebral cells containing acetylcholine have reduced activity during sleep, but a subset of brainstem cells containing acetylcholine (laterodorsal and pedunculopontine tegmental nuclei (LDT and PPT)) increase activity during REM-sleep (REM on cells). REM-on and REM-off cells probably inhibit each other reciprocally (McCarley, 2007). Sleep promoting VLPO and arousal nuclei also have mutually inhibitory reciprocal connections (Brennan and Charles, 2009).

3.2 Arousals

Arousals are transient phenomena resulting in fragmented sleep without behavioral awakening (Chokroverty, 2009a). Cholinergic and monoaminergic nuclei of the brainstem and basal forebrain are the main mediators of arousal and two main streams have been identified (Brennan and Charles, 2009). Thalamus receives excitatory projections from the pedunculopontine (PPT) and laterodorsal tegmentum (LDT) preventing thalamus from entering a sleep-associated bursting mode. The primary source of orexin/hypocretin is the lateral regions of hypothalamus. Orexin is a key component in

arousal switching and is reduced in most patients with narcolepsy. This hypothalamic region mainly receives diffuse excitatory projections from basal forebrain and brainstem (noradrenergic locus coeruleus, serotonergic raphe nuclei, dopaminergic ventrolateral periaqueductal gray matter (vIPAG) and histaminergic tuberomammillary nucleus) (Lydic and Baghdoyan, 2005, McCarley, 2007, Brennan and Charles, 2009). Orexin also has effects in several of the same brainstem areas (McCarley, 2009a) as well as modulating effects in vIPAG (Brennan and Charles, 2009).

There are different ways of scoring arousals (Parrino et al., 1998, Sforza et al., 2000, Iber et al., 2007). Cyclic alternating pattern (CAP) the English translation of the French term “*trace alternant*” was first used to describe periodic discontinuity of quiet sleep in premature and newborn babies and has a equivalent in NREM sleep in adults (Parrino et al., 1998). Both fast and slow arousals, and the time intervals between them, are used to define the different phases in the CAP scoring. Hence, CAP can be considered as a quite advanced and time consuming system without special designed software.

AASM accepts only fast arousals (scored as single events) (Iber et al., 2007). However, our intention in the present study was to study both fast arousals and slow arousals as separate events without considering the time interval between the different episodes i.e. D- and K-bursts as defined before (Sforza et al., 2000), it seemed logical to choose these events as the slow counterpart to the fast AASM-arousals and calculate similar indexes.

3.3 *Insomnia*

Insomnia is defined as a repeated difficulty with sleep initiation, duration, consolidation or quality that occurs despite adequate time and opportunity for sleep and results in some

form of daytime impairment. All three conditions: adequate sleep opportunity, a persistent sleep difficulty, and associated daytime dysfunctions are collectively implied in the term insomnia (Sateia, 2005). Operational diagnostic criteria have also been defined in “International Classification of Diseases” (ICD, latest: 10th edition, ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM, latest: fifth edition, DSM-V).

3.4 Sleep apnea

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction which by definition last more than ten seconds during sleep (Sateia, 2005). These respiratory events often result in reductions in blood oxygen saturation and are usually terminated by brief arousals from sleep (Sateia, 2005). Operationally different ways of measuring (thermistor or nasal pressure transducer etc.) and different definitions of respiratory episodes exists (AASM, 1999, Iber et al., 2007, Berry et al., 2012). The 2007-recommendation was also ambiguous as hypopneas were scored by a nasal pressure transducer as either a 30% or a 50% reduction in amplitude *accompanied* by either a 4- or 3% oxygen desaturation or an arousal. Furthermore, both the AASM 2007 and 2012 criteria also accept alternative hypopnea scoring by thermistor. Apneas are separated into obstructive, central and mixed. Usually we regard an apnea/hypopnea index (AHI) of 5 to 15 as mild, 15 to 30 as moderate, and >30 as severe (Parish and Somers, 2004, Iber et al., 2007). Excessive sleepiness is a major, but not obligatory, presenting complaint in OSA syndrome. OSA is also associated with systemic hypertension and type II diabetes and in severe cases with comorbid conditions as pulmonary hypertension and cor pulmonale (Sateia, 2005).

3.5 Restless legs and periodic limb movements

Restless legs syndrome (RLS) is a sensory motor disorder characterized by complaint of a strong, nearly irresistible, urge to move the legs (Sateia, 2005). Rest makes symptoms worse while movements relieves. A motor expression that is associated with the disorder is called periodic limb movements (PLMs). These may occur in sleep (PLMS) or resting wakefulness (PLMW) and they are most common in the legs. PLMS occur in up to 80-90% of patients with RLS, depending on the chosen cut-off. Periodic limb movement disorder (PLMD) is characterized by periodic episodes of repetitive, highly stereotyped, limb movements that occur during sleep (PLMS) and by clinical sleep disturbance that cannot be accounted for by another primary sleep disorder (Sateia, 2005). PLMS index of more than 5 per hour in children and more than 15 per hour in adults might be regarded abnormal if they are followed by adequate sleep complaints (Sateia, 2005).

4 Sleep, pain thresholds (PT) and headache

Already in 1853 Romberg probably stated about migraine: "The attack is generally closed by a profound and refreshing sleep" (Dodick et al., 2003). However, sleep does not always cure headache. In a heterogeneous group labeled "sleep related headache" in the International Classification of Sleep Disorders (Sateia, 2005), headache starts either during sleep or by awakening. Several PSG studies have been performed to find the relation between sleep and headache, but the results are diverging (Aldrich and Chauncey, 1990, Paiva et al., 1995, Ulfberg et al., 1996, Paiva et al., 1997, Loh et al., 1999, Neau et al., 2002, Jensen et al., 2004, Manni et al., 2004, Goksan et al., 2009, Chen et al., 2011, Holle et al., 2011, Johnson et al., 2012). Migraineurs with attacks related to sleep (defined in the present thesis as sleep migraine, SM) have also been studied before (Dexter and Riley, 1975, Goder et al., 2001, Della Marca et al., 2006). Compared to controls SM patients had findings consistent with a hypofunction in the arousal system (Della Marca et al., 2006) and reduced cortical activation in the preictal phase compared to the interictal phase (Goder et al., 2001). Why SM patients should have altered function in their arousal-system and the pathophysiological meaning of these findings are not clear. More PSG studies have been performed to explore the relation between migraine in general and sleep (Dexter and Riley, 1975, Dexter, 1979, Kristiansen et al., 2011a, Karthik et al., 2012)(Table 3). Kristiansen et al (Kristiansen et al., 2011b) found no signs of increased sleep-apnea, while Karthik et al (Karthik et al., 2012), found signs of reduced sleep quality. Few PSG studies have been performed in TTH patients (Table 3): Drake et al (Drake et al., 1990) found increased awakenings and reduced slow wave sleep compared to normal values, while Kristiansen et al (Kristiansen et al., 2011b) found no signs of increased obstructive sleep apnea in TTH patients.

Subjective sleep disturbances increase the risk of provoking a headache attack in both TTH and migraine patients (Spierings et al., 2001, Alstadhaug et al., 2007, Kelman, 2007) and both TTH and migraine patients report more sleep-related symptoms than healthy controls (Kelman and Rains, 2005, Odegard et al., 2010). Furthermore, the relation between subjective sleep disturbances and headache seems bidirectional as subjective sleep disturbances have been found to increase the risk of headache (Odegard et al., 2011), but headache have also been found to increase the risk of insomnia (Odegard et al., 2013).

Reduced PT have been found in migraineurs compared to controls (Fernandez-de-las-Penas et al., 2009, Grossi et al., 2011, Schwedt et al., 2011) and thresholds seem to be reduced before an attack (Sand et al., 2008, Zappaterra et al., 2011). In TTH patients only the chronic group has been found to have significantly reduced PT (Bendtsen et al., 1996, Fernandez-de-Las-Penas et al., 2007, Bezov et al., 2011, Zappaterra et al., 2011). Sleep deprivation has also been found to reduce PT in healthy controls (Onen et al., 2001, Kundermann et al., 2004, Roehrs et al., 2006).

Table 3. Overview over polysomnographic studies in subjects with migraine and tension type headache (TTH)		
First author, year	Design and numbers studied =n	Main results
<u>Headache</u>		
<u>Migraine</u>		
Kristiansen, 2011	Blinded populational based cross sectional, n=431.	No association between OSA and migraine in the general population
Karthik, 2012	Cross sectional design, 30 migraineurs without aura and 30 controls.	Migraineurs had reduced sleep quality in PSG (sleep onset and efficiency, reduced NREM and sleep stage 4)
<u>Sleep related migraine</u>		
Dexter, 1970	Repeated measures, n=7 of whom 3 migraineurs.	Headache evoked by arousal from REM sleep
Dexter, 1979	Repeated measures, 4 sleep migraineurs.	Increased amount of deep (SWS) sleep and REM sleep before attack onset
Paiva, 1995	Case reports, 25 with nightly headache of whom 10 migraineurs.	Morning and nocturnal headache are frequent indicators of sleep disturbance
Goder, 2001	Repeated measures, 8 migraineurs with attacks related to sleep of whom 7 migraineurs without aura.	Reduced fast arousals in migraineurs with attacks related to sleep before an attack.
Della Marca, 2006	Cross sectionalase design, 10 migraineurs with attacks related to sleep and 10 controls.	Reduced fast arousals in migraineurs with attacks related to sleep compared to controls
<u>Tension-type headache</u>		
Drake, 1990	Cases compared to norms, 10 TTH + 10 migraineurs + 10 combined.	TTH had reduced deep sleep while migraineurs had essentially normal
Kristiansen, 2011	Blinded, population based cross sectional, n=431.	Main result: No association between OSA and migraine in the general population
SWS: slow wave sleep. REM: Rapid eye movement. OSA: obstructive sleep apnea. TTH: Tension type headache. NREM: Non-rapid-eye-movement		

Table 4. Overview of recent relevant studies on pain measurements in subjects with migraine and tension-type headache (TTH) and sleep deprived healthy controls		
Group, subgroup First author, year	Design and numbers studied = n.	Main result
<u>Migraine:</u>		
Fernandez, 2009	Blinded cross sectional, 20 with unilateral migraine and 20 controls	Reduced PPT on the symptomatic side compared to non-symptomatic side and lower than in controls. Reduced PPT over peripheral nerves compared to controls
Grossi, 2011	Blinded cross sectional, 15 with episodic and 14 with chronic migraine and 20 controls	Reduced PPT in craniocervical muscles in women with migraine.
Schwedt, 2011	Cross sectional control, 20 interictal episodic and 20 chronic migraineurs and 20 controls	Reduced PPT and pressure pain tolerance test in interictal migraineurs
Zappaterra, 2011	Cross sectional, a total of 98, of these 21 interictal migraineurs.	Reduced pain thresholds in migraineurs in temple and cheekbone areas, but not in neck areas.
<u>Preictal/ictal:</u>		
Sand, 2008	Repeated measures, 11 migraineurs.	Reduced thermal pain thresholds within 24 hour before an attack compared to more than 24 hour from an attack.
Zappaterra, 2011	Questionnaire (Jakubowski), n=98.	The prevalence of acute allodynia related to headache increase in both subjects with migraine and TTH when headache frequency rises towards chronicization
<u>Tension type headache:</u>		
Bendtsen, 1996,	Cross sectional, 40 CTTH patients and 40 controls	Reduced PPT in dorsal middle phalanx second finger in patients with CTTH
Fernandez, 2007	Blinded case control, 25 CTTH and 25 controls	Decreased PPT and increased tenderness in cephalic and neck points.
Zappaterra, 2011	Case control, a total of 98, of these: 11 chronic and 22 interictal episodic TTH patients.	Reduced pain thresholds (calibrated monofilament) in TTH patients in temple and cheekbone areas but not in neck areas.
<u>Sleep deprived healthy controls:</u>		
Onen, 2001	Prospective double blind cross over, total sleep deprivation, REM or SWS interruption. 9 healthy males.	Total sleep deprivation significantly reduced mechanical pain thresholds tested on fingers.
Kunderman, 2004	Repeated measures, 24 healthy volunteers.	Two nights of total sleep deprivation reduced heat pain thresholds.
Roehrs, 2006	Repeated measures in two groups, 7 reduced total sleep time and 6 reduced sleep time and thereafter disturbed REM and finally NREM sleep.	Reduced finger withdrawal time after 4 hour sleep and disturbed REM-sleep
PPT: Pressure pain thresholds, TTH: Tension type headache, CTTH: Chronic tension type headache, REM: Rapid eye movement, NREM: Non rapid eye movement, SWS: Slow wave sleep.		

5 Main objectives

Main aims for the three studies in the thesis:

The first study:

1. To compare subjective and objective sleep quality variables and PT in headache free controls and migraine patients in interictal phase.
2. To evaluate PSG sleep quality and PT in interictal, preictal and postictal phases. Thirdly, we intended to perform an exploratory correlation study to enlighten the association between sleep parameters and PT in controls and migraineurs in the three migraine phases.

The second study:

1. To compare subjective and objective sleep quality, arousal indices and PT between SM- and NSM patients.
2. To compare sleep and pain variables between healthy controls (C) and SM- and NSM patients respectively.
3. To explore the correlation between subjective and objective sleep, PT, and headache severity variables.

The third study:

1. To compare subjective and objective sleep quality variables and PT in headache-free controls and TTH.
2. To assess the association between sleep variables and headache severity and PT. We also compared controls with subgroups with episodic TTH (ETTH) and chronic TTH (CTTH).

Methods and materials

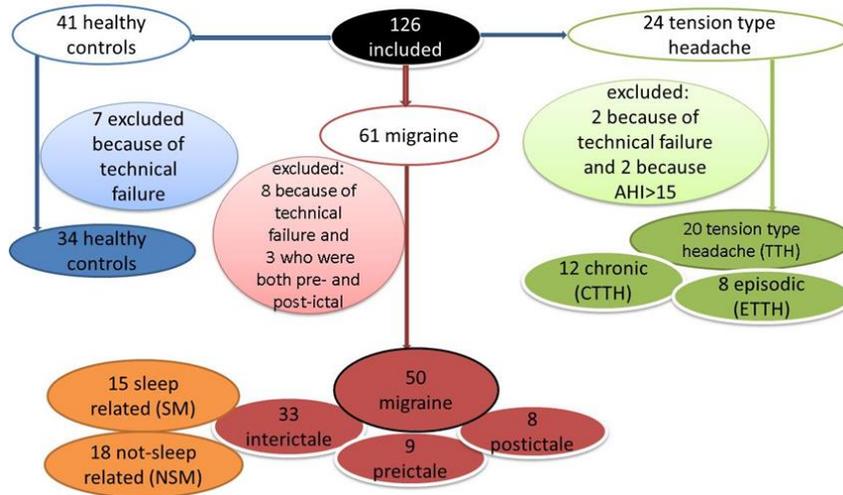
6 Design

All papers in this thesis are based on the same blinded study where cases are compared with controls and subgroups are compared with each other. Interictal migraineurs are compared with preictal migraineurs and controls. The TTH group was compared with the whole migraine group and with the interictal sleep and non-sleep related migraine subgroups.

The PSG scoring was done blinded by the main author and a sleep expert was consulted when in doubt.

7 Participants (Figure 1)

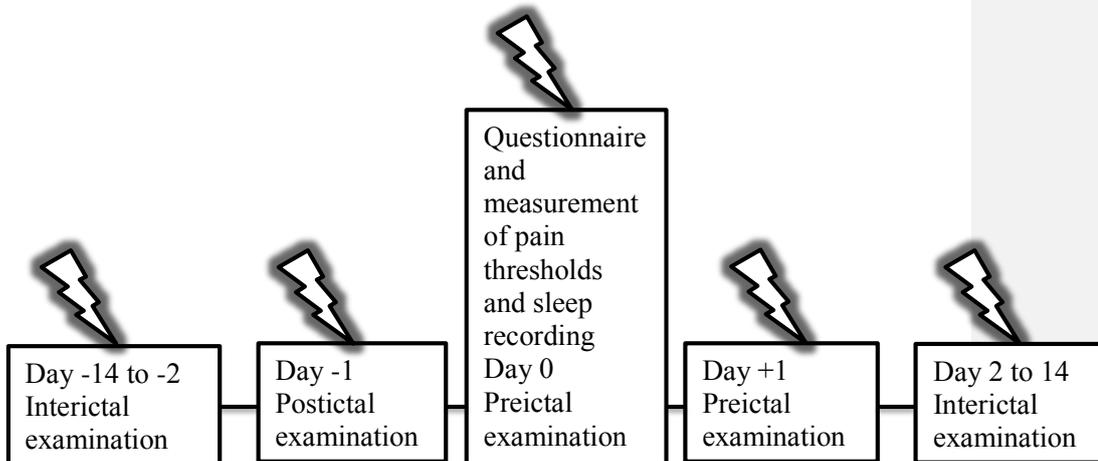
Figure 1. Participants in the headache sleep study.



SM: Sleep related migraine, NSM: Non-sleep related migraine, TTH: Tension type headache, ETTH: Episodic tension type headache, CTTH: Chronic tension type headache, AHI>15: 29.9 and 43.4.

One-hundred and twenty-six persons, 85 women and 41 men, (age range 18 to 64, mean age 38.9 years), 41 healthy controls, 24 TTH and 61 migraine patients participated in this study (Figure 1). Inclusion and examination were done in 2005-2007 and data analysis was done from 2009-2013. The participants were mainly recruited by advertising in local newspapers. Potential participants with headache were diagnosed according to the ICDH-II criteria (2004). Based on headache diaries, the sleep recordings and PT measurements were divided into interictal, preictal (2 days or less before the next attack), and postictal (2 days or less after the previous attack) (Figure 2). Five patients with headache during “Day 0” were included in the preictal group.

Figure 2. The relationship between the nearest migraine attack (lightening Z-symbol) and the classification of the recording as interictal, preictal or postictal



Based on a question about *usual migraine attack onset*, SM patients were defined as those answering either "upon awakening or "during the night (waking me up)", whereas NSM patients were those who answered "during daytime before noon, "during daytime after noon" or "no regular onset time" (15 interictal SM and 18 interictal NSM).

Three migraine patients with midictal PSG, fulfilling both preictal and postictal criteria, were excluded from this analysis. Of 24 TTH patients 20 were included while four were excluded for technical reasons or sleep apnea. Pregnancy, major health problems, coexisting migraine or frequent tension-type headache (TTH), were exclusion criteria.

The study was approved by the regional ethics committee and participants signed an informed consent before inclusion.

8 Procedure

Every subject completed several questionnaires including Epworth sleepiness scale (ESS) (Johns, 1991), questions adapted from Karolinska sleep questionnaire (KSQ) (Engström et al., 2011), Pittsburgh sleep quality index (PSQI) (Buysse et al., 1989), Hospital anxiety and depression subscales (HADS) (Zigmond and Snaith, 1983) and 10 questions from the autonomic symptom profile (Suarez et al., 1999, Nilsen et al., 2007). They also answered the question: “Do you have bothersome tiredness during daytime?” Patients and controls underwent a full night ambulatory sleep study unattended in our patient-hotel.

Sleep staging was performed according to “The AASM Manual for the scoring of sleep and associated events” from 2007 (Iber et al., 2007) with a few exceptions, as described in paper 1 (Engstrom et al., 2013b) and sleep scoring reliability was adequate (Table 5).

Fast arousals were defined according to the AASM-manual (Iber et al., 2007) as an abruptly increased EEG frequency (alpha, theta and/or faster than 16 Hz activity) lasting 3-30 seconds, separated with at least 10 seconds of sleep. Slow arousals, D- and K-bursts (Parrino et al., 1998, Sforza et al., 2000,), were also scored. Thermal PT and pressure PT (algometry) were recorded before the participants had their PSG equipment mounted. Heat and cold PT (HPT and CPT) were measured on thenar and the medial forehead on both sides. Pressure PT (PPT) was measured at four sites on both sides in a fixed order: m. temporalis, m. splenius, m. trapezius and over distal phalanx middle finger.

Table 5. 20 incidental PSG scored by Morten Engstrøm in 2009/2010. Raw data files were blindly rescored by Trond Sand in 2013.

	ICC
Sleep efficacy (perc)	0.957
Sleep latency (min)	0.983
REM latency (min)	0.997
Awakenings (no)	0.762
Wake after sleep onset (min)	0.917
Total sleep time (min)	0.982
Wake (min)	0.883
Stage N1 (min)	0.847
Stage N2 (min)	0.765
Stage N3 (min)	0.831
REM (min)	0.876
Apne-hypopnea index	0.841

ICC: Intraclass coefficient of reliability

In general ICC values=0.75 or above are taken to represent excellent reliability (Fleiss JL. The design and analysis of clinical experiments, Wiley 1985, page 7)

9 Statistics

Univariate two-group comparisons were made by non-parametric Mann-Whitney tests. Categorical data were analyzed with Pearson chi-square test or Fisher's exact test when any cell had expected count less than five. The primary comparisons reported in this thesis were: 1) controls versus TTH, interictal NSM and interictal SM and 2) between interictal and preictal migraine groups. Post hoc we also compared sleep- and non-sleep-related TTH (STTH and NSTTH categorized as for migraineurs). We did not perform adjustments for multiple comparisons because this was an exploratory study.

Summary of the main results for subjects with migraine and TTH

(Table 6-7 and Table A-B (Appendix))

10 Questionnaire and diary

TTH as well as interictal SM and NSM patients reported more anxiety symptoms in HADS (≥ 5.3 vs. ≤ 3.0 , $p < 0.01$) and higher autonomic index score (≥ 5.2 vs. ≤ 4.3 , $p < 0.001$), more symptoms of insomnia (KSQ insomnia score 5.8 vs. 3.4, $p < 0.001$), more symptoms in PSQIs (5.9 vs 3.8, $p < 0.001$) and more pain-related sleep trouble in PSQI than controls (Engstrom et al., 2013a, Engstrøm et al., 2013). The TTH group had more frequent headache ($p < 0.000$), more insomnia ($p = 0.006$) and more frequent daytime tiredness than migraineurs ($p < 0.05$) (Table 6 and Table A in appendix).

11 Measurements

11.1 Fast arousals, SWS and PT

Both TTH- and NSM patients had more SWS than controls (≥ 104 vs. ≤ 86 minutes, $p < 0.05$), less fast arousals (≥ 18.3 vs. ≤ 15.5 per hour, $p < 0.05$) and more frequent daytime tiredness (0-4) (≥ 1.3 vs. 0.7 $p < 0.01$). Furthermore TTH patients had more SWS than SM patients ($p < 0.05$) (Table 6 and table B in appendix). NSM also had lower TPT than controls (HPT 11.2 °C vs 16.6°C, CPT 16.1 vs 20.7 °C, $p < 0.05$). Among TTH only CTTH had lower PPT than controls (506 vs 678 kPa) ($p < 0.05$) (Engstrom et al., 2013a, Engstrøm et al., 2013).

11.2 Slow arousals, light sleep and awakenings

NSM patients had more time in bed (488 vs. 453 minutes, $p < 0.05$) and more K-bursts (4.0 vs. 3.0 per hour, $p < 0.05$) than controls. SM patients also had less D-bursts (7.3 vs.

11.8 per hour, $p < 0.05$) more awakenings (1.45 vs. 0.99 per time, $p < 0.05$) and tended to have more N1 sleep than controls (35 vs. 27 minutes, $p = 0.05$) (Engstrom et al., 2013a).

11.3 NSM versus SM

SM patients had less SWS (88 vs. 104 minutes, $p < 0.05$) and less K-bursts (2.4 vs. 4.0 per hour, $p < 0.05$) than NSM patients (Engstrom et al., 2013a).

11.4 Preictal versus interictal migraineurs

Preictal migraineurs had shorter latency to sleep onset than interictal migraineurs (2.0 vs. 10.3 minutes, $p < 0.01$). TPT were lower in interictal migraine compared to controls ($p < 0.04$) (Engstrom et al., 2013b).

11.5 TTH post hoc

A post hoc comparison revealed that NSTTH ($n = 15$) had fewer fast arousals than STTH ($n = 5$) ($p = 0.025$).

Table 6. Summed main results for tension type headache (TTH) patients, migraineurs in interictal (MI) and preictal (MP) phases or sleep- and non-sleep (SM and NSM)¹ migraineurs (M) compared to controls (C).

Report data	
Anxiety symptoms ²	C<TTH**/NSM**/SM**
Insomni symptoms ³	C<TTH***/NSM**/SM** and M<TTH**
Subjective sleep disturbances ⁴	C<TTH***/NSM*/SM**
Total sleep time (diary)	C=TTH/NSM/SM
Subjective daytime tiredness ⁵	C<TTH**/NSM** and M<TTH*
Autonomic index	C<TTH/NSM/SM***
Examination data	
Awake index (>8 Hz, >30 sec, per hour)	C<SM*
N3, slow wave sleep, minutes	C/SM<TTH**/NSM*
Fast arousals (lasting 3-30 sec)	C>TTH**/NSM*
D-bursts	C>SM*
K-bursts	C/SM<NSM*
Pressure pain thresholds (kPa) ⁶	C>TTH(*)/NSM(*)
Thermal pain thresholds (°C) ⁷	C<NSM*
Latency to sleep onset	MP<MI**

¹ Both NSM and SM patients were in the interictal phase

² Sum of seven questions about anxiety symptoms during the last week from the Hospital Anxiety and Depression scale questionnaire.

³ Sum of insomnia questions in Karolinska sleep questionnaire

⁴ Evaluated by Pittsburgh sleep quality and questions adapted from the Karolinska sleep questionnaire.

⁵ Question: Do you have bothersome tiredness during daytime? (0(no)-4(daily))

⁶ Mean value of m. temporalis, m. splenius, m. trapezius, distal dorsal middle finger three tests on each place, both left and right side.

⁷ Mean value heat and cold pain thresholds for frontal and thenar region, three tests on each side.

Mann-Whitney U- test: (*)p=0.05, *p<0.05, **p<0.01, ***p<0.001

Table 7

Comparison of important symptoms and objective findings for the tension type headache, sleep and non-sleep related migraine compared to controls.

Sleep migraineurs (SM):	Signs of reduced sleep quality (number of awakenings ↑, amount of superficial sleep (↑), but not increased daytime tiredness or sleepiness
Non-sleep migraineurs (NSM):	Signs of increased sleep quality (amount of slow wave sleep ↑ and fast arousals ↓), increased frequency of daytime tiredness and reduced pain thresholds (PT)
Tension-type headache (TTH):	Signs of increased sleep quality, increased frequency of daytime tiredness and tendency to reduced pressure pain thresholds (PT)

Discussion

12 Methods

12.1 Design

We have performed a blinded study comparing affective symptoms, subjective and objective sleep parameters and pain thresholds in patients and controls. The study design included prospective elements as we used sleep diaries data antedating the sleep recording by two weeks and as well as headache diaries for weeks before and two weeks after PT and PSG measurements. Headache diary data was necessary to classify our PSG and PT data in migraineurs as “interictal” and “preictal” while data from sleep diaries gave us a background for interpreting PSG data. However, we had only one PSG registration in each subject and some may therefore not accept to classify our study as “prospective”. Also, the term “case-control study” is most commonly applied to retrospective studies. Hence, calling this a “cross-sectional study” might have been preferred. The migraine studies were “most” prospective as they characterized the PSG and PT findings in relation to both headache attacks and performed sleep, while the time relation between the examination and headache was not evaluated in the TTH study. As far as we know, no comparable study is reported.

It should also be mentioned that a study design with repeated PSGs had been more powerful for the detection of phase-related differences.

12.2 Diagnosis/misclassification

The division of migraineurs into sleep-related and not-sleep-related could have been objective by analyzing long lasting headache diaries (months) rather than asking the participants of their headache usual start. A definition of sleep-related headache is found in The International Classification of Sleep Disorders 2nd edition: Diagnostic and coding manual (Sateia, 2005), but a distinction between sleep-related and non-sleep-related migraine is not found in ICHD-2 (Olesen J, 2004). The distinction between SM and NSM patients is accordingly not a universally established concept, but rather a useful subgrouping also applied by other researchers (Goder et al., 2001, Della Marca et al., 2006).

The division of migraineurs in different phases could have been more exact if a different type of headache diary (displaying headache per hour) had been used. However, it is our experience that this type of diary is difficult for patients to complete in a reliable way. For this reason five migraineurs with headache onset during “day zero” (the day with PT measurements and PSG mounting) were also classified as preictals. These migraineurs could be in preictal phase or early ictal phase. Furthermore, amore exact definition of a “point zero” would have been preferable, e.g. by the participants attendance at noon, when the PT measurements were performed or the time for sleep on or off set. It is possible that the procedure of PT measurements, mounting of PSG equipment and sleeping in the hospital hotel provoked an attack in some patients in a preictal phase.

To retain power in the interictal vs. control group comparisons, we sat the pre/post ictal cut-off to two days. Furthermore, the vast majority of prodromes do not occur until about 24 hours before the attack (Giffin et al., 2003). Also, a different cutoff for the

Kommentert [ME1]: These two sentences are not correct, based on a misunderstanding about the headache diary structure. The data files used for analysis were too crude and did not include exact headache onset hours, but most of the sleep diaries are filled in correctly and contain the sufficient information. In retrospect, these two sentences should have been replaced with the following one: “The division of migraineurs in different phases could have been more exact if all data in the headache diary had been used in the analysis.”

preictal/interictal distinction, like 72 hours, could have been explored if we had included more subjects.

12.3 Controls

The control group consisted mainly of healthy blood donors and as such not entirely representative for the general population but generally disease-free as requested by the inclusion criteria. To achieve comparable groups, successfully included headache patients' age and sex were continuously observed by the study nurse so that comparable controls could be included. Individualized matched controls for age and sex could have been somewhat preferable rather than a comparable control group.

12.4 Bias

In contrast to a hospital-based migraine population which may include more severe and longstanding cases, participants in the present study were mainly recruited by advertising in local newspapers. The subgroup of headache patients responding on a newspaper advertisement might not be representative for the whole headache population. It is evidently impossible to recruit a completely unbiased patient-population. However as most migraine patients had been prescribed triptans for their attacks our study group were probably fairly representative. Participants got 500 NOK (about 50 EURO) to compensate for transportation, parking and other expenses related to this project. This compensation could possibly attract some groups to participate more than others. However, if so, both headache and control group would be biased and the groups still comparable. An underestimation of sleep problems is expected in our study because patients with known and diagnosed previous sleep disorders were excluded. However, this exclusion is a strength regarding the major aims of the study.

12.5 Measurements

All PSGs were inspected twice for sleep stage scoring. Then all PSGs were inspected once for fast arousal scoring, and finally once for slow burst scoring. The scorer (first author) was blinded for diagnoses. This blinding ensured that the group comparison was unbiased. Any divergent scoring trend should not affect the relative results. In addition, the interrater sleep scoring reliability was found to be good (Table 5).

An upper limit for fast arousal duration was not defined by AASM in 2007 (Iber et al., 2007) and arousals (lasting at least 3 seconds preceded by 10 s stable sleep) were only allowed to be scored in sleep (Iber et al., 2007). Normally, epochs with increased EEG frequency to ≥ 8 Hz EEG (excluding spindles) lasting more than 15 seconds are scored as awake, while episodes lasting 3-15 seconds are scored as arousals without affecting the scoring of that epoch. If a 3-15 second arousal episode occurs in sleep stage N2 the following sleep stage is scored as sleep stage N1. To avoid counting both the arousal directly and also measure arousals indirectly as amount of N1 sleep we decided not to change sleep stage N2 to N1 after an arousal in the present study. In REM sleep the presence of slow eye movements or not after a corresponding arousal (accompanied by an increase in submental EMG amplitude lasting at least 1 second) decides whether the following epoch continues as REM or N1 sleep. Thus, it is not the arousal episode per se that define the transition from REM to NREM sleep. Single arousals that occupy 3-15 seconds at the end of one epoch would be scored as an arousal, but to incorporate arousals that also occupied up to 15 seconds in the start of next epoch we decided our fast arousal upper limit duration to be 30 seconds. In the present study episodes consisting of acceleration to ≥ 8 Hz EEG frequencies and lasted more than 30 seconds, implied that at least one epoch would be scored as awake and not as an arousal.

Furthermore, mean duration of fast arousals or awake periods did not differ between the groups (Appendix, Table B), suggesting that our definition did not create a bias. However, our definition will probably underestimate the awake index slightly as compared to the AASM 2007 (Iber et al., 2007) and AASM 2012 (Berry et al., 2012) definitions (Table 8). In 2012, a note was added so that arousals also could be scored in epochs scored as awake if 10 seconds of stable preceding sleep is observed (AASM 2012). Hence, according to this most recent definition of arousals our definition probably also have underestimated amount of fast arousals. However, the limits of EEG activation duration and its definition should be a theme for further discussions within the scientific community. For instance the CAP-system evaluates episodes lasting 2-60 seconds (Terzano et al., 2002) while the AASM scoring manual do not define an upper duration limit of fast arousals.

Table 8. Comparing definitions and consequences of three different rules for scoring of fast arousals in polysomnography				
Fast arousal defined by:	Arousal duration	Consequence for sleep staging	Amount of arousals scored	Amount of awake periods scored
AASM 2007	≥3 seconds	Change sleep stage N2 to N1	Only in sleep epochs. Underestimate amount of fast arousals compared to AASM 2012	
AASM 2012	≥3 seconds	Change sleep stage N2 to N1	Overestimate amount of fast arousals compared to AASM 2007 and The headache sleep study caused by arousal scoring both in sleep and in wake epochs.	
The Headache sleep (present) study	3-30 seconds	None. Therefore sleep stage N1 is relatively underestimated compared to AASM 2007 and 2012	Underestimate amount of fast arousals compared to AASM 2012 caused by arousal scoring only in sleep epochs. Overestimate amount of fast arousals compared to AASM 2007 and AASM 2012 caused by consequently accepting arousals up to 30 seconds.	Underestimation of number of awake periods compared to AASM 2007 and AASM 2012 caused by consequently accepting arousals up to 30 seconds.
AASM: American Academy of Sleep Medicine (scoring manual)				

We have used mean values for many parameters. Mean total sleep time in diaries the last two weeks before the examination does not describe the day to day variation or the relation to migraine attacks. These data are available for analysis in a future paper. Comparably, mean pain thresholds do not describe any possible anatomical distribution of reduced pain threshold in affected groups, but a detailed analysis was not within the study aims and averaging reduced the number of statistical tests.

A comparison with some recent papers on arousal could have been easier if we had chosen to also use CAP, although so far only one group seems to have studied CAP in migraine (Della Marca 06). Furthermore, CAP-scoring is complicated and too time consuming for us with the available software.

Different definitions of hypopneas exist (AASM, 1999, Iber et al., 2007, Berry et al., 2012). The present study was planned and data-collection started before the AASM recommendation was published in 2007. The equipment used for this study had accordingly only a thermistor available. A thermistor is less sensitive than a pressure transducer, but the advantage is that it reflects both nasal and oral airflow. To compensate for the use of thermistor, we chose to analyze hypopneas according to a modified “Chicago criteria” (AASM, 1999) (either at least 50% flow reduction or at least 30% reduction in thermistor signals associated with 4% desaturation). The AASM recommended standard for hypopnea scoring is quite conservative compared to the “Chicago criteria”. Hence our scoring algorithm probably compensate for the apparent loss of sensitivity by not applying the nasal pressure transducer. It should also be mentioned that AASM, in both 2007 (Iber et al., 2007) and in the 2012 update, stated that a thermistor is an acceptable alternative to a nasal flow-pressure transducer.

Snoring and OSA are related (Young et al., 2002). Both snoring (Rains and Poceta, 2010) and OSA have also been related to headache (Sand et al., 2003) and particularly morning headache (Rains, 2011). However, in patients who reported snoring a migraine diagnosis was found to be a stronger predictor for morning headache than OSA syndrome (Chen et al., 2011). Snoring without OSA could therefore be sufficient to evoke headache in sensitive groups. However snoring can be difficult to define objectively. So far snoring data have not been analyzed in the present study.

12.6 The role of chance

Three subgroups (preictal and postictal migraineurs and ETTH) had less than 10 participants. These numbers are not very far from those in a comparable, but less extensive study (n=10 for both migraineurs and controls) (Della Marca et al., 2006), but the statistical power to detect differences between these groups will be low. We could not detect any differences in the postictal phase compared to the other phases or compared to controls, possibly because of to low statistical power. However, for migraineurs we could not preplan how many participants we could register in the different phases. The present study was not designed to capture enough subjects with sleep and non-sleep-migraine in pre- and postictal phases respectively to analyze these subgroups separately.

This study was exploratory and we did not adjust for multiple comparisons. Also, we did not want to increase type II failures on the cost of reducing type I failures (Perneger, 1998, Schulz and Grimes, 2005), and univariate comparison of several sleep variables, without p-value corrections, seem to have been a “de facto standard” in the literature. However, the possibility of both type I and type II errors is acknowledged. Thus, the present study is more suitable to generate hypotheses than to confirm or establish general scientific facts about all migraineurs and TTH patients.

12.7 Confounding

The headache group had more anxiety than controls. Both insomnia and headache are probably related to anxiety (Monti and Monti, 2000, Lucchetti et al., 2013). Hence, our findings could be related to the anxiety rather than the headache per se. However, comparable levels of increased anxiety score could hardly alone explain both increased and reduced objective sleep quality in different headache groups. Furthermore, even

though anxiety scores in patients in the present study were high they were within the normal range. Hence they are not comparable to patients with generalized anxiety disorder who have been shown to have reduced objective sleep quality (Monti and Monti, 2000).

13 Main results

13.1 Subjective and objective sleep quality in controls and headache patients

Increased symptoms of anxiety, insomnia and subjective tiredness among TTH patients and migraineurs have been shown before (Kelman and Rains, 2005, Lanteri-Minet et al., 2005, Barbanti et al., 2007, Odegard et al., 2010, Lucchetti et al., 2013). However, in contrast to these clear differences in subjective symptoms, differences in the more objective sleep diary variables, and the most objective PSG sleep parameters were smaller.

A history of chronic insomnia does not predict poor EEG sleep in all patients (Rosa and Bonnet, 2000). However, increased SWS as found in the present study among NSM and TTH patients is one factor that usually indicates better sleep quality (Keklund and Akerstedt, 1997). SM patients differed from NSM and TTH patients by having signs of reduced sleep quality in PSG (more awakenings than controls and less SWS than TTH and NSM). Hence, even though average total sleep time in PSG and sleep diary were normal, SM patients at least had some objective sleep findings supporting reported subjective sleep symptoms. However, no specific sleep disturbing factor was detected in PSG among SM patients. In spite of being the only group with PSG findings indicating disturbed sleep, the SM patients did not report increased daytime tiredness, an apparent paradoxical observation.

Reduced amounts of fast arousals and increased slow wave sleep have also been found the night after experimental sleep deprivation (De Gennaro et al., 2001) and are in line with what we found in TTH and NSM patients. After foregoing sleep deprivation a hypoarousal state, with reduced fast arousals, increased SWS and increased daytime tiredness, can be regarded as normal. However, in the present study sleep diaries revealed

normal average total sleep times before the PSG. Increased need for sleep and a relative sleep deprivation among NSM and TTH patients could explain our findings. This hypothesis is partly consistent with the notion that EEG among migraineurs is found to be either normal or have subtle findings that may reflect drowsiness (Sand, 1991), but it does not fit with the impression that TTH patients have less EEG-abnormal findings than migraineurs (Schlack and Court, 1983) or mostly normal EEGs (Rossi et al., 2011). However, a high-quality QEEG study of adult TTH patients still is lacking. In addition, sleepiness seemed to evolve close to headache onset in migraineurs as sleep onset latency was reduced compared to interictal phase. Increased objective sleepiness close to attack phase fits both with objective EEG findings (Bjork et al., 2011) and with subjective symptoms in the preictal phase (Giffin et al., 2003).

When discussing sleep deprivation it is surprising that those headache patients with the best sleep quality also had the highest frequency of daytime tiredness while those with signs of disturbed sleep had not increased frequency of daytime tiredness. Symptoms related to sleep or foregoing sleep time, symptoms of anxiety or autonomic activity or objective sleep disturbing factors as apnea/hypopneas or PLM and could hardly explain these differences alone as TTH, NSM and SM groups had comparable findings. Hence, we hypothesize that there is constitutional differences between the two groups: NSM and TTH patients who seem to either have a hypoarousal state per se (trait) or possibly recovery-SWS related to a relative sleep deprivation caused by increased need for sleep. Increased symptom load could be relevant for this increased need for sleep. In the present study SM patients on the other hand seem to have preserved arousability, but Göder et al (Goder et al., 2001) found reduced number of (fast) arousals in SM patients the night before a migraine attack. Relative reduced arousability signaling awake-time overload or insufficient rest during sleep before a headache attack could therefore be a

common feature for NSM and SM patients. Division into sleep (STTH) - and non-sleep related TTH (NSTTH) was not part of the planned project and only five of 20 TTH patients had sleep related headache onset. The relatively few STTH patients did probably not have a significant effect on the main results, but a post hoc comparison showed that also NSTTH had significantly less fast arousals than STTH.

Preserved arousability in SM patients seems to be associated by slightly disturbed sleep. No increase in sleep disturbing factor indexes was found in SM patients. An increased sensitivity to sleep disturbing factors could be a disadvantage of preserved arousability. This notion also fits with the observed increase in sleep related migraine with age as sleep gets lighter with age (Crowley, 2011, Gori et al., 2012).

Slow bursts are said to reflect the slow wave sleep propensity, occurring with highest frequency before SWS in the first sleep cycles (Terzano et al., 2005). A lower D-burst index than controls and lower K-bursts index than NSM patient in SM patients seem reasonable if slow bursts could be apprehended as a signal of ability to achieve SWS. Then reduced amount of slow bursts signals is consistent with preserved or increased arousability. A lower number of low frequency, high amplitude EEG bursts in NREM and a lower index of high frequency EEG arousals during REM sleep have previously been found among interictal migraineurs with attacks related to sleep compared to controls (Della Marca et al., 2006). These findings have been interpreted as hypofunction of the arousal system (Della Marca et al., 2006). In the present study signs of hypoarousability was prominent in NSM, but not among the SM patients.

Many findings in the TTH group were comparable to the NSM group and most of the TTH patients were also NSTTH. However, compared to the migraineurs the TTH group had a higher insomnia load and more frequent headache. 12 of 20 TTH patients

had 15 or more headache days per month while the migraineurs had 2-6 attacks per month. Insomnia symptoms seem to increase the risk for headache and probably chronic headache in particular (Odegard et al., 2011). The CTTH group also tended to have less slow bursts than controls, significant for D-bursts. Increased insomnia load and higher headache frequency in the CTTH group compared to the migraine group probably are relevant for the diverging findings in slow bursts between CTTH and NSM patients.

13.2 Sleep, arousability and pain

We found decreased TPT in the NSM group in accordance with Schwedt et al. (Schwedt et al., 2011) and we found decreased PPT in the CTTH group as found before (Langemark et al., 1989, Fernandez-de-Las-Penas et al., 2007, Bezov et al., 2011).

Reduced PT are also found in healthy volunteers after sleep deprivation (Onen et al., 2001, Kundermann et al., 2004, Roehrs et al., 2006). Migraineurs with head allodynia during attack is found to report more sleep disturbances than non-allodynic migraineurs when compared to controls (Lovati et al., 2010). Both PSG and PT findings in NSM and TTH (mostly NSTTH) are similar and points to a relative sleep deprivation (Okifuji and Hare, 2011). Reduced latency to sleep onset among preictal migraineurs in the present study and preictally reduced TPT in a previous study (Sand et al., 2008) are compatible with sleep deprivation as a trigger for both allodynia and headache.

Looking ahead of sleep deprivation or not, those groups with a tendency to be “hypoaroused” (TTH and NSM groups) also tended to have reduced PT while those with preserved “arousability had preserved normal PT. If hyperarousability also is related to increased PT there is a pattern. Furthermore, arousability probably also is related to hypertension (Janackova and Sforza, 2008). Thus, arousability could be relevant in explaining the inverse relation between hypertension and pain (France, 1999, Stovner and Hagen, 2009, Messerotti Benvenuti et al., 2012).

14 Etiology and pathophysiology

14.1 How is a headache attack initiated?

NSM and TTH patients had quite corresponding results, possibly because the majority of our TTH patients were NSTTH. This interesting finding may suggest that sleep and attack precipitating mechanisms have similarities across different headache diagnoses. Except for the frequency of headache, insomnia symptoms and daytime tiredness comparable to controls in SM patients and headache onset time, symptoms did not differ between our headache groups. Migraine (in general) has no main specific actuating cause relevant for every patient (Purdy, 2010) and the same statement is probably valid for TTH too. Several different causal factors in different individuals may sum up to create a sufficient load that exceeds a threshold and initiates headache. Either if the load is a bit too high or the threshold is a bit too low, a mismatch ensues and the result, a headache, will be the same. Increased susceptibility to daytime load and subsequently increased need for sleep is probably characteristic for headache with tendency to onset during daytime, while increased susceptibility to sleep disturbances probably is characteristic when headache begins during sleep. This notion is in line with Cortelli et al (Cortelli et al., 2010) who wrote that a migraine attack might be a genetically determined behavioral response orchestrated by the threatened brain. Even if migraine and TTH are defined by different symptomatology (Olesen J, 2004), TTH probably also could be included in this statement. Accordingly, we hypothesize that the hypoarousability observed among the NSM and TTH patients (mainly NSTTH) may be related to a relative sleep deprivation and that these patients need more sleep than healthy controls (Figure 3).

Figure 3

Hypothesized different nervous system responses to increased daily-life-strain

Susceptible arousal system

Strain ↑ → Arousability ↓

Hypoarousal stress response

- Increased sleep need
- Increased susceptibility for sleep deprivation and reduced pain thresholds
- Increased susceptibility for daytime onset of headache
- Increased risk for hypotension (low blood pressure)

Robust arousal system

Strain ↑ → Preserved arousability

Preserved arousal stress response

- Normal sleep need
- Preserved pain thresholds
- Increased risk for sleep disturbances
- Increased risk for headache onset during sleep
- Increased risk for hypertension (high blood pressure) (Janackova 2008)

This hypothesis might explain the relation between hypertension and reduced pain.

14.2 Possible pathophysiological explanations

Activation of vl PAG has been found to induce a passive emotional coping with decreased vigilance and -reactivity while lateral and dorsolateral areas induce active coping with increased vigilance and hyper reactivity (Keay 2001). As a speculation, a constitutional difference between NSM and SM could partly depend on in which degree different PAG areas are activated.

Sleep deprivation in healthy volunteers has been shown to increase pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α), C-reactive protein (CRP) and PGE2 which all probably are able to increase pain sensitivity by both central and peripheral mechanisms (Haack et al., 2009).

It has been proposed that NO could induce headache by dilatation of cerebral and extra cerebral blood vessels (Olesen et al., 1994). However, NO also increases in the basal forebrain during sleep deprivation and is a causal event in the induction of recovery sleep in an animal study (Kalinchuk et al., 2006). To avoid cerebral exhaustion, sleep could restore equilibrium by reducing NO concentrations along with adenosine concentrations. NO also probably plays a role in pain modulation (Chen, 2009). If sleep or rest is postponed, a migraine attack could be an appropriate behavioral response for the threatened brain (Cortelli et al., 2010) in order to enforce rest. This reasoning might also be relevant for TTH. NO might also play a role in the observed possible relation between arousability and PT in the present study. Increased arousability is probably related to increased blood pressure (Janackova and Sforza, 2008). NO dilates blood vessels (Rand, 1992) (and thereby reduce blood pressure) and signalize need for sleep (Kalinchuk et al., 2006). NO is also involved in regulation of cerebral acetylcholine release and thereby probably also in supraspinal cholinergic antinociception (Lydic and Baghdoyan, 2005). Possibly, NO production and sensitivity might differ between patients with headache

onset during awake and sleep time. In SM patients headache and increased blood pressure would then be a earlier signs of sleep deprivation than daytime tiredness and reduced pain thresholds.

CSD increase corticocortical evoked potential for several hours in animal experiments (Faraguna et al., 2010). CSD has also been found to increase synaptic transmission and cyclooxygenase (COX)-2 expressions (Cui et al., 2008). CSD also seems to increase the need for sleep, probably by increasing prostaglandins in the brain (Cui et al., 2008). As for NO it is possible that CSD threshold and sensitivity differ between patients with headache onset during awake and sleep time. This notion fits with that increased slow wave sleep and tendency to reduced PT was found interictally in NSM patients. Reduced PT could then be related to increased levels of prostaglandins and increased synaptic transmission. For those with headache onset related to sleep, reduced tolerance for CSD during sleep could be relevant because SWS and PT were normal interictally. Headache onset could thereby be provoked by one or few CSD in SM patients. In this way mechanisms related to CSD might be relevant for increased sleep need, hyperesthesia and allodynia. This hypothetical notion is coherent with the observation that early drug intake reduces an evolving attack-related hypersensitivity even though there is no evidence that acute migraine drugs affect CSD per se (Costa et al., 2013).

A relation between CSD and NO probably exists and could be relevant for “hypoarousability” as a sign of CSD tolerance. Increased formation of endogenous NO is critical for subsequent, rapid recovery of cellular ionic homeostasis after CSD (Costa et al., 2013). Furthermore, female hormones probably increase susceptibility for CSD (Costa et al., 2013).

Short term 5-HT deficiency reduced the regulation of diurnal cyclic sleep-awake rhythm (Nakamaru-Ogiso et al., 2012). Hence, a stronger homeostatic drive may be necessary to induce sleep if 5-HT is reduced and insomnia could be the consequence. However, at least in rats sleep deprivation also seems to increase the brain serotonin turn over (Asikainen et al., 1997).

Rat experiments suggest that a stress-induced sleep disturbance simultaneously activates sleep and arousal systems (Cano et al., 2008), and a similar co-activation is hypothesized as essential in human insomnia where emotional or physiological. Increased neural activity can induce increased sleep need (Porkka-Heiskanen and Kalinchuk, 2011) probably by increased cerebral adenosine. However, none of the headache groups had more physical activity than the controls. On the other hand both NSM and TTH (mostly NSTTH) had increased autonomic and anxiety symptoms in the present study. In concert with our present results a recent review also conclude that anxiety disorders are nearly twice as common as depression in migraineurs (Smitherman et al., 2013). Hence, increased sleep need signaled by increased objective sleep quality and daytime tiredness might be secondary to lengthy emotional and autonomic physiologic activation in NSM and TTH (mainly NSTTH).

The possible pathophysiologic mechanisms are extremely many. Headache certainly also involve many mechanisms in real life. The most relevant mechanism probably also differ in different people.

14.3 Possible clinical implications

Diagnoses usually make communication and research easier, but could on the other hand oversimplify the individual complexity in different subjects' state and trait. It is well known that one symptom can have different causes and that one "cause" can give different symptoms. In this way the underlying or actuating causes might differ for subjects with the same type of headache and be common for subjects with different headache diagnoses as TTH and migraine (Karli et al., 2005). Headache features also overlap between migraine and TTH and symptoms often coexist over time (Karli et al., 2005, Sacco, 2008). Furthermore, headaches are associated with different diseases (Schankin and Straube, 2012), disorders and symptoms (Odegard et al., 2010, Lucchetti et al., 2013, Yoon et al., 2013). Interestingly, rather than the specific headache diagnosis it is the headache onset time that separate our results into quite distinct groups. Primary headache certainly can be the main problem for individuals and "isolated" treatment of headache itself has obviously a great value. But "primary" headache may also often be an "end symptom" signaling a sum of individually inborn vulnerability and daily life factors. If so, primary headache is "primary" because the causes are multifarious (Cutrer, 2010), discrete and difficult to detect and treat. From this point of view it is probably more useful to hypothesize that different loads, to a variable extent, increase the risk for headache rather than only being "associated with the headache". Similarly, based on our results, it is probably often more correct and useful to think that increased sleepiness may trigger headache rather than more passive descriptions like: "drowsiness and frequent yawning may occur the preceding day"(Adams et al., 1997). However, headache also contributes to the individual "total load" and probably increases the risk for other symptoms (Odegard et al., 2013). Discussion about coping strategies to decrease the total load could probably be fruitful in treatment of some patients.

For example, if headache evolves regularly during sleep, a thorough search for sleep-disturbing factors with PSG may be indicated even in patients with a primary headache diagnosis (Paiva et al., 1995). Also, if events like snoring, hypopneas, or PLMs are found, active treatment should be considered. For those with bothersome headache with onset during sleep, treatment for sleep disturbing factors, applying thresholds lower than those usually applied, could be a future option.

15 What is achieved and where to go

15.1 What this thesis adds

A controlled and blinded study combining questionnaires, sleep- and headache diaries, PSG and PT measurements has not been performed previously in migraine and tension-type headache patients. Increased affective symptom load and subjectively reduced sleep quality were common features for all our headache groups and specific markers related to ICHD-II headache groups were accordingly not found. The difference between controls on the one side and NSM- and TTH patients on the other was in principle the same as reported between healthy controls before and after sleep deprivation: Increased frequency of daytime tiredness is a common experience, increased SWS, reduced amount of fast arousals (De Gennaro et al., 2001) and reduced PT (Onen et al., 2001, Kundermann et al., 2004, Roehrs et al., 2006). A chronic sleep deprived or hypoarousal status may be a common feature among NSM and TTH (mainly NSTTH) patients which seem to be further worsened in migraineurs before an attack. SM patients seem to have a preserved arousability and PT, but possibly are more susceptible to sleep disturbing factors.

15.2 Future perspectives

Comparison of sleep quality and pain thresholds in controlled studies with high statistical power is needed to confirm or reject our results. The most reliable results probably come from longitudinal studies where intra- individual comparison in different headache stages can be performed. However, such design is time consuming for the participants and they probably need to be highly motivated. Men and women probably also should be studied separately and compared.

In such studies measurements of blood pressure is recommended. If there is a difference in blood pressure between those with onset of headache during sleep and other times is found, this could strengthen the notion that different part of PAG is activated in these two groups and that hypertension could be a subtle sign of sleep deprivation. Furthermore the relation between arousability, pain thresholds and blood pressure could be clarified.

So far, only mean values of diaries sleep time and PT measurements are evaluated, but in future studies more details could be revealed. Both the day to day variation of sleep time in relation to attack and the anatomical distribution of reduced pain thresholds in the present study is planned to be evaluated. Comparing threshold in the trigeminal area with thresholds at distant sites like the hand or foot may provide a distinction between local sensitization to pain as opposed to a central sensitization disorder. As we found no differences in objective sleep disturbing factor between NSM and SM patients, possible differences in frequency of snoring between these groups could be of relevance.

Intervention studies where headache patients with nightly onset and subclinical apnoe/hypopnea indexes or PLM indexes are treated could also be valuable. Intervention

studies treating anxiety and insomnia symptoms in headache patients probably also could be advantageous.

Furthermore, PSG studies comparing subjects with anxiety symptoms high and low in the normal range could be interesting to reject or confirm that the high symptom group might need more sleep than the low symptom group.

15.3 Conclusions

Data presented in this thesis indicates “classical” signs of sleep deprivation without obvious reason in NSM and TTH while SM patients have more obvious reasons to be sleep deprived, but have no “classical” signs of sleep deprivation. However, as discussed above, sleep deprivation might interfere with both central and peripheral mechanisms relevant for headache and the connections are complex. However, even if we detected differences on group level, no diagnostic markers for individual subject with headache is found.

To our knowledge the relationship between sleep and PT has not been investigated in migraineurs and tension type headache by others in a blinded, controlled design. However, data in this thesis should be considered as preliminary and studied further in a longitudinal design.

Reference list

- AASM (1999) Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. In: *Sleep*, vol. 22, pp 667-689.
- Adams RD, Victor M, Ropper AH (1997) Headache and other craniofacial pains In: *Principles of neurology* (Adams, R. D. et al., eds), pp 3-1618 United States of America: The McGraw-Hill companies, Inc. .
- Afridi SK, Giffin NJ, Kaube H, Friston KJ, Ward NS, Frackowiak RS, Goadsby PJ (2005) A positron emission tomographic study in spontaneous migraine. *Arch Neurol* 62:1270-1275.
- Aldrich MS, Chauncey JB (1990) Are morning headaches part of obstructive sleep apnea syndrome? *Arch Intern Med* 150:1265-1267.
- Alstadhaug K, Salvesen R, Bekkelund S (2007) Insomnia and circadian variation of attacks in episodic migraine. *Headache* 47:1184-1188.
- Asikainen M, Toppila J, Alanko L, Ward DJ, Stenberg D, Porkka-Heiskanen T (1997) Sleep deprivation increases brain serotonin turnover in the rat. *Neuroreport* 8:1577-1582.
- Bahra A, Matharu MS, Buchel C, Frackowiak RS, Goadsby PJ (2001) Brainstem activation specific to migraine headache. *Lancet* 357:1016-1017.
- Barbanti P, Fabbrini G, Aurilia C, Vanacore N, Cruccu G (2007) A case-control study on excessive daytime sleepiness in episodic migraine. *Cephalalgia* 27:1115-1119.
- Bendtsen L, Jensen R, Olesen J (1996) Decreased pain detection and tolerance thresholds in chronic tension-type headache. *Arch Neurol* 53:373-376.
- Berry RB, Brooks R, Gamaldo CE, Harding SM, Marcus CL, Vaughn BV (2012) *The AASM manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications* (American Academy of Sleep Medicine, W., IL 60154, U.S.A, ed) USA.
- Bezov D, Ashina S, Jensen R, Bendtsen L (2011) Pain perception studies in tension-type headache. *Headache* 51:262-271.
- Bjork M, Stovner LJ, Hagen K, Sand T (2011) What initiates a migraine attack? Conclusions from four longitudinal studies of quantitative EEG and steady-state visual-evoked potentials in migraineurs. *Acta Neurol Scand Suppl* 56-63.
- Borbely AA (1982) A two process model of sleep regulation. *Hum Neurobiol* 1:195-204.
- Brennan KC, Charles A (2009) Sleep and headache. *Semin Neurol* 29:406-418.
- Brodal P (2007) *Sentralnervesystemet*. Universitetsforlaget AS, PB 508 Sentrum, 0105 Oslo: Universitetsforlaget.
- Burstein R, Jakubowski M, Garcia-Nicas E, Kainz V, Bajwa Z, Hargreaves R, Becerra L, Borsook D (2010) Thalamic Sensitization Transforms Localized Pain into Widespread Allodynia. *Ann Neurol* 68:81-91.
- Burstein R, Strassman A, Moskowitz M (2012) Can cortical spreading depression activate central trigeminovascular neurons without peripheral input? Pitfalls of a new concept. *Cephalalgia* 32:509-511.
- Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 28:193-213.
- Cano G, Mochizuki T, Saper CB (2008) Neural circuitry of stress-induced insomnia in rats. *J Neurosci* 28:10167-10184.
- Cao Y, Aurora SK, Nagesh V, Patel SC, Welch KM (2002) Functional MRI-BOLD of brainstem structures during visually triggered migraine. *Neurology* 59:72-78.
- Chen PK, Fuh JL, Lane HY, Chiu PY, Tien HC, Wang SJ (2011) Morning headache in habitual snorers: frequency, characteristics, predictors and impacts. *Cephalalgia* 31:829-836.

Formatert: Norsk (bokmål)

- Chen Y (2009) Advances in the pathophysiology of tension-type headache: from stress to central sensitization. *Curr Pain Headache Rep* 13:484-494.
- Chokroverty S (2009a) An overview of normal sleep. In: *Sleep Disorders Medicine: basic science, technical considerations, and clinical aspects* (Chokroverty, S., ed), pp 5-21 1600 John F. Kennedy Blvd. Ste 1800, Philadelphia, PA 19103-2899: Saunders Elsevier.
- Chokroverty S (2009b) Sleep Deprivation and Sleepiness. In: *Sleep Disorders Medicine: Basic science, technical considerations and clinical aspects* (Chokroverty, S., ed), pp 22-28 1600 John F. Kennedy Blvd. Ste 1800, Philadelphia, PA 19103-2899: Saunders Elsevier.
- Cologno D, Mazzeo A, Lecce B, Mundi C, Petretta V, Casucci G, d'Onofrio F (2012) Triptans: over the migraine. *Neurol Sci* 33 Suppl 1:S193-198.
- Cortelli P, Pierangeli G, Montagna P (2010) Is migraine a disease? *Neurol Sci* 31 Suppl 1:S29-31.
- Costa C, Tozzi A, Rainero I, Cupini LM, Calabresi P, Ayata C, Sarchielli P (2013) Cortical spreading depression as a target for anti-migraine agents. *J Headache Pain* 14:62.
- Crowley K (2011) Sleep and sleep disorders in older adults. *Neuropsychol Rev* 21:41-53.
- Cui Y, Kataoka Y, Inui T, Mochizuki T, Onoe H, Matsumura K, Urade Y, Yamada H, Watanabe Y (2008) Up-regulated neuronal COX-2 expression after cortical spreading depression is involved in non-REM sleep induction in rats. *J Neurosci Res* 86:929-936.
- Cutrer FM (2010) Pathophysiology of migraine. *Semin Neurol* 30:120-130.
- De Gennaro L, Ferrara M, Bertini M (2001) EEG arousals in normal sleep: variations induced by total and selective slow-wave sleep deprivation. *Sleep* 24:673-679.
- Della Marca G, Vollono C, Rubino M, Di Trapani G, Mariotti P, Tonali PA (2006) Dysfunction of arousal systems in sleep-related migraine without aura. *Cephalalgia* 26:857-864.
- Dexter JD (1979) The relationship between stage III + IV + REM sleep and arousals with migraine. *Headache* 19:364-369.
- Dexter JD, Riley TL (1975) Studies in nocturnal migraine. *Headache* 15:51-62.
- Dodick DW, Eross EJ, Parish JM, Silber M (2003) Clinical, anatomical, and physiologic relationship between sleep and headache. *Headache* 43:282-292.
- Drake ME, Jr., Pakalnis A, Andrews JM, Bogner JE (1990) Nocturnal sleep recording with cassette EEG in chronic headaches. *Headache* 30:600-603.
- Engstrom M, Hagen K, Bjork M, Gravidahl GB, Sand T (2013a) Sleep-related and non-sleep-related migraine: interictal sleep quality, arousals and pain thresholds. *J Headache Pain* 14:68.
- Engstrom M, Hagen K, Bjork MH, Stovner LJ, Gravidahl GB, Stjern M, Sand T (2013b) Sleep quality, arousal and pain thresholds in migraineurs: a blinded controlled polysomnographic study. *J Headache Pain* 14:12.
- Engstrøm M, Hagen K, Bjørk M, Stovner LJ, Stjern M, Sand T (2013) Sleep quality, arousal and pain thresholds in tension-type headache. Submitted.
- Engstrøm M, Ødegård SS, Sand T, Stovner LJ, Zwart JA, Hagen K (2011) The reliability of a New Sleep Screening Questionnaire for Large Population-Based Studies: The Third Nord-Trøndelag Health Study *The Open Sleep Journal* 4:14-19.
- Faraguna U, Nelson A, Vyazovskiy VV, Cirelli C, Tononi G (2010) Unilateral cortical spreading depression affects sleep need and induces molecular and electrophysiological signs of synaptic potentiation in vivo. *Cereb Cortex* 20:2939-2947.
- Faravelli C, Alessandra Scarpato M, Castellini G, Lo Sauro C (2013) Gender differences in depression and anxiety: The role of age. *Psychiatry Res*.
- Fernandez-de-las-Penas C, Arendt-Nielsen L, Cuadrado ML, Pareja JA (2009) Generalized mechanical pain sensitivity over nerve tissues in patients with strictly unilateral migraine. *Clin J Pain* 25:401-406.
- Fernandez-de-Las-Penas C, Cuadrado ML, Arendt-Nielsen L, Ge HY, Pareja JA (2007) Increased pericranial tenderness, decreased pressure pain threshold, and headache clinical parameters in chronic tension-type headache patients. *Clin J Pain* 23:346-352.

- France CR (1999) Decreased pain perception and risk for hypertension: considering a common physiological mechanism. *Psychophysiology* 36:683-692.
- Gee JR, Chang J, Dublin AB, Vijayan N (2005) The association of brainstem lesions with migraine-like headache: an imaging study of multiple sclerosis. *Headache* 45:670-677.
- Giffin NJ, Ruggiero L, Lipton RB, Silberstein SD, Tvedskov JF, Olesen J, Altman J, Goadsby PJ, Macrae A (2003) Premonitory symptoms in migraine: an electronic diary study. *Neurology* 60:935-940.
- Goder R, Fritzer G, Kapsokalyvas A, Kropp P, Niederberger U, Strenge H, Gerber WD, Aldenhoff JB (2001) Polysomnographic findings in nights preceding a migraine attack. *Cephalalgia* 21:31-37.
- Goksan B, Gunduz A, Karadeniz D, Agan K, Tascilar FN, Tan F, Purisa S, Kaynak H (2009) Morning headache in sleep apnoea: clinical and polysomnographic evaluation and response to nasal continuous positive airway pressure. *Cephalalgia* 29:635-641.
- Gori S, Lucchesi C, Morelli N, Maestri M, Bonanni E, Murri L (2012) Sleep-related migraine occurrence increases with aging. *Acta Neurol Belg* 112:183-187.
- Grossi DB, Chaves TC, Goncalves MC, Moreira VC, Canonica AC, Florencio LL, Bordini CA, Speciali JG, Bigal ME (2011) Pressure pain threshold in the craniocervical muscles of women with episodic and chronic migraine: a controlled study. *Arq Neuropsiquiatr* 69:607-612.
- Haack M, Lee E, Cohen DA, Mullington JM (2009) Activation of the prostaglandin system in response to sleep loss in healthy humans: potential mediator of increased spontaneous pain. *Pain* 145:136-141.
- Haas DC, Kent PF, Friedman DI (1993) Headache caused by a single lesion of multiple sclerosis in the periaqueductal gray area. *Headache* 33:452-455.
- Hamel E (2007) Serotonin and migraine: biology and clinical implications. *Cephalalgia* 27:1293-1300.
- Holle D, Wessendorf TE, Zaremba S, Naegel S, Diener HC, Katsarava Z, Gaul C, Obermann M (2011) Serial polysomnography in hypnic headache. *Cephalalgia* 31:286-290.
- Iber C, Ancoli-Israel S, Chesson A, Quan SF (2007) The AASM Manual for the Scoring of Sleep and Associated Events. Rules, Terminology and Technical Specifications. (Medicine, A. A. o. S., ed), pp 1-59 Westchester, IL 60154, U.S.A: American Academy of Sleep Medicine, Westchester, IL.
- Janackova S, Sforza E (2008) Neurobiology of sleep fragmentation: cortical and autonomic markers of sleep disorders. *Curr Pharm Des* 14:3474-3480.
- Jensen R, Olsborg C, Salvesen R, Torbergsen T, Bekkelund SI (2004) Is obstructive sleep apnea syndrome associated with headache? *Acta Neurol Scand* 109:180-184.
- Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 14:540-545.
- Johnson KG, Ziemba AM, Garb JL (2012) Improvement in Headaches With Continuous Positive Airway Pressure for Obstructive Sleep Apnea: A Retrospective Analysis. *Headache*.
- Kalinchuk AV, Lu Y, Stenberg D, Rosenberg PA, Porkka-Heiskanen T (2006) Nitric oxide production in the basal forebrain is required for recovery sleep. *J Neurochem* 99:483-498.
- Karli N, Zarifoglu M, Calisir N, Akgöz S (2005) Comparison of pre-headache phases and trigger factors of migraine and episodic tension-type headache: do they share similar clinical pathophysiology? *Cephalalgia* 25:444-451.
- Karthik N, Sinha S, Taly AB, Kulkarni GB, Ramachandraiah CT, Rao S (2012) Alteration in polysomnographic profile in 'migraine without aura' compared to healthy controls. *Sleep Med*.
- Keklund G, Akerstedt T (1997) Objective components of individual differences in subjective sleep quality. *J Sleep Res* 6:217-220.
- Kelman L (2007) The triggers or precipitants of the acute migraine attack. *Cephalalgia* 27:394-402.

- Kelman L, Rains JC (2005) Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. *Headache* 45:904-910.
- Kristiansen HA, Kvaerner KJ, Akre H, Overland B, Russell MB (2011a) Migraine and sleep apnea in the general population. *J Headache Pain* 12:55-61.
- Kristiansen HA, Kvaerner KJ, Akre H, Overland B, Russell MB (2011b) Tension-type headache and sleep apnea in the general population. *J Headache Pain* 12:63-69.
- Kundermann B, Sernal J, Huber MT, Krieg JC, Lautenbacher S (2004) Sleep deprivation affects thermal pain thresholds but not somatosensory thresholds in healthy volunteers. *Psychosom Med* 66:932-937.
- Langemark M, Jensen K, Jensen TS, Olesen J (1989) Pressure pain thresholds and thermal nociceptive thresholds in chronic tension-type headache. *Pain* 38:203-210.
- Lanteri-Minet M, Radat F, Chautard MH, Lucas C (2005) Anxiety and depression associated with migraine: influence on migraine subjects' disability and quality of life, and acute migraine management. *Pain* 118:319-326.
- Lauritzen M, Dreier JP, Fabricius M, Hartings JA, Graf R, Strong AJ (2011) Clinical relevance of cortical spreading depression in neurological disorders: migraine, malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury. *J Cereb Blood Flow Metab* 31:17-35.
- Levy D, Moskowitz MA, Nosedá R, Burstein R (2012) Activation of the migraine pain pathway by cortical spreading depression: do we need more evidence? *Cephalalgia* 32:581-582.
- Linnman C, Moulton EA, Barmettler G, Becerra L, Borsook D (2012) Neuroimaging of the periaqueductal gray: state of the field. *Neuroimage* 60:505-522.
- Loh NK, Dinner DS, Foldvary N, Skobieranda F, Yew WW (1999) Do patients with obstructive sleep apnea wake up with headaches? *Arch Intern Med* 159:1765-1768.
- Lovati C, D'Amico D, Bertora P, Raimondi E, Rosa S, Zardoni M, Bussone G, Mariani C (2010) Correlation between presence of allodynia and sleep quality in migraineurs. *Neurol Sci* 31 Suppl 1:S155-158.
- Lucchetti G, Peres MF, Lucchetti AL, Mercante JP, Guendler VZ, Zukerman E (2013) Generalized anxiety disorder, subthreshold anxiety and anxiety symptoms in primary headache. *Psychiatry Clin Neurosci* 67:41-49.
- Lydic R, Baghdoyan HA (2005) Sleep, anesthetics, and the neurobiology of arousal state control. *Anesthesiology* 103:1268-1295.
- Mainero C, Boshyan J, Hadjikhani N (2011) Altered functional magnetic resonance imaging resting-state connectivity in periaqueductal gray networks in migraine. *Ann Neurol* 70:838-845.
- Manni R, Sances G, Terzaghi M, Ghiotto N, Nappi G (2004) Hypnic headache: PSG evidence of both REM- and NREM-related attacks. *Neurology* 62:1411-1413.
- McCarley RW (2007) Neurobiology of REM and NREM sleep. *Sleep Med* 8:302-330.
- McCarley RW (2009a) Neurobiology of Rapid Eye Movement and Non-Rapid Eye Movement Sleep. In: *Sleep Disorders Medicine* (Chokroverty, S., ed), pp 29-58 1600 John F. Kennedy Blvd. Ste 1800, Philadelphia, PA 19103-2899: Saunders Elsevier.
- McCarley RW (2009b) Neurobiology of Rapid eye Movement and Non-Rapid Eye Movement Sleep. In: *Sleep disorders medicine: Basic science, technical considerations and clinical aspects* (Chokroverty, S., ed), pp 29-58 1600 John F. Kennedy Blvd. Ste 1800, Philadelphia, PA 19103-2899: Saunders Elsevier.
- Messerotti Benvenuti S, Ring C, Palomba D, Baldanzi F, Zanatta P (2012) Cortical and autonomic responses to noxious stimulation during anesthesia in cardiac surgery patients are moderated by preanesthetic blood pressure levels. *Psychophysiology* 49:697-703.
- Monti JM, Monti D (2000) Sleep disturbance in generalized anxiety disorder and its treatment. *Sleep Med Rev* 4:263-276.

- Nakamaru-Ogiso E, Miyamoto H, Hamada K, Tsukada K, Takai K (2012) Novel biochemical manipulation of brain serotonin reveals a role of serotonin in the circadian rhythm of sleep-wake cycles. *Eur J Neurosci* 35:1762-1770.
- Neau JP, Paquereau J, Bailbe M, Meurice JC, Ingrand P, Gil R (2002) Relationship between sleep apnoea syndrome, snoring and headaches. *Cephalalgia* 22:333-339.
- Nilsen KB, Sand T, Stovner LJ, Leistad RB, Westgaard RH (2007) Autonomic and muscular responses and recovery to one-hour laboratory mental stress in healthy subjects. *BMC Musculoskelet Disord* 8:81.
- Odegard SS, Engstrom M, Sand T, Stovner LJ, Zwart JA, Hagen K (2010) Associations between sleep disturbance and primary headaches: the third Nord-Trøndelag Health Study. *J Headache Pain* 11:197-206.
- Odegard SS, Sand T, Engstrom M, Stovner LJ, Zwart JA, Hagen K (2011) The long-term effect of insomnia on primary headaches: a prospective population-based cohort study (HUNT-2 and HUNT-3). *Headache* 51:570-580.
- Odegard SS, Sand T, Engstrom M, Zwart JA, Hagen K (2013) The impact of headache and chronic musculoskeletal complaints on the risk of insomnia: longitudinal data from the Nord-Trøndelag health study. *J Headache Pain* 14:24.
- Okifuji A, Hare BD (2011) Do sleep disorders contribute to pain sensitivity? *Current rheumatology reports* 13:528-534.
- Olesen J e (ed.) (2004) *The International Classification of Headache Disorders: 2nd edition.*
- Olesen J, Iversen HK, Thomsen LL (1993) Nitric oxide supersensitivity: a possible molecular mechanism of migraine pain. *Neuroreport* 4:1027-1030.
- Olesen J, Thomsen LL, Iversen H (1994) Nitric oxide is a key molecule in migraine and other vascular headaches. *Trends Pharmacol Sci* 15:149-153.
- Onen SH, Alloui A, Gross A, Eschallier A, Dubray C (2001) The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *J Sleep Res* 10:35-42.
- Paiva T, Batista A, Martins P, Martins A (1995) The relationship between headaches and sleep disturbances. *Headache* 35:590-596.
- Paiva T, Farinha A, Martins A, Batista A, Guillemainault C (1997) Chronic headaches and sleep disorders. *Arch Intern Med* 157:1701-1705.
- Parish JM, Somers VK (2004) Obstructive sleep apnea and cardiovascular disease. *Mayo Clin Proc* 79:1036-1046.
- Parrino L, Boselli M, Spaggiari MC, Smerieri A, Terzano MG (1998) Cyclic alternating pattern (CAP) in normal sleep: polysomnographic parameters in different age groups. *Electroencephalogr Clin Neurophysiol* 107:439-450.
- Perneger TV (1998) What's wrong with Bonferroni adjustments. *Bmj* 316:1236-1238.
- Porkka-Heiskanen T, Kalinchuk AV (2011) Adenosine, energy metabolism and sleep homeostasis. *Sleep Med Rev* 15:123-135.
- Purdy RA (2010) Migraine is curable! *Neurol Sci* 31 Suppl 1:S141-143.
- Rains JC (2011) Morning headache in habitual snorers. *Cephalalgia* 31:981-983.
- Rains JC, Poceta JS (2010) Sleep and headache. *Curr Treat Options Neurol* 12:1-15.
- Rand MJ (1992) Nitroergic transmission: nitric oxide as a mediator of non-adrenergic, non-cholinergic neuro-effector transmission. *Clin Exp Pharmacol Physiol* 19:147-169.
- Raskin NH, Hosobuchi Y, Lamb S (1987) Headache may arise from perturbation of brain. *Headache* 27:416-420.
- Rechtschaffen A, Kales A (1968) Sleep scoring manual. In: *A manual for standardized terminology, Techniques and scoring system for sleep stages of human subject*, pp 1-23.
- Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T (2006) Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 29:145-151.
- Rosa RR, Bonnet MH (2000) Reported chronic insomnia is independent of poor sleep as measured by electroencephalography. *Psychosom Med* 62:474-482.

Formatert: Norsk (bokmål)

- Rossi P, Vollono C, Valeriani M, Sandrini G (2011) The contribution of clinical neurophysiology to the comprehension of the tension-type headache mechanisms. *Clin Neurophysiol* 122:1075-1085.
- Sacco S (2008) Diagnostic issues in tension-type headache. *Curr Pain Headache Rep* 12:437-441.
- Sand T (1991) EEG in migraine: a review of the literature. *Funct Neurol* 6:7-22.
- Sand T, Hagen K, Schrader H (2003) Sleep apnoea and chronic headache. *Cephalalgia* 23:90-95.
- Sand T, Zhitniy N, Nilsen KB, Helde G, Hagen K, Stovner LJ (2008) Thermal pain thresholds are decreased in the migraine preattack phase. *Eur J Neurol* 15:1199-1205.
- Sateia MJ (2005) The international classification of sleep disorders 2nd edition: Diagnostic and coding manual. (American Academy of Sleep Medicine, W., IL 60154, U.S.A, ed).
- Schankin CJ, Straube A (2012) Secondary headaches: secondary or still primary? *J Headache Pain* 13:263-270.
- Schlack I, Court J (1983) [EEG in vasomotor cephalgias and in tension headache]. *EEG EMG Z Elektroenzephalogr Elektromyogr Verwandte Geb* 14:17-21.
- Schulz KF, Grimes DA (2005) Multiplicity in randomised trials I: endpoints and treatments. *Lancet* 365:1591-1595.
- Schwedt TJ, Krauss MJ, Frey K, Gereau RWt (2011) Episodic and chronic migraineurs are hypersensitive to thermal stimuli between migraine attacks. *Cephalalgia* 31:6-12.
- Sforza E, Jouny C, Ibanez V (2000) Cardiac activation during arousal in humans: further evidence for hierarchy in the arousal response. *Clin Neurophysiol* 111:1611-1619.
- Smitherman TA, Kolivas ED, Bailey JR (2013) Panic disorder and migraine: comorbidity, mechanisms, and clinical implications. *Headache* 53:23-45.
- Snell RS (2001) Clinical neuroanatomy. 351 West Camden Street, Baltimore, Maryland 21201-2436; 530 Walnut street, Philadelphia, Pennsylvania 19106 USA Lippincott Williams& Wilkins.
- Spierings EL, Ranke AH, Honkoop PC (2001) Precipitating and aggravating factors of migraine versus tension-type headache. *Headache* 41:554-558.
- Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, Steiner T, Zwart JA (2007) The global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia* 27:193-210.
- Stovner LJ, Hagen K (2009) Hypertension-associated hypalgesia: a clue to the comorbidity of headache and other pain disorders. *Acta Neurol Scand Suppl* 46-50.
- Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA (1999) The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. *Neurology* 52:523-528.
- Terzano MG, Parrino L, Smerieri A, Carli F, Nobili L, Donadio S, Ferrillo F (2005) CAP and arousals are involved in the homeostatic and ultradian sleep processes. *J Sleep Res* 14:359-368.
- Terzano MG, Parrino L, Smerieri A, Chervin R, Chokroverty S, Guilleminault C, Hirshkowitz M, Mahowald M, Moldofsky H, Rosa A, Thomas R, Walters A (2002) Atlas, rules, and recording techniques for the scoring of cyclic alternating pattern (CAP) in human sleep. *Sleep Med* 3:187-199.
- Ulfberg J, Carter N, Talback M, Edling C (1996) Headache, snoring and sleep apnoea. *J Neurol* 243:621-625.
- Veloso F, Kumar K, Toth C (1998) Headache secondary to deep brain implantation. *Headache* 38:507-515.
- Weiller C, May A, Limmroth V, Juptner M, Kaube H, Schayck RV, Coenen HH, Diener HC (1995) Brain stem activation in spontaneous human migraine attacks. *Nat Med* 1:658-660.
- Yoon MS, Manack A, Schramm S, Fritsche G, Obermann M, Diener HC, Moebus S, Katsarava Z (2013) Chronic migraine and chronic tension-type headache are associated with concomitant low back pain: results of the German Headache Consortium study. *Pain* 154:484-492.

- Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM, Sleep Heart Health Study Research G (2002) Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch Intern Med* 162:893-900.
- Zappaterra M, Guerzoni S, Cainazzo MM, Ferrari A, Pini LA (2011) Basal cutaneous pain threshold in headache patients. *J Headache Pain* 12:303-310.
- Zhang B, Wing YK (2006) Sex differences in insomnia: a meta-analysis. *Sleep* 29:85-93.
- Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67:361-370.
- Zwart JA, Dyb G, Hagen K, Odegard KJ, Dahl AA, Bovim G, Stovner LJ (2003) Depression and anxiety disorders associated with headache frequency. The Nord-Trøndelag Health Study. *Eur J Neurol* 10:147-152.

Appendix

Operationally AASM in 2007 defined a significant leg movement event as: duration 0.5-10 seconds, starts when EMG increase more than 8 uV above resting EMG voltage and ends when at least 0.5 seconds does not exceed 2uV above resting EMG. A PLM series has at least 4 leg movements with 5-90 seconds between (Iber et al., 2007). The international classification of sleep disorder has another operationally definition (Sateia, 2005).

Table A. Population, sleep-diary, questionnaire and headache-related data for all patients : Counts or mean (SD)

	Controls for migraine (n=34)	Controls for TTH (n=29)	Migraine (n=53)	Tension-type headache (n=20)
Age (years)	39.6 (13.7)	41.2 (13.6)	38.2 (12.0)	40.9 (13.5)
Sex: F/M	20/14	15/14	41/12	11/9
Headache frequency (1-4)	Na	na	2.2 (0.7)	3.5 (0.7) ⁵
Headache history duration (years)	Na	na	21.6 (13.8)	15.8 (12.2)
Average diary sleep time (hour)	7.3 (0.8)	7.2 (0.8)	7.2 (1.0)	6.8 (1.1)
Long awakenings in diary (no)	0.1 (0.2)	0.1 (0.2)	0.4 (0.8)	0.4 (0.4)
Daytime tiredness frequency (0-4)	0.7 (0.8)	0.7 (0.9)	1.1 (0.9)	1.7 (1.0) ⁶
Insomnia KSQ score (0-16) ¹	3.4 (2.3)	3.4 (2.4)	6.1 (2.9)	7.9 (2.4) ⁷
Pain-related sleep trouble (1-4) ²	3.8 (2.6)	3.9 (2.7)	6.3 (3.2)	7.2 (3.2)
PSQIgs (0-21) ²	1.5 (1.4)	1.4 (1.4)	6.6 (4.4)	5.3 (3.5)
HADS anxiety score (0-21) ³	1.6 (2.1)	1.5 (2.2)	2.3 (2.3)	2.8 (3.0)
Autonomic index (0-30) ⁴	1.3 (0.7)	1.3 (0.6)	1.9 (1.0)	2.0 (1.0)

¹Sum of four insomnia-questions in Karolinska sleep questionnaire (KSQ), ²Pittsburgh sleep quality index global score, ³Sum of seven questions about anxiety symptoms during the last week from the Hospital Anxiety and Depression Scale questionnaire. ⁴Sum of ten questions about autonomic instability during the last year. Tension-type headache was compared statistically to migraine: Mann-Whitney test ⁵p<0.0005, ⁶p<0.05, ⁷p=0.006.

Table B. Polysomnography and pain threshold mean values (SD) for controls, interictal migraineurs, with sleep-migraine and non-sleep migraine subgroups, and tension-type headache.

	<u>Controls⁶</u> <u>(n=34)</u>	<u>Migraine</u> <u>(n=33)</u>	<u>Sleep-</u> <u>migraine</u> <u>(n=15)</u>	<u>Non-sleep</u> <u>migraine</u> <u>(n=18)</u>	<u>Tension-type</u> <u>headache (n=20)</u>
<u>Total sleep time</u> <u>(min)</u>	409 (68)	435 (61)	417 (67)	451 (52)	432 (46)
<u>Sleep efficiency</u> <u>(%)</u>	90.0 (8.1)	91.0 (6.1)	89.4 (7.6)	92.4 (4.2)	91.2 (5.6)
<u>Awakening index</u> <u>(no/h)</u>	0.99 (0.59)	1.27 (0.74)	1.45 (0.84)	1.12 (0.63)	1.1 (0.6)
<u>WASO duration</u> <u>(minutes)</u>	4.4 (3.8)	3.8 (1.7)	3.4 (1.3)	3.6 (1.6)	4.1 (2.7)
<u>Stage 1 (min)</u>	27 (19)	32 (15)	35 (17)	29 (13)	29 (15)
<u>Stage 2 (min)</u>	197 (47)	201 (44)	194 (44)	206 (45)	185 (34)
<u>Stage 3 (min)</u>	86 (31)	97 (28)	88 (25)⁵	104 (28)	107 (21)⁵
<u>REM (min)</u>	99 (26)	106 (35)	99 (38)	112 (32)	111 (30)
<u>Fast arousal index</u> <u>(per hour)¹</u>	18.3 (5.7)	16.3 (9.1)	17.4 (8.6)	15.5 (9.7)	14.5 (4.3)
<u>Mean fast arousal</u> <u>duration (seconds)</u>	9.3 (1.1)	9.0 (1.3)	9.3 (1.5)	8.7 (1.3)	9.6 (1.2)
<u>D-burst index (per</u> <u>hour)²</u>	11.8 (8.0)	9.5 (7.5)	7.3 (5.7)	11.3 (8.3)	7.9 (6.3)
<u>K-burst index (per</u> <u>hour)²</u>	3.0 (3.8)	3.3 (2.5)	2.4 (2.2)	4.0 (2.5)	3.7 (4.5)
<u>Pressure pain</u> <u>threshold (kPa)³</u>	661 (249)	549 (135)	586 (141)	519 (125)	543 (191)
<u>Heat pain</u> <u>threshold (°C)⁴</u>	13.4 (3.1)	11.7 (3.6)	12.4 (3.3)	11.0 (3.8)	12.7 (3.7)
<u>Cold pain</u> <u>threshold (°C)⁴</u>	20.8 (6.3)	17.2 (6.9)	18.4 (6.3)	16.2 (7.3)	19.4 (7.4)

¹Fast EEG-arousal. ²Slow EEG arousal. ³Mean from four bilateral sites. ⁴Expressed as the difference above/below the 32 C baseline Tension-type headache was compared statistically to migraine, sleep migraine and non-sleep migraine ⁵Mann-Whitney test p=0.026. ⁶Control group for migraine. ⁷ WASO: Wake after sleep onset.